VOLUME 34 SEPTEMBER 1969 NUMBER 9

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THE JOURNAL OF Organic Chemistry

PUBLISHED MONTHLY BY THE AMERICAN CHEMICAL SOCIETY

CARBOXYLIC ORTHO ACID DERIVATIVES

by **ROBERT DEWOLFE,** *Department of Chemistry, University of California at Santa Barbara, Goleta, California*

The voluminous literature on reactions of ortho acid derivatives, poorly indexed by abstract journals is not readily accessible to one unfamiliar with the field. Yet these reactions are both synthetically useful and mechanistically interesting, meriting the attention of chemists interested in a broad spectrum of problems. This book, specifically devoted to ortho acid derivatives intends to fulfill this need. It is an updated, comprehensive, critical and interpretive survey of the synthesis, properties, and reactions of the principal classes of ortho acid derivatives and should prove invaluable to synthetic and theoretical organic chemists who are concerned with reactions of organic compounds at the carboxyl level of oxydation. It should be included in all college, university, and technical libraries.

CONTENTS: SYNTHESIS AND PROPERTIES OF CARBOXYLIC ORTHO ESTERS AND RELATED COMPOUNDS • REACTIONS OF ORTHO ESTERS WHICH RESULT IN CARBON-OXYGEN OR CARBON-HALOGEN BOND FORMATION • REACTIONS OF ORTHO ESTERS WHICH RESULT IN CARBON-NITROGEN OR CARBON-PHOSPHORUS BOND FORMATION • REACTIONS OF ORTHO ESTERS WHICH INVOLVE CARBON-CARBON OR CARBON-HYDROGEN BOND FORMATION • CARBOHYDRATE ORTHO ESTERS • THIOORTHOCARBOXYALTES • THIOORTHOCARBONATES AND RELATED COMPOUNDS • AMIDE ACETALS • ESTER ANIMALS AND ORTHO AMIDES •

October 1969, about 466 pp., in preparation

ADVANCES IN PHYSICAL ORGANIC CHEMISTRY

VOLUME 7

edited by **V. GOLD,** *King's College, University of London, England*

1969, 352 pp., $13.50

NUCLEAR QUADRUPOLE COUPLING CONSTANTS

by **E.A.C. LUCKEN,** *Cyanamid European Research Institute, Geneva, Switzerland*

This monograph begins by defining and describing the derivation of the quadrupole coupling constant and continues by surveying the methods available for its measurement. The author then discusses the attempts which have been made to relate it to the electronic structure of the molecule, the nucleus of which is under examination. The second half of the book is devoted to a review of available data using as a basis for its correlation the simple bookkeeping method of Townes and Dailey.

1969, 360 pp., $14.50

ADVANCES IN CARBOHYDRATE CHEMISTRY

VOLUME 24

edited by **R. STUART TIPSON,** and **M. L. WOLFROM,** *Ohio State University, Columbus, Ohio*

December 1969, about 460 pp., in preparation

RING FORMING POLYMERIZATION RINGS

PART A: CARBOCYCLIC AND METALLORGANIC

By **ROBERT J. COTTER** and **MARKUS MATZNER,** *Both at the Research and Development Department, Chemicals and Plastics Operations Division, Union Carbide Corporation, Bound Brook, New Jersey*

Ring-forming polymerizations comprise a field of polymer chemistry that is undergoing tremendous growth. This original two-part work is an invaluable key to literature covering the rapidly increasing number of polymerizations that result in the formation of polymers having a new ring structure. Although not a comprehensive book on ring-containing polymers, it is an accurate, exhaustive survey of those polymers whose ring or rings are formed during polymerization. This book discusses polymers possessing widely different and complex structures and contains data on polymer classes of commercial interest.

1969, 395 pp., $19.50

LINEAR FREE ENERGY RELATIONSHIPS

By **PETER R. WELLS,** *Reader in Physical Chemistry, University of Queensland, Australia*

The correlation of relative reactivities in terms of relative free energy has provided 9 quantative basis in terms of which observations maybe discussed and theories of reactivity developed. This approach has become a well-defined section of physical organic chemistry, and is being applied with advantage in fields of inorganic and biochemical reactivity studies. In this monograph the well-established relationships are critically surveyed under the major headings of substrate structure, reagent structure and reaction medium. Substituent effects are examined in detail for various substrate types and theoretical treatments are discussed in terms of implications of the linear free energy relationships. The correlation of solvent effects upon solvolysis rates and upon acid strength are described and related to the concept of acidity functions. The relationships between quantities derived from reactivity and from spectroscopic studies are examined.

1968, 116 pp., $5.95

ANNUAL REVIEW OF NMR SPECTROSCOPY

VOLUME II

edited by **E. F. MOONEY,** *Department of Chemistry, University of Birmingham, England*

NMR spectroscopy is firmly established as a tool in all branches of chemistry. This series will enable the chemist to keep abreast of the various developments in the technique and the increasing range of applications of the method to structural analysis. This work is intended for chemists in all fields of research but will be particularly useful to the organic and analytical chemists.

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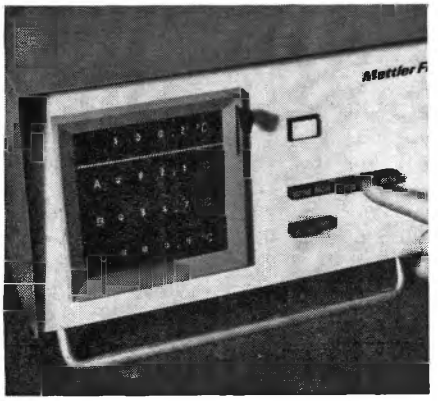

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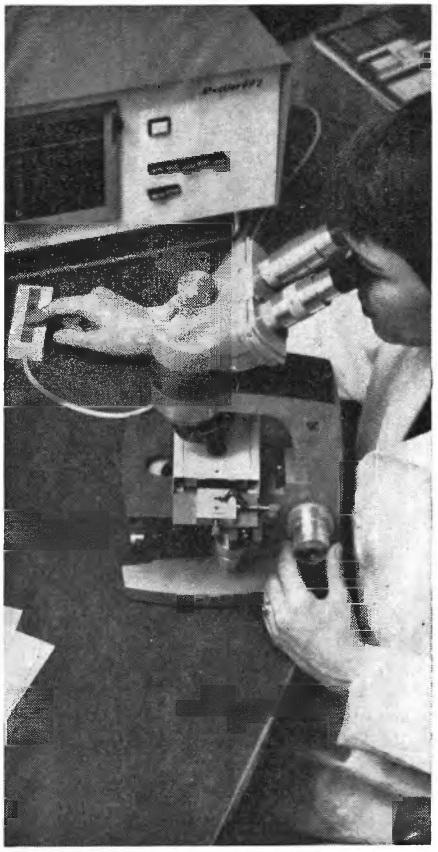

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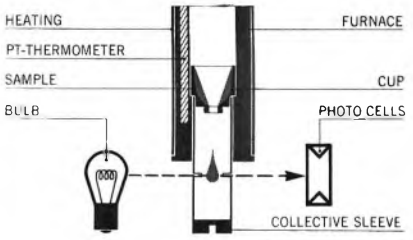

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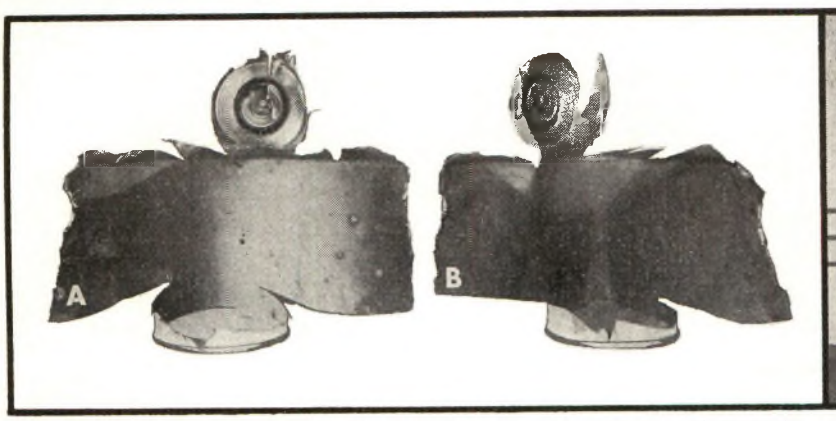

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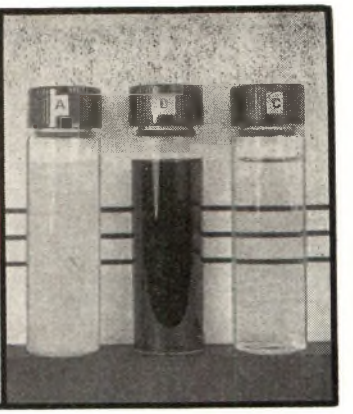

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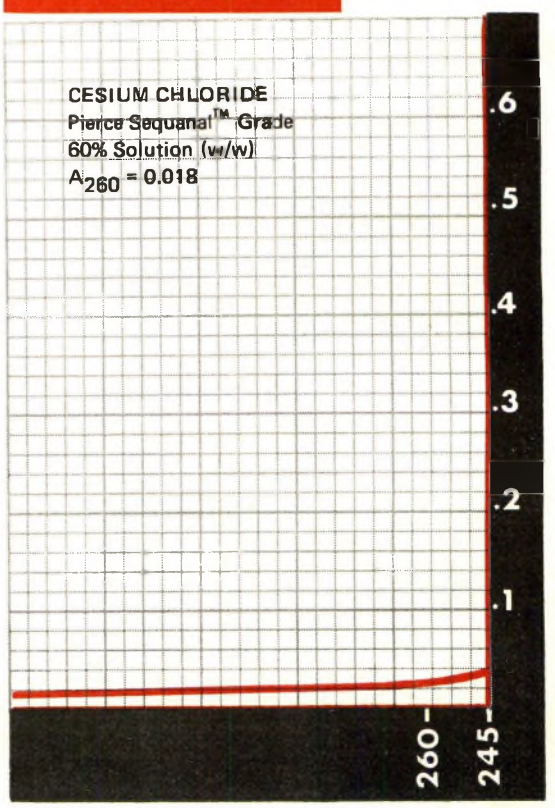

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Synthesis, Configuration, and Optical Purity of Asymmetric Primary Alcohols[1a]

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Samples of optically active and racemic isobutyl-1-d_1 alcohols required for the determination of the stereochemistry of the biosynthesis of the cholesterol side chain were prepared. Asymmetric reduction of isobutyraldehyde with (−)- and (+)-diisopinocampheyldeuterioboranes gave (−)-(1*R*)-isobutyl-1-d_1 alcohol (optical purity 27.1%) and (+)-(1*S*)-isobutyl-1-d_1 alcohol (optical purity 27.6%), respectively. Two specimens of optically pure (1*S*)-isobutyl-1-d_1 alcohol containing 80.5 and 70.2% deuterium were obtained by yeast reduction of samples of isobutyraldehyde-1-*d* containing 100 and 98.4% deuterium. The (+)-(3*R*)- and (−)-(3*S*)- isocaproic-3-d_1 acids, previously described by us, were shown to be 34.0 and 32.6% optically pure, respectively. The (+)-(1*S*)- and the (−)-(1*R*)-isobutyl-1-d_1 alcohol were related to (*R*)- and (*S*)-glyceraldehyde, respectively. The method of Horeau, studies utilizing the specificity of NAD^+ and yeast alcohol dehydrogenase (YADH), and a modified interpretation of the mode of reduction of ketones and aldehydes with (+)- and (−)-diisopinocampheylboranes led to identical configurational conclusions.

The transformation of lanosterol into cholesterol entails, among other steps, the reduction of the C-24 double bond. The stereochemistry of the addition of the hydrogen at C-24 is under investigation in our laboratory. The approach we chose was to biosynthesize cholesterol from 4(*R*)-2-^{14}C-mevalonic-4-t_1 acid (MVA) (t = ^{3}H), then cleave the side chain with an adrenal preparation, and isolate the resulting isocaproic acid. Ultimately, the stereochemistry at C-3 of the isocaproic acid, corresponding to that at C-24 of the cholesterol, would be established.[2]

Obviously the C-3 asymmetry of isocaproic-3-t_1 acid cannot be determined by relating it to a measurable rotation. An indirect approach was therefore required, and it was planned to degrade the acid to isobutyl-1-t_1 alcohol and define its configuration. The success of this approach depended heavily on two factors: our ability to degrade the isocaproic-3-t_1 acid without disturbing the asymmetry at C-3, and the feasibility of establishing the configuration at C-1 of the resulting alcohol. The stereospecific degradation of the acid to isobutyl-1-t_1 alcohol clearly was not an "insurmountable" problem, and we turned to the more involved question of determining the asymmetry at C-1 of the isobutyl-1-t_1 alcohol. At the outset, it was obvious that classical methods of defining the configuration of the isobutyl alcohol would be of no use, and that more specific microprocedures would be required. Under the circumstances, it appeared to us that the method of choice would be the NAD^+–alcohol dehydrogenase (ADH) oxidation of the alcohol to isobutyraldehyde. Because of the proven greater specificity of *yeast* alcohol dehydrogenase,[3] the studies were carried out with this enzyme.

Oxidation of ethanol with NAD^+ and *liver* ADH has been shown to proceed with the loss of the *pro*-(1*R*) proton.[4] The removal of the *pro*-(1*R*) proton was observed also on oxidation of geranyl-1-t_1 alcohol and farnesyl-1-t_1 alcohol with horse *liver* ADH.[5] In the reverse reaction, the enzymic reductions of 1-*d*-aldehydes, the (1*S*)-1-d_1-alcohols were obtained, indicating that the newly introduced hydrogen assumed the *pro*-(1*R*) orientation.[6] By analogy it seemed probable that NAD^+–YADH oxidation of isobutyl alcohol would also proceed with the removal of the *pro*-(1*R*) proton. Since this question was of paramount importance in our scheme of establishing the stereochemistry at C-24, prior to committing ourselves to this line of study we deemed it necessary to establish this point unequivocally.

As models for the studies, we required specimens of (+)- and (−)-isobutyl-1-d_1 alcohols of known absolute

(1) (a) This work was supported by Grants P-500H from the American Cancer Society and CA-K3-16614 from the National Institutes of Health; (b) Postdoctoral Fellow, 1966–1968.

(2) We have now proved that a 24-*pro*-(*S*) proton is added, resulting in the 24-(*R*) configuration [E. Caspi, K. R. Varma, and J. B. Greig, *Chem. Commun.*, 45 (1969)].

(3) See, for example, F. M. Dickinson and K. Dalziel, *Nature*, **214**, 31 (1967); *Biochem. J.*, **104**, 165 (1967).

(4) J. W. Cornforth, R. H. Cornforth, C. Donninger, G. Popjak, G. Ryback, and G. J. Schroepfer, *Proc. Roy. Soc.*, **163B**, 436 (1966), and references therein.

(5) C. Donninger and G. Popjak, *ibid.*, **163B**, 465 (1966); C. Donninger and G. Ryback, *Biochem. J.*, **11P**, 91 (1964).

(6) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 3595 (1966); W. A. Sanderson and H. S. Mosher, *ibid.*, **88**, 4185 (1966).

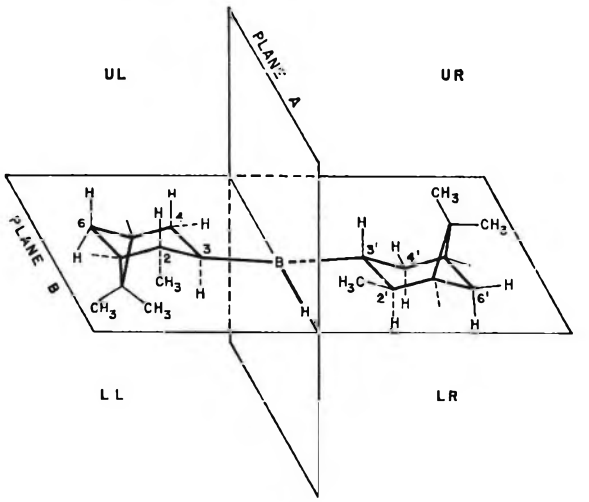

Figure 1.

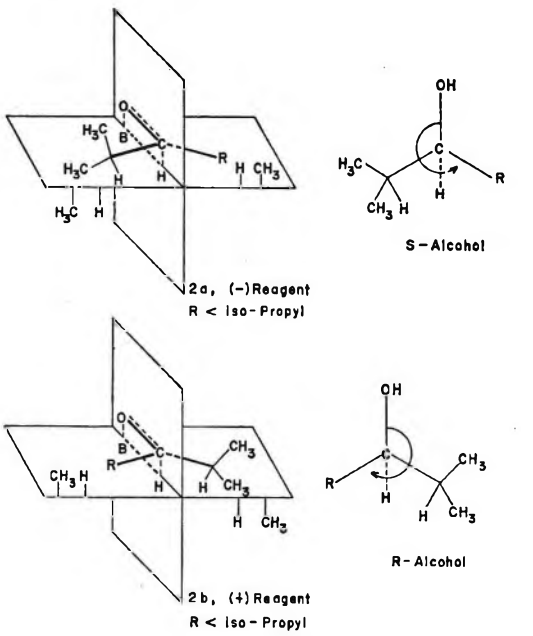

Figure 2.

stereochemistry. The optically active (+)- and (−)-alcohols were prepared by reduction of isobutyraldehyde with (+)- and (−)-diisopinocampheyldeuterioboranes, respectively.[7] The alcohols were purified through their respective acid phthalates, from which they were regenerated by treatment with lithium aluminum hydride. The acid phthalates were devoid of optical activity, but the recovered alcohols showed rotations: $[\alpha]^{20}D$ 0.168 ± 0.02° (neat), and $[\alpha]^{20}D$ −0.165 ± 0.02° (neat). Two additional specimens of alcohols were obtained by reduction of samples of isobutyraldehyde-1-*d* (98–100% deuterium) with fermenting yeasts.[6] Although the aldehyde was totally deuterated at C-1 (100% d_1), in one case the alcohol retained 80.5% *d*, $[\alpha]^{25}D$ 0.49° (neat, l = 1), and in the other case 70.2% *d*, $[\alpha]^{25}D$ 0.43° (neat, l = 1). There is ample evidence available demonstrating the stereospecificity of the reduction of aldehydes with fermenting yeasts, and it is implied that such alcohols are optically pure.[6] On the basis of this hypothesis, the rotation of the optically pure 100% C-1 monodeuterated isobutyl alcohol would be $[\alpha]^{20}D$ 0.61° (neat, l = 1). Presumably, in analogy to other cases,[6] this alcohol has the (1*S*) configuration. Consequently, the configurations and optical purities of the chemically synthesized alcohols would be (−)-(1*R*)-isobutyl-1-d_1 alcohol, 27.1%; and (+)-(1*S*)-isobutyl-1-d_1 alcohol, 27.6%.

Since the implied (1*S*) configuration of the isobutyl alcohol obtained by yeast reduction is of great importance in our considerations, we wished to corroborate it by other, more direct means. For evaluation of the configurational assignment, we had at our disposal three approaches: (a) Horeau's esterification procedure,[8] (b) deductions from the mode of reduction of aldehydes with (+)- and (−)-diisopinocampheyldeuterioboranes, and (c) degradation of the previously prepared (+)-(3*R*)-and (−)-(3*S*)-isocaproic-3-d_1 acids to the respective isobutyl alcohols, and comparison of their behavior toward NAD$^+$–YADH oxidation with those of the "synthetic" samples.

The Horeau method, though attractive and convenient for secondary alcohols, is of limited value when applied to C-1 deuterated primary alcohols. Its drawback is the low, frequently marginal, optical activity observed for the recovered α-phenylbutyric acid in experiments with primary alcohols.[9] In our hands, with the use of a Hilger MK-III polarimeter, no meaningful readings of optical rotation were obtained for the α-phenylbutyric acid recovered from esterification of the chemically prepared (+)- and (−)-isobutyl-1-d_1 alcohols.

Brown, *et al.*, have devised a procedure for the asymmetric synthesis of alcohols through hydroboration of olefins and reduction of carbonyls with (+)- and (−)-diisopinocampheylboranes.[7] The same authors suggested a model for the mode of action of the reagent. The model was of limited utility since it was applicable only to the hydroboration of cyclic olefins, *cis* olefins, and terminal methylenes.

Other investigators[10,11] suggested alternative, frequently complicated, rationalizations. We had occasion to use the reagent for the preparation of (+)-(3*R*)- and (−)-(3*S*)-4-methylpentane-1,3-diol-1-tetrahydropyranyl ethers (**2** and **3**), by reduction of 4-methyl-3-ketopentane-1-ol-tetrahydropyranyl ether[12a] (**1**). The configurations of the products were determined by Horeau's method. To explain the configurations at C-3, we had to revise the mode of formation of the four-membered transition state.[12b] A schematic presentation of the disposition in space of groups of (−)-diisopinocampheylborane is given in Figure 1. The B–H bond is drawn to lie at the intersection of planes A and B, and bonds C_3–B–C'_3 are assumed to lie in plane B. Under these circumstances, the C_2 and C'_2 methyls of the (−) reagent will lie in the lower left (LL), and upper right (UR) quadrants (Figure 1). The opposite situation (not shown in Figure 1) will prevail in the (+) reagent, in which the C_2 and C'_2 methyls will be located

(7) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 397 (1964), and **86**, 1071 (1964); H. C. Brown and D. B. Bigley, *ibid.*, **83**, 3166 (1961).

(8) A. Horeau and B. Kagan, *Tetrahedron*, **20**, 2431 (1964), and references therein.

(9) A. Horeau and A. Nouaille, *Tetrahedron Lett.*, No. 33, 3953 (1966).

(10) A. Streitweiser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).

(11) D. R. Brown, S. F. A. Kettle, J. McKenna and J. M. McKenna, *Chem. Commun.*, 667 (1967).

(12) (a) E. Caspi and K. R. Varma, *J. Org. Chem.*, **33**, 2181 (1968); (b) K. R. Varma and E. Caspi, *Tetrahedron*, **24**, 6365 (1968).

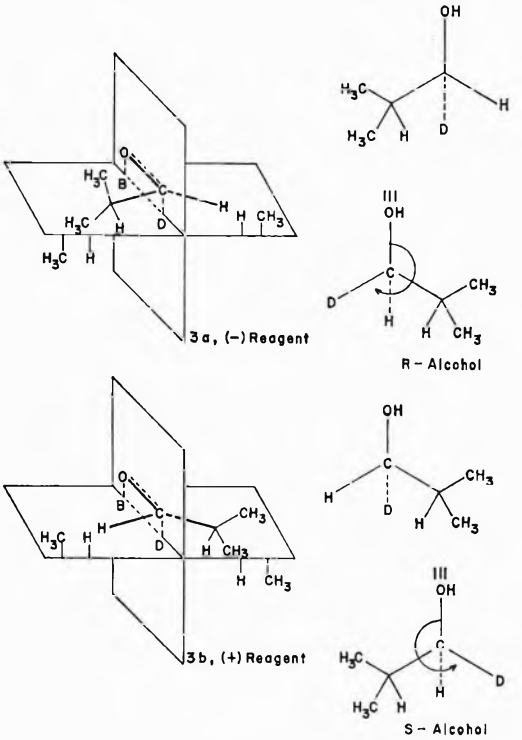

Figure 3.

in the upper left (UL) and lower right (LR) quadrants. It is evident that the carbonyl will approach the (−) reagent (Figure 2a) and the (+) reagent (Figure 2b) either from above or below the plane B, along plane A. For simplicity we have indicated in Figures 2a and b the formation of the four-membered transition states only *via* a top approach of the ketone to the reagents. The correct configurations of the produced alcohols can now be predicted effectively by assuming that in the actual reaction *the larger substituent* of the ketone is located in a *quadrant opposite to that which contains the* C_2 *and* C'_2 *methyls* of the reagent. Indeed, our results fully agreed with these predictions.[12]

We have reason to believe that this interpretation should also be applicable to the asymmetric reduction of isobutyraldehyde with (+)- and (−)-diisopinocampheyldeuterioboranes. Since the isopropyl group of the aldehyde is distinctly the larger substituent, the transition states of reactions with the (−) and (+) reagents can be represented as in Figures 3a and 3b. The anticipated result would therefore be the (−)-(1*S*)- isobutyl-1-d_1 alcohol from the (+)-*d* reagent (Figure 3b), and (−)-(1*R*)-isobutyl-1-d_1 alcohol from the (−)-*d* reagent (Figure 3a). We were encouraged in this interpretation of the reactions, and hence in the assignment of the configurations of the alcohols, by the fact that the isobutyl-1-d_1 alcohol obtained by yeast reduction of the 1-*d*-aldehyde, which was expected to have the (1*S*) configuration, indeed showed a positive rotation.

The correlation of the three specimens of the alcohols with the previously prepared (3*R*)- (**4**) and (3*S*)-isocaproic-3-d_1 acids (**5**)[12a] was now undertaken. The (+)-(3*R*)- and (−)-(3*S*)-acids were degraded to the corresponding alcohols **9** and **12** in the same manner. The (3*R*)-methyl ester **4a** (Figure 4) was first treated with phenylmagnesium bromide, then with acid to yield the olefin **6**. The olefin was ozonized, and after a reductive work-up (zinc–acetic acid) the isovaleraldehyde **7**

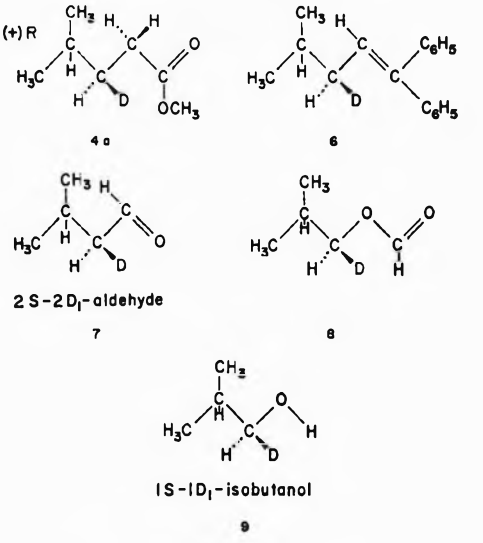

Figure 4.

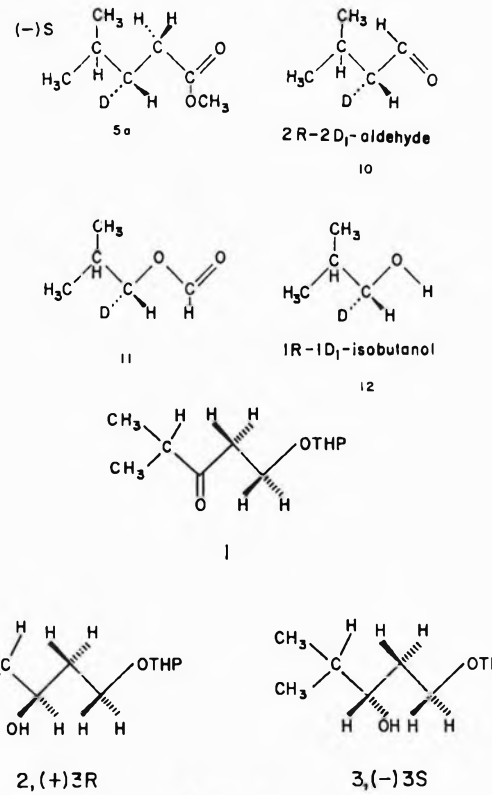

Figure 5.

was obtained. Because of the change of priorities of substituents at C-2 of the aldehyde, the (3*R*)-acid **4** gave the 2*S*-isovaleraldehyde-2-d_1 (**7**). The deuterated aldehyde **7** was treated with trifluoroperacetic acid, and the resulting formate **8** was reduced with lithium aluminum hydride to yield the (1*S*)-isobutyl-1-d_1 alcohol (**9**).[13a] The Baeyer–Villiger oxidation is known to proceed with retention of configuration.[13b] The (−)-(*S*) ester **5a** (Figure 5) was degraded in a similar manner *via* the aldehyde **10** and formate **11** to yield the (1*R*)-isobutyl-1-d_1 alcohol (**12**). Because of the availability of only small amounts of the alcohols so obtained, a comparison of their rotations with those of the previously described specimens was impossible. Consequently,

(13) (a) H. Weber, J. Seibl, and D. Arigoni, *Helv. Chim. Acta*, **49**, 741 (1966); (b) K. Mislow and J. Brenner, *J. Amer. Chem. Soc.*, **75**, 2318 (1953).

the correlation was accomplished by comparing their behavior toward NAD^+–YADH oxidation.

As mentioned above, in the several instances investigated until now, oxidation of primary alcohols to aldehydes with NAD^+–YADH proceeded with the removal of the *pro*-(1*R*) proton. As a working hypothesis, we assumed that the same would occur in the oxidation of the isobutyl-1-d_1 alcohols to isobutyraldehydes. Thus oxidation of the (1*S*)-isobutyl-1-d_1 alcohol would proceed by abstraction of the hydrogen, to yield isobutyraldehyde-1-*d*. On the other hand, oxidation of the (1*R*)-1-d_1 alcohol would require breakage of the C–D bond and formation of isobutyraldehyde. Involvement of a primary isotope effect could be anticipated in the breakage of the C–D bond and a secondary isotope effect in the scission of the C–H bond [of the (1*S*)-alcohol]. The isotope effects would not have presented a problem if the oxidation of the mixtures of enantiomeric, optically active (but not optically pure) alcohols could be brought to completion. Unfortunately, exploratory studies with 5–20-mg samples of isobutyl alcohol showed that the reaction is arrested when about 35–40% of alcohol is oxidized. In view of this, it was necessary to determine the magnitude of the isotope effects in the oxidation with NAD^+ and YADH.

Oxidation of samples of (1*S*)-isobutyl-1-d_1 alcohol containing 80.5% D and 70.2% D with NAD^+–YADH gave specimens of isobutyraldehyde-1-*d* having 78.7% D and 71.2% D, respectively. It is evident that the aldehydes retained all the deuterium, and this confirms the stereospecific removal of the *pro*-(1*R*) proton in the reaction. In addition, it is clear that the influence of a secondary isotope effect must be small, and its magnitude falls within the limits of mass spectroscopic deuterium determination. Consequently, for the present calculations we will disregard the secondary isotope effect.

In the absence of the optically pure (1*R*)-isobutyl-1-d_1 alcohol, the primary isotope effect could not be determined directly. Under the circumstances, we chose to define the primary isotope effect from the oxidation of racemic isobutyl-1-d_1 alcohol. The rationale of the approach was based on the assumption that the oxidation of the (1*S*)-1-d_1-alcohol will proceed at a different rate, probably faster, than that of the (1*R*)-1-d_1-alcohol. Should the two rates happen to be equal, the resulting aldehyde will retain 50% of the initially present deuterium. If, on the other hand, the oxidation of the (1*R*)-1-d_1-alcohol is slower, as expected, more than 50% of the initially present deuterium will be retained. From this excess (above 50%) the primary isotope effect X can be calculated.

The required (±)-isobutyl-1-d_1 alcohol (100% 1-d_1) was obtained by reduction of isobutyraldehyde with lithium aluminum deuteride. Oxidation of this alcohol proceeded to the extent of 40% within 20 hr, and gave 1-*d*-isobutyraldehyde containing 68% deuterium. For reasons discussed above it may be assumed that the (1*S*)-alcohol is oxidized at the "same rate" as the protonated isobutyl alcohol, and gives the 1-*d*-isobutyraldehyde. On the other hand, the (1*R*)-alcohol is oxidized at a rate X and gives the *h*-aldehyde. The primary isotope effect X (*d*/*h*) can now be calculated from eq 1,

$$\frac{(50)}{(50) + (50)(X)} \cdot 100 = 68 \qquad (1)$$

and therefore X = 0.47. This calculation will be valid as long as both enantiomeric alcohols are present in solution and are still available for oxidation. The magnitude of X = 0.47 indicates that, at any particular time, as long as both enantiomers are present in the medium, 2.13 molecules of the (1*S*)-alcohol will be oxidized for each molecule of the (1*R*)-alcohol.

Having evaluated the primary and secondary isotope effects, we turned to the question of confirmation of the configuration of the (−)-(1*R*)- and (+)-(1*S*)-isobutyl-1-d_1 alcohols prepared by reduction of isobutyraldehyde with (−)- and (+)-diisopinocampheyldeuterioboranes, respectively.

The (−)-(1*R*)-isobutyl-1-d_1 alcohol (100% 1-d_1) with an optical purity of 27.1% was oxidized in the standard manner (40% oxidation), and gave isobutyraldehyde containing 55.1% deuterium. The initial alcohol contained a 27.1% excess of the (*R*)-alcohol, and 72.9% racemate which consisted of 36.5% each of the (*R*)- and (*S*)-alcohols. Hence the actual composition of the sample was 63.5% (1*R*)-1-d_1-alcohol and 36.5% (1*S*)-1-d_1-alcohol. The anticipated amount of deuterium in the resulting aldehyde is given by eq 2, shown below,

$$\frac{(36.5)}{(36.5) + (63.5)(0.47)} \cdot 100 = Y \qquad (2)$$

and consequently Y = 55.0% deuterium. The calculated value for Y = 55.0% agrees well with the experimentally determined amount of deuterium present in the aldehyde (55.5%).

When a similar oxidation was performed on the (+)-(1*S*)-isobutyl-1-d_1 alcohol (100% 1-d_1) having an optical purity of *ca.* 27.6%, the isolated isobutyraldehyde retained 77.8% deuterium. The oxidized alcohol had an excess of 27.6% of the (1*S*) enantiomer, and the remaining racemate (72.4%) consisted of 36.2% each of the (1*S*)- and (1*R*)-alcohols. Consequently, the sample contained a total of 63.8% (1*S*)-isobutyl-1-d_1 alcohol and 36.2% (1*R*)-isobutyl-1-d_1 alcohol. The expected amount Z of deuterium in the aldehyde is given by eq 3,

$$\frac{(63.8)}{(63.8) + (36.2)(0.47)} \cdot 100 = Z \qquad (3)$$

where Z = 79.0% deuterium. The calculated (79.0%) and the experimentally found (77.8%) amount of deuterium in the aldehyde are in satisfactory agreement.

We now wished to correlate the above specimens of (−)-(1*R*)- and (+)-(1*S*)-1-d_1-alcohols with the (1*R*)- and (1*S*)-isobutyl-1-d_1 alcohols obtained by degradation of (−)-(3*S*)- and (+)-(3*R*)-isocaproic-3-d_1 acid, respectively. We have previously shown that the isocaproic-3-d_1 acids contained 11% D at the C-4 methine carbon.[12a] Consequently, the derived isobutyl alcohols, and hence isobutyraldehydes, should have 11% D at the methine carbons. Since the isobutyraldehydes are recovered as 2,4-DNPH derivatives from an acidified reaction medium, some deuterium may be lost by enolization. To evaluate the magnitude of the losses, we required isobutyl-2-*d* alcohol which was prepared as follows. Isobutyraldehyde was converted into isobutenyl acetate, and the enol ester was hydrolyzed in D_2O–D_2SO_4. The obtained $(CH_3)_2CD$–CHO (100% D) was diluted with protiated aldehyde and reduced with lithium aluminum hydride. A specimen of $(CH_3)_2CD \cdot CH_2OH$ (10.9% D) was treated with NAD^+–YADH, and

the resulting aldehyde was isolated in the usual manner. The aldehyde contained 8.1% D, indicating a net loss of 2.8% D from C-2. It follows that results for the isobutyraldehydes obtained by oxidation of isobutyl alcohols derived from the isocaproic acids should be increased by 2.8%.

The (1*R*)-isobutyl-1-d_1 alcohol from the (3*S*)-acid had 89.0% D at C-1 and 11% D at C-2, and on oxidation yielded isobutyraldehyde containing 55.0% deuterium. Thus the composition of the alcohol was 11% D at C-2, *A*% (1*R*)-1-d_1-alcohol and *B*% (1*S*)-1-d_1-alcohol. Obviously eq 4 obtains, and therefore, also, eq 5.

$$A + B + 11 = 100 \quad (4)$$

$$\frac{(11) + (B)}{(11) + (B) + (A)\,(0.47)} \cdot 100 = 57.8 \quad (5)$$

Solution of eq 4 and 5 leads to $B = 28.2\%$ and $A = 60.8\%$. It follows that the sample contained 28.2% (1*S*)-alcohol and 60.8% (1*R*)-alcohol. The optical purity of the (1*R*)-alcohol, and hence of the (3*S*)-isocaproic-3-d_1 acid, was 32.6% (60.8–28.2%).

The (1*S*)-1-d_1-alcohol derived from the (3*R*)-isocaproic-3-d_1 acid had 100% D, of which 11%[12a] was at C-2 and 89% at C-1. The composition of this sample was *A*% (1*R*)-1-d_1, *B*% (1*S*)-1-d_1, and 11% D at C-2. Oxidation of this specimen of (1*S*)-1-d_1-alcohol gave isobutyraldehyde which contained 82.1% deuterium. The over-all composition of the sample can be expressed by eq 4 and therefore by eq 6 which follows.

$$\frac{(B) + 11}{(B) + (11) + (0.47)\,(A)} \cdot 100 = 84.9 \quad (6)$$

Solution of eq 4 and 6 gives $A = 27.5\%$ and $B = 61.5\%$. Consequently, the optical purity of this specimen of (1*S*)-isobutyl-1-d_1 alcohol, and therefore of the (3*R*)-isocaproic-3-d_1 acid, was 34.0% (61.5–27.5%).

It is evident that the configurations of the (1*R*)- and (1*S*)-alcohols, obtained from the isocaproic acids, have been correctly assigned. As expected, oxidation of the (1*R*)-alcohol proceeded with a greater loss of deuterium than that of the (1*S*)-alcohol. This is in agreement with the anticipated removal of the *pro*-(1*R*) hydrogen (or of isotopic hydrogen) during the NAD^+ and YADH oxidation.[4] Furthermore, the results relate the configurations of (3*R*)- and (3*S*)-isocaproic-3-d_1 acids to those of the (1*S*)- and (1*R*)-isobutyl-1-d_1 alcohols. Since, in principle, the assignment of configurations of the acids was based on Horeau's procedure,[12a] and that of the isobutyl-1-d_1 alcohols on behavior toward NAD^+–YADH, it follows that both procedures lead to identical configurational conclusions. The results confirm also the configurations of the (−)-(1*R*)- and (+)-(1*S*)-isobutyl-1-d_1 alcohols synthesized by reduction of isobutyraldehyde with (−)- and (+)-diisopinocampheyldeuterioboranes. Thus our proposed interpretation of the "nature" of the transition state in the reduction of aldehydes and ketones with diisopinocampheylboranes gains added validity.

The (−)-4-methylpentane-1,3-(*S*)-diol was previously correlated with (*S*)-glyceraldehyde.[14,12a] The method of synthesis of the asymmetric isocaproic-3-d_1 acids[12a] from the asymmetric 4-methylpentane-1,3-diols proceeded with inversion of configuration at C-3. It follows that (+)-(3*R*)-isocaproic-3-d_1 acid (**4**) and the derived (2*S*)-2-d_1-aldehyde (**7**) and (+)-(1*S*)-isobutyl-1-d_1 alcohol (**9**) are related to (*R*)-glyceraldehyde. Similarly, the (−)-(3*S*)-isocaproic-3-d_1 acid (**5**) and the derived (2*R*)-2-d_1-aldehyde (**10**) and (−)-(1*R*)-isobutyl-1-d_1 alcohol (**12**) must be related to (*S*)-glyceraldehyde.

In summary, it may be concluded that the three methods, deductions on the reduction of ketones and aldehydes with (+)- or (−)-diisopinocampheylboranes, Horeau's procedure for secondary alcohols, and NAD^+–YADH oxidation, all gave analogous results and can be used for configurational assignments.

Experimental Section

Materials and Apparatus.—The sodium borodeuteride and lithium aluminum hydride were of high isotopic purity and were supplied by Metal Hydrides, Inc., Beverly, Mass. A solution of deuterioborane in tetrahydrofuran was prepared according to the general procedure used for diborane.[12a] The α-pinenes showed $[\alpha]^{25}D$ −45.5° and 46.0° (neat, $l = 1$), and were purchased from Chemical Samples Co., Columbus, and Aldrich Chemical Co., Milwaukee, respectively. The NAD^+ (85.5% β-NAD by enzymatic assay and 97.0% by uv assay) and crystalline yeast ADH (80%, specific activity 300 μ/mg) were used as supplied by Calbiochem Co., Los Angeles, Calif.

Analytical and preparative glc were carried out on an F & M Model 720 instrument on columns packed with TCEP, using helium as carrier gas. In all cases, identity of samples was confirmed by mixed injection with authentic (nondeuterated) samples. The melting points were determined on a hot stage and are corrected. The ir spectra were determined on a Perkin-Elmer Model 237 instrument. The mass spectra were run on a Varian M-66 or Hitachi–Perkin-Elmer RMH6 spectrometer. The nmr spectra were recorded at 60 Hz on a Varian DA-60 instrument using tetramethylsilane as internal standard. The deuterium content in all compounds was established mass spectroscopically. The uv spectra of the enzymatic oxidation media were recorded on a Perkin-Elmer Model 202 instrument in 1-cm cells. A Hilger polarimeter Model MK-III was used.

Isobutyraldehyde-1-*d*.—To a cooled stirred suspension of lithium aluminum deuteride (5.0 g, 119 mmol) in dry ether (100 ml), a solution of absolute ethanol (16.43 g, 357 mmol) in dry ether (50 ml) was added during 20 min. After stirring for another 20 min at 0°, isobutyronitrile (8.28 g, 120 mmol) was added during 5 min. The resulting thick solid was allowed to warm to room temperature and was stirred for 1.5 hr. The reaction was terminated with 5 *N* sulfuric acid, and the solid was removed by filtration and washed with ether. The combined filtrate and washings were concentrated by distillation through a 90-cm column packed with glass helices. The resulting concentrate was then distilled through a 1-ft packed column, and the fraction at bp 50–78° (750 mm) was collected. Analysis of this fraction by glpc at 60° on a 2.4-m column of 5% TCEP on Chromosorb indicated a yield of 5.06 g (60.6%) of isobutyraldehyde-1-*d*. The product was contaminated with large amounts of ethanol, but no other impurity was detected. Subsequently, this fraction was used for the preparation of (1*S*)-isobutyl-1-d_1 alcohol by yeast reduction (*vide infra*).

An aliquot of the aldehyde was converted into the 2,4-dinitrophenylhydrazone derivative, mp 183–186° (lit. 187 or 182° for nondeuterated material).[15] The mass spectrum of this derivative indicated that the aldehyde was 100% deuterated.

(+)-(1*S*)-Isobutyl-1-d_1 Alcohol. A. Reduction of Isobutyraldehyde-1-*d* with Fermenting Yeast.—In a 5-l. flask, dextrose (450 g) and distilled water (1.91 g) were stirred at 37° until completely dissolved. Baker's yeast (450 g, National Corporation) was added in small lumps with stirring. After a few minutes, a solution of isobutyraldehyde-1-*d* (2.53 g) in ethanol (10 ml) was added to the actively fermenting mixture. Active fermention slowed down considerably after 5 hr, but the reaction was continued with stirring for 12 hr (35–37°). The mixture was then steam distilled, and 1.3 l. of distillate was collected. The dis-

(14) G. Buchi, L. Crombie, P. J. Godin, J. S. Katlenbronn, K. S. Siddalingaiah, and D. A. Whiting, *J. Chem. Soc.*, 2843 (1961).

(15) M. Frankel and S. Patai, "Tables for Identification of Organic Compounds," Chemical Rubber Publishing Co., Cleveland, Ohio, 1960.

tillate was saturated with salt and continuously extracted with ether (12 hr). The ether was changed and the extraction was continued for 12 hr. The two ether extracts were combined and fractionated through a 90-cm packed column in order to remove the ether and most of the ethanol. The residual solution was dried, and glpc analysis indicated the presence of 1.62 g of isobutyl-1-d_1 alcohol. The pure compound (1.2 g) was obtained by two successive glpc purifications on a 2.4-m column of 20% TCEP at 100°. The homogeneous product was distilled, and showed $[\alpha]^{25}D$ 0.49° (neat, $l = 1$). The mass spectrum indicated 80.5% deuterium content. The 100% deuterated optically pure compound should have $[\alpha]^{25}D$ 0.61°. A second fermentation experiment gave a sample containing 70.2% D, $[\alpha]^{25}D$ 0.43° (neat, $l = 1$).

B. Reduction of Isobutyraldehyde with (+)-Diisopinocampheyldeuterioborane.—The apparatus consisted of a 100-ml flask equipped with a magnetic stirring bar, a side arm capped with a rubber septum, and an inlet for dry nitrogen. The flask was flamed in a stream of nitrogen and cooled to 0°. A positive pressure of nitrogen was maintained thereafter.

A solution of deuteriodiborane in tetrahydrofuran (59.1 ml, 23.34 mmol BD_3) was placed in the flask and cooled to 0°. To the stirred solution, (−)-α-pinene (51.3 mmol, 6.95 g) was slowly added from a syringe (20 min), and the stirring was continued for 5 hr (0–3°).

To the white suspension, isobutyraldehyde (23.34 mmol, 1.68 g) was added in the course of 5 min, and the stirring was continued overnight at 0–2°. On addition of water, little hydrogen was produced. The reaction mixture was oxidized by adding 3 *N* NaOH (16 ml) followed by 30% H_2O_2 (8 ml) and by stirring at 40° for 1.5 hr. The tetrahydrofuran layer was separated; the aqueous layer was washed with several portions of ether. The organic extracts were combined, washed once with a little brine and dried, and most of the solvent was removed by distillation through a 30-cm packed column. The residual liquid was distilled through a short Vigreux column, and the fraction at bp 70–110° (750 mm) was collected. The product was twice purified by glpc on the TCEP column and then distilled to furnish (1*S*)-isobutyl-1-d_1 alcohol, $[\alpha]^{25}D$ 0.168 ± 0.02° The mass spectrum indicated that the sample contained 100% $(CH_3)_2\cdot CH\cdot CDHOH$. Assuming that pure (1*S*)-isobutyl-1-d_1 alcohol has $[\alpha]^{25}D$ 0.61° (neat), this product has an optical purity of 27.6%.

The alcohol was converted into the acid phthalate, which was recrystallized from ligroin (90–120°), mp 63–64° (lit.[16] 62.5–65° for the racemate). A 20% ether solution in a 1-dm tube did not show measurable rotation. The nmr spectrum indicated 99.5–100% deuterium content. The regenerated alcohol, obtained by lithium aluminum hydride reduction of the acid phthalate (see below), had the same optical rotation as the starting material.

(−)-(1*R*)-Isobutyl-1-d_1 Alcohol.—The same apparatus as above was employed. A stirred suspension of sodium borodeuteride (37.5 mmol, 1.58 g) in dry tetrahydrofuran (40 ml) was cooled to 0° and freshly distilled boron trifluoride ethereate (50 mmol, 6.3 ml) was added during 15 min. After stirring for 1 hr, (+)-α-pinene (120 mmol, 16.32 g) was added (20 min), and the mixture was stirred overnight at 0–3°. To the white suspension of the reagent, isobutyraldehyde (50 mmol, 3.6 g) was added during 20 min, and stirring was continued for 4 hr at 0–2°. Addition of water did not generate hydrogen, suggesting that the reduction was complete. The organoborane was oxidized ($NaOH$–H_2O_2), and the product was isolated in the manner described for the (+) enantiomer. The fraction at bp 90–110° (750 mm) was converted into the acid phthalate (90% yield). The acid phthalate was dissolved in a sodium bicarbonate solution and recovered after acidification. The purified product was twice crystallized from ligroin (90–120°), mp 62–63°. A 37% solution of the phthalate in ether in a 1-dm tube did not show a measurable optical rotation.

To the purified acid phthalate (8.0 g) in ether (75 ml), lithium aluminum hydride (2.5 g) was added in small amounts and the mixture was refluxed for 2 hr. The reaction was terminated with dilute hydrochloric acid until an easily filterable white precipitate was obtained. The ether layer was isolated by decantation, the precipitate was washed with ether, and the combined ether solutions were evaporated through a 30-cm packed column. Short-path distillation of the residue gave 2.2 g (81% yield) of (1*R*)-isobutyl-1-d_1 alcohol, bp 105–106° (750 mm) [lit.[16] 106–108° (748 mm)], $[\alpha]^{25}D$ −0.165 ± 0.02°. The sample was homogeneous when analyzed by glpc on a 2.4-m column of 5% TCEP at 115°. The mass spectrum indicated 100% $(CH_3)_2\cdot CHDOH$. Hence the sample is 27.1% optically pure.

(+)-Isobutyl-1-d_1 Alcohol.—The racemic alcohol was prepared by the reduction of isobutyraldehyde with lithium aluminum deuteride and was purified by distillation. The mass spectrum indicated 100% $(CH_3)_2\cdot CH\cdot CDHOH$.

Isobutenyl Acetate.—A mixture of isobutyraldehyde (28.8 g, 400 mmol), acetic anhydride (50.5 g, 500 mmol), and *p*-toluenesulfonic acid hydrate (100 mg) was refluxed for 18 hr. Sodium acetate (2.0 g) and water (50 ml) was added and the solution was stirred for 18 hr. The layers were separated and the aqueous layer was extracted with ether. The extract and the main organic layer were combined and washed with a cold dilute sodium bicarbonate solution and water and dried. The solvent was removed through a 60-cm packed column. The residual material was distilled to furnish isobutenyl acetate (85%): bp 123–125° (760 mm) (lit.[17] bp 124–126°, 124°); ν_{max}^{film} 1750 (strong, –OAc), 1685 cm^{-1} (medium, C=C).

Isobutyraldehyde-2-*d*.—A mixture of isobutenyl acetate (7.5 g), deuterium oxide (5.0 g), and concentrated sulfuric acid (2 drops) was stirred and distilled (water bath) through a Vigreux column during 6 hr. The bulk of the D_2O was removed from the distillate by freezing, anhydrous potassium acetate (200 mg) was added, and the isobutyraldehyde-2-*d* was distilled: bp 62–64° (760 mm); ν_{max}^{film} 1730 cm^{-1}; yield 3.3 g.

Isobutyl-2-*d* Alcohol.—To a solution of isobutyraldehyde-2-*d* (150 mg) and isobutyraldehyde (850 mg) in ether (50 ml), lithium aluminum hydride (500 mg) was added, and the mixture was refluxed for 1 hr. The recovered alcohol was purified by glpc on a 2.5-m column of 20% TCEP on Chromosorb, and by distillation. The homogeneous alcohol contained 17.8% D.

The sample was further diluted with isobutyl alcohol to give a specimen of $(CH_3)_2CD\cdot CH_2OH$ containing 10.9% D which was treated with NAD^+–YADH (see Table I).

Degradation of Methyl (+)-(3*R*)-Isocaproate-3-d_1 (4a) to (1*S*)-Isobutyl-1-d_1 Alcohol (9). A. Diphenylalkene 6.—The ester 4a (25 mmol, 3.25 g) was added with cooling to phenylmagnesium bromide (60 mmol) in ether (60 ml). The reaction mixture was stirred for 2 hr at room temperature and refluxed for 30 min. Excess dilute hydrochloric acid was added, the ether was separated, and the aqueous phase was extracted twice with ether (25 ml). The combined ether solution was washed with water and dried, and the solvent was removed *in vacuo*. The crude liquid alkyldiphenylcarbinol was dissolved in benzene (150 ml) containing a few crystals of *p*-toluenesulfonic acid. The mixture was slowly distilled, and, when the dehydration was complete (no -OH band in the ir) (2 hr), the reaction was terminated. The solution was washed with aqueous sodium carbonate and water, and evaporated *in vacuo*. The remaining liquid was distilled and furnished the diphenylalkene 6 (4.4 g, 75% yield): bp 115–116° (0.2 mm); no hydroxyl absorption in ir; mass spectrum 237 (M^+), 194 (M − 43), (M − 83), etc. Analysis by glpc at 225° on a 2.4-m column of 5% SE-30 on Chromosorb showed that the sample was contaminated with a small amount of bromobenzene and traces of unidentified impurities. This material was employed in the next step.

B. (2*S*)-Isovaleraldehyde-2-d_1 (7).—A solution of diphenylalkene 6 (2.6 g) in methylene chloride (20 ml) was cooled in Dry Ice–Methyl Cellosolve and ozonized for 2.5 hr until the blue color persisted. The solution was then stirred for 4 hr with zinc dust (2.5 g) and glacial acetic acid (2.0 ml) at room temperature. The excess acid was removed by stirring the mixture with sodium bicarbonate (3 g) and a few drops of water for 1 hr. Then anhydrous sodium sulfate was added and stirring was continued for 30 min. The mixture was filtered into a receiver and cooled in ice, and the solid was washed with several small portions of methylene chloride. Most of the methylene chloride was removed by distillation through a 30-cm packed column. The column was removed, the flask was immersed in an oil bath maintained at 160°, and the distillate (*ca.* 25 ml) was collected in a receiver cooled in ice. The distillation flask was cooled to room temperature, 3 ml of methylene chloride was added, and the mixture was again distilled (160°) almost to dryness. The operation was repeated three times. The distillate, *ca.* 40 ml, contained 593 mg (64%) of isovalerylaldehyde-2-d_1 (7) by glpc.

(16) E. L. Eliel and D. W. Delmonte, *J. Amer. Chem. Soc.*, **80**, 1744 (1958).

(17) P. Z. Bedoukian, *ibid.*, **66**, 1325 (1944).

TABLE I
DEUTERIUM CONTENT AND OPTICAL PURITY OF COMPOUNDS

Entry no.	Compd	Origin	Average %D from MS	% optical purity
1	(+)-(3*R*)-Isocaproic-3-d_1 acid[a]	(+)-(3*R*)-4-Methyl-3-d_1-pentan-1-ol	100	34.0
2	(−)-(3*S*)-Isocaproic-3-d_1 acid[a]	(−)-(3*S*)-4-Methyl-3-d_1-pentan-1-ol	100	32.6
3	(1*S*)-Isobutyl-1-d_1 alcohol	Entry 1	100	34.0
4	(1*R*)-Isobutyl-1-d_1 alcohol	Entry 2	100[h]	32.6
5	Isobutyraldehyde-1-*d*	Entry 3–NAD$^+$, YADH[b]	84.9[c]	...
6	Isobutyraldehyde-1-*d*	Entry 4–NAD$^+$, YADH	57.8[c]	...
7	(+)-(1*S*)-Isobutyl-1-d_1 alcohol	Ald[d]–(+)-reagent[e]	100	27.6
8	(−)-(1*R*)-Isobutyl-1-d_1 alcohol	Ald[d]–(−)-reagent[e]	100	27.1
9	Isobutyraldehyde-1-*d*	Isobutyronitrile–LTEAH[f]	100[c]	...
10	Isobutyraldehyde-1-*d*	Isobutyl-1-d_2 alcohol–LTA[i]	98.4[c]	...
11	(+)-(1*S*)-Isobutyl-1-d_1 alcohol	Entry 9–yeast	80.5	100[i]
12	(+)-(1*S*)-Isobutyl-1-d_1 alcohol	Entry 10–yeast	70.2	100[i]
13	(±)-Isobutyl-1-d_1 alcohol	Ald[d]–LAD[g]	100	...
14	Isobutyraldehyde-1-*d*	Entry 7–NAD$^+$, YADH	77.8[c]	...
15	Isobutyraldehyde-1-*d*	Entry 8–NAD$^+$, YADH	55.5[c]	...
16	Isobutyraldehyde-1-*d*	Entry 11–NAD$^+$, YADH	78.7[c]	...
17	Isobutyraldehyde-1-*d*	Entry 12–NAD$^+$, YADH	71.2[c]	...
18	Isobutyraldehyde-1-*d*	Entry 13–NAD$^+$, YADH	68.0[c]	...
19	Isobutyl-2-*d* alcohol[k]		10.9	...
20	Isobutyraldehyde-2-*d*	Entry 19–NAD$^+$, YADH	8.1[c]	...

[a] Reference 12. [b] NAD$^+$, nicotinamide adenine dinucleotide; YADH, yeast alcohol dehydrogenase. [c] Of the 2,4-dinitrophenylhydrazone. [d] Ald, isobutyraldehyde. [e] Reagent, diisopinocamphenyldeuterioborane. [f] Lithium triethoxyaluminohydride [H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **86**, 1085 (1964)]. [g] Lithium aluminum deuteride. [h] Of the 3,5-dinitrobenzoate. [i] Assumed, corrected for 100% deuterium. [j] By oxidation of isobutyl-1-d_2 alcohol with lead tetraacetate in pyridine [R. E. Partch, *Tetrahedron Lett.*, 3071 (1964)]. The isobutyl-1-d_2 alcohol was prepared by the reduction of neooctylisobutyrate with lithium aluminum deuteride in ether. [k] See Experimental Section.

The 2,4-dinitrophenylhydrazone derivative had mp 118–121° (lit.[15] for nondeuterated derivative, 123°).

C. (1*S*)-Isobutyl-1-d_1 Alcohol (9).—The above dried solution of isovaleraldehyde-2-d_1 (**7**)(560 mg) in methylene chloride (40 ml) was mixed with freshly dried sodium hydrogen phosphate (5.0 g) and stirred at 0°. A solution of trifluoroperacetic acid (prepared by mixing 2.7 g of trifluoroacetic anhydride and 540 mg of 80% hydrogen peroxide in 10 ml of methylene chloride at 0°) was added during 15 min, and stirred overnight at 0–3°. The mixture was filtered into a cooled flask, and the solid was washed with small amounts of methylene chloride. The filtrate was stirred with sodium bicarbonate (3.0 g) and a few drops of water. After 1 hr, anhydrous sodium sulfate was added, and then filtered into a cooled flask. The solid was washed with small amounts of methylene chloride, and the washings were combined with the main filtrate. The solution was concentrated by distilling through a 30-cm packed column. Analysis (glpc, 20% TCEP column) of the concentrated solution indicated the presence of isobutyl-1-d_1 alcohol (10%), the formate of **8** (45%), a small amount of isovaleraldehyde-2-d_1, and methylene chloride. The formate and the isobutyl-1-d_1 alcohol were isolated by preparative glc (20% TCEP column).

To a solution of the formate in ether, lithium aluminum hydride was added and the mixture was stirred for 30 min at ambient temperature. The reaction was terminated by addition of a few drops of water, and the resultant solid was separated by filtration. The solution was added to the alcohol obtained from glc, and the solvent was removed by distillation through a packed colum (30 cm). The residue was distilled to yield (1*S*)-isobutyl-1-d_1 alcohol (120 mg). The product was contaminated with a small amount of diethyl ether (glpc). The mass spectrum indicated the presence of 100% D.

Degradation of Methyl (−)-(3*S*)-Isocaproate-3-d_1 (5a) to (1*R*)-Isobutyl-1-d_1 Alcohol (12).—The degradation was carried out as described for the (+)-(3*R*)-3-d_1 ester. The derived (2*R*)-isovaleraldehyde-2-d_1 (**10**) was submitted to a Baeyer–Villiger oxidation, and, after $LiAlH_4$ reduction of the formate **11**, (1*R*)-isobutyl-1-d_1 alcohol (**12**) was obtained. The mass spectrum showed 100% d_1; the 3,5-dinitrobenzoate derivative had mp 84–86° (lit.[15] 87° for nondeuterated alcohol); the mass spectrum of the 3,5-dinitrobenzoate derivative showed 99.5–100% D.

General Procedure for the Oxidation of Isobutyl-1-d_1 Alcohols with NAD$^+$ and Yeast ADH.—Preliminary experiments demonstrated that the rate of oxidation of isobutyl alcohol or isobutyl-1-d_1 alcohol was slow. The reagents appeared to decompose and discolor rapidly at 37° at pH 9.5. The decomposition was considerably slower when the oxidation was carried out at 24–25°.

The following procedure was found to be reproducible and was therefore used throughout. The oxidation medium was prepared by dissolving NAD$^+$ (253 μmol, 181.3 mg of an 87% pure sample), and yeast ADH (13 mg, 80% pure) in a 0.25 *M* glycine–sodium hydroxide buffer of pH 9.8 (65 ml). A 2-ml aliquot was removed, diluted with the buffer to 10 ml, and used as a blank for uv. The isobutyl-1-d_1 alcohol (253 μmol, 18.7 mg) was added to the medium, and the oxidation was followed by measuring the optical density at 340 mμ of aliquots five times diluted with the buffer. The amount of NADH formed was calculated[18] on the basis of ϵ 6220. The amount of aldehyde produced was assumed to be equivalent to the amount of NADH.

Normally, the oxidation came to an equilibrium after 17–20 hr, at which time 35–40% of the alcohol was oxidized. In some instances it was found advantageous to add more NAD$^+$ in order to expedite the reaction. The reaction was terminated with a solution of 2,4-dinitrophenylhydrazine (200 mg) in 10% sulfuric acid (25 ml). The flask was warmed briefly at 40–50° and stored in a refrigerator for 2–3 hr. The solids were isolated by centrifugation and washed with water. The solid was mixed with anhydrous sodium sulfate and digested several times with warm methylene chloride. The extracts were combined and evaporated. The resulting residue was twice chromatographed [tlc, silica gel, benzene–hexane (4:1)], the zone corresponding to authentic material was collected, and the product was recovered. All experiments were carried out at least in duplicate, and the average results are given in Table I.

Registry No.—Isobutyraldehyde-1-*d*, 20440-12-4; **9**, 20446-26-8; **12**, 20446-27-9; (±)-isobutyl-1-d_1 alcohol, 20446-28-0; isobutyl-2-*d* alcohol, 20440-13-5; isobutyraldehyde-2-*d*, 4303-51-9.

(18) B. L. Horecker and A. Kornberg, *J. Biol. Chem.*, **175**, 385 (1948).

Stable Silicon Heterocyclic Derivatives of Branched Alkanediols

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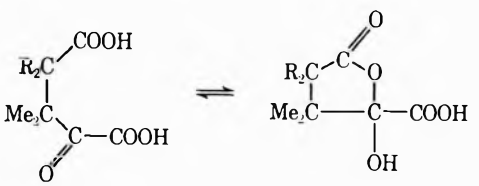
The cyclic stabilizing effect of alkyl substituents has been exploited for the preparation of a series of spirosilicates derived from 1,2-, 1,3-, and 1,4-diols. Vicinal 1,2 disubstitution and geminal 1,1 disubstitution are apparently more effective than geminal 2,2 disubstitution. A series of related heterocyclic organosilicon derivatives is also described.

The literature contains numerous examples of silicon heterocyclic derivatives of various diols,[1] but, with the exception of two papers,[1a,1h] there has been little apparent effort to relate heterocyclic stability[2] to diol structure. The paucity of such correlations is somewhat surprising, because dioxasila-heterocyclic substrates are well suited for studying the effect of structure upon ring–chain equilibria, since (1) structural variation is simple, (2) facile interconversion of ring and chain forms is easily catalyzed, and (3) the interconversion results in no new functional moieties. Regarding this last point, much of the earlier ring–chain work has dealt with systems such as the following[3] equilibrium in which any interpretation is necessarily complicated by changes in functionality.



The present paper reports the deliberate effort to exploit the well-known cyclic-stabilizing effect of alkyl substituents[4] for the preparation of a number of interesting silicon heterocyclic diol derivatives. Included are examples of 1,2-, 1,3-, and 1,4-diol spirosilicates (I–IX) as well as several related organosilicon heterocyclics (Table I). The relative effect of several types of dialkylation on cyclic stability is also illustrated.

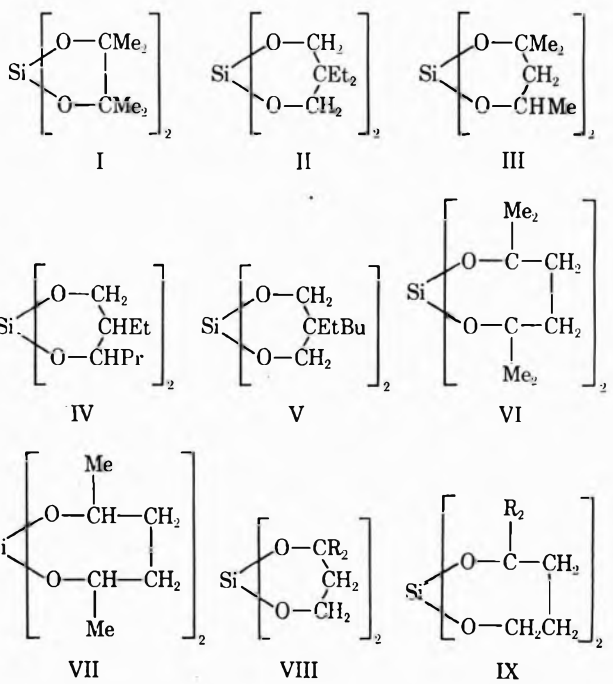
Diol Alcoholysis of Ethyl Silicate.—In this work, spirosilicates were prepared by catalyzed (NaOMe or isopropyl titanate) alcoholysis of ethyl silicate with appropriate diols under conditions whereby ethanol was removed from the system as it formed. The resulting spirosilicates were then isolated by distillation or crystallization. In appropriately decorated systems, monomeric spirosilicate species are so favored that the initial *neat* undistilled product is essentially free of higher oligomers, even in the presence of agents capable of catalyzing rapid redistribution of SiOC bonds (in this category fall I,[5] III,[5] IV, VI, VIII, and IX). In some systems, the decoration is less effective and, at equilibrium, the crude alcoholysis product contains much material of higher molecular weight. In such instances, distillation in the presence of a catalyst can,

TABLE I

ORGANOSILICON MODIFICATIONS

Alkanedioxysilane[a,b] (G = —OCH(*n*-Pr)—CHCH$_2$O(Et)—)	Bp, °C (mm), uncorrected	Viscosity (centistokes) 25°	75°	125°	200°
[Me(G)Si]$_2$G	170 (0.5)	66.2	7.76	2.59	1.06
[*n*-Pr(G)Si]$_2$G	185 (0.3)	61.8	8.79	3.14	1.23
[*n*-Pr(G)Si]$_2$G	130 (0.01)	20.6	4.36	1.82	0.79
[*n*-Pentyl(G)Si]$_2$G	180 (0.05)	95.1	11.9	3.89	1.44
[Ph(G)Si]$_2$G	250 (0.01)	7.75	26.5	6.01	1.88
n-Pr(G)SiOMe	114 (10)				

[a] Prepared by reaction of the organomethoxysilanes with 2-ethylhexane-1,3-diol and, in the case of the disiloxane, the appropriate amount of water. [b] In all cases, an elemental analysis consistent with the assigned structure was obtained.



(1) (a) H. Staudinger and W. Hahn, *Makromol. Chem.*, **11**, 24 (1953); (b) W. Hahn, *ibid.*, **10**, 261 (1953); (c) W. Hahn, *ibid.*, **11**, 51 (1953); (d) R. Schwarz and W. Kuchen, *Z. Anorg. Allgem. Chem.*, **279**, 84 (1955); (e) F. S. Kipping and J. T. Abrams, *J. Chem. Soc.*, 81 (1944); (f) J. J. Zuckermann, *ibid.*, 873 (1962); (g) C. M. Silcox and J. J. Zuckerman, *J. Organometal. Chem.*, **5**, 483 (1966); (h) R. Calas and P. Nicon, *Compt. Rend.*, **249**, 1011 (1959); (i) R. C. Mehrotra and R. C. Pant, *J. Indian Chem. Soc.*, **41**, 563 (1964); (j) R. C. Mehrotra and R. C. Pant, *ibid.*, **1**, 380 (1963); (k) Yn. N. Vol'nov and B. N. Dolgov, *J. Gen. Chem. USSR* (Engl. Transl.), **10**, 550 (1940); (l) M. M. Koton, *et al.*, *Zh. Obshch. Khim.*, **36**, 87 (1966); (m) M. F. Shostakovskii, *et al.*, U.S.S.R. Patent 165,452; *Chem. Abstr.*, **62**, 6514*a* (1965); (n) R. H. Krieble and C. A. Burkhard, *J. Amer. Chem. Soc.*, **69**, 2689 (1947); (o) G. W. Pedlow, Jr., and C. S. Miner, Fr., U. S. Patent 2,566,365 (1946); (p) R. Müller and L. Heinrich, *Chem. Ber.*, **94**, 2225 (1961); (q) C. L. Frye, R. M. Salinger, and T. J. Patin, *J. Amer. Chem. Soc.*, **88**, 2343 (1966).

(2) Throughout this paper the terms "stable heterocyclic" and "cyclic stability" refer to the thermodynamic stability relative to acyclic alternatives. No inferences regarding solvolytic or oxidative stability are intended.

(3) E. Rothstein and C. W. Shoppee, *J. Chem. Soc.*, 531 (1927).

(4) (a) G. S. Hammond, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 468. (b) N. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960). (c) For other leading references, see F. G. Bordwell, C. E. Osborne, and R. D. Chapman, *J. Amer. Chem. Soc.*, **81**, 2698 (1959).

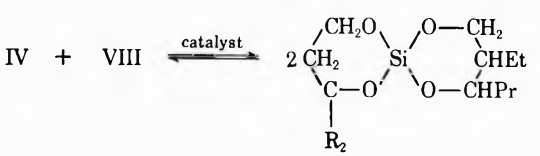
(5) Pinacol spirosilicate (I) has been prepared previously[1c,i] but not from alkyl orthosilicates. Likewise, compound III has also been previously described.[10]

by displacing the mobile equilibrium, be used to give high yields of the monomeric species (thus, II, V, and VII were prepared in this fashion). Finally, there are systems, *i.e.*, $[Si(OCH_2CH_2O)_2]_x$, which are so thoroughly polymeric at equilibrium as to completely frustrate all attempts to form and distil monomer from the *neat* system. The claim[11] that spirosilicates derived from ethylene, propylene, and butylene glycols had indeed been prepared is certainly unwarranted in view of the complete lack of volatility or solubility of the reported materials.

While examination of molecular models indicates the six- and seven-membered rings to be essentially strain-free, the five-membered ring species I appears to be appreciably strained. This strain is presumably related to the marked ease with which I is converted into stable pentacoordinate silicon derivatives.[6,7]

As will be seen below, geminal 1,1 dialkylation effectively stabilized the six-membered cyclics; however, this degree of substitution did not stabilize spirosilicates with five-membered rings; *i.e.*, the reaction of ethyl silicate and isobutylene glycol afforded only cross-linked gels from which we were unable to distil any spirosilicate. The fact that I does *not* undergo polymerization under equilibrating conditions despite its strained nature underscores the overriding importance of alkyl decoration upon ring–chain equilibria.

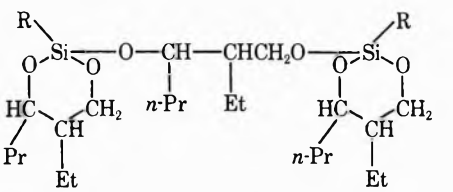
Vicinal Decoration and Heterocyclic Stability.—Some types of decoration appear to stabilize cyclics much more effectively than others. For instance, the vicinal 1,2 disubstitution in IV is apparently superior in this respect to the geminal 2,2 disubstitution of V. Upon heating these pure distilled spirosilicates briefly to 100° after the addition of catalytic KOH, IV (vicinal substitution) was unaffected, while V rearranged rapidly to an obviously cross-linked polymer. The greater stability of IV is possibly related to restriction of rotation about the vicinally substituted C–C bond; *i.e.*, constraint of rotation about this bond should diminish any loss of segmental rotational entropy which might result from cyclization. Although geminal 2,2 disubstitution did not confer much stability to the cyclic species (*i.e.*, V), very marked stability did accrue, however, from geminal 1,1 disubstitution (*e.g.*, VIII and IV); thus, under equilibrating conditions, VIII and IX afford no ring-opened oligomers. This stability is perhaps a consequence of the greater steric interactions to be expected in the hypothetical open-chain oligomers of VIII and IX; certainly decoration at the 1 site should produce more crowding about the silicon than should decoration at the 2 site. That these observations were indeed made under dynamic equilibrium conditions (*i.e.*, that cyclic stability was not merely the consequence of a slow and incomplete ring-opening reaction) was easily demonstrated. Thus, admixture of two stable cyclic species such as IV and VIII in the presence of a catalyst



resulted in the rapid formation of an additional species of intermediate volatility (*i.e.*, the mixed spirosilicate). Similar attempts to prepare a stable spirosilicate from the 1,5-diol, $HOCH_2CH_2CH_2CH_2C(Bu)_2OH$, led only to a viscous nonvolatile oil containing little, if any, of the desired monomer. Thus, this negative result would appear to indicate, at least qualitatively, a limit to the geminal 1,1 dialkyl "cyclic stabilizing" effect.

Although V did indeed gel, the number of cross links is apparently inversely proportional to the temperature, since upon heating to 200–220° the gel reverted to a mobile liquid. The catalyzed polymer thus behaves as a thermoplastic resin. The explanation for this thermal reversibility is believed to be similar to that advanced above to account for the stability of IV relative to polymeric forms. That is, certain motions (rotation of the geminal substituents, perhaps) more readily accommodated in the monomeric structure become increasingly important at higher temperature, thus favoring the spirosilicate species. Other motions also presumably facilitated in the lower molecular weight species, such as stretching vibrations and molecular translation, would become increasingly important at higher temperatures.

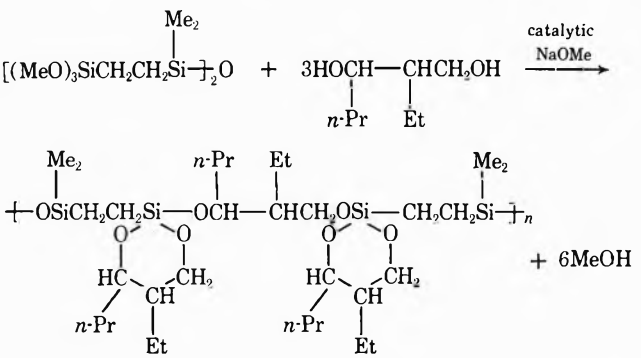
Organosilicon Modifications.—A number of related 2-ethylhexane-1,3-diol derivatives involving organo-substituted silicon (X, R = Me, *n*-Pr, *n*-pentyl, Ph)



X

were also prepared. Because of their possible utility as hydraulic fluids, viscosity data from 25–200° was obtained, and this information is also included in Table I.

The marked cyclization tendency engendered by this type of alkyl decoration was particularly well illustrated by the following reaction.

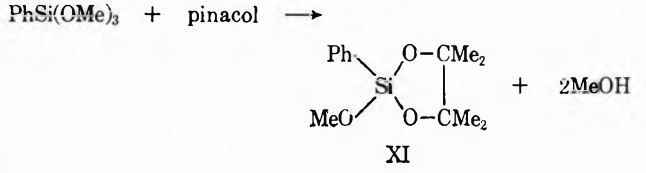


A *soluble* polymer was obtained, and this observation seemed immanently consistent with the presumed cyclic structure suggested, since any appreciable ring-opening would have certainly resulted in cross linking and consequent gelation.

(6) R. Müller and L. Heinrich, *Chem. Ber.*, **94**, 1943 (1961).

(7) Unpublished work from this laboratory to be described in a forthcoming paper.

Of especial interest were the organosilicon heterocyclic species derived from pinacol, *e.g.*



XI

Like I, the analogous spirosilicate, XI, appears to be highly strained and, as a presumed consequence of this strain, undergoes a number of interesting transformations to stable isolable pentaccordinate silicon derivatives.[7]

Experimental Section

2,2,3,3,7,7,8,8-Octamethyl-1,4,6,9,5-tetraoxasilaspiro[4.4]nonane (I, Pinacol Spirosilicate).—This material has been prepared before,[1a,i] but the following procedure utilizing alkoxy exchange is believed to be the most convenient method now available. To a 1-l. erlenmeyer flask were added 118 g (1.00 mol) of pinacol and 100 ml of benzene. After boiling this solution vigorously for about 5 min to azeotropically expel any moisture, 104 g (0.500 mol) of ethyl silicate was added. Upon heating to 135°, the absence of ethanol evolution suggested no reaction to be occurring. Therefore, tetraisopropyl titanate (0.5 ml) was added as a catalyst, resulting in the immediate commencement of ethanol evolution. The flask was then heated to a pot temperature of 190° and allowed to cool, whereupon crystallization occurred. Recrystallization from hexane yielded 70 g of pinacol spirosilicate; mp 112°. The filtrate was concentrated and taken up in pentane, and upon refrigeration deposited an additional 31 g of product. These two crops represent a 78% yield, and no further effort was expended with the filtrate, although it presumably contained additional spirosilicate. The infrared spectrum was consistent with the anticipated structure (absorption due to hydroxy and ethoxy being absent), and the anticipated molecular weight (260) was confirmed by mass spectroscopy.

2,2,4,8,8,10-Hexamethyl-1,5,7,11,6-tetraoxasilaspiro[5.5]undecane (III, Hexylene Glycol Spirosilicate).—This material[1i,10] was prepared in similar fashion to that employed above for I, the only difference being that NaOMe was employed as catalyst rather than isopropyl titanate. The product was freed of catalyst by filtration of its hexane solution. The clear filtrate was then stripped of hexane to give a crystalline product (90% yield) which was recrystallized from methanol or pentane; mp 73–77°. The broad melting point is not unexpected in view of the diastereomeric possibilities.

2,2,5,5,9,9,12,12-Octamethyl-1,6,8,13,7-tetraoxasilaspiro[6.6]tridecane (VI).—Ethyl silicate (16.0 g, 0.077 mol) and 2,5-dimethyl-2,5-hexanediol (22.0 g, 0.150 mol) were combined and heated to 140° with no indication of ethanol formation. The addition of a catalytic amount of powdered sodium methoxide resulted in the immediate commencement of boiling. Allowing ethanol to escape as it formed, the reaction mixture was heated to 220° and held at that temperature for 20 min. The low viscosity of this solvent-free melt attests to the absence of polymeric products. Recrystallization of the resulting solid product from methanol yielded 13.9 g (59% yield) of pure VI; mp 81–83°. An infrared spectrum showed this material to be completely free of hydroxyl content and to have a strong Si–O absorption at 9.5 μ.

Anal. Calcd for $SiC_{16}H_{32}O_4$: C, 60.8; H, 10.23; Si, 8.89; mol wt, 316. Found: C, 61.1; H, 10.23; Si, 8.83; mol wt, 359.

In an earlier attempt to prepare this material using tetraisopropyl titanate as catalyst, little or no reaction was observed.

3,9-Diethyl-3,9-dibutyl-1,5,7,11,6-tetraoxasilaspiro[5.5]undecane (V).—Into a 1-l. distillation flask were placed 320 g (2.00 mol) of 2-ethyl-2-butyl-1,3-propanediol and 100 ml of benzene. This material was then briefly heated to boiling under a 36 in. × 10 mm Nester–Faust spinning-band column to azeotropically remove any moisture from the system. A slurry of 0.1 g of NaOMe in 208 g (1.00 mol) of ethyl silicate was then added, and, upon further heating, benzene and ethanol was removed while the still temperature climbed to 255°. Fractionation at reduced pressure yielded 329 g (95%) of spirosilicate; bp 150–155° (0.5 mm), $n^{25}D$ 1.4631.

Anal. Calcd for $SiC_{18}H_{36}O_4$: C, 62.8; H, 10.46; Si, 8.16. Found: C, 62.7; H, 10.64; Si, 8.15.

A sample of this spirosilicate (16.8 g) was heated for several minutes at a temperature of 100–150° with a trace of KOH (0.04 g), resulting in gelation. Heating this gel at a temperature of 200–230° caused the obviously cross-linked material to revert to a mobile liquid which, of course, gelled again as the temperature was lowered. Another sample of the spirosilicate showed no discernible viscosity change upon heating at 100–150° for 2 hr in the absence of KOH.

3,9-Diethyl-2,8-dipropyl,1,5,7,11,6-tetraoxasilaspiro[5.5]undecane (IV).—This material was prepared in the same manner as was V; bp 134–137° (0.8 mm), $n^{25}D$ 1.4536. Temperature and viscosity (in centistokes) follow: 0°, 425; 25°, 54.0; 100°, 3.41.

Anal. Calcd for $SiC_{16}H_{32}O_4$: C, 60.8; H, 10.12; Si, 8.88; mol wt, 316. Found: C, 61.3; H, 10.46; Si, 8.93; mol wt, 350.

When a sample of this material was heated with catalytic KOH for 2 hr at 100–150°, there was no discernible change, in striking contrast to the behavior of V noted in the preceding example.

3,3,9,9-Tetraethyl-1,5,7,11,6-tetraoxasilaspiro[5.5]undecane (II).—To a 250-ml distillation flask were added 20.8 g (0.100 mol) of ethyl silicate, 26.4 g (0.200 mol) of 2,2-diethyl-1,3-propanediol, and 0.1 g of powdered KOH. The flask was placed under a 36 in. × 10 mm Nester–Faust spinning-band column and heat was applied. Commencing at a pot temperature of 85–90°, ethanol formation was noted. During the next 30 min, 17 g (92% of theoretical) of ethanol was collected while the still temperature rose to 230°. Fractionation at reduced pressure then yielded 26.4 g (92% yield) of the spirosilicate; bp 130–133° (0.8 mm), $n^{26}D$ 1.4633. An infrared spectrum showed this material to be free of hydroxyl. Refrigeration of its pentane solution caused crystallization; mp 61–63°.

Anal. Calcd for $SiC_{14}H_{28}O_4$: C, 58.35; H, 9.72; Si, 9.75. Found: C, 58.24; H, 9.52; Si, 9.70.

2,5,9,11-Tetramethyl-1,6,8,13,7-tetraoxasilaspiro[6.6]tridecane (VII).—Ethyl silicate (62.4 g, 0.30 mol) of 2,5-hexanediol (71.5 g, 0.60 mol), and catalytic KOH (0.10 g) were heated to 210°, removing ethanol as it formed. Subsequent fractional distillation afforded the desired product in fair yield (29%); bp 110° (4.5 mm), $n^{26.5}D$ 1.4430. Infrared spectroscopy confirmed the absence of carbinol groups.

Anal. Calcd for $SiC_{12}H_{24}O_4$: C, 55.4; H, 9.29; Si, 10.78. Found: C, 55.6; H, 8.8; Si, 10.73.

2,2,8,8-Tetrabutyl-1,5,7,11,6-tetraoxasilaspiro[5.5]undecane (VIII, R = Bu).—3-Butylheptane-1,3-diol (9.0 g, 0.048 mol) was heated with ethyl silicate (5.0 g, 0.024 mol) after adding 80 μl of $(i\text{-PrO})_4Ti$ to catalyze the alcoholysis reaction. Ethanol was distilled from the reaction mixture, and distillation of the residue afforded a 62% yield (6 g) of the anticipated spirosilicate, VIII, which eluted as a single component from a gas chromatograph. Positive structural confirmation was provided by mass spectroscopy (a parent ion of the theoretically anticipated molecular weight of 400), as well as nmr spectroscopy which showed the following absorptions of the proper intensity ratios: A poorly resolved triplet at τ 9.07 ($C\text{–}CH_3$), a triplet at τ 6.01 (OCH_2), and a complex multiplet at τ 8.2–8.9 ppm ($\text{–}CH_2\text{–}CH_2CH_2\text{–}$).

The glycol needed for the above preparation (*i.e.*, 3-butylheptane-1,3-diol) was prepared as follows. A solution of β-propiolactone (29 g, 0.40 mol) in toluene (50 ml) was slowly added to a 1.6 *M* hexane solution of *n*-BuLi (containing 0.8 mol of the lithium reagent) while maintaining the temperature at 0°. The resulting product was washed well with water, dried (Na_2SO_4), and fractionally distilled to afford 20 g (27% yield) of the desired diol; bp 88–90° (0.15 mm). [Mol wt: calcd, 188; found (mass spectrum), 188.]

The nmr spectrum showed the following absorptions of the anticipated intensity ratios: A poorly resolved triplet at τ 9.08 ($C\text{–}CH_3$), a triplet at τ 6.29 ($O\text{–}CH_2$), a complex multiplet at τ 8.2–8.9 ($\text{–}CH_2CH_2CH_2\text{–}$), and a singlet at τ 5.92 ppm (OH).

2,2,8,8-Tetramethyl-1,5,7,11,6-tetraoxasilaspiro[5.5]undecane (VIII, R = Me).—This spirosilicate was prepared (75% yield) in the same fashion as was VIII; bp 67° (2.4 mm). [Mol wt: calcd, 232; found (mass spectrum), 232.] The nmr spectrum showed a singlet at τ 8.73 ($C\text{–}Me_2$), a triplet at τ 8.31 ($C\text{–}CH_2$), and a triplet at τ 5.99 ($O\text{–}CH_2$); and these absorptions

were of the expected intensity ratios. The diol required for this preparation was obtained from the slow addition of β-propiolactone (29 g, 0.40 mol) to 550 ml of ethereal MeLi (containing 0.88 mol of lithium reagent) while maintaining the reaction temperature at −18°; the reaction product was then allowed to rise to room temperature and enough water (0.88 mol) was added to hydrolyze the lithium alkoxide, whereupon LiOH precipitated and was removed by filtration. Subsequent distillation of the filtrate afforded a 25% yield (10 g) of the desired diol,[8] 3-methylbutane-1,3-diol, which was characterized by mass and nmr spectroscopy. [Mol wt: calcd, 104; found (mass spectrum), 104].

The nmr spectrum showed the following absorptions of the expected intensity ratios: a singlet at τ 8.88 (C-Me_2), a triplet at τ 8.41 (C-CH_2), a triplet at 6.49 (OCH_2), and a broad unresolved band at τ 5.65 ppm (OH).

2,2,9,9-Tetrabutyl-1,6,8,13,7-tetraoxasilaspiro[6.6]tridecane (IX).—This spirosilicate was prepared in the same fashion as were the previous two examples; bp 153° (0.6 mm). The diol precursor to this derivative (*i.e.*, 4-butyloctane-1,4-diol) was prepared in 39% yield by the addition of *n*-BuLi to γ-butyrolactone, as in the above related examples; bp 119° (0.65 mm), $n^{25}D$ 1.4596. The diol was characterized by mass spectroscopy (the calculated molecular weight value of 202 was confirmed), and nmr spectroscopy (in dimethyl sulfoxide), which showed peaks at τ 5.63 (CH_2OH), τ 6.20 (R_2COH), τ 6.6 (CH_2O), and τ 8.7–9.1 ppm (aliphatic) in the expected intensity ratios of 1:1:2:22, respectively.

Attempted Polymerization of VIII and IX.—Neither VIII nor IX could be caused to polymerize when heated for long periods (*i.e.*, 48 hr) at 60° with catalytic amounts of KOH or $(i\text{-PrO})_4Ti$. To demonstrate that alkoxysilicon linkages were indeed undergoing exchange, VIII and IX were admixed with IV in the presence of such catalysts; glpc assay revealed in each case the almost immediate appearance of an additional peak attributable to the mixed spirosilicate.

Phenyl(tetramethylethylenedioxy)methoxysilane (XI).—Phenyltrimethoxysilane (1.00 mol) and pinacol (1.00 mol) were heated in the presence of an alkaline catalyst (0.1 g of NaOMe), distilling the methanol from the reaction zone as it formed. This required a time of 5–6 hr, with a maximum temperature of 215° being reached. "Methanol volatiles" in the amount of 64.7 g were collected; there was some indication of a small amount of Ph–Si cleavage in the latter part of the reaction; *i.e.*, the refractive index of the volatiles was somewhat higher, suggesting the presence of some benzene. The crude product was strip distilled and then carefully fractionated on a 36 in. × 10 mm Nester–Faust spinning-band column to afford a 63% yield (160 g) of IV, bp 85° (0.15 mm), $n^{25}D$ 1.4890.

(8) This preparative method is superior in terms of yield and convenience to those previously employed; see S. Searles, Jr., E. K. Ives, and S. Nukina, *J. Org. Chem.*, **24**, 1170 (1959), and references therein.

Anal. Calcd for $SiC_{13}H_{29}O_3$: C, 61.9; H, 7.94; Si, 11.14. Found: C, 62.0; H, 6.9; Si, 11.08.

The nuclear magnetic resonance spectrum showed a doublet at τ 8.82 and 8.40 (*cis* and *trans* methyls of the pinacoloxy moiety) a singlet at τ 6.45 (OMe), and a complex multiplet at τ 2.1–2.8 ppm (C_6H_5); the integrated intensity ratios were consistent with the structure. This compound is *very* hygroscopic and must be protected from atmospheric exposure to avoid hydrolysis.

2-Ethylhexane-1,3-diol Derivatives of Organo-Substituted Silanes (X).—The preparation of the 2-ethylhexane-1,3-diol derivatives of $PrSi(OMe)_3$ described below illustrate the methods used to prepare related organosilicon species from other alkoxysilanes.

2-Ethyl-1,3-bis(2,4-dipropyl-5-ethyl-1,3,2-dioxasila-2-cyclohexoxy)hexane (X, R = Pr).—Propyltrimethoxysilane (67.6 g, 0.41 mol), 2-ethylhexane-1,3-diol (87.6 g, 0.60 mol), and sodium methoxide (0.05 g) were heated to 260° during a 2–3-hr period, and methanol was distilled from the system as it formed. Subsequent fractional distillation afforded 103 g (90% yield) of the desired product (X, R = Pr); bp 180–190° (0.3 mm), $n^{25}D$ 1.4525. An infrared spectrum confirmed the absence of residual OH groups.

Anal. Calcd for $Si_2C_{30}H_{62}O_6$: C, 62.7; H, 10.85; Si, 9.78. Found: C, 63.3; H, 11.05; Si, 9.77.

When glycol sufficient to react with only two-thirds of the methoxy groups was added, the monomeric species, $Pr(MeO)SiOCH_2CHEtCHPrO$, was obtained in 50% yield; bp 114° (10 mm), $n^{25.8}D$ 1.4339. This monomethoxysilane (123 g, 0.5 mol) was heated to 150° for 3 hr with H_2O (4.5 g, 0.25 mol) after adding a small amount of powdered KOH to serve as catalyst; during this time 15 g (94% yield) of methanol distilled from the reaction. Subsequent distillation afforded 98 g (88% yield) of the expected disiloxane, bis-2,4-dipropyl-5-ethyl-1,3,2-dioxasila-2-cyclohexyl ether; bp 155° (0.5 mm), $n^{25.4}D$ 1.4475.

Anal. Calcd for $Si_2C_{22}H_{46}O_5$: C, 59.2; H, 10.3; Si, 12.59. Found: C, 59.5; H, 10.3; Si, 12.2.

Registry No.—I, 837-00-3; II, 20505-17-3; III, 887-37-6; IV, 20505-19-5; V, 20505-20-8; VI, 20483-232; VII, 20505-21-9; VIII, R = Bu, 20505-22-0; 3-butylheptane-1,3-diol, 20483-24-3; VIII, R = Me, 20505-23-1; IX, 20505-24-2; X, R = Pr, 20505-25-3; bis-2,4-dipropyl-5-ethyl-1, 20505-26-4; 3,2-dioxasila-2-cyanohexyl ether; $Pr(MeO)SiOCH_2CHEtCHPrO$, 20505-27-5; X, R = Me, 20505-28-6; X, R = pentyl-*n*, 20505-29-7; X, R = PL, 20483-25-4; XI, 20505-30-0.

Acknowledgment.—It is a pleasure to acknowledge the technical assistance of Mr. David S. Robinson and Mrs. Theresa DeYoung on certain phases of this work.

Alkyl–Oxygen Bond Cleavage in Trityl Acetate-^{18}O during Reaction with Phenyl Grignard Reagent[1a]

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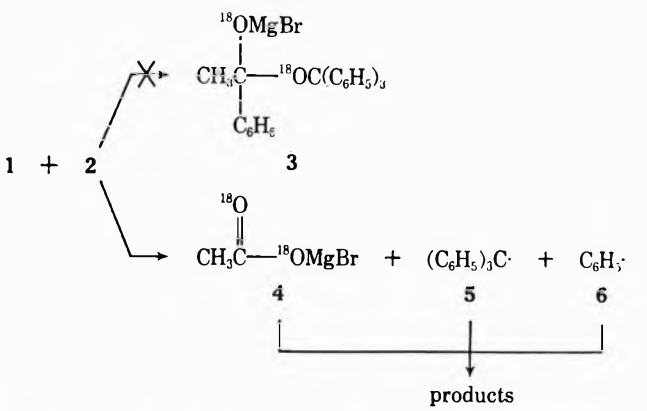
Triphenylmethyl (trityl) acetate-^{18}O and phenylmagnesium bromide (1:1.3 molar ratio) react in ether at room temperature. Trityl peroxide and acetic acid are the major products detected in the reaction mixture after hydrolysis in the presence of air. Acetophenone, triphenylmethane, benzophenone, triphenylmethanol, tetraphenylmethane, and very small quantities of several other compounds were also identified by glpc and mass spectral analysis. Since trityl peroxide did not contain ^{18}O, a classical acyl–oxygen [C(=O)O] bond cleavage was considered untenable. The acetic acid examined contained ^{18}O in the amount essentially identical with that determined in trityl acetate-^{18}O used as starting material. A mechanism is postulated to involve electron transfer by the Grignard reagent to trityl cation to give trityl radical.

In a continuing study,[2] it was observed[3] that several carboxylic esters of triphenylmethanol behave in an anomalous fashion toward aryl Grignard reagents.[4] Unequivocal evidence is now available by the use of trityl acetate-^{18}O (**1**) to substantiate a mechanism in which alkyl–oxygen bond cleavage[5a] occurs in the ester

SCHEME I



prior to or during attack by phenylmagnesium bromide (**2**). A classical intermediate[5b] **3** resulting from addition of the Grignard reagent to the carbonyl group is untenable, but a different mechanism tentatively postulated[3] is supported. (See Scheme I.)

The distribution of ^{18}O in the final products is found in Table I. It is clear that decomposition by the intermediate **3** in a classical manner would be expected to give triphenylmethanol containing ^{18}O. In two separate experiments with labeled **1**, glpc and mass spectral analyses confirmed the presence of triphenylmethanol, but with only 1–2% ^{18}O, which most likely results from hydrolysis of a small amount of unreacted **1**.

TABLE I

QUANTITATIVE ANALYSIS OF PER CENT YIELDS AND PER CENT ^{18}O IN THE PRODUCTS RESULTING FROM THE REACTION OF TRITYL ACETATE-^{18}O (**1**) AND PHENYLMAGNESIUM BROMIDE (**2**), 1:1.3 MOLAR RATIO

Product	Typical yield, %[a]	% ^{18}O[b]	% ^{18}O[c]
Trityl Peroxide (**7**)	60	0	0
Acetic Acid	80[d]	0[e]	50
Acetophenone (**9**)	14	15	20.6
Triphenylmethane	23	..	...
Benzophenone	12	0	0
Triphenylmethanol	~5	3	0
Biphenyl	23	..	...
1,1-Diphenylethanol (**9**)	~2	..[f]	...[f]
Tetraphenylmethane	~2	..	...
1,1-Diphenylethene (**10**)	~2	..	...
Bromobenzene	...[g]	..	...
Phenol	...	..	...[h]

[a] Yields based on trityl acetate. The yield of **7** is that obtained by actual isolation of the material. It was inadvertently implied in the preliminary communication[3] of our data that this yield was determined by glpc analysis. The yield of **7** varied from a minimum of 60% to a maximum of 72% of isolated pure product. This situation was created owing to the lack of a good purification solvent for **7**, since hot benzene proved to be only a fair solvent and no other solvent proved superior. [b] Started with trityl acetate-^{18}O (47%) and mixture hydrolyzed with 6 *N* HCl. [c] Started with trityl acetate-^{18}O (50%) and mixture decomposed with anhydrous H_2SO_4. [d] Yield of acetic acid was obtained by an nmr study of the water layer, using dimethyl sulfoxide as an internal standard. A deviation of ±2% of the actual yield under controlled conditions was observed for acetic acid. [e] ^{18}O exchanged with H_2O in water layer. [f] Mass spectrum of the oxygen-containing molecular ion could not be obtained owing to ease of dehydration of the alcohol. [g] Not determined. [h] Found in all reaction mixtures (<2%) but did not contain ^{18}O as determined within the limits of mass spectral analysis.

Electron transfer from the Grignard reagent **2** to trityl cation to give **4**, **5**, and **6** permits a prediction as to

(1) (a) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967. (b) To whom inquiries should be addressed at the Department of Chemistry, Oklahoma State University, Stillwater, Okla. 74074. (c) Predoctoral NASA Trainee, 1965–1968.

(2) K. D. Berlin and B. S. Rathore, *J. Org. Chem.*, **29**, 993 (1964), contains reference to prior work.

(3) K. D. Berlin, R. D. Shupe, N. L. Doss, W. J. Leivo, M. D. Bell, R. D. Grigsby, E. D. Mitchell, Jr., and G. R. Waller, *Chem. Commun.*, 624 (1968).

(4) Facile reduction of trityl cations at the dropping mercury cathode was observed recently; see M. I. James and P. H. Plesch, *Chem. Commun.*, 508 (1967). Trityl cation is reported to undergo an electron exchange with trityl radical; see J. W. Lown, *Proc. Chem. Soc.*, 283 (1963).

(5) (a) Ion-pair formation in trityl esters is well documented. Much of the data has been summarized; see S. Winstein and B. R. Appel, *J. Amer. Chem. Soc.*, **86**, 2718 (1964), **86**, 2720 (1964). Ion-pair formation by **1** could yield trityl cation, which could then be reduced. (b) It is recognized that esters of triphenylmethanol undergo heterolytic bond cleavage to give trityl cation in alcohols in the synthesis of trityl ethers. For a discussion of this, see E. S. Gould, "Mechanism and Structure in Organic Chemistry," H. Holt & Co., New York, N. Y., p 344.

distribution of ^{18}O in the products.[6] First, trityl peroxide (**7**), a major product (see Table I), did not contain ^{18}O, a fact which does not support heterolytic or homolytic acyl–oxygen bond cleavage for $[C(=^{18}O)^{18}O]$ in **1** or **3**. Trityl peroxide must arise by reaction of trityl radical with oxygen during the workup. Trityl radicals probably exist in equilibrium with hexaphenylethane in solution; during work-up, reaction with oxygen occurs to give tritylperoxy radicals.[7]

$$(C_6H_5)_3C\cdot + O_2 \rightleftharpoons (C_6H_5)_3COO\cdot \xrightarrow{(C_6H_5)_3C\cdot} \mathbf{7}$$

With a molar ratio of 1.3:1 for **2**:**1**, only a slight excess (maximum 0.3 equiv) of **2** would be available to react with any intermediates, assuming 1 equiv would be consumed in the reduction step. This means that further reaction of **2** with **4** should be small and therefore the amount of acetophenone produced would be low. This low yield was substantiated by careful glpc analysis using standards (see Table I).[8] Mass spectral analysis

$$\mathbf{2} + \mathbf{4} \longrightarrow \underset{\mathbf{8}}{CH_3\overset{\overset{^{18}O}{\|}}{C}-C_6H_5} + \underset{\mathbf{9}}{(C_6H_5)_2\overset{\overset{^{18}OH}{|}}{C}CH_3} + \underset{\mathbf{10}}{(C_6H_5)_2C=CH_2}$$

of the ^{18}O content of **8** revealed an incorporation of 20.6% in the experiment starting with **1** (50 atom % ^{18}O). The cause of this isotopic dilution is difficult to assess, but one tentative explanation may rest in an unusual reaction involving formation of acetophenone from ethyl ether and **2** or radical fragments therefrom. As a model experiment to evaluate this question, trityl bromide and **2** were allowed to react in anhydrous ethyl ether by Gomberg's method.[9] Glpc analysis revealed *acetophenone* and *benzophenone* as important products along with those compounds already reported,[9] in addition to several others previously unreported. Participation of ethyl ether in the reaction leading to acetophenone appears likely, but no direct evidence is available from which to support a mechanism.

In a second experiment (see Table I) with a separately prepared sample of labeled **1** (47 atom % ^{18}O), the incorporation of ^{18}O in **8** was 15%. We have noted in this laboratory that decomposition of commercial phenylmagnesium bromide in ether or freshly prepared reagent with dilute aqueous hydrochloric acid leads to only 1–2% acetophenone.

Decomposition of the reaction mixture of **2** and **1** (50 atom %) with a few drops of concentrated sulfuric acid (previously treated with fuming sulfuric acid to minimize the water content) gave a heterogeneous mixture in which the acetic acid remained in solution while trityl peroxide and the magnesium salts precipitated. The acetic acid was 50 atom % ^{18}O (±2%). Thus, it appears that essentially all of the acetic acid derived from **1** does not experience an exchange of ^{18}O. This is reasonable if the mechanism postulated is applicable, in which **4** is formed and is decomposed by concentrated sulfuric acid without ^{18}O exchange.

Trityl radicals may abstract hydrogen from ether in addition to reacting with oxygen. From the former situation, triphenylmethane is expected, except that the source of the hydrogen is somewhat speculative, but two observations are pertinent. First, the yield of acetic acid was 80% or greater in experiments with a 1:1.3 ratio of **1**:**2**. This implies that removal of hydrogen from **1** or **4** is probably not important; this is tenable since the concentrations of **1** or **4** are small. Additional support is provided for this by the detection of 1–2% of ^{18}O in triphenylmethanol which is thought to arise from hydrolysis of unreacted **1**. Moreover, the dilution effect on the ^{18}O content of acetophenone is more easily understood if ether participates at some stage of the over-all reaction by furnishing hydrogen to the trityl radical. In total, labeled acetic acid, acetophenone, and triphenylmethanol account for the bulk of ^{18}O in the products.

A solution of **1** in anhydrous ether was treated with dried oxygen for 8 hr. The ester **1** was recovered unchanged. Although the degree of ionization of **1** is unknown, if a reaction occurred between trityl cation and O_2, even trace amounts of the cation should give some detectable **7** (at least this should be a detectable quantity within the period used for the general reaction). After 1 hr of reaction, a mixture of **1** and **2** was subjected to a stream of dried oxygen for 6 hr. Trityl peroxide began to precipitate immediately. This was taken as additional evidence for the presence of trityl radical. A special experiment was conducted in a drybox in which deoxygenated N_2 was used to degas the ether prior to use, the reaction mixture during reaction, and the water used to decompose the mixture. The resulting organic layer appeared clear, but, upon exposure to the atmosphere, immediate precipitation of **7** occurred. Thus, in the absence of oxygen, trityl radical reacts principally (although very slowly) by abstracting hydrogen as suggested previously.[3,10] The assumption that trityl bromide, like **1**, can form trityl cations in solution is not without precedence.[11]

(6) It is important to note that an electron transfer from potassium heptaphenylcycloheptatrienide to heptaphenyltropylium cation to give heptaphenylcycloheptatrienyl radical in dimethoxyethane has been recorded recently; see R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, **87**, 2200 (1965). A free-radical mechanism has been suggested in the reaction of methylmagnesium bromide with 7,7-dibromobicyclo[4.1.0]heptane; see D. Seyferth and B. Prokai, *J. Org. Chem.*, **31**, 1702 (1966). A very recent report presents strong evidence for fleeting radical intermediates in reactions of certain Grignard reagents with allylic bromides; see R. G. Gough and J. A. Dixon, *J. Org. Chem.*, **33**, 2148 (1968). A paper just published contains a summary of many electron transfer reactions involving cations, carbanions, metals, Lewis bases, etc.; see K. A. Bilevitch, N. N. Bubnov, and O. Yu. Okhlobystin, *Tetrahedron Lett.*, 3465 (1968). An example which appears to be related to our study is that of Shilov and coworkers who found trityl radicals in the reaction of $(C_6H_5)_3CCl$ with C_2H_5Li; see F. S. Dyachkovskii, N. N. Pubnov, and A. E. Shilov, *Dokl. Akad. Nauk SSSR*, **123**, 870 (1958); *Chem. Abstr.*, **55**, 7996 (1961).

(7) This equilibrium appears to be well substantiated now; see C. L. Ayers, E. G. Janzen, and F. J. Johnston, *J. Amer. Chem. Soc.*, **88**, 2610 (1966); **89**, 1176 (1967).

(8) Unfortunately, the peak for **9** was buried under that of benzophenone in the glpc analysis. Extensive dehydration of **9** to **10** occurred during the reaction and on the glpc columns used, and prevented any quantitative estimate of ^{18}O in **9** by mass spectral examination.

(9) M. Gomberg and D. Kamm, *J. Amer. Chem. Soc.*, **39**, 2009 (1917). These workers found trityl peroxide and other triaryl-substituted hydrocarbons by extremely careful distillations. Acetophenone was not reported however. See also C. S. Schoepfle and S. G. Trepp, *ibid.*, **58**, 791 (1936).

(10) It has been suggested by a referee that products from reaction of O_2 with C_6H_5MgBr [these react at −78°; *cf.* C. Walling and F. A. Buckler, *J. Amer. Chem. Soc.*, **77**, 6039 (1955)] could be involved in the mechanism of reaction of **1** and **2**. If this were true to an appreciable extent, it is reasonable to expect considerable dilution effect in the ^{18}O content in the products. The ^{18}O balance is near 90% in analysis of acetic acid, acetophenone, and triphenylmethanol from the labeling experiment. This does not include the 1,1-diphenylethanol, which must arise from attack of **2** on **4**, nor does the loss of ^{18}O in dehydration to 1,1-diphenylethene. In addition, since in the experiments with deoxygenated N_2 no **7** was detectable in the organic layer (after decomposition) until air was admitted, trityl radical is relatively unreactive toward other radicals in solution.

(11) A. G. Evans, I. H. McEwan, A. Price, and J. H. Thomas, *J. Chem. Soc.*, 3098 (1955); P. B. D. De La Mare and E. D. Hughes, *ibid.*, 1059 (1949); F. Fairbrother and B. Wright, *ibid.*, 1059 (1949).

Dry oxygen was bubbled into a solution of trityl bromide in anhydrous ether for 6 hr. The solution remained clear and no **7** precipitated. Thus, oxygen does not appear to be an effective electron-transfer agent for trityl cation as expected.

Phenyl radical could abstract hydrogen to give benzene or couple to give biphenyl, both of which are present in the reaction mixture. However, the yields of these materials from reaction of **1** and **2** cannot be evaluated simply, since both compounds are formed in solutions of phenylmagnesium bromide in ether. Since analysis of the phenol for ^{18}O content did not reveal any incorporation of the isotope, it is surmised that the compound does not arise from any reaction in which **1** furnishes the oxygen.

In the mass spectrum of **1**, the base peak occurs at *m/e* 243 $[(C_6H_5)_3C^+]$; masses of 302, 304, and 306 (relative ratios are 1:0.4:0.86, respectively) confirm the presence of the ^{18}O (47 atom %) in **1**. Additional ions occur at *m/e* 259 $[(C_6H_5)_3CO^+]$ and 261 $[(C_6H_5)_3C^{18}O^+]$.

In the mass spectrum of **7**, the base peak at *m/e* 105 $[C_6H_5C^+{=}O]$ is likely formed by decomposition of the fragment at *m/e* 259 $[(C_6H_5)_3CO^+]$. It was not possible to obtain a molecular ion of trityl peroxide (placed as a solid directly into the source), as the O—O bond cleaved upon electron bombardment.

Experimental Section

Apparatus and Procedure.—Mass spectral analyses were performed on two instruments: a Bendix time-of-flight and a LKB-9000 prototype magnetic sector. Solid samples were placed in the ionization chamber with the aid of a direct probe. The ethereal reaction mixtures were analyzed *via* a glpc inlet system to the ionization chamber. The ionization voltage was 70 eV.

The nuclear magnetic resonance spectra were determined using a Varian Model A-60 high resolution spectrometer with a field-sensing stabilizer ("Super-Stabilizer").

Gas chromatographic analyses were performed using a Varian-Aerograph Model 1520 with a hydrogen flame ionization detector and a disk integrator. Acetic acid was determined with a 6 ft × 1/4 in. glass column of 6% FFAP on A/W Chromosorb W, 80–100 mesh and DMCS treated. All other glpc analyses of the ether solutions were performed using a 6 ft × 1/8 in. column of 6% SE-30 on A/W Chromosorb G, 60–80 mesh and DMCS treated.

Nitrogen gas used for this work was carefully dried by passing it through concentrated sulfuric acid and then through three Linde 3A Molecular Sieve traps. The N_2 was deoxygenated to a low level according to the method reported.[12] Trityl bromide was prepared according to the method in the literature.[2] Anhydrous ether[13] was degassed with the deoxygenated N_2 in the special experiment before use in the reaction; during the reaction, the mixture was also degassed with deoxygenated N_2.

Silver acetate (82% ^{18}O-labeled) was obtained from the Weizmann Institute of Science, Rehovoth, Israel.

Small-Scale Preparation of 1.—The procedure was slightly modified from that originally developed in this laboratory.[2] This description is typical of all preparations attempted for **1** in this work. All glassware was carefully dried for several hours in a drying oven above 105°. Nitrogen, dried by passing through three 3A molecular sieve containing drying towers, was passed through the system for 2 hr before any reagents were added. To the reaction vessel was added 1.00 g (0.0031 mol) of trityl bromide followed by 40 ml of reagent grade benzene dried over 3A molecular sieve. The solution was then brought to reflux, and 0.30 g (0.0018 mol) of regular silver acetate and 0.40 g (0.0024 mol) of 82% ^{18}O-labeled anhydrous silver acetate were added all at once. The resulting heterogeneous reaction mixture was stirred at near reflux for 8 hr, after which time the silver bromide and any unreacted silver acetate were filtered from the hot benzene solution. Again, all glassware used in the filtration process was carefully oven dried, as the ester is easily hydrolyzed. The benzene was immediately stripped from the dissolved trityl acetate (by using a flash evaporator) to leave a viscous oil. This oil was allowed to stand under nitrogen for 1 hr, and then cold, anhydrous petroleum ether was added. White crystals of trityl acetate formed in about 2 hr. The crystals were powdered with a mortar and pestle and then placed under high vacuum for about 1 hr. No recrystallization was necessary. Trityl acetate (0.51 g, 0.00169 mol, 47 atom % ^{18}O) was obtained in 55% yield, mp 82.5–83° (lit.[14] mp 82–84°). Nmr and infrared spectra were superimposable on those of an authentic sample.

Reaction of Trityl Acetate (1) with Phenylmagnesium Bromide (2) (1:1.3 Molar Ratio).—Trityl acetate (0.45 g, 0.00147 mol, 47 atom % ^{18}O) dissolved in ether was added dropwise to 0.00191 mol of Grignard solution over a period of 1 hr. The reaction mixture was then allowed to stir at room temperature for 12 hr while ether was added as necessary to keep the volume near 50 ml. The mixture was cooled in an ice bath and 50 ml of ice-cold 6 *N* hydrochloric acid was added very slowly to destroy any excess Grignard reagent. The organic layer was washed successively with water and 10% sodium bicarbonate solution, and again with water. A pale yellow solid, trityl peroxide (**7**), was filtered from the organic layer, after which the organic layer was dried ($MgSO_4$). Glpc analysis of the organic layer revealed many products (Table I) which were identified by mixed injections of known standards. Per cent yields of the products were calculated by using standard solutions of the reaction products and comparing peak areas with the aid of the disk integrator on the Aerograph 1520 unit. One of the products, acetic acid, was present in both the aqueous and the organic layers. The identification and determination of yield of acetic acid was accomplished by a nmr study of the aqueous layer. The methyl protons of acetic acid were identified by examination of the nmr spectrum of the aqueous layer of the reaction mixture. After determination of the partition coefficient of acetic acid between 6 *N* hydrochloric acid and ether (equal volumes) under the conditions of the reaction as described above, the per cent yield of acetic acid could be determined as follows. A known amount of dimethyl sulfoxide (DMSO) was added to the aqueous layer, and then the area under the nmr peaks due to the methyl protons in DMSO was compared with that due to the methyl protons in acetic acid. Then the per cent yield of acetic acid based on trityl acetate (**1**) was calculated by using the partition coefficient so determined. For this particular determination, the organic layer was not washed with water and sodium bicarbonate solution, as described above; instead, the aqueous layer was analyzed directly for acetic acid. This procedure was checked against a standard solution of acetic acid.

Peak integration gave the DMSO/acetic acid ratio as 1.25:1. Since 0.0356 g (0.000456 mol) of DMSO had been added, and since DMSO has six protons to every three for acetic acid, the number of moles of acetic acid present in the aqueous layer was given by (0.000456/1.25) × 2, or 0.00073 mol, but, since the partition coefficient, organic/aqueous, is 0.61, there remained (0.38/0.62) × (0.00073) = 0.00045 mol of acetic acid in the ether layer. Thus the total yield of acetic acid obtained was 0.00118 mol (80%).

In the special experiment with deoxygenated N_2, the procedure was identical with that described, except for the increased precautions to remove O_2. After decomposition with the aqueous acid (previously degassed with the deoxygenated N_2), the organic layer was carefully separated and dried ($MgSO_4$) all under N_2. Upon exposure of the clear solution to the atmosphere, trityl peroxide (**7**) precipitated at once. The remainder of the work-up was as described previously.

Determination of the Partition Coefficient of Acetic Acid between Ether and 6 *N* Hydrochloric Acid.—The general procedure was to make up equal-volume solutions of 6 *N* hydrochloric acid and ether, each presaturated with the other component, and then add to these immiscible liquids the materials that would be present after hydrolysis of a reaction mixture obtained from trityl acetate (**1**) and phenylmagnesium bromide. For example, in one experiment, based on 0.0066 mol of **1** as starting material, the mixture contained 60 ml of 6 *N* hydrochloric acid and 60 ml of ether. To these liquids were added acetophenone, biphenyl,

(12) P. Arthur, *Anal. Chem.*, **36**, 701 (1964).

(13) Peroxides could not be detected in the ether by the method reported; see L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath Co., Boston, Mass., 1957, p 287.

(14) K. D. Berlin, L. H. Gower, J. W. White, D. E. Gibbs, and G. P. Sturm, *J. Org. Chem.*, **27**, 3595 (1962).

benzophenone, triphenylmethane, triphenylmethanol, and magnesium bromide hexahydrate in amounts corresponding to their per cent yields given in Table I. To this mixture was added 1.00 g (0.0167 mol) of acetic acid and 0.508 g (0.0065 mol) of DMSO. Nmr peak area integration gave an average DMSO/acetic acid ratio of 23:18. Thus, only 62.4% of the acetic acid remained in the aqueous layer. An average of three different determinations, each of slightly different volumes of two liquids, resulted in an average partition coefficient (ether/aqueous) of 0.38/0.62 = 0.61, which indicates that acetic acid preferentially remains in the aqueous layer by a factor of 0.62/0.38 = 1.63.

Reaction of Acetic Acid with Phenylmagnesium Bromide (1:2:3 Molar Ratio).—Acetic acid (1.0 g, 0.0167 mol) was slowly added to 0.035 mol of phenylmagnesium bromide (2) in 50 ml of anhydrous ether. The reaction mixture was stirred for 3 hr, cooled, and hydrolyzed with cold 6 *N* hydrochloric acid. Analysis of the organic layer was accomplished by glpc analysis. The following products were found: benzene, phenol, acetophenone, biphenyl, 1,1-diphenylethanol, and 1,1-diphenylethene. The alkene is apparently formed by dehydration of part of the tertiary alcohol. Acetophenone was found to be present (15 ± 1% yield based on the acid), and the combined quantities of the tertiary alcohol and 1,1-diphenylethene amounted to about 40 ± 1% (based on the acid). Standard solutions were used to check each of these compounds. These yields are not unreasonably low when one considers that 1 mol of the Grignard reagent was destroyed by the acidic proton of acetic acid.

Reaction of Trityl Bromide with Phenylmagnesium Bromide (2) and Oxygen.—Phenylmagnesium bromide (0.0121 mol) was added to a reaction vessel along with 50 ml of anhydrous ether. Then 3.0 g (0.0093 mol) of trityl bromide dissolved in anhydrous ether was added dropwise. After 1 hr, the reaction mixture was dark orange-red color, but no solid material had formed. At this time, oxygen was introduced into the reaction mixture and a solid began to form. After 6 hr, the reaction mixture had assumed a pale yellow color and trityl peroxide (7) was readily visible. The reaction mixture was cooled in an ice bath and then hydrolyzed with 40 ml of ice-cold 6 *N* hydrochloric acid; yield of trityl peroxide was 47% (1.10 g, 0.00212 mol). Other products observed by glpc analysis were benzene, phenol, acetophenone (11%), biphenyl, benzophenone (17%), triphenylmethane (26%), triphenylmethanol (7%), and tetraphenylmethane (3%). A solution of trityl bromide in ether was bubbled with dry O_2 for 6 hr. The solution remained unchanged and no trityl peroxide precipitated.

Registry No.—Trityl acetate-^{18}O, 20449-05-2; phenylmagnesium bromide, 100-58-3.

Acknowledgment.—We are grateful to Keith Kinneberg for aid in the determination and interpretation of the mass spectra. Grateful acknowledgment is extended to the National Science Foundation, Grant GB-3482, for funds provided to Oklahoma State University for purchase of the LKB-9000 mass spectrometer–glpc unit. We thank Professor Glen Russell for helpful discussions.

The Thermal Decomposition of Dimsyl Ion in Dimethyl Sulfoxide

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The decomposition of sodium dimsyl in dimethyl sulfoxide at temperatures above 80° produces a mixture of methylated butadienes and a white precipitate which, by titration and reaction with benzyl chloride, is evidently a mixture of sodium methanesulfenate, sodium methanesulfinate, and sodium methylmercaptide.

One of the useful strong bases in dimethyl sulfoxide (DMSO) is its anion, first prepared by Corey and Chaykovsky.[2] These authors mentioned the thermal decomposition of this reagent and it was the purpose of this investigation to establish the nature of the reactions involved.

When *ca.* 1 *M* solutions of sodium dimsyl are heated to 80° for several hours, the solutions turn dark red–brown, a voluminous white precipitate separates, and a volatile product and an extremely foul odor are evolved. The initial reaction can become violent at temperatures above 100°.

The volatile products have been collected by trapping at −78° and separated by gas chromatography. Many of the fractions were identified unequivocally by comparison of their nmr and mass spectra with those reported for methylated butadienes. Typical examples are summarized in Table I.

TABLE I

IDENTIFICATION OF GLPC FRACTIONS FROM VOLATILE LIQUID FROM SODIUM DIMSYL DECOMPOSITION

Peak No.	Wt % A[a]	Wt % B[b]	Mass	Identity
1	6.4	0.9	...	...
2	8.4	1.9	C_5H_8	Isoprene
3	11.0	15.2	C_5H_8	*trans*-1,3-Pentadiene
4	0.3	4.2	...	...
5	0.2	1.6	C_2H_6S	Dimethyl sulfide
6	11.8	16.3	C_6H_{10}	*trans*-2-Methyl-1,3-pentadiene
7	6.6	12.5	C_6H_{10}	4-Methyl-1,3-pentadiene
8	11.0	16.6	C_6H_{10}	*trans*-2,4-Hexadiene
9	40.0	28.2	C_7H_{12}	2,4-Dimethyl-1,3-pentadiene

[a] Decomposed for 5 hr at 85°, 33% total yield of hydrocarbons. [b] Decomposed for 7.5 hr at 78°, 27% total yield of hydrocarbons.

The nmr spectrum of peak 1 indicates that it is *not* butadiene; it shows mainly paraffinic proton resonance in four major peaks between δ 1.3 and 1.85 with only very weak absorbance in the olefinic proton 5–6 region. This material is probably from residual petroleum ether used to wash sodium hydride free of mineral oil. The other peaks identified as methylated butadienes gave excellent nmr spectra with chemical shifts, splitting constants, and peak heights identical with authentic spectra.

A number of sulfur ylides have been reported to be sources of ethylene and/or polymethylene, although the exact mechanism of the conversions and whether they involve methylene as an intermediate are matters of controversy.[3] The formation of dienes from a methylene donor, however, appears to be a unique reaction for

(1) Supported in part by National Science Foundation Grant GP-5269. From the Ph.D. Dissertation of T. Yukuta, University of Pennsylvania, 1968.

(2) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962).

(3) A. W. Johnson, "Ylid Chemistry," Academic Press Inc., New York, N. Y., 1966, p 304.

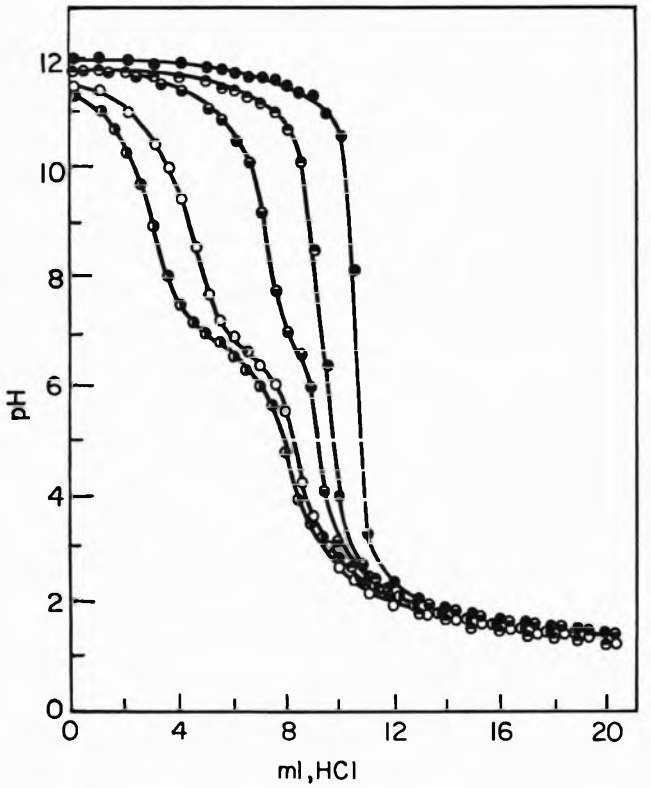

Figure 1.—The titration with 0.1 *N* hydrochloric acid of dimsyl solutions decomposed at 97° for 0.0 (●), 0.5 (◓), 5 (◒), 113 (○), and 211 (◐) hours.

"methylene" generated from dimsyl anion. In this case, the over-all reaction requires an oxidative step, and the stoichiometry can be represented by eq 1 and 2.

$$3CH_3\overset{O}{\overset{\|}{S}}CH_2^- \longrightarrow 3[CH_2] + 3CH_3SO^- \quad (1)$$

$$CH_3\overset{O}{\overset{\|}{S}}CH_2^- + 3[CH_2] \longrightarrow [C_4H_6] + CH_3S^- + H_2O \quad (2)$$

The formation of methylene dimer and polymer from neutral ylides has been postulated by some[3] to proceed through direct exchange of methylene between ylides[3] without intervention of "free" methylene. Such a course in this instance seems even less likely because it would require bimolecular reaction of two anions.

The failure to isolate any butadiene is readily explained by its rapid reaction with dimsyl ion to give the homologs actually isolated, since it is reported[4] that butadiene is converted to 1,3-pentadiene in 1 hr at 55° by strong base and dimethyl sulfoxide, while further alkylation of 1,3-pentadiene under the same conditions required 17 hr. It can be assumed that the intermediate nucleophilic attack by dimsyl on the dienes would be still further hindered by introduction of two or three methyl groups. The considerable increase in branched-chain butadienes in our experiments may be due either to intervention of "free" methylene in addition to dimsyl ion itself as alkylating agent at the higher temperatures used, or to rearrangement or methylene insertion in the unknown intermediates in eq 2 of the thermal decomposition reaction.

By reaction of the decomposition mixture with benzyl chloride, 50–60% of the sulfur of decomposed dimsyl anion was recovered in the reduced sulfide state, while about 10–12% was recovered as sulfoxide and sulfone. This leads to the conclusion that the sulfenate ion may disproportionate under the conditions employed by us, even though O'Connor and Lyness[5] report sodium methanesulfenate to be stable in dimethyl sulfoxide for an hour at 30–40°. The relatively low yields of the

$$2CH_3SO^- \rightleftharpoons CH_3S^- + CH_3SO_2^- \quad (3)$$

sulfoxide and sulfone we ascribe at least in part to losses in the eight washings of product with salt water, necessary to remove dimethyl sulfoxide. The formation of benzyl sulfide, sulfoxide, and sulfones from decomposed dimsyl solutions is in marked contrast to the formation of *trans*-stilbene (which we have confirmed) as the main product from fresh dimsyl solutions.[6]

Addition of water and then titration with hydrochloric acid (Figure 1) indicates that the single strong base initially present is converted to the three weaker dimethyl sulfoxide insoluble bases of eq 3 with very nearly a statistical redistribution of oxygen. After 211 hr at 97°, when iodimetric titration (Table II) indicated 92% total conversion to the three species in eq 3, the pK titration indicated 26% of the base has $pK_a = 2.9$, 52% has $pK_a = 6.7$, and 23% has $pK_a = 10.7$. A pK_a of about 11 for CH_3S would be in reasonable accord with the pK_a of 11.5 reported for butyl mercaptan[7] and the pK_a of butanesulfinic acid is reported to be 2.1.[8] This leaves some question about the acid titrating with a pK_a near 7, but it does seem reasonable that the pK_a of a sulfenic acid would be intermediate between its reduction and oxidation products.

TABLE II
IODIMETRIC TITRATION OF SODIUM DIMSYL SOLUTION DECOMPOSED AT 97°

Heating time, hr	0	0.5	5	113	211
Ml of 0.1 *N* HCl to pH 6	11	10	9	7	6
Ml of 0.13 *N* I_2	0.30	1.40	4.80	6.30	7.40
Mequiv/mol of dimsyl	0.037	0.173	0.59	0.78	0.91

If the titration data indeed accurately reflect the equilibrium in eq 3, then the isolation of a 50–60% yield of sulfide from the benzyl chloride reaction could be explained by the reasonable postulates that (a) mercaptide ion is a more reactive nucleophile than sulfenate, and (b) the disproportionation reaction (eq 3) is fast compared with the reaction of sulfenate with benzyl chloride.

In addition to benzyl methyl sulfide and sulfone, two other major products isolated from benzyl chloride reactions deserve comment. One is dibenzyl sulfide, which normally was isolated in the same chromatogram fraction as benzyl methyl sulfide. The ease with which this mixed sulfide fraction is converted to trimethylsulfonium ion by methyl iodide suggests that a somewhat

$$(PhCH_2)_2S + PhCH_2SCH_3 \xrightarrow{CH_3I} (CH_3)_3S^+I^- + PhCH_2S^+(CH_3)_2I^- \quad (4)$$

similar disproportionation may explain the presence of dibenzyl sulfide. The volatility of methyl chloride may

(4) P. A. Argabright, J. E. Hofmann, and A. Schriesheim, *J. Org. Chem.*, **30**, 3233 (1965).

(5) D. E. O'Connor and W. I. Lyness, *ibid.*, **30**, 1620 (1965).

(6) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 3782 (1962); **87**, 1353 (1965).

(7) W. H. Fletcher, *ibid.*, **68**, 2726 (1946).

(8) P. Rumpf and J. Sadet, *Bull. Soc. Chim. Fr.*, 450 (1958).

indeed promote shift of these equilibria toward dibenzyl sulfide.

$$PhCH_2SCH_3 + PhCH_2Cl \rightleftharpoons (PhCH_2)_2S^+CH_3Cl^- \rightleftharpoons (PhCH_2)_2S + CH_3Cl\uparrow \quad (5)$$

A second type of product is illustrated by the isolation of the sulfone I, which is presumably formed by the base-catalyzed further benzylation of benzyl methyl sulfone. The bisbenzyl sulfone (II) was also isolated

$$PhCH_2SO_2CH_3 \xrightarrow{\text{base}} Ph\bar{C}HSO_2CH_3 \xrightarrow{PhCH_2Cl} \underset{\text{mp 125°}}{PhCH(CH_2Ph)SO_2CH_3} \quad (6)$$

I, mp 125°

and identified, although it appears to have been obtained in the reaction mixture first as the sulfoxide. Presumably a second alkylation of I was hindered by the two sulfone oxygens, whereas the analogous sulfoxide readily alkylated a second time. Generally speaking,

$$CH_3S^- \longrightarrow \left[CH_3SCH_2Ph\right] \xrightarrow[PhCH_2Cl]{\text{base}} \xrightarrow{H_2O_2} \underset{\text{Ph}}{CH_3SC(CH_2Ph)_2} \quad (7)$$

II, mp 168°

these further benzylated products were obtained from benzyl chloride treatment of short-time decompositions, when undecomposed dimsyl ion would remain as the strong base necessary to remove the benzyl proton α to the sulfone or sulfoxide.

The nmr spectra of I and II show that the two benzyl hydrogens are in different environments. For the case of I, the benzyl hydrogens appear at δ 3.42 and 3.84, splitting each other by $J = 13.8$ cps. Each is also split by the adjacent methine hydrogen (δ 4.57) by $J = 10.2$ and 4.8 cps, respectively. For the case of II, the benzyl hydrogens appear as two doublets, δ 3.57 and 3.87, with $J = 15.0$ cps.

Preliminary experiments attempting to treat decomposed dimsyl solutions with methyl iodide led to the isolation of beautiful needles of $NaI \cdot 2CH_3SOCH_3$, mp 147°, recrystallizable from ethanol.

Experimental Section

Elemental analyses were performed by A. Bernhardt, Microanalytical Laboratory, Ruhr, Germany, and Galbraith Laboratories, Inc., Knoxville, Tenn. The melting points of all crystalline compounds were uncorrected.

Volatile Hydrocarbons.—A 3.75-g sample of a 50% dispersion of sodium hydride in oil was placed in a 100-ml flask and washed three times by decantation with low-boiling petroleum ether. After evaporation by water aspirator, 40 ml of redistilled dimethyl sulfoxide was added by syringe. The reaction mixture was cautiously heated to 75° until gas evolution ceased. A liquid collector trap, cooled in Dry Ice–acetone, was attached and the solution was heated cautiously to 80–85° and held there for 5 hr. The trap contained 364 mg of liquid, which was separated by preparative gas chromatography in a 20 ft × 3/8 in. column packed with 30% Carbowax 20M maintained at 65°. The results of two such fractionations are shown in Table I.

The identity of fraction 5 as dimethyl sulfide was indicated by the mass spectrum, which showed major peaks for CH_3S^+ (relative intensity 100), $(CH_3)_2S^+$ (82), CHS^+ (50), H_3S^+ (42), and $C_2H_3^+$ (28).

Acid–Base Titration.—A pale blue-green 1.05 *M* solution of sodium dimsyl in dimethyl sulfoxide, prepared as above, was divided into 1-ml aliquots, sealed in nmr tubes and heated to 97° for a specified time, cooled, and diluted with 40 ml of water prior to titration with 0.1 *N* HCl. The results are summarized in Figure 1.

Iodine Titration.—Similar 1-ml aliquots, heated in the same way and then dissolved in 40 ml of water, were titrated with 0.13 *N* iodine solution (after neutralization to pH 6 by 0.1 *N* HCl) using starch indicator. The results are summarized in Table II.

Test for Solvent Participation.—Decomposition mixtures of sodium dimsyl run for times as long as 336 hr at 105° were added to ^2H_2O and dioxane. Comparison of the dimethyl sulfoxide peak with the dioxane peak indicated no significant change in dimethyl sulfoxide over this interval, indicating that the decompositions observed were indeed those of the dimsyl ion.

Reaction of Decomposed Dimsyl with Benzyl Chloride. A.—A solution of 0.10 mol of sodium dimsyl in 50 ml of dimethyl sulfoxide was decomposed thoroughly by heating for 150 hr to a maximum of 105°. After cooling, 12.7 g (0.1 mol) of benzyl chloride was added dropwise over 10 min with stirring in a water bath to control the initial exothermic reaction. After 20 min, a 45° oil bath was placed around the reaction mixture, which was stirred at this temperature for 16 hr to yield a viscous dark brown solution.

The contents were poured into 250 ml of ether to give a precipitate which was filtered and washed with a total of 800 ml of ether to afford 6.81 g of powder (theory for NaCl, 5.85 g) after drying under vacuum. The ether solution was washed with 250 ml of NaCl-saturated water eight times in order to remove dimethyl sulfoxide, giving a dark brown solution which was dried over anhydrous sodium sulfate. Evaporation of ether with a rotary evaporator gave 13.31 g of viscous dark red–brown liquid with some crystalline solids.

The 13.31 g of oily liquid was dissolved in benzene and submitted to column chromatography with benzene and then methanol as eluents (column: 4 × 33 cm, 80–200 mesh A-540 Fisher alumina). Three main fractions were obtained as follows: **i**, 11.20 g (viscous dark red–brown liquid, from which small amounts of needle crystals separated); ii, 0.35 g (pale yellow solid); and iii, 1.27 g (by flushing with absolute methanol, dark red–brown liquid, from which needle crystals separated); recovery 96.3%.

A solution of 3.36 g of **i** in 50 ml of glacial acetic acid was treated with 10 ml of 50% H_2O_2 dropwise, producing an exothermic reaction. After several days, the contents were poured into 150 ml of water and extracted three times with 200 ml of ether. The combined extracts were washed three times with 200 ml of water and twice with 200 ml of 10% aqueous K_2CO_3, dried (anhydrous Na_2SO_4), and evaporated, leaving 3.00 g of pale yellow crystalline solid, mp 90–130°. Recrystallization from 95% ethanol gave dibenzyl sulfone as colorless needle crystals, mp 148–150° (lit. m 150°), nmr (CF_3COOD) δ 7.44 (s, 5 H) and 4.43 ppm (s, 2 H). The evaporation of solvent left a crystalline yellow-tinged powder, mp 115–118° (hot CCl_4), identified by nmr spectra in CF_3COOH as methyl benzyl sulfone.

The nmr spectrum of **i** indicated that it was a mixture of dibenzyl sulfide (61.2 mol %) and methyl benzyl sulfide (38.8 mol %). The nmr spectrum of crystals, obtained by oxidation of **i**, before recrystallization (*i.e.*, mp 90–130°) showed that it was a mixture of dibenzyl sulfone (76.4 mol %) and methyl benzyl sulfone (23.6 mol %).

Recrystallization of **ii** gave colorless needle crystals of methyl benzyl sulfone, mp 123–125° (95% ethanol) (lit.[9] mp 125–127°). The nmr spectrum in CF_3COOD showed bands at δ 7.48 (s, 5), 4.53 (s, 2), 3.03 (s, 3), and in DMSO-d_6 at 7.44 (s, 5), 4.49 (s, 2), and 2.91 ppm (s, 3).

The decantation of the supernatant from **iii** yielded 0.10 g of white needle crystals, mp 123–125° (95% ethanol), identified as methyl benzyl sulfone. The ir spectrum (infracord, neat) of the filtrate showed strong sulfoxide stretching absorption at 1020 cm^{-1}.

B.—Following the same procedures as above but for dimsyl solution decomposed only 7.5 hr at 78°, benzyl chloride (12.90 g, 0.10 mol) was added to the viscous red–brown solution. Stirring was continued for 13 hr at 42–44°. After filtering, washing with ether, and evaporation, 6.66 g of powder (theory for NaCl, 5.85

(9) T. R. Lewis and S. Archer, *J. Amer. Chem. Soc.*, **73**, 2109 (1951).

g), and 13.71 g of viscous red–brown liquid were obtained. From the latter, crystalline needles separated on standing.

The entire 13.20 g of the liquid containing some needle crystals was dissolved in benzene and submitted to column chromatography as above to afford three main fractions using benzene and then methanol as an eluent: **i**, 9.00 g (red–brown liquid), **ii**, 0.18 g (light brown liquid), **iii**, 3.06 g (by flushing with absolute methanol, viscous dark grown liquid); recover 95.9%.

From the nmr spectrum of **i** (CCl_4), δ 7.21 and 7.16 (broad, 12.2), 4.42 (s, 0.7), 3.49 and 3.44 (s, 2.9), 2.04 (s, 1.9), and 1.79 ppm (s, 2.0), the composition of the mixture was estimated as dibenzyl sulfide (28.6 mol %), methyl benzyl sulfide (46.4 mol %), and unreacted benzyl chloride (25.0 mol %).

Fraction **i** (3.22 g) was dissolved in 4 ml of absolute ethanol, and 3 ml of methyl iodide was added. After standing at room temperature overnight, white needle crystals separated from the dark red–brown supernatant. Another 1 ml of methyl iodide was added, and the fraction was left overnight again. The fine white needles were filtered and washed with absolute ethanol to yield 2.35 g of trimethylsulfonium iodide, mp 209–215° with sublimation (95% ethanol) (lit.[10] 203–207°), nmr (D_2O) δ 2.92 ppm (s). The nmr and ir spectra were identical with those reported for trimethylsulfonium iodide.[10]

To the dark red–brown mother liquid, ether was added to yield white needle crystals. A total of 800 ml of ether was used until no further precipitate occurred to give 1.15 g of the crystals, identified as **dimethylbenzylsulfonium iodide**. Recrystallization afforded flat needles: mp 99–101°; nmr (D_2O) δ 7.57 (s, 5 H), 4.61 (s, 2 H), and 2.83 ppm (s, 6 H).

Anal. Calcd for $C_9H_{13}SI$: C, 38.58; H, 4.69; I, 45.29; S, 11.45. Found: C, 38.63; H, 4.82; I, 45.36; S, 11.61.

After solvent evaporation, the mother liquid afforded 2.79 g of highly lachrymatory dark red–brown liquid, which was not further studied (presumably benzyl iodide).

(10) R. Kuhn and H. Trischmann, *Ann. Chem.*, **611**, 117 (1958).

A 3.06-g sample of **iii** was dissolved in CCl_4 to give white needle crystals on standing (0.92 g). Solvent evaporation and addition of 95% ethanol gave an additional 0.83 g of the crystals. Recrystallization afforded white wooly needle crystals of **methylsulfonylbenzylphenylmethane** (I), mp 120–122° (CCl_4).

Anal. Calcd for $C_{15}H_{16}SO_2$: C, 69.18; H, 6.21; S, 12.31. Found: C, 69.06; H, 6.21; S, 12.47.

The mother liquid was condensed to give 1.24 g of red–brown liquid (showing sulfoxide by ir) which was dissolved in 30 ml of glacial acetic acid and oxidized with 6 ml of 50% H_2O_2 to yield 1.00 g of yellow oily solid. Recrystallization gave white needle crystals of **methylsulfonyldibenzylphenylmethane** (II), mp 165–168° [95% ethanol, followed by petroleum ether (bp 60–110°)–$CHCl_3$].

Anal. Calcd for $C_{22}H_{22}SO_2$: C, 75.38; H, 6.34; S, 9.15. Found: C, 75.38; H, 6.37; S, 9.16.

Reaction of DMSO with NaI.—By heating for 39 min at 80°, 6.10 g of NaI was dissolved in 40 ml of redistilled dimethyl sulfoxide. No precipitate appeared on standing at room temperature for a week. However, when the concentration was higher, *e.g.*, 10 g of NaI in 40 ml of dimethyl sulfoxide, colorless crystals appeared. The solution was poured into 100 ml of benzene to yield 13.71 g (theory, 12.5 g) of white solid after filtration under N_2. Recrystallization from absolute ethanol afforded hygroscopic white needles, mp 144–147°.

Anal. Calcd for $C_4H_{12}IONaS_2$: C, 15.69; H, 3.96; I, 41.45; Na, 7.51; S, 20.94. Found: C, 15.56; H, 3.79; I, 41.50; Na, 7.41; S, 20.75.

Registry No.—Dimsyl ion, 13810-16-7; dimethyl sulfoxide, 67-68-5; I, 15733-05-8; II, 20505-04-8; methyl benzyl sulfone, 3112-90-1; $NaI \cdot 2CH_3SOCH_3$, 4659-76-1; dimethyl benzyl sulfonium iodide, 20483-21-0.

The Thermal Decomposition of β-Hydroxy Ketones

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β-Hydroxy ketones decompose thermally to mixtures of aldehydes and ketones in a reaction that is the reverse of the aldol condensation. A study has been carried out of the kinetics of the thermal decomposition of some β-hydroxy ketones in xylene solution. The results indicate that the reaction is unimolecular and involves a cyclic transition state. Comparison of the rates of decomposition of the different β-hydroxy ketones indicates that little charge separation is obtained during the breaking of the carbon–carbon bond in the transition state.

β-Hydroxy ketones decompose thermally[1] to give mixtures of aldehydes and/or ketones in a reaction which is the reverse of the aldol condensation. A kinetic study of the pyrolysis of 4-hydroxy-4-methyl-2-pentanone in the gas phase[2] showed that the decomposition is homogeneous and follows first-order kinetics, and it was proposed that the reaction involves a six-membered cyclic transition state. As a further test of this mechanism, we have carried out a study of the products and kinetics of the thermal decomposition of 4-hydroxy-4-methyl-2-pentanone in dilute xylene solution. It would be expected[3] that, if in the gas phase the pyrolysis of 4-hydroxy-4-methyl-2-pentanone does involve a cyclic intramolecular mechanism, the same reaction carried out in nonpolar solvent would involve a similar type of mechanism, thus giving rise to similar products and first-order kinetics.

(1) C. D. Hurd, "The Pyrolysis of Organic Compounds," The Chemical Catalog Co., Inc., Reinhold Publishing Corp., New York, N. Y., 1929, p 164.
(2) G. G. Smith and B. L. Yates, *J. Org. Chem.*, **30**, 2067 (1965).
(3) S. W. Benson, "The Foundation of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 506.

Furthermore, no kinetic measurements have been carried out for the thermal decomposition of other β-hydroxy ketones.

We have therefore studied the kinetics of the thermal decomposition of 4-hydroxy-3-methyl-2-pentanone and 4-hydroxy-2-pentanone, in order to examine the influence of the differently substituted methyl groups on the mechanism and velocity of pyrolysis.

Discussion

Quantitative analysis, using gas–liquid chromatography, of the products of the thermal decomposition of 4-hydroxy-4-methyl-2-pentanone in dilute xylene solution showed that acetone is by far the principal product of the reaction, being obtained in a yield of >95%, although a small amount (<5% in total) of two other unidentified products was also observed.

The rate of decomposition of the 4-hydroxy-4-methyl-2-pentanone was followed using glpc, by measuring both the rate at which acetone is formed and the rate of disappearance of the 4-hydroxy-4-methyl-2-pentanone.

It was found by both methods that the decomposition followed good first-order kinetics for at least three half-lives, and that furthermore the first-order rate constants obtained by each method were in very good agreement. The determined rate constants are listed in Table I.

Table I
Rates of Pyrolysis of Some β-Hydroxy Ketones at Different Temperatures

β-Hydroxy ketone	$k \times 10^{-4}$ sec^{-1} at 148.7°	160.7°	179.4°	206.5°
4-Hydroxy-2-pentanone	...	0.141	0.530	3.62
4-Hydroxy-4-methyl-2-pentanone	0.126	0.373	1.55	10.0
4-Hydroxy-3-methyl-2-pentanone	0.100	...	1.03	8.20

They were found to be reproducible to within ±4%, and rate constants determined at different temperatures were found to follow a good Arrhenius relationship. The derived activation parameters can be seen in Table II. Assuming that the rate constants are accurate to

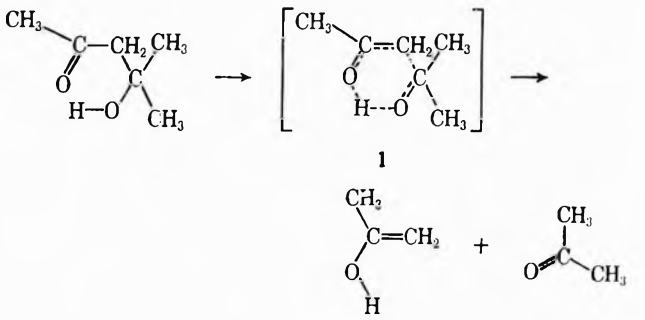
Table II
Activation Parameters for the Pyrolysis of Some β-Hydroxy Ketones

β-Hydroxy ketone	E_a (kcal/mol) (±1.0 kcal)	$\log_{10} A$ (±0.34)	$\Delta S^{\ddagger}$ (eu) (±1.6 eu)
4-Hydroxy-2-pentanone	30.2	10.24	−12.6
4-Hydroxy-4-methyl-2-pentanone	31.1	11.12	−8.7
4-Hydroxy-3-methyl-2-pentanone	31.0	10.96	−9.4

±4%, the energy and entropy of activation are estimated to be accurate to within ±1.0 kcal and ±1.6 eu, respectively.

The first-order rate constants showed little variation with the initial concentration of the 4-hydroxy-4-methyl-2-pentanone: at a temperature of 179.5° and initial concentrations of the β-hydroxy ketone of 2, 4, 6, 8, and 10% (v/v), the values of the first-order rate constants obtained for the decomposition were 1.52, 1.55, 1.57, 1.49, and 1.50 × 10^{-4} sec^{-1} respectively. Also, the reaction does not appear to be influenced by surface effects. In ampoules packed with glass wool which increased the surface area of the reaction vessel by a factor of at least 15, the rate of decomposition of the 4-hydroxy-4-methyl-2-pentanone was found to be 1.48 × 10^{-4} sec^{-1}, compared with 1.55 × 10^{-4} sec^{-1} in an unpacked vessel.

These results indicate that, as was found for the reaction in the gas phase, the thermal decomposition of 4-hydroxy-4-methyl-2-pentanone in dilute xylene solution is a homogeneous first-order reaction which gives acetone as practically the only product. The entropy of activation for both reactions is very similar: −8.3 eu for the reaction in the gas phase and −8.7 eu for the reaction in solution. These values are typical of those reactions that are thought to involve cyclic transition states,[4] and it would thus appear that, in solution, 4-methyl-4-hydroxy-2-pentanone decomposes through the cyclic six-membered transition state 1 similar to the one previously proposed[2] for its decomposition in the gas phase.



1

As would be expected[3] for such intramolecular unimolecular reactions, the presence of a nonpolar solvent does not have a great influence on the velocity of the reaction. The energies of activation for the decomposition in the gas phase and in solution are 32.2 and 31.2 kcal respectively, giving extrapolated first-order rate constants for the decomposition in the gas phase and in solution of 5.37 and 6.76 × 10^{-4} sec^{-1} respectively at 200°. It can thus be seen that the results obtained for the reaction in solution are in agreement with the mechanism previously proposed for the reaction in the gas phase, the reaction involving a cyclic six-membered intramolecular transition state in both phases.

Similar first-order kinetic results were also obtained for the two other β-hydroxy ketones studied, 4-hydroxy-2-pentanone and 4-hydroxy-3-methyl-2-pentanone. These compounds were found to decompose thermally to mixtures of acetone and acetaldehyde and acetaldehyde and methyl ethyl ketone respectively. In both cases it was determined by glpc that the products were obtained in yields of >95%, although, as in the case of 4-hydroxy-4-methyl-2-pentanone, small quantities (<5%) of other products were also obtained. The decomposition of both compounds followed good first-order kinetics up to >3 half-lives, with the first-order rate constants showing a reproducibility of ±4%. Rate constants determined at different temperatures were found to follow good Arrhenius relationships, and the derived energies and entropies of activation can be seen in Table II. Again, the rate of decomposition was shown not to depend on the initial concentration of the β-hydroxy ketone.

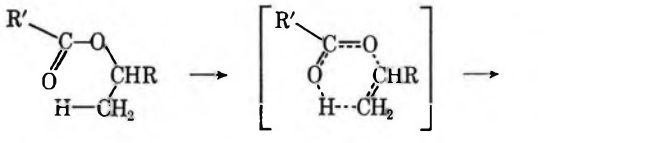
As in the case of 4-hydroxy-4-methyl-2-pentanone, the entropies of activation for the decomposition of 4-hydroxy-2-pentanone and 4-hydroxy-3-methyl-2-pentanone were found to be negative, −12.6 and −9.4 respectively. These entropies of activation, together with the first-order kinetics and the nature of the products, would seem to indicate that 4-hydroxy-2-pentanone and 4-hydroxy-3-methyl-2-pentanone decompose thermally through a six-membered cyclic transition state similar to that proposed for the thermal decomposition of 4-hydroxy-4-methyl-2-pentanone.

Compared with 4-hydroxy-2-pentanone, 4-hydroxy-3-methyl-2-pentanone and 4-hydroxy-4-methyl-2-pentanone have a methyl group substituted on either side of the breaking carbon–carbon bond. Comparing the rates of decomposition of these two β-hydroxy ketones

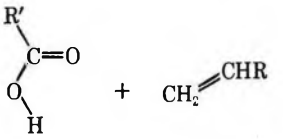
(4) See ref 3, p 257.

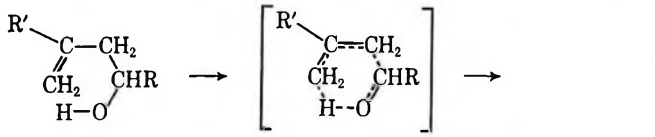
with that of 4-hydroxy-2-pentanone it can be seen that the methyl groups do not have a great influence on the rate of decomposition. For example, at 179.5° the relative rates of decomposition of 4-hydroxy-4-methyl-2-pentanone, 4-hydroxy-3-methyl-2-pentanone and 4-hydroxy-2-pentanone are 2.9:1.9:1.0.

It is of interest to compare the effect of methyl groups in the pyrolysis of β-hydroxy ketones with their effects in two other pyrolytic reactions that are thought to involve analogous cyclic six-membered transition states, the pyrolysis of esters **2**[5] and β-hydroxy olefins **3**.[6]

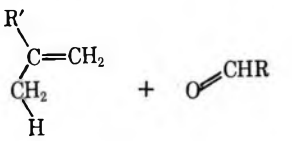


2





3



In the case of the esters, the relative rates of pyrolysis of ethyl, isopropyl, and *t*-butyl formate at 650°K are 1:18:760,[7] while the relative rates of pyrolysis at the same temperature of the β-hydroxy olefins 3-buten-1-ol, 4-penten-2-ol, and 2-methyl-4-penten-2-ol are 1:2.9:5.4.[6] It can thus be seen that branching at the α-carbon of the esters (*i.e.*, the carbon of the bond C-O) has a much greater effect than the corresponding substitutions in the case of the β-hydroxy ketones and β-hydroxy olefins. Part of the effect must be statistical, there being more hydrogens available for reaction in the case of the more highly branched esters. Nevertheless, the effect is much greater than can be accounted for on a purely statistical basis, and it has been suggested[8] that some carbonium ion character is developed by the α-carbon during the breaking of the C–O bond. In the case of the pyrolysis of the β-hydroxy olefins and β-hydroxy ketones, the effect of the extra methyl group is much less, which would seem to indicate that much less charge is developed during breaking of the C–C bond in these two reactions. This is reasonable when one considers that, in the breaking of the carbon–oxygen bond in ester pyrolysis, two atoms of different electronegativity are involved, whereas in β-hydroxy olefin and β-hydroxy ketone pyrolysis the breaking of the carbon–carbon bond involves two atoms of identical electronegativity.

This conclusion, of course, is only valid if the transition state in ester pyrolysis does indeed develop some carbonium ion character. For example, it has been suggested[9] that the rate-enhancing influence on ester pyrolysis of extra methyl groups on the α-carbon could be accounted for by the increased stability of the olefin being formed. However this view has been disputed,[10] and in any case this effect would also be expected to have a similar influence on the rate of pyrolysis of the β-hydroxy olefins, whereas in fact, as can be seen from the rates of pyrolysis of the β-hydroxy olefins given above, increased methyl substitution on the breaking C–C bond has only a small effect on the rate of pyrolysis of the β-hydroxy olefin. It would thus seem that, in the pyrolysis of β-hydroxy olefins and β-hydroxy ketones, little charge is developed during the breaking of the carbon–carbon bond, whereas in ester pyrolysis some charge is developed during the breaking of the C–O bond.

Experimental Section

4-Hydroxy-4-methyl-2-pentanone was obtained commercially, while 4-hydroxy-2-pentanone and 4-hydroxy-3-methyl-2-pentanone were obtained by the aldol condensation[11] of acetaldehyde and acetone and acetaldehyde and methyl ethyl ketone respectively. All the β-hydroxy ketones were distilled carefully before use and their purity checked by glpc using a 5-ft 10% tricresyl phosphate column, and by infrared spectroscopy.

As solvent, Matheson Coleman and Bell purified-grade xylene was used. It was fractioned before use using a 4-ft packed glass column.

The reaction was carried out in sealed glass ampoules made from capillary tubing. The sealed ampules containing the β-hydroxy ketone in xylene solution were placed in a boiling solvent thermostat bath whose temperature was checked using a N. B. S. standardized thermometer, allowances being made for variation in atmospheric pressure. At regular intervals the ampoules were removed and the amount of acetone or methyl ethyl ketone produced was determined by glpc, using benzene as an internal standard, on a 5 ft column of 10% tricresyl phosphate on Chromosorb W. The rate of decomposition of each of the β-hydroxy ketones was also determined by observing the rate of disappearance of the β-hydroxy ketone, again by glpc using a 5-ft 10% tricresyl phosphate column with mesitylene as an internal standard.

Registry No.—4-Hydroxy-2-pentanone, 4161-60-8; 4-hydroxy-4-methyl-2-pentanone, 123-42-2; 4-hydroxy-3-methyl-2-pentanone, 565-79-7.

Acknowledgment.—The authors express their thanks to the Rockefeller Foundation for financial support of this work through Grant 66077 and to the Fund for Overseas Research Grants and Education (FORGE).

(5) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).
(6) G. G. Smith and B. L. Yates, *J. Chem. Soc.*, 7242 (1965).
(7) Calculated from the data of E. Gordon, S. J. W. Price, and A. F. Trotman-Dickenson, *ibid.*, 2813 (1957).
(8) G. G. Smith, F. D. Bagley, and R. Taylor, *J. Amer. Chem. Soc.*, **83**, 3047 (1961).
(9) C. H. DePuy and R. E. Leary, *ibid.*, **79**, 3705 (1957).
(10) R. Taylor, G. G. Smith, and W. H. Wetzel, *ibid.*, **84**, 4817 (1962).
(11) J. E. Dubois, *Bull. Soc. Chim. Fr.*, 66 (1949).

Study of Stereospecificity in the α-Phenylethylation of the Dicarbanions of Certain β-Diketones in Liquid Ammonia[1]

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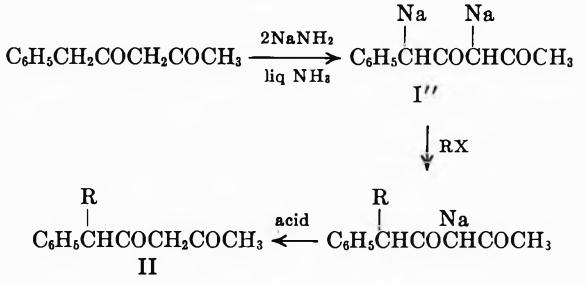
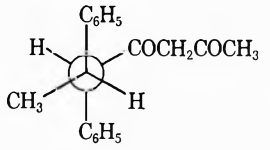
The α-phenylethylations of 1-phenyl-2,4-pentanedione and 1,4-diphenyl-2,4-butanedione were effected with α-phenylethyl chloride through their dicarbanions, which were prepared by means of 2 mol equiv of sodium amide in liquid ammonia. In both of these condensations, only one of the two possible diastereomeric products was isolated, and none of the other isomer could be detected. Each of these diastereomers was shown by independent, stereospecific synthesis to have the *erythro* configuration. Since the *threo* isomer of one of these products was not epimerized appreciably under conditions similar to those of the reaction, the alkylation is considered to follow a stereospecific course.

Recently,[3] alkylation at the benzyl site of β-diketone I was effected with certain alkyl halides to form II through disodio salt I″, which was prepared by means of 2 mol equiv of sodium amide in liquid ammonia (Scheme I). No alkylation at the methyl or α-methylene group was observed.[3]

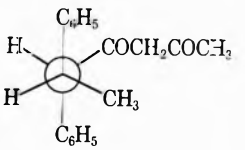
SCHEME I



In the present investigation, the stereochemical course of this type of alkylation was studied. Thus, disodio salt I″ was alkylated with α-phenylethyl chloride to form *erythro* isomer IIa; none of *threo* isomer IIb was found.



IIa (*erythro*)

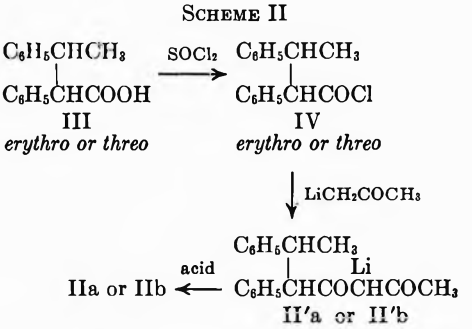


IIb (*threo*)

The general structure of IIa was supported by analysis and absorption spectra (see Experimental Section) and its specific configuration was established by comparison with authentic samples of the two isomers (IIa–b) employing thin layer chromatography (tlc). The tlc method involved visualization of the β-diketones on the silica gel G coated plates by spraying the developed plate with an ethanolic solution of ferric chloride. The resulting colors, characteristic of β-diketones,[4] made an excellent and sensitive method of locating β-diketones on the tlc plate. By examining prepared mixtures of diastereomers IIa–b, it was shown that the tlc technique could detect the *threo* isomer in amounts greater than 5%.

The authentic samples of the two isomers, IIa and IIb, were prepared from *erythro*- and *threo*-2,3-diphenylbutyric acids (III)[5] by means of condensations involving the corresponding acid chlorides (IV) with lithioacetone (Scheme II).

SCHEME II



These acylations of the lithioacetone were evidently stereospecific, since the *erythro* acid chloride IV afforded exclusively the *erythro* β-diketone IIa, and the *threo* acid chloride IV only the *threo* β-diketone IIb. To minimize further acylations of the lithio products II′a–b, 2 mol equiv of the lithio ketone to one of the acid chloride were used.[6]

The α-phenylethylation of disodio salt I″ (see Scheme I) to form *erythro* IIa was realized in 44–48% yield. Although this yield is not high, none of the *threo* isomer IIb appeared to be formed. Thus, the dark oil remaining after isolation of crystalline *erythro* IIa was shown by tlc to contain more of the *erythro* isomer IIa and starting β-diketone I but not the *threo* isomer IIb.

This preferential formation of the *erythro* isomer IIa evidently involved a stereospecific α-phenylethylation of the disodio salt I″, not the possible production of both the *erythro* and *threo* isomers followed by epimerization of the latter isomer. Thus, *threo* IIb failed to be converted to *erythro* IIa in the presence of disodio salt I″ under the conditions employed for the alkylation.[7]

(1) Supported in part at Duke University by the National Science Foundation and at Texas A & M University by the Petroleum Research Fund, administered by the American Chemical Society, and by The Robert A. Welch Foundation.

(2) National Science Foundation Cooperative Fellow, 1965–1966.

(3) K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **31**, 663 (1966).

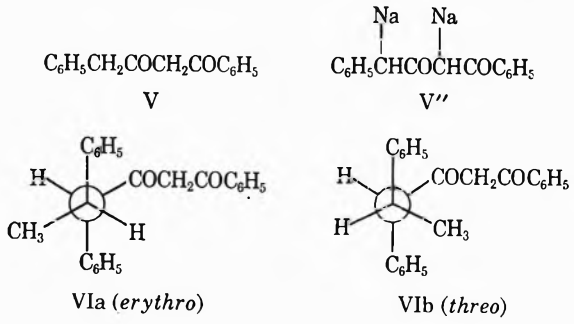
(4) See G. T. Morgan, H. D. K. Drew, and C. R. Porter, *Chem. Ber.*, **58**, 333 (1925).

(5) C. R. Hauser, D. Lednicer, and W. R. Brasen, *J. Amer. Chem. Soc.*, **80**, 4345 (1958).

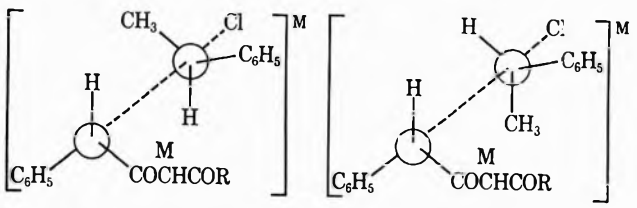
(6) See B. O. Linn and C. R. Hauser, *ibid.*, **78**, 6066 (1956).

(7) It should be mentioned that *threo* IIb was completely converted to *erythro* IIa on treatment with 2 mol equiv of sodium amide in liquid ammonia; apparently some ionization of the benzylic hydrogen occurred to permit this epimerization. However, this did not occur under the usual conditions of alkylation where essentially no excess alkali amide was present.

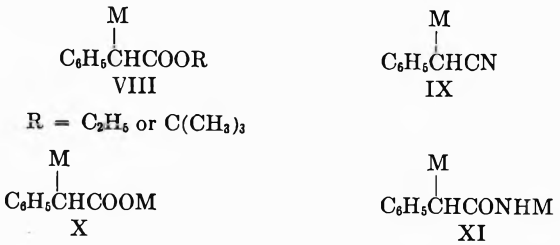
Similarly, β-diketone V was converted to its disodio salt V″ which was α-phenylethylated to form the *erythro* isomer VIa in 31% yield. None of the *threo* isomer VIb was detected (see Experimental Section).



These stereospecific alkylations, which are presumably SN2 type displacements, evidently occur because the nonbonded interactions in the transition states leading to the *erythro* isomer are less than those leading to the *threo* isomer, as indicated in VII″a and VII″b, respectively. The conformations of these transition states are assumed to resemble the conformations of the alkylation products.



The present results, which are of interest because of the wide usage of such alkylations in synthesis,[8] apparently furnish the first demonstrated stereospecific alkylation of a dicarbanion. Other α-phenylethylations of carbanions that have afforded largely or exclusively the *erythro* isomer of the alkylation product include those of the monocarbanions VIII[9] and IX,[10] and of the dianions X[5,11] and XI.[12] However, only VIII and X have been shown to involve stereospecific alkylations.



Experimental Section[13]

α-Phenylethylation of β-Diketone I.—To a stirred suspension of 0.10 mol of $NaNH_2$ in liquid ammonia (prepared from 0.1 g-atom of sodium in 400 ml of commercial, anhydrous liquid ammonia[14]) was added 8.8 g (0.05 mol) of 1-phenyl-2,4-pentanedione (I).[15] After the resulting green solution had stirred for 30 min, 7.0 g (0.05 mol) of α-phenylethyl chloride in 20 ml of anhydrous ethyl ether was added dropwise. The reaction mixture was stirred for 2 hr and then neutralized by the addition of 10 g of NH_4Cl. The ammonia was evaporated (water bath) as 200 ml of dry ether was added, and the resulting ethereal suspension was washed with several portions of 10% HCl. The ethereal solution was dried ($MgSO_4$) and concentrated (rotary evaporator) to a semisolid. The mixture was dissolved in hexane and allowed to crystallize. The precipitate was filtered to give 6.1 g (44%) of 2,3-diphenyl-4,6-heptanedione (IIa), mp 120–122°. Thin layer chromatography (tlc), as described below, indicated that the isolated β-diketone was at least 95% *erythro* IIa.

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.55; H, 7.20.

The reaction was repeated, except that the reaction mixture was allowed to stir for 11 hr before neutralization with NH_4Cl. This gave 6.7 g (48%) of IIa, mp 120–122°, a second crop of 2.3 g, mp 98–105°, and an oil (5 g). A sample of the second crop and the oil was analyzed on a silica gel G (Merck) tlc plate or silica gel (Eastman chromatogram sheet) using a 1:1 (v/v) mixture of CH_2Cl_2 and CCl_3 as a developing solvent. Visualization of the β-diketone, accomplished by spraying the developed plate with a 5% solution of $FeCl_3$ in ethanol, revealed red spots corresponding to starting β-diketone (R_f 0.29) and *erythro* IIa (R_f 0.23). None of the *threo* isomer IIb (R_f 0.20) was present.

Identification of the spots was accomplished by direct tlc comparison to samples of *erythro* and *threo* II prepared as described below. Various prepared mixtures of authentic *threo* IIb and *erythro* IIa were separated by tlc. It was observed that a mixture of 0.95 g of *erythro* IIa and 0.05 g of *threo* IIb could be separated adequately by tlc, but mixtures with smaller amounts of *threo* IIb were not consistently separated.

The infrared spectrum of a sample of the isolated *erythro* IIa, mp 120–122°, which was identical with that of authentic *erythro* IIa prepared as described below, showed peaks at 750 and 690 cm^{-1} (monosubstituted phenyl)[16] and a broad band centered at 1600 cm^{-1} (β-diketone).[16] The nuclear magnetic resonance (nmr) spectrum of *erythro* IIa in deuteriochloroform showed, in addition to the aromatic proton signals at 7.30 and 7.22 ppm (all chemical shifts are reported in δ downfield from an internal tetramethylsilane standard), a signal at 5.22 ppm, attributed to the vinyl proton of the enolic form; a complex multiplet centered at 3.57 ppm, assigned to the two benzylic protons on C-2 and C-3; a singlet at 3.19 ppm, assigned to the methylene protons at C-5 in the unenolized form; a pair of singlets at 1.68 and 1.60 ppm, assigned to the methyl protons at C-7 in the enol and keto forms, respectively; and a pair of doublets at 1.02 and 0.95 ppm, assigned to the C-1 methyl group.

Preparation of Authentic Samples of *erythro* IIa and *threo* IIb.—A sample of 8.4 g (0.035 mol) of *erythro*-2,3-diphenylbutyric acid (III)[5] was refluxed in 50 ml of thionyl chloride. After 3 hr, the excess thionyl chloride was removed by distillation and by evacuating the reaction flask to 1 mm for 30 min. The resulting *erythro*-2,3-diphenylbutyryl chloride (IV) remaining in the flask was condensed with lithioacetone as described below.

Tritylllithium[17] was prepared by the addition of 44.0 ml (0.07 mol) of 1.6 *N* *n*-butyllithium in hexane[18] to 17.2 g (0.07 mol) of triphenylmethane in 100 ml of anhydrous ethyl ether. After stirring for 90 min, the dark red solution of tritylllithium was cooled (ice bath), and 4.08 g (0.07 mol) of dry acetone was added. To the resulting solution of lithioacetone was added the acid

(8) See especially K. G. Hampton, R. J. Light, and C. R. Hauser, *J. Org. Chem.*, **30**, 1413 (1965); S. Boatman, T. M. Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 82 (1965), and earlier references.

(9) W. G. Kenyon, R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, **28**, 3108 (1963).

(10) W. R. Brasen and C. R. Hauser, *J. Amer. Chem. Soc.*, **79**, 395 (1957); C. R. Hauser and W. R. Brasen, *ibid.*, **78**, 494 (1956).

(11) C. R. Hauser and W. J. Chambers, *ibid.*, **78**, 4942 (1956).

(12) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **26**, 3696 (1961).

(13) Melting points were taken on a Thomas–Hoover melting point apparatus in open tubes and are uncorrected. Analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and Triangle Chemical Laboratories, Chapel Hill, N. C. Infrared spectra were obtained with a Perkin-Elmer Model 137 or 237 spectrophotometer, using the potassium bromide pellet method. Nmr spectra were obtained on a Varian A-60 nuclear magnetic resonance spectrometer.

(14) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(15) K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **29**, 3511 (1964).

(16) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Second Edition, John Wiley & Sons, New York, N. Y., 1958.

(17) H. Gilman and G. J. Gaj, *J. Org. Chem.*, **28**, 1725 (1963).

(18) Obtained from Foote Mineral Co., Exton, Pa.

chloride IV, prepared as described above, and the mixture was heated to reflux. After 6 hr, the suspension was cooled and neutralized with 10% HCl. The ethereal layer was dried ($MgSO_4$) and the solution concentrated (rotary evaporator); the triphenylmethane, which precipitated as the ether evaporated, was removed by filtration. Removal of all the ether left a solid residue which was shown by tlc to contain triphenylmethane and *erythro* IIa but no other β-diketone. Recrystallization of a portion of this residue from hexane yielded a sample of IIa whose infrared spectrum was superimposable upon that of IIa prepared from Ia.

Similarly, a sample of 1.6 g (0.067 mol) of *threo*-2,3-diphenylbutyric acid (III) was condensed through its acid chloride with 0.14 mol of lithioacetone to give exclusively *threo* IIb. Although IIb generated in this manner could not be completely separated from the triphenylmethane, its infrared spectrum was very similar to that of *erythro* IIa, with only minor differences in the 1350–1100-cm^{-1} region, and its nmr spectrum was similar to that of *erythro* IIa. Tlc indicated that none of the *erythro* IIa had been formed by the reaction.

α-Phenylethylation of β-Diketone V.—To a stirred suspension of 0.04 mol of $NaNH_2$ in liquid ammonia was added 5.0 g (0.021 mol) of 1,4-diphenyl-2,4-butanedione (V).[15] The resulting green–brown solution was stirred for 30 min, and 5.87 g (0.042 mol) of α-phenylethyl chloride in 50 ml of anhydrous ethyl ether was then added dropwise. After 8 hr, the mixture was neutralized with 10 g of NH_4Cl, the ammonia was replaced by ether, and the resulting suspension was washed with 10% HCl. The ether layer was dried ($MgSO_4$) and concentrated (rotary evaporator) to give, in several crops, 2.20 g (31%) of 1,4,5-triphenyl-1,3-hexanedione (VI), mp 172–174°. The oil obtained on removing all of the ether was distilled to give 3.62 g of α-phenylethyl chloride (1 equiv plus 24% of a second equiv) leaving 4.3 g of pot residue. Thin layer chromatography indicated that the isolated β-diketone was *erythro* VIa. A sample, recrystallized several times from hexane–ethanol, melted at 174–175°.

Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.17; H, 6.47. Found: C, 83.98; H, 6.54.

A portion of the pot residue (see above) was analyzed on a silica gel G (Merck) coated tlc plate using a 4:1 (v/v) mixture of CCl_4 and CH_2Cl_2 as developing solvent. Visualization of the plate with an ethanolic solution of $FeCl_3$ indicated that the major component of the oil was *erythro* VIa (R_f 0.41). The only other β-diketone indicated to be present was the starting material V (R_f 0.30).

The infrared spectrum of a sample of the isolated *erythro* VIa, mp 174–175°, had a broad band centered at 1600 cm^{-1} (β-diketone)[16] and peaks at 750 and 690 cm^{-1} (monosubstituted phenyl).[16] The nmr spectrum of *erythro* VIa in deuteriochloroform solution showed aromatic proton signals centered at 7.28 ppm, a singlet at 5.90 ppm assigned to the vinylic proton at C-4, a complex multiplet centered at 3.30 ppm assigned to the benzylic protons at C-2 and C-3, and what appeared to be a pair of doublets at 1.04 and 0.95 ppm, similar to those found in the spectrum of *erythro* IIa, assigned to the methyl protons at C-1.

Preparation of an Authentic Sample of *erythro* VIa.—Similar to the preparation of authentic *erythro* IIa (see above), *erythro* VIa was prepared by condensing 0.017 mol of the acid chloride of *erythro* acid III with 0.034 mol of lithioacetophenone. The β-diketone product, identified by tlc using the $FeCl_3$ reagent, had the same R_f value as VIa prepared from the alkylation of V. Although the β-diketone could not be completely separated from triphenylmethane, that portion of its infrared spectrum not due to triphenylmethane was superimposable on that of VIa prepared from the α-phenylethylation of V.

Epimerization Studies of *threo* IIb.—To a solution of 0.10 mol of $NaNH_2$ in 400 ml of liquid ammonia was added 8.8 g (0.05 mol) of β-diketone I. After 30 min, the solution was considered to contain 0.05 mol of disodio salt I″. To this solution was added 2.0 g of *threo* IIb. *threo* IIb was contaminated with triphenylmethane (about 50%), and hence, only about 0.004 mol of IIb was present. The mixture was stirred for 2 hr and neutralized with 10 g of NH_4Cl. The ammonia was replaced by ether (water bath), and the resulting ethereal suspension was washed with 10% HCl. The ether solution was concentrated, and some of β-diketone I was removed *in vacuo*. The residue was shown by tlc to contain only *threo* IIb and β-diketone I. None of the *erythro* isomer IIa was indicated to be present. The fact that pure *threo* IIb was not used in this experiment does not affect the validity of the results, since more than enough I″ was present to compensate for impurities.

Similarly, a sample of *threo* IIb (0.37 g) was added to 0.002 mol of $NaNH_2$ in 50 ml of liquid ammonia. Since the sample of *threo* IIb was contaminated with triphenylmethane (see above), this represents *ca.* 2 equiv of sodium amide per equiv of β-diketone. After stirring for 1 hr, the mixture was neutralized with NH_4Cl. The ammonia was replaced by ether and the ether suspension was washed with 10% HCl. The ether layer was concentrated and subjected to tlc analysis, which indicated that *threo* IIb had been converted completely to *erythro* IIa.

Registry No.—Ammonia, 7664-41-7; IIa (*erythro*), 20406-81-9; VIa (*erythro*), 20462-26-4.

Investigations into Possible Intermediates in the Photoreduction of Conjugated Cyclopropyl Ketones in 2-Propanol[1]

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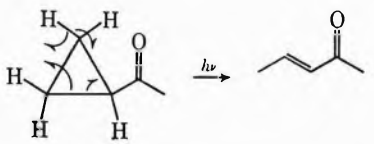
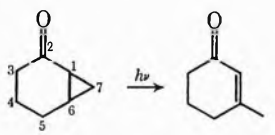
The photoreductions of a series of bicyclo[4.1.0]- and bicyclo[3.1.0]alkan-2-ones (1) in 2-propanol and the ground-state radical rearrangements of the corresponding bicyclo[4.1.0]- and bicyclo[3.1.0]alkan-2-ols (6) (using di-*t*-butyl peroxide as initiator) were compared. The product ratios, in either the photoreductive process or the radical rearrangement, change markedly with temperature. The similarity in product distributions of the two processes at different temperatures indicates that a common intermediate is involved, *i.e.*, the α-hydroxycyclopropylcarbinyl radical **7**. Overlap between the p orbital of the radical and the outside cyclopropane bond leads to selective cleavage of this bond at room temperature. However, at elevated temperatues appreciable amounts of the product originating from inside bond opening may be found, provided that in this cleavage a thermodynamically preferred species is formed. The similarity of specific ring opening of the outside bond of the cyclopropane ring in photoisomerization and photoreduction stems from the energy features of the ring system rather than a common intermediate. Initial studies on the rearrangement of the related carbonium ion are given for comparison.

It is well known that in the irradiation of conjugated cyclopropyl ketones in the vapor phase or in inert solvents a cyclopropane bond adjacent to the carbonyl group is cleaved, followed by a hydrogen migration and formation of a conjugated enone.[2-4] In the bicyclo-

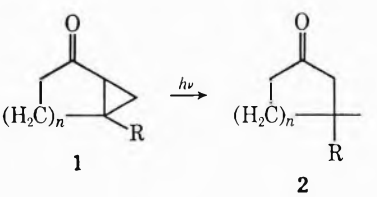


[4.1.0]heptane-2-one series, the two adjacent cyclopropyl bonds have a different geometry with respect to the carbonyl group, and in these cases photochemical ring opening appears to be selective. It is found that the C-1–C-7 bond, which has better overlap with the carbonyl π electrons, cleaves and cyclohexenones are formed.



This photoisomerization of the cyclopropylcarbonyl chromophore is highly dependent upon the substitution pattern of the system. For example, a methyl group at C-6 inhibits photoisomerization.[4] Various reasons can be postulated for the cause of this substituent effect; and, to obtain further information on the initial stage of the reaction, it was desired to learn if in all cases stereospecific opening of the cyclopropane did occur first and the fate of this first intermediate determined the ultimate over-all reaction pathway. For example, the photostability of 6-methylbicyclo[4.1.0]heptan-2-one might be due either to the photo-opening of the C-1–C-6 bond, yielding an intermediate which rapidly recloses to re-form starting material, or to the lack of migration of a methyl group if the better overlapped bond is broken. To evaluate these concepts, the photoreaction was conducted in the presence of a good hydrogen donor in order to trap any intermediate radicals; *i.e.*, in the irradiation of 6-methylbicyclo[4.1.0]heptan-2-one, if the latter route were followed, photochemical reduction would be expected to lead to 3,3-dimethylcyclohexanone.

Preliminary experiments in this laboratory indicated that photoreductive ring opening in bicyclic cyclopropyl ketones are selective.[5] Furthermore, 2-propanol appeared to be a far better hydrogen donor than methanol or pentane.[5-7] A further advantage for the use of 2-propanol in the photoreduction studies is the resemblance of the conditions to those of the photoisomerizations which were conducted in 2-methyl-2-propanol.[4] Table I summarizes the results of the photoreductions of a series of bicyclo[4.1.0]heptan-2-ones and bicyclo[3.1.0]hexan-2-ones (**1**). In no case could the product expected to be formed by cleavage of the inside bond be detected, even though such a product was shown to be stable to the reaction conditions. The low total recovery in the case of bicyclo[3.1.0]hexan-2-one (**1**, n = 1, R = H) was due to the photoreactivity of the 3-methylcyclopentanone formed.



1 **2**

TABLE I

PHOTOCHEMICAL REDUCTIONS OF SOME BICYCLO[4.1.0]- AND BICYCLO[3.1.0]ALKAN-2-ONES (1) IN 2-PROPANOL

Ketone 1	Irradiation time, hr	Starting material, %	Product 2, %
n = 2; R = H	4	30	60
n = 2; R = CH_3	0.5	63	32
n = 1; R = H	2	39	28
n = 1; R = CH_3	2.5	38	51

The results obtained from photoisomerization[4] and photoreduction in the bicyclo[4.1.0]heptan-2-one series suggest the involvement of a common intermediate

(1) This work was supported in part by National Institutes of Arthritis and Metabolic Diseases, PHS Grant AM-00709, U. S. Public Health Services.

(2) J. N. Pitts, Jr., and I. Norman, *J. Amer. Chem. Soc.*, **76**, 4815 (1954).

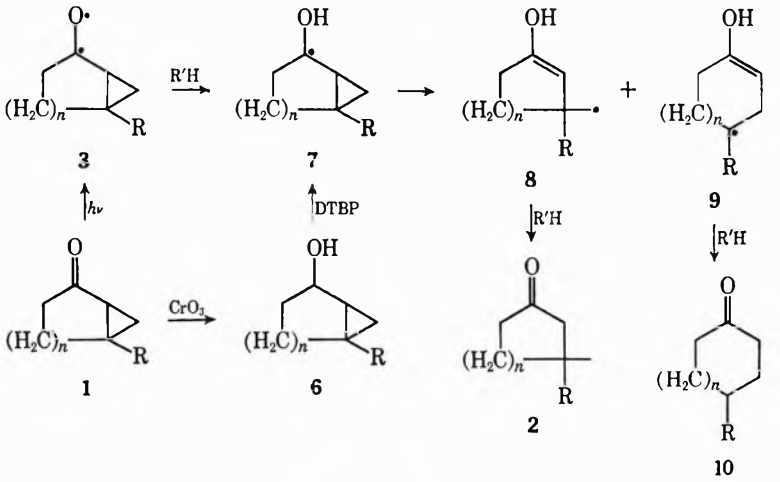
(3) L. D. Hess and J. N. Pitts, Jr., *ibid.*, **89**, 1973 (1967).

(4) W. G. Dauben and G. W. Shaffer, *Tetrahedron Lett.*, 4415 (1967).

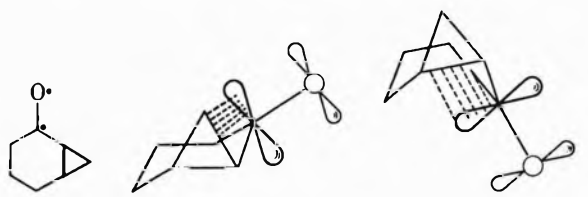
(5) E. J. Deviny, Ph.D. Thesis, University of California, Berkeley, 1965.

(6) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1966, p 533.

(7) W. G. Dauben, L. Schutte, and R. E. Wolf, *J. Org. Chem.*, **34**, 1849 (1969).



during the cleavage of the cyclopropane ring. That one such an intermediate could be the triplet state **3**, resulting from the known highly efficient singlet–triplet intersystem crossing in ketones, was shown by quenching and sensitization experiments. This triplet might better be represented as having the electrons delocalized, as in **4**, since such delocalization is known to occur



in the excited singlet state. Alternatively, the triplet could also adopt another extreme geometry shown in **5**, when the preferred orbital overlap occurs with the C-1–C-6 bond. In the isomerization reaction, the opening of the cyclopropane bond should proceed with continuous overlap of the carbonyl group; and, if this is the case, the reaction from conformation **4** would be favored, since overlap as in **5** demands a boatlike conformation. This feature must be more important than the relative stabilities of the potential ring-opened intermediates arising from the two conformations. In the photochemical reductions of bicyclo[3.1.0]hexan-2-ones, this preferred opening from a conformation related to **4** is also found. In these opening processes, internal hydrogen migrations would yield a conjugated enone, and hydrogen abstraction from 2-propanol would give the saturated cyclic ketone **2**. Thus, the photostability of 6-methylbicyclo[4.1.0]heptan-2-one to rearrangement would appear to be due to the inability of the methyl group to migrate and not to an inhibition of the opening of the cyclopropane ring.

From the above conclusion, it follows that opening of the cyclopropane ring has begun in the triplet state for both photorearrangement and photoreduction and that a homoallyl species would be formed directly. In the presence of a good hydrogen donor, however, the carbonyl triplet normally abstracts a hydrogen with high efficiency to yield a hydroxycarbinyl radical. Therefore, an alternative to the suggestion of a common mechanism is that there is no mechanistic relationship between the two photoreactions and that any similarity in results stems solely from the basic energy features of the ring systems involved. For example, in the presence of a good hydrogen donor, the carbonyl triplet could abstract a hydrogen to yield directly the hydroxycyclopropylcarbinyl radical **7**; and the reactions of this radical could be controlled by steric rather than by thermodynamic features to yield the reduction products. To evaluate the possible involvement of the α-hydroxycyclopropylcarbinyl radical **7**, its independent formation by peroxide-induced hydrogen abstraction[8] from the corresponding alcohol **6** and comparison of the product distribution in this ground-state reaction with that in the photoreductions was undertaken.

A series of bicyclo[4.1.0]heptan- and bicyclo[3.1.0]-hexan-2-ols (**6**),[9] corresponding to the series of bicyclic ketones photoreduced previously, were mixed with di-*t*-butyl peroxide (DTBP) and heated at 130° for 24 hr to generate the α-hydroxycyclopropylcarbinyl radical. The results are summarized in Table II.

TABLE II

RADICAL REARRANGEMENTS OF SOME BICYCLO[4.1.0]- AND BICYCLO[3.1.0]ALKAN-2-OLS (6) WITH DI-*t*-BUTYL PEROXIDE AT 130°

Alcohol 6	DTBP, mol equiv	Starting material, %	Products 10 + 2, %	Ratio, 10:2
$n = 2$; R = H	0.1	63	24	<0.2:10
	0.2	44	40	<0.2:10
$n = 2$; R = CH_3	0.1	34	63	0.5:9.5
	0.3	14	76	0.5:9.5
$n = 1$; R = H	0.1	60	36	2:8
	0.3	20	70	2:8
$n = 1$; R = CH_3	0.1	41	46	4.5:5.5
	0.4	28	71	4.5:5.5

The opening of the cyclopropane ring in the radical rearrangement reactions of cyclopropyl carbinols at 130° (Table II) does not show the same specificity as the photoreductions of cyclopropyl ketones. However, the radical generated by DTBP still gave a far greater amount of the product corresponding to outside bond opening of the cyclopropyl group (**2**) than can be accounted for on the basis of thermodynamic stabilities of the intermediates **8** and **9** formed. Two factors can be considered in determining the over-all thermodynamic stabilities of these intermediates: the stability of the

(8) D. C. Neckers, A. Schaap, and J. Hardy, *J. Amer. Chem. Soc.*, **88**, 1265 (1966).

(9) The *cis* bicyclic alcohols **6** were employed in this series. Rearrangements with a *cis–trans* (30:70) mixture of **6** ($n = 2$; R = H) showed that the *trans* isomer behaved in a similar fashion.

radicals[10] generated (primary *vs.* secondary or tertiary), and the stability of the ring system found as based on strain energy considerations of a cycloalkene.[11] When $n = 2$ and R = CH_3, the over-all stability favors the opening of the inside bond to yield **9** and, when R = H, a slight preference for opening of the outside bond to yield **8** is indicated. When $n = 1$, regardless of the degree of substitution, the opening of the inside bond to yield the six-membered ring compound **9** is strongly favored.

The selectivity of the ring opening could be accounted for on the basis of better overlap between the outer cyclopropane bond and the adjacent carbonyl center. However, selective product formation would also result if the reactivity of a primary radical is a predominant factor and if the secondary and tertiary radicals, though also formed, reclose to **7**, rather than abstract a hydrogen atom from the solvent. To evaluate this possibility the radical rearrangement was performed with an optically active alcohol **6** and the photochemical reduction was carried out with an optically active ketone **1**. The results of these experiments are summarized in Table III.

TABLE III

PHOTOCHEMICAL REDUCTION AND RADICAL REARRANGEMENT OF OPTICALLY ACTIVE BICYCLO[4.1.0]HEPTANE COMPOUNDS ($n = 2$, R = H)

Starting material	Type of reaction	$[\alpha]_D$ of starting material	$[\alpha]_D$ of recovered starting material	$[\alpha]_D$ of product **2**
1[a]	$h\nu$ in 2-propanol	−2.0	−2.1	−0.8[b]
6	130° with DTBP	5.2	5.2	−0.9

[a] The optically active ketone **1** was obtained by Jones oxidation of alcohol **6** and should have the same optical purity. [b] Reduction of **1** with lithium in liquid ammonia yielded ketone **2**, possessing this same optical activity (see ref 19); all optical activities were taken with vpc collected material and are accurate to ±0.1°.

Complete retention of optical activity of the starting material was observed under conditions of both rearrangement and irradiation; in addition, the product **2** obtained by either procedure was optically active to the same extent. These findings indicate that no equilibrium exists between the radical species **7** and **9**, since the absence of an asymmetric center in **9** would lead to racemization.[12]

Before using the data, summarized in Table I and II, pertaining to the difference in selectivity in photoreductions of cyclopropyl ketones **1** and in radical rearrangement of cyclopropyl carbinols **6** for mechanistic evaluation, it was essential to investigate the temperature dependence of the reactions, since room temperature was used for the former reaction and 130° for the latter. Thus, 5-methylbicyclo[3.1.0]hexan-2-ol (**6**, $n = 1$, R = CH_3), in which the difference in product distribution for the thermal and the photochemical reactions was greatest, was allowed to react at room temperature with DTBP, using filtered light as the radical initiator. In addition, the corresponding ketone (**1**, $n = 1$, R = CH_3) was irradiated at elevated temperatures. In the photolytic experiments at high temperature, some difficulties in product determination were encountered, as many by-products were observed, owing to instability of the primary products in uv light at 130°. These complications were minimized by using short irradiation times. Table IV summarizes the results of these experiments.

TABLE IV

RADICAL REARRANGEMENT AND PHOTOREDUCTION AT VARIOUS TEMPERATURES OF 5-METHYLBICYCLO[3.1.0]HEXANE COMPOUNDS ($n = 1$, R = CH_3)

Type of reaction	Temp, °C	Time, hr	Starting material, %	Products **10** + **2**, %	Ratio, **10**:**2** [a]
6 in DTBP + $h\nu$	25	24	87	13	0.5:9.5
		42	76	23	0.5:9.5
6 in DTBP	130	24	28	71	4.5:5.5
1 + $h\nu$ in *i*-PrOH	25	0.5	82	12	1:9
		1	69	23	1:9
	80	0.5	80	15	4:6
		0.8	69	18	3.5:6.5
	130	0.5	82	12	5:5
		2	60	7	5:5

[a] Irradiation of a mixture of **10** and **2** at elevated temperatures showed that both products disappear at approximately the same rate.

The radical rearrangement of the cyclopropyl alcohol investigated (**6**, $n = 1$, R = CH_3), when carried out at room temperature, showed the same selectivity of product formation as the photoreduction of the corresponding ketone (**1**, $n = 1$, R = CH_3). In both cases, 3,3-dimethylcyclopentanone (**2**, $n = 1$, R = CH_3) was formed almost exclusively. In addition, the photoreduction of the cyclopropyl ketone at elevated temperatures appeared to be much less selective than at room temperature. In fact, the similarity of the temperature dependence of product distribution in both types of reactions is remarkable. When bicyclo[4.1.0]-heptan-2-one (**1**, $n = 2$, R = H) was irradiated in 2-propanol at 130°, again only the formation of 3-methylcyclohexanone (**2**, $n = 2$, R = H) was observed. For this compound, change in temperature does not result in a diminished selectivity of ring opening, a result anticipated since the 130° radical rearrangement of the corresponding alcohol also showed a similar selectivity.

The striking similarity of temperature dependence on product formation in the two cases studied strongly suggests that photoreduction of conjugated cyclopropyl ketones **1** and radical rearrangements of the corresponding alcohols **6** proceed through the same intermediate; the α-hydroxycyclopropylcarbinyl radical **7**. Both processes are highly selective at room temperature, giving cleavage of the cyclopropane bond that overlaps best with the radical at C-2, but this selectivity can be severely affected by raising the temperature.

In the irradiation of 5-methylbicyclo[3.1.0]hexan-2-one (**1**, $n = 1$, R = CH_3) at elevated temperatures, the

(10) It is assumed that the tertiary radical is 4 kcal/mol more stable than the secondary radical, which, in turn, is 4 kcal/mol more stable than a primary radical (see C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 50).

(11) It is assumed that cyclohexane is 6.3 kcal/mol more stable than cycloheptane and 6.5 kcal/mol more stable than cyclopentane (see summary of values in J. D. Roberts and M. C. Casserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 112) and that the heat of hydrogenation of cyclohexene is 1.2 kcal/mol larger than that of cycloheptene and 1.4 kcal/mol larger than that of cyclopentene (see R. B. Turner and R. R. Meador, *J. Amer. Chem. Soc.*, **79**, 4133 (1957)].

(12) If reclosure of the inside bond was faster than inversion and rotation to the optical enantiomer, optical purity could be retained. From an operational viewpoint, however, such a process appears unlikely.

formation of small amounts of the alcohol **6** (about 5%) was indicated, but, in the irradiation of bicyclo[4.1.0]-heptan-2-one (**1**, $n = 2$, R = H) at 130°, no alcohol **6** could be detected. This is consistent with the previous observation that the corresponding optically active alcohol did not racemize during radical rearrangement at 130° (Table III), implying that in the latter case the α-hydroxycyclopropylcarbinyl radical does not abstract hydrogen to generate the alcohol.

In the presence of a triplet quencher (oxygen or isoprene), no photoreduction of bicyclo[4.1.0]heptan-2-one (**1**, $n = 2$, R = H) was observed. Benzene, acetone, or fluorene sensitized the reaction, but it was remarkable that the rate of overirradiation, leading to 3-methylcyclohexanol, increased more than that of the primary photoreduction step. These experiments leave little doubt that the excited species involved is in the triplet state.

The findings of the present work indicate that the photoreduction of ketone **1** and the ground-state radical rearrangement of alcohol **6** both go through the same intermediate radical **7**. The following mechanism may be considered for these reactions (see Figure 1). After excitation of **1**, a triplet species **3** is formed. This species abstracts a hydrogen atom from 2-propanol, and during this process it cascades down to the ground-state radical **7**. When $n = 1$, the thermodynamically controlled process leads to the more stable radical **9**, especially when R = CH_3 and a tertiary radical is formed. However, the pathway leading to a primary radical **8** has a lower energy of activation, since **2** is the preferred product when the reactions are run at room temperature. The lower energy of the transition state between **7** and **8** compared with that between **7** and **9** may be explained by overlap between the outer cyclopropane bond and the p orbital of the radical at C-2. The inner cyclopropane bond and the p orbital at C-2 are orthogonal, and the molecule must be twisted to form the transition state leading to opening of that bond.

When $n = 2$, an analogous conflict between kinetically and thermodynamically controlled product formation does not exist, owing to the stability of the six-membered ring in **8**.

It should be exphasized that the mechanism proposed is only applicable when a good hydrogen-donating solvent is present. In poor hydrogen donors, hydrogen abstraction is not important, and the triplet, in addition to returning to the ground state (**1**), may rearrange, the rearrangement proceeding *via* the more preferred triplet **4**.

The present study has illustrated the selectivity of bond cleavage in the photochemical reduction of conjugated cyclopropyl ketones in 2-propanol. In all cases examined, the bond that has better overlap with the carbonyl π system is preferentially cleaved. It is remarkable that the specificity of bond breaking is temperature dependent. However, this temperature dependence is not due to the photochemical process, but rather to subsequent ground-state radical reactions, as is indicated by the parallel rearrangements of the ground-state generated species.

It is interesting to compare the results of the radical rearrangements, which are largely governed by steric factors, with those of the rearrangement of the related α-hydroxycyclopropylcarbinyl carbonium ion **11**.

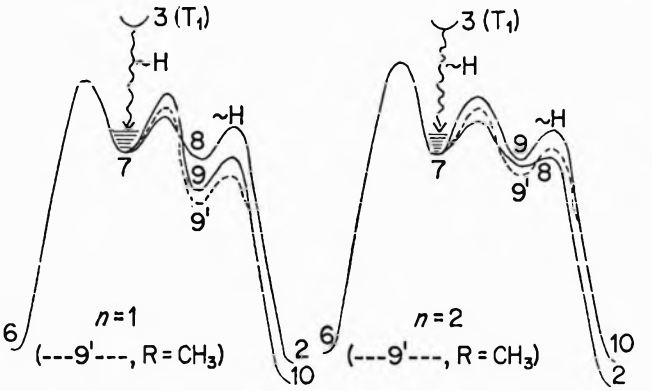
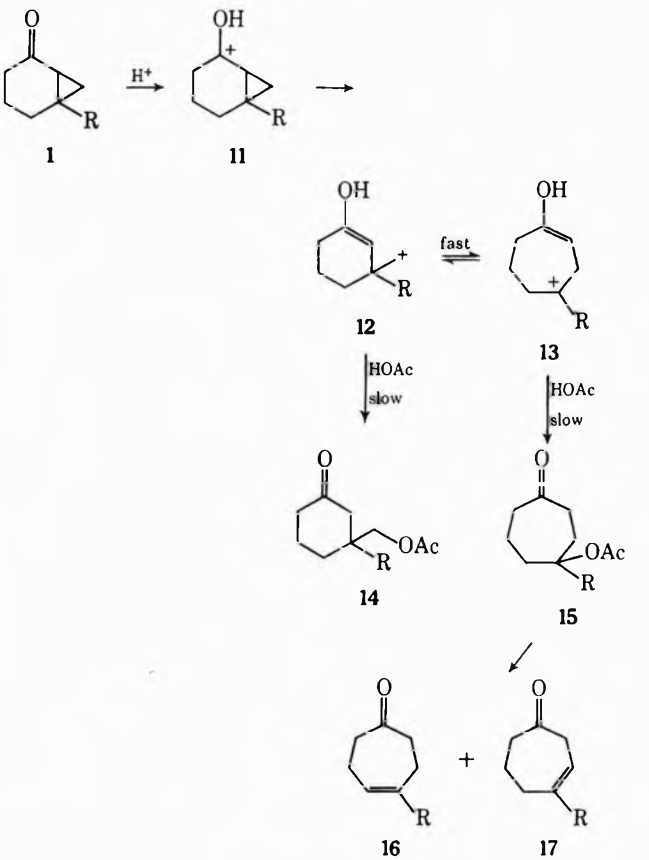


Figure 1.



For this purpose, the bicyclic ketones **1** ($n = 2$, R = H and CH_3) were allowed to react with acetic acid, using perchloric acid as a catalyst. The results of these reactions are summarized in Table V.

TABLE V

ACID-CATALYZED REARRANGEMENT OF BICYCLO[4.1.0]HEPTAN-2-ONE AND 6-METHYLBICYCLO[4.1.0]HEPTAN-2-ONE IN ACETIC ACID WITH 0.1 *M* $HClO_4$

Compd	Temp, °C	Time, hr	Starting material, %	Products **14** + **15**, %	Ratio, **15**:**14**
1, R = H	27	57	11	86	3.5:6.5
1, R = H	33	6	35	62	3.5:6.5
1, R = H	68	2.5	0	89	4:6
1, R = H	72	2	0	97	4:6
1, R = H	140	0.5	0	80	4:6
1, R = CH_3	70	0.5	0	96[a]	8.5:1.5

[a] Instead of **15**, the elimination products **16** and **17** were found in a 1:1 ratio.

The ratio of the products formed and the small effect of temperature in this reaction show that product formation follows closely the thermodynamic stabilities of the intermediate carbonium ions **12** and **13**. Although the difference in stability of these ions is difficult to evaluate because of solvation effects, they should be of the same order of magnitude as or larger than the radical stabilities. Since the ionic reaction may be reversible, it is necessary to study the process in greater detail before a direct comparison with the radical process can be achieved.

If the same type of reaction is conducted with HCl in dry chloroform, the chloride analog of **14** is formed almost exclusively. Further work is needed to decide whether this is due to the enhanced nucleophilicity of chloride compared with acetate or to less stabilization of the carbonium ions in a less polar solvent, thus causing the acid addition step to become faster than the rearrangement equilibrium under these conditions.

Experimental Section

The syntheses of the bicyclic ketones and alcohols for $n = 2$, R = **H**, CH_3, and for $n = 1$, R = H, have been described.[13]

5-Methylbicyclo[3.1.0]hexan-2-one was prepared by Dr. G. W. Shaffer[14] of this laboratory from 3-methyl-2-cyclopentenone[15] and dimethyloxosulfonium ylide according to the procedure described by Corey and Chaykovsky[16] in 51% yield. The following data were observed: bp 64–65° (13 mm); ir (CCl_4) 3058 (▷CH), 1727 (C=O), 1175, 933, 897, 856 cm^{-1}; uv λ_{max} (95% C_2H_5OH) 194 (ϵ 3710), 280 mμ (ϵ 56).

Anal. Calcd for $C_7H_{10}O$: C, 76.33; **H**, 9.15. Found: C, 76.14; H, 8.92.

***cis*-5-Methylbicyclo[3.1.0]hexan-2-ol** was prepared according to the procedure of Dauben and Berezin[13] from 3-methyl-2-cyclopentenol, which, in turn, was prepared by reduction of 3-methyl-2-cyclopentenone[15] following a procedure described by Davidson and coworkers.[17] The bicyclic alcohol was characterized by the following data: bp 76° (18 mm); ir (CCl_4) 3600, 3360 (OH), 1055, 1025, 1000 cm^{-1}; nmr (CCl_4) δ 4.38 (m, 1, CHOH), 3.43 (s, 1, OH), 1.63 (m, 4, ring CH_2), 1.13 (s, 3, CH_3), 0.7 and 0.2 ppm (m, 3, ▷CH); mass spectrum (70 eV) *m/e* 112, 111, 97, 94, 79, 70, 68 (B), 67, 55.

The optically active materials were prepared by asymmetric induction, converting cyclohexene to 2-cyclohexenol[18] ($[\alpha]_D$ 7.0°), followed by a Simmons–Smith[19] reaction to the *cis*-bicyclo[4.1.0]-heptan-2-ol[20] ($[\alpha]_D$ 5.2°) and Jones[21] oxidation to the bicyclo[4.1.0]heptan-2-one ($[\alpha]_D$ −2.0°). Optical rotations were measured in chloroform on a Zeiss polarimeter LEP A2.

Irradiation Procedures.—The irradiations described in Table I were conducted with 0.4% solutions in 125 ml of 2-propanol by Corex filtered light of an immersed Hanovia 450-W lamp. The radical rearrangements (Table II) were carried out by heating various portions of DTBP with the bicyclic alcohol at 130° for 24 hr in a sealed tube. The products of irradiation and of rearrangement were both independently collected from a preparative vpc column (Wilkens Aerograph A-90-P gas chromatograph, 10 ft × 0.375 in., 10% Carbowax 20M–10% KOH column at 160°) and were identified by ir, nmr, and mass spectra.

The irradiations at elevated temperatures were conducted in sealed Pyrex tubes in the vapor of refluxing 2-methyl-2-pentanol (bp 130°) or of refluxing 2-propanol (bp 80°) using a Hanovia 450-W lamp. Because of sample size (3-ml solutions), the product assignments were based on comparison of vpc retention times with those of authentic samples on two different analytical columns (5% XF-1150 Cyanosilicone, 10 ft × 0.125 in., 100°; 20% Carbowax 20 M–10% KOH, 10 ft × 0.125 in., 150°: Hewlett–Packard F & M 5751 gas chromatograph). Solutions of the starting materials and products were stable at 130°. The radical rearrangements, initiated by photodecomposition of DTBP (Table V), were conducted at room temperature employing a UVS-11 mineral light lamp filtered with a Vycor filter (λ >240 mμ).

Procedures in Acid-Catalyzed Rearrangements.—The perchloric acid catalyzed reaction with acetic acid was run with 1 g of the bicyclic ketone in 77 ml of glacial acetic acid and 2.2 ml of acetic anhydride containing 0.725 ml of 70% perchloric acid under magnetic stirring and in a nitrogen atmosphere. To terminate the reaction, the solution was neutralized with 95 ml of concentrated ammonium hydroxide and extracted with chloroform. The solution was washed and dried, the chloroform was evaporated, and the resulting oil was molecularly distilled. The amounts of volatile products formed were calculated from vpc traces of this distillate. The products were collected from a 20% DFGS-preparation vpc column.

Identification of Reaction Products.—Authentic samples were available of cycloheptanone, 3-methylcyclohexanone, cyclohexanone, and 4-methylcyclohexanone. The vpc retention times and spectral data of the products were in agreement with those of the authentic samples. The structures of the other products were assigned based on the following data.

4-Methylcycloheptanone: ir (CCl_4) 1705 (C=O), 1449 cm^{-1}; nmr (CCl_4) δ 2.35 (m, 4, CH_2, $COCH_2$), 1.68 (m, 7, ring protons), and 0.94 ppm (m, 3, CH_3); mass spectrum (prominent peaks) *m/e* 126, 111, 98, 97, 83 (B), 82, 70, 69, 56, 55.

3,3-Dimethylcyclohexanone: ir (CCl_4) 1715 (C=O), 1460, 1422, 1387, 1366 cm^{-1}; nmr (CCl_4) δ 2.7 (m over s, 4, CH_2, $COCH_2$), 1.7 (m, 4, ring protons), 0.97 [s, 6, $(CH_3)_2$]; mass spectrum (prominent peaks) *m/e* 176, 111, 83 (B), 69, 56, 55.

3-Methylcyclopentanone: ir (CCl_4) 1750 (C=O), 1455, 1410, 1050 cm^{-1}; nmr (CCl_4) δ 2.1 (m, 4, CH_2COCH_2), 2.0–1.2 (m, 3, ring protons), and 1.13 ppm (d, 3, J = 6 Hz, CH_3CH); mass spectrum (prominent peaks) *m/e* 98, 83, 70, 69 (B), 56, 55, 42.

3,3-Dimethylcyclopentanone: ir (CCl_4) 1745 (C=O), 1458, 1399, 1379, 1364, 1260, 1135 cm^{-1}; nmr (CCl_4) δ 2.1 (d, 2, J = 7 Hz, CH_2CH_2CO), 1.92 (s, 2, CCH_2CO), 1.90 (d, 2, J = 7 Hz, ring CH_2), 1.1 [s, 6 $(CH_3)_2C$]; mass spectrum (prominent peaks) *m/e* 112 (p), 97, 83, 69, 56 (B).

4-Acetoxycycloheptanone: ir (CCl_4) 1739, 1706, 1242, 1028 cm^{-1}; nmr (CCl_4) δ 4.57 (m, 1, CHOAc), 2.43 (m, 4, α-CH_2), 2.00 (s, 3, CH_3), and 1.88 ppm (m, 6, ring protons).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.63; H, 8.06.

3-Acetoxymethylcyclohexanone: ir (CCl_4) 1742, 1718, 1231, 1047 cm^{-1}; nmr (CCl_4) δ 3.88 (d, J = 3.5 Hz, 2, CH_2OAc), 2.13 (m, 4, α-CH_2), 1.96 (s, 3, CH_3), 1.92 (m, 5).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.29; H, 8.09.

4-Methyl-4-cycloheptenone: ir (CCl_4) 1706, 1230, 1214, 1091, 880, 823 cm^{-1}; nmr (CCl_4) δ 5.62 (m, 1, HC=C), 2.44 (m, 8, ring protons), 1.77 (s, 3, CH_3).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.16; H, 9.91.

4-Methyl-3-cycloheptenone: ir (CCl_4) 1712, 1667, 1285, 1244, 1212, 1122, 1072, 936, 891, 827 cm^{-1}; nmr (CCl_4) δ 5.36 (split t, J = 6 Hz, 1, CH=C), 3.11 (split d, J = 6 Hz, 2, α-CH_2), 2.50, 2.42, 2.22 (m, 6, ring protons), and 1.76 ppm (s, 3, CH_3).

Anal. Calcd for $C_8H_{12}O$: C, 77.83; H, 9.74. Found: C, 77.44; H, 9.63.

Registry No.—2-Propane, 67-63-0; 4-methylcycloheptanone, 5452-36-8; 3,3-dimethylcyclohexanone, 2979-19-3; 3-methylcyclopentanone, 1757-42-2; 3,3-dimethylcyclopentanone, 20500-49-6; 4-acetoxycyclo-

(13) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **89**, 3449 (1967); **85**, 468 (1963).

(14) G. W. Shaffer, Ph.D. Thesis, University of California, Berkeley, 1967.

(15) R. M. Acheson and Sir R. Robinson, *J. Chem. Soc.*, 1127 (1952).

(16) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(17) R. S. Davidson, W. H. H. Gunther, S. M. Waddington-Feather, and B. Lythgoe, *J. Chem. Soc.*, 4907 (1964).

(18) D. B. Denney, R. Napier, and A. Cammarata, *J. Org. Chem.*, **30**, 3151 (1965).

(19) H. E. Simmons, E. P. Blanchard, and R. D. Smith, *J. Amer. Chem. Soc.*, **86**, 1347 (1964).

(20) R. K. Hill and J. W. Morgan, *J. Org. Chem.*, **33**, 927 (1968); the present results indicate a higher degree of purity in the ketone from the oxidation.

(21) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

heptanone, 18341-63-4; 3-acetoxymethylcyclohexanone, 20500-51-0; 4-methyl-4-cycloheptenone, 13015-11-7; 4-methyl-3-cycloheptenone, 20500-53-2; **1**, $n = 2$, R = H, 5771-58-4; **1**, $n = 2$, R = CH_3, 14845-41-1; **1**, $n = 1$, R = H, 4160-49-0; **1**, $n = 1$, R = CH_3, 14845-46-6.

Anomalous Low Solvolytic Reactivity of 2,2-Dichlorocyclopropylcarbinyl Chlorides

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The solvolyses (50 vol % aqueous ethanol, 100°) of 2,2-dichlorocyclopropylcarbinyl chloride, 1-methyl-2,2-dichlorocyclopropylcarbinyl chloride, and *trans*-3-methyl-2,2-dichlorocyclopropylcarbinyl chloride have been studied as to rate and products. The absence of rearranged solvolysis products suggests that the cyclopropyl group is not interacting with the carbinyl carbon during solvolysis. In agreement with the product picture the solvolysis rates are substantially normal for a primary alkyl chloride and are at least 10^3 slower than is suggested by a σ^+ correlation of literature data on methyl- and ethoxy-substituted cyclopropylcarbinyl systems. The solvolysis rate of cyclopropylcarbinyl chlorides is, therefore, unexpectedly sensitive to electron-withdrawing substituents on the cyclopropane ring.

The most striking special features of cyclopropylcarbinyl systems in solvolysis are greatly enhanced solvolysis rates and formation of rearranged products having allylcarbinyl and cyclobutyl structures. The effect of methyl, phenyl, and ethoxy substituents on solvolysis rates have been studied.[1] However, no systematic study has been made of the effect of deactivating substituents such as chlorine on solvolysis in cyclopropylcarbinyl systems.

We have been interested[2] in the reactions of the *gem*-dichlorocyclopropyl functional group and have now studied its behavior as part of a cyclopropylcarbinyl solvolytic system. We report in this paper solvolysis rates (50% aqueous ethanol, 100°) and products for 2,2-dichloro-1-chloromethylcyclopropane, 2,2-dichloro-1-methyl-1-chloromethylcyclopropane, and *trans*-2,2-dichloro-3-methyl-1-chloromethylcyclopropane. The results are surprising in that participation of the cyclopropane ring appears to be completely suppressed.

Experimental Section

General.—The nmr data were obtained on a Varian A-60; chemical shifts and J values are reported in cycles per second (cps) relative to tetramethylsilane. The glpc unit was fitted unless otherwise stated with a 2-ft Carbowax 20M column. Distillations were normally through an 18-in. spinning-band column. The chemicals were obtained from laboratory supply houses except for acrolein dimethyl acetal which was furnished by Shell Chemical Co.

Kinetic Runs.—Solutions were prepared by dilution of a weighed sample of dichlorocyclopropylcarbinyl chloride to volume with 50% (v/v) aqueous ethanol. The initial run was made using a standard sealed ampoule technique titrating 5-ml aliquot portions with standard base (phenolphthalein indicator, calculated infinity). Subsequent runs were carried out using duplicate glpc analyses of 10-μl portions (2-ft Carbowax 20M, programmed from 50° at 11°/min) of 30-μl aliquots sealed in Kimax capillaries. First-order rate constants were calculated using the area of the dichlorocyclopropylcarbinyl chloride peak *vs.* an internal standard (2,5-dimethoxytoluene or *o*-diethoxybenzene). Material balances were run on the high-conversion points. Identity of the products was verified by comparison with authentic samples on the Carbowax 20M column and on an SE 30 column. The constant-temperature bath was a steam chamber.

1,1-Dichloro-2-chloromethylcyclopropane.—Into a 200-ml three-necked creased flask fitted with a Stir-O-Vac[3] high shear stirrer and an ice condenser was put allyl chloride (20.3 ml, 0.25 mol), chloroform (20 ml, 0.25 mol), sodium hydroxide pellets (40 g, 1.00 mol), and tetraglyme (25 ml). The mixture was stirred and the temperature was increased first to 80° during 1.5 hr and then to 98° for 2 hr more. Work-up by water dilution, ether extraction, and distillation of the dried ether extract gave 1,1-dichloro-2-chloromethylcyclopropane [9.1 g, 23%, bp 72–74° (46 mm), lit.[4] 56° (17 mm)]: infrared 3096 (cyclopropyl CH_2), 1372 (CH_2Cl), 1029 (cyclopropane ring), and 755 and 709 cm^{-1} (CCl_2 group in cyclopropane ring).

1,1-Dichloro-2-dimethoxymethylcyclopropane.—Into the usual apparatus was put acrolein dimethyl acetal (30 ml, 0.25 mol), chloroform (20 ml, 0.25 mol), sodium hydroxide pellets (60 g, 1.5 mol), and tetraglyme (25 ml). The mixture was stirred vigorously 3 hr at 25–40° and the evolved gas (1.6 l., 0.064 mol as carbon monoxide) was measured. The reaction mixture was diluted with water, the organic products were ether extracted, and the ether extracts were dried and fractionally distilled yielding 1,1-dicloro-2-dimethoxymethylcyclopropane [12.2 g, 26%, bp 92–93° (35 mm)]: nmr 198 and 203 (methoxy groups, three protons each, peak separation was temperature independent to 140°, split by adjacent asymmetric center), 72–132 (cyclopropyl H, complex, three protons), and 254 cps (tertiary acetal H, one-proton doublet, $J = 6$). A mixture of 1,1-dichloro-2-dimethoxymethylcyclopropane (10 g, 54 mmol), *p* toluenesulfonylhydrazine (10.1 g, 54 mmol), and hydrochloric acid (1 ml of concentrated acid in 40 ml of 50% aqueous ethanol) was heated on a steam bath 1.5 hr yielding crude *p*-toluenesulfonylhydrazone (17.1 g). A 2 g sample was recrystallized (50 ml of 50% aqueous ethanol) giving pure *p*-toluenesulfonylhydrazone derivative (1.5 g, indicated yield 77%, mp 134–137° dec).

2,2-Dichlorocyclopropylcarboxaldehyde.—A mixture of the 1,1-dichloro-2-dimethoxymethylcyclopropane (44.3 g, 0.24 mol), water (200 ml), concentrated sulfuric acid (5 ml), and tetraglyme (10 ml) was stirred at 25–30° for 30 hr. Examination (glpc) of the mixture indicated about 80% conversion to aldehyde. The crude product was extracted with ether and the extract was washed (water), dried (sodium sulfate), and distilled giving 2,2-dichlorocyclopropylcarboxaldehyde [8.3 g, 30%, bp 70–71° (25 mm)]: nmr 100–170 (three-proton multiplet, cyclopropyl H) and 559 cps (one-proton doublet, aldehyde, $J = 4$); 2,4-dinitro-

(1) For a recent review, *cf.* M. Hanack and H. J. Schneider, *Angew. Chem. Intern. Ed. Engl.*, **6**, 666 (1967).

(2) (a) G. C. Robinson, *J. Org. Chem.*, **32**, 3218 (1967); (b) *ibid.*, **33**, 607 (1968).

(3) Cole-Parmer Instrument and Equipment Co., Chicago, Ill. 60626.

(4) W. M. Wagner, H. Kloosterziel, and S. van der Ven, *Rec. Trav. Chim. Pays-Bas*, **80**, 740 (1961).

phenylhydrazone, mp 145.5–147° (ethanol); hydantoin[5] (analytical sample, mp 215–216.5°, aqueous ethanol).

Anal. Calcd for $C_6H_8Cl_2N_2O_2$: C, 34.47; H, 2.89. Found: C, 34.11, 34.20; H, 3.05, 3.06.

1,1-Dichloro-6-hydroxymethylcyclopropane.—A mixture of methyl orthoformate (8.9 g, 0.083 mol), allyl alcohol (20 g, 0.345 mol), and ammonium nitrate (0.30 g) was stirred and heated under a distilling column until the distillate temperature reached 80°. The residual material was distilled under reduced pressure yielding triallyl orthoformate [8.88 g, 57%, bp 101–110° (34 mm), lit.[6] bp 196–205°]. The triallyl orthoformate (0.048 mol) was allowed to react with chloroform (20 ml, 0.25 mol) and sodium hydroxide pellets (40 g, 1.00 mol) in tetraglyme (25 ml) in an ice bath with vigorous stirring (Stir-O-Vac high shear stirrer) during 1.5 hr. The mixture stood at 25° for 16 hr and was then diluted with water and extracted with ether. The ether extract was shaken twice with 20% aqueous hydrochloric acid. Examination of the ether phase (glpc) showed two products (area ratio 1:2). Removal of solvent gave 6.50 g of crude product having a carbonyl band in the infrared (formate ester). Column chromatography on alumina decomposed the formate ester giving pure 1,1-dichloro-2-hydroxymethylcyclopropane (5.42 g, 27% on triallyl orthoformate): infrared 3.0 (bonded OH), 3.33, 3.42, 3.48, 6.85, 7.00, 7.20, 8.08, 8.22, 9.00, 9.60, 10.32, 10.70, 11.30, 12.40, and 13.40 μ; nmr 245 (OH), 218–230 (pair of doublets, $-CH_2O-$), 65–135 ppm (complex cyclopropyl H) and integrates for 3.1 protons $-CH_2OH$ and 3.0 protons on cyclopropane ring (calcd three protons and three protons).

The phenylurethan was an oil. The α-naphthylurethane was a solid (mp 100–102°): nmr 70–135 (cyclopropyl H), 235–285 ($-CH_2O-$), 420–430 (broad, NH), and 430–480 ppm (aromatic), integrated area aromatic plus NH to $-CH_2O-$ is 7.9/2 (calcd 8/2) and of $-CH_2O-$ to cyclopropyl H is 2/3 (calcd 2/3).

Anal. Calcd for $C_{15}H_{13}Cl_2NO_2$: C, 58.06; H, 4.22; Cl, 22.86. Found: C, 58.14, 58.38; H, 4.36, 4.37; Cl, 22.5.

1,1-Dichloro-2-ethoxymethylcyclopropane.—Allyl ethyl ether (21.5 g, 0.25 mol), chloroform (20 ml, 0.25 mol), sodium hydroxide pellets (40 g, 1.00 mol), and tetraglyme (25 ml) were allowed to react with high-shear stirring at 98° for 3 hr yielding crude 1,1-dichloro-2-ethoxymethylcyclopropane[7] [21 g, 50%, bp 82–90° (40 mm)] containing a minor impurity. The major component was isolated by careful distillation, bp 90–90.5° (43 mm).

Anal. Calcd for $C_6H_{10}Cl_2$: C, 42.63; H, 5.96. Found: C, 42.9, 42.8; H, 5.92, 6.11.

1,1-Dichloro-2-methyl-2-chloromethylcyclopropane.—A mixture of methallyl chloride (26.5 g, 0.292 mol), chloroform (40 ml, 0.50 mol), sodium hydroxide pellets (80 g, 2.0 mol), and 100 ml of tetraglyme was stirred vigorously at 30° for 2 hr. Steam distillation followed by fractional distillation of the organic distillate gave 1,1-dichloro-2-methyl-2-chloromethylcyclopropane [24.6 g, 49%, bp 86° (30 mm), $n^{25}D$ 1.4855, lit.[8] bp 89° (50 mm), $n^{26}D$ 1.4858]: nmr 87.2 and 91.7 (cyclopropyl H *cis* and *trans* to methyl group, J = 13), 92.8 (methyl group), and 223.1 and 232.8 cps (chloromethyl protons adjacent to asymmetric center, J = 16); integral 2.0 (chloromethyl, calcd 2.0) and 4.8 (cyclopropyl H plus methyl, calcd 5.0).

Anal. Calcd for $C_5H_7Cl_3$: C, 34.62; H, 4.07; Cl, 61.32. Found: C, 34.61, 34.42; H, 4.19, 4.17; Cl, 60.7.

1,1-Dichloro-2-methyl-2-hydroxymethylcyclopropane.—A mixture of methallyl alcohol (18.0 g, 0.25 mol), chloroform (20 ml, 0.25 mol), sodium hydroxide pellets (40 g, 1.00 mol), and tetraglyme (25 ml) was stirred for 1 hr. The usual work-up followed by distillation gave crude material, bp 103° (30 mm), contaminated with 25% impurity. The phenylurethan formed readily (mp 78.5–79.5°): nmr ($DCCl_3$) 77.6 and 89.2 (cyclopropyl H *trans* and *cis* to methyl, J = 7.4), 86.3 (methyl), 246.7 and 269.3 ($-OCH_2-$ adjacent to asymmetric center, J = 11.4), and 430–500 cps (aromatic and NH protons), integral five cyclopropyl plus methyl protons and two methylene protons.

Anal. Calcd for $C_{12}H_{13}Cl_2NO_2$: C, 52.57; H, 4.78. Found: C, 52.21, 52.36; H, 4.73, 4.96.

1,1-Dichloro-2-methyl-2-ethoxymethylcyclopropane.—To a solution of sodium ethoxide in ethanol (0.25 mol of sodium to 125 ml of absolute ethanol) was added methallyl chloride (22.64 g, 0.25 mol) and the mixture was allowed to stir at 25° for 4 days. After dilution with water an ether extract was distilled giving ethyl methallyl ether, 14.60 g, 58%, bp 86–88° (lit.[9] bp 84.6–86.8°). The ethyl methallyl ether (0.15 mol), chloroform (16 ml, 0.20 mol), sodium hydroxide pellets (40 g, 1.0 mol), and tetraglyme (25 ml) were stirred at 0° for 2.5 hr. Dilution with water and ether extraction followed by distillation of the ether extract gave 1,1-dichloro-2-methyl-2-ethoxymethylcyclopropane, 21.9 g, 80%, bp 83–85° (34 mm).

Anal. Calcd for $C_7H_{12}Cl_2O$: Cl, 38.73. Found: Cl, 38.8, 38.4.

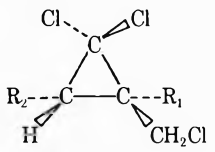
1,1-Dichloro-2-methyl-3-chloromethylcyclopropane.—Crotyl chloride (0.25 mol, contains about 25% *cis*-crotyl chloride), chloroform (20 ml, 0.25 mol), sodium hydroxide pellets (40 g, 1.00 mol), and tetraglyme (50 ml) was stirred at 37° for 2.5 hr. Steam distillation followed by careful fractional distillation gave 1,1-dichloro-2-methyl-3-chloromethylcyclopropane [19.8 g, 46%, bp 85° (30 mm), $n^{25}D$ 1.4813] contaminated with a small amount of a second material (shoulder on glpc trace) which could not be removed by extraction of a dilute petroleum ether solution with concentrated sulfuric acid: nmr 1.36 (methyl group doublet, J = 2.5), 1.2–1.8 (cyclopropyl H multiplet), and 3.75 ppm (chloromethyl doublet, J = 7.5); integral 2.0 chloromethyl protons and 5.2 methyl plus cyclopropyl protons (calcd 5.0).

Anal. Calcd for $C_5H_7Cl_3$: Cl, 61.32. Found: Cl, 61.0.

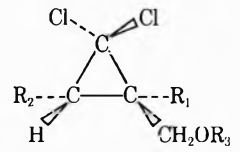
1,1-Dichloro-2-methyl-3-hydroxymethylcyclopropane.—A mixture of crotyl alcohol (18.0 g, 0.25 mol), chloroform (20 ml, 0.25 mol), sodium hydroxide pellets (40 g, 1.00 mol), and tetraglyme (25 ml) was allowed to react in the usual way and crude product was distilled giving a low yield (3 g) of product containing 80% of the major component. Column chromatography on alumina yielded this major component in about 95% purity. The presumed 1,1-dichloro-2-methyl-3-hydroxymethylcyclopropane did not yield a crystalline phenylurethane. An α-naphthylurethane solidified but melted over a wide range. A variety of methods of purification failed to yield a tractable product. The material is probably a mixture of *cis–trans* isomers.

Results

Solvolysis of 1,1-dichloro-2-chloromethylcyclopropane in 50% (v/v) aqueous ethanol was found to give two product peaks on glpc. Comparison on SE-30 and Carbowax 20M glpc columns with authentic samples identified the products as 1,1-dichlorocyclopropyl-2-ethoxymethylcyclopropane (IIb) and 1,1-dichlorocyclopropyl-2-hydroxymethylcyclopropane (IIa). No



Ia, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = CH_3$



IIa, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = H$; $R_3 = C_2H_5$
c, $R_1 = CH_3$; $R_2 = R_3 = H$
d, $R_1 = CH_3$; $R_2 = H$; $R_3 = C_2H_5$
e, $R_1 = R_3 = H$; $R_2 = CH_3$
f, $R_1 = H$; $R_2 = CH_3$; $R_3 = C_2H_5$

other products were detected and 87% of reacted starting material could be accounted for.

The alcohol IIa had not previously been reported and its synthesis was approached by two routes. One proposed route involved dichlorocyclopropanation of

(5) The hydantoin was prepared by the procedure of H. R. Henze and R. J. Speer [*J. Amer. Chem. Soc.*, **64**, 522 (1942)], but formation of a coproduct (mp 80°) presumed (from its infrared and nmr spectra) to be aldehyde trimer complicated the work-up. Facile trimerization was a continual complication with this aldehyde.

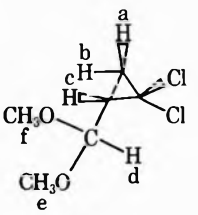
(6) F. Beilstein, *et al.*, *Ber.*, **18**, 482 (1885).

(7) D. Seyferth, *et al.*, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

(8) H. A. Bruson and H. L. Plant, U. S. Patent 3,376,348 (April 2, 1968).

(9) M. Tamele, C. J. Ott, K. E. Marple, and G. Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).

acrolein dimethyl acetal, hydrolysis to the aldehyde, and reduction with sodium borohydride to IIa. The dichlorocyclopropanation proceeded in reasonable (26%) yield giving 1,1-dichloro-2-dimethoxymethylcyclopropane. This substance, interestingly, showed two methoxyl peaks in its nmr spectrum and the appearance of the doublet was unchanged up to 140°. The methoxyl doublet is attributed to the adjacent asymmetric center[10] and not to restricted rotation. A detailed analysis of this unusual spectrum has been carried out.[11]

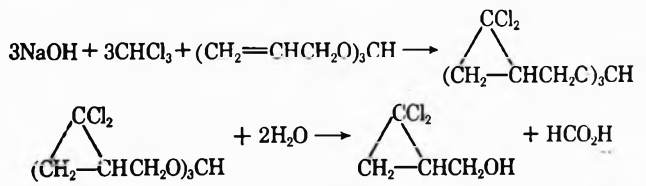


Chemical shift	H_a	H_b	H_c	H_d	H_e	H_f
cps	83.6	105.9	103.3	253	199	203

Coupling constants	J_{ab}	J_{ac}	J_{bc}	J_{cd}
cps	6.5	9.1	5.1	6.0

Difficulties were met during hydrolysis of the acetal to 2,2-dichlorocyclopropylcarboxaldehyde. The yield of aldehyde was rather poor and the aldehyde was difficult to handle, appearing to trimerize very readily to the rather unreactive substituted trioxane. This approach was abandoned when an alternate synthesis of the desired alcohol proved simpler.

The successful synthesis used dichlorocyclopropanation of triallyl orthoformate with subsequent hydrolysis directly to IIa. This synthesis proceeded smoothly except that the product alcohol was contaminated initially with some formate ester owing to incomplete hydrolysis. This was converted into alcohol by chromatography on alumina. The nmr spectrum of the alcohol was in accord with the postulated structure and the α-naphthylurethan derivative gave the expected nmr pattern and the correct analysis.



Preparation of 1,1-dichloro-2-methyl-2-chloromethylcyclopropane (Ib) according to our standard procedure went in good (49%) yield. The protons of the chloromethyl group were nonequivalent in the nmr, presumably again owing to the adjacent asymmetric center. Solvolysis in aqueous ethanol gave two products, 1,1-dichloro-2-methyl-2-hydroxymethylcyclopropane (IIc) and the corresponding ethyl ether (IId), which were identified by glpc comparison with authentic materials. Material balances were initially about 80% declining to 60% at 604 hr. The initial solvolysis products rapidly reacted further with solvent at 120°. The alcohol (IIc) was prepared in low yield directly by dichlorocyclopropanation of methallyl alcohol and readily formed a phenylurethane which gave the correct elemental analysis and had an nmr spectrum similar to that of parent Ib. The ethyl ether (IId) was prepared in the standard way from methallyl ethyl ether in excellent (80%) yield.

Preparation of 1,1-dichloro-2-methyl-3-chloromethylcyclopropane utilized dichlorocyclopropanation of crotyl chloride containing 25% *cis* crotyl chloride. The product, isolated by careful distillation in fair (46%) yield, revealed a small shoulder on glpc which was not removed by extraction of a dilute pentane solution of the product with sulfuric acid. The impurity cannot, therefore, be an olefinic product from dichloromethylene insertion at a carbon–hydrogen bond and is presumably an isomeric *gem*-dichlorocyclopropane. The nmr spectrum was consistent with the expected structure as was the elemental analysis.

Solvolysis of the 1,1-dichloro-2-methyl-3-chloromethylcyclopropane yielded two products, one of which was shown by glpc to be 1,1-dichloro-2-methyl-3-hydroxymethylcyclopropane and the second was presumed from its retention time to be the corresponding ethyl ether. Material balances were 95% based on areas. Authentic 1,1-dichloro-2-methyl-3-hydroxymethylcyclopropane was prepared by dichlorocyclopropanation of crotyl alcohol. Conversion to an α-naphthylurethan gave a solid derivative which melted over a wide range in spite of repeated attempts at purification. It seems likely that *cis* isomer is present and is difficulty separable.

Rate data were obtained at 100° (steam chamber) in 1:1 (v/v) aqueous ethanol. Most of the rates were obtained using glpc analysis with an internal standard. This procedure permits continual scrutiny of the solvolysis products. An initial study of 1,1-dichlorocyclopropyl-2-chloromethylcyclopropane solvolysis used a conventional sealed ampoule titrimetric procedure. A summary of the rate data together with some comparative literature data are given in Table I. Representative kinetic runs are detailed in Tables II and III.

Conclusions

The solvolysis products show a simple pattern and no rearranged cyclobutyl or homoallylic chlorides, alcohols, or ethyl ethers were detected. The material balances are adequate to exclude any substantial formation of these products.

The rather unexpected product data are supported by the kinetic data. The rate of solvolysis of Ia is anomalously slow. From the solvolytic rate data of Schleyer and Van Dyne[12] (on polymethyl- and ethoxycyclopropylcarbinyl 3,5-dinitrobenzoates which are well correlated by a σ^+ plot[13]) one can estimate that the solvolysis rate of 2,2-dichlorocyclopropylcarbinyl 3,5-dinitrobenzoate should be 0.16 times that of cyclopropylcarbinyl 3,5-dinitrobenzoate.

This value can be transferred to a chloride leaving group by assuming that the relative rates of substituted cyclopropylcarbinyl systems are substantially

(10) H. S. Gutowsky, *J. Chem. Phys.*, **37**, 2196 (1962).

(11) The HaHbHc portion of the spectrum was calculated as an ABX pattern. J_{ax} and J_{bx} were of unlike sign.

(12) P. von R. Schleyer and G. W. Van Dyne, *J. Amer. Chem. Soc.*, **88**, 2321 (1966).

(13) H. C. Brown, personal communication.

TABLE I

SOLVOLYSIS RATES OF SUBSTITUTED CYCLOPROPYLCARBINYL CHLORIDES (50% AQUEOUS ETHANOL, 100°)

RCH_2Cl, R	$k_1 \times 10^6$, sec^{-1}	Relative rate
Cyclopropyl	$\gg 1.3 \times 10^2$ [a]	$\gg 67$
C_2H_5	9.7[b]	5.0
2,2-Dichlorocyclopropyl	1.8 ± 0.1[c]	
2,2-Dichlorocyclopropyl	1.92 ± 0.06	1
2,2-Dichlorocyclopropyl	1.97 ± 0.13	
1-Methyl-2,2-dichlorocyclopropyl	1.32 ± 0.04	0.68
2,2-Dichloro-3-methylcyclopropyl	4.0 ± 0.2	2.05

[a] 50° rate is 1.3×10^{-4} sec^{-1}; J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951). [b] 101.6°, C. A. Vernon, *J. Chem. Soc.*, 423 (1954). [c] Titrimetric rate, calculated infinity.

TABLE II

TITRIMETRIC DATA.
1,1-DICHLORO-2-CHLOROMETHYLCYCLOPROPANE SOLVOLYSIS[a]

Time, hr	Titer, (ml of 0.0957 *M* NaOH)	$k_1 \times 10^6$, sec^{-1}
0		
21	0.40	1.9
45	0.75	1.9
117	1.36	1.7
285	2.00	1.7
		Av 1.8 ± 0.1

[a] 1:1 v/v aqueous ethanol, 100°, calcd ∞ 2.68 ml.

TABLE III

REPRESENTATIVE DATA.
1,1-DICHLORO-2-CHLOROMETHYLCYCLOPROPANE SOLVOLYSIS[a]

Time, hr	RCl/ internal standard (relative area)	$10^6 k_1$, sec^{-1}
0	0.678	
24	0.588	1.67
48	0.481	1.99
74	0.386	2.12
98.2	0.336	1.99
141.2	0.217	2.24
194.2	0.188	1.84
263	0.108	1.94
		Av 1.97 ± 0.13

[a] 1:1 v/v aqueous ethanol, 100°, glpc internal standard.

unaffected by changes in the leaving group and solvent. In support of this assumption Roberts[14] showed that in solvolysis of 1-methylcyclopropylcarbinyl tosylate changing solvent from methanol to ethanol to acetic acid gave a substantially constant rate relative to cyclopropylcarbinyl tosylate of 4–5. Schleyer and Van Dyne found the same rate ratio for a 3,5-dinitrobenzoate leaving group in aqueous acetone.

Thus one predicts a solvolysis rate for Ia (50°, 50% aqueous ethanol) of 2.7×10^{-5} sec^{-1}. Activation energy data are not available for the extrapolation from 50 to 100° but a factor of 100 is assumed as a lower limit giving an estimated rate as $>2.7 \times 10^{-3}$. This is a factor of $>1.4 \times 10^3$ higher than the observed rate.

(14) D. D. Roberts, *J. Org. Chem.*, **31**, 2000 (1966).

Alternatively one can assume that the solvolysis mechanism is similar to that of *n*-propyl chloride. From the pK_a of 2,2-dichlorocyclopropane carboxylic acid[15] one calculates σ^* of the 2,2-dichlorocyclopropyl group as +0.72. Although ρ^* for primary alkyl chloride solvolysis in 50% aqueous ethanol at 100° is not available, it should be near the value (−0.74) for primary alkyl brosylate solvolysis in ethanol at 100°.[16] To a first approximation using ρ^* as −0.74 one calculates the solvolysis rate of *gem*-dichlorocyclopropylcarbinyl chloride as 0.246 times that of *n*-propyl chloride or 2.4×10^{-6} sec^{-1} in good agreement with the observed 1.8×10^{-6} sec^{-1} solvolysis rate.

Clearly the solvolysis of *gem*-dichlorocyclopropylcarbinyl chloride gives a product pattern and kinetic behavior characteristic of primary alkyl chloride solvolysis without involvement of the cyclopropane ring. This conclusion is strengthened by the effects of methyl substitution on reaction products and rates. The products are completely analogous to those from the parent compound. The solvolysis rate is depressed by a factor of 0.68 on 1-methyl substitution whereas in the simple cyclopropylcarbinyl system solvolysis rate is increased by a factor of 5 on 1-methyl substitution. Rate is increased by a factor of 2.05 by 3-methyl substitution, much less than the factor of 8–11 noted in cyclopropylcarbinyl systems. This pattern of rate effects on methyl substitution strongly suggests a simple solvolytic substitution at the carbinyl carbon not involving charge delocalization into the cyclopropane ring.

No convincing reason for the noninvolvement of the ring in *gem*-dihalocyclopropylcarbinyl chloride solvolysis can as yet be given. Steric explanations seem unpromising since models reveal no obvious steric problems and solvolytic studies on polymethylcyclopropylcarbinyl *p*-nitrobenzoates indicate normal participation by the cyclopropane ring although chlorine and methyl are substantially identical sterically[17] (Pauling and van der Waals radii 1.8 and 2.0, respectively). It appears that participation in cyclopropylcarbinyl chloride solvolysis must be abnormally sensitive to electron-withdrawing substituents, even more sensitive than can be accounted for by a σ^+ correlation. Even a mildly electronegative group like chlorine is sufficient to nullify participation. The way in which this unusual deactivation is implemented remains to be elucidated.

Registry No. —1,1-Dichloro-2-chloromethylcyclopropane, 3722-05-2; 1,1-dichloro-2-dimethoxymethylcyclopropane, 20414-44-2; 1,1-dichloro-2-dimethoxymethylcyclopropane-*p*-toluenesulfonylhydrazone derivative, 20414-45-3; 2,2-dichlorocyclopropylcarboxaldehyde, 20414-46-4; 2,2-dichlorocyclopropylcarboxaldehyde-(2,4-dinitrophenylhydrazone), 20414-47-5; 2,2-dichlorocyclopropylcarboxaldehyde (hydantoin derivative), 20414-48-6; 1,1-dichloro-2-hydroxymethylcyclopropane, 5365-23-1; 1,1-dichloro-2-hydroxymethylcyclopropane (α-naphthylurethan), 20414-49-7; 1,1-dichloro-2-ethoxymethylcyclopropane, 932-59-2; 1,1-dichloro-2-methyl-2-chloromethylcyclopropane, 15997-19-0; 1,1-dichloro-2-methyl-2-chloromethylcyclopro-

(15) R. C. Woodworth and P. S. Skell, *J. Amer. Chem. Soc.*, **79**, 2542 (1957).

(16) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., 1962, p 126.

(17) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1945.

pane (phenylurethan), 20439-52-5; 1,1-dichloro-2-methyl-2-ethoxymethylcyclopropane, 20439-53-6; 1,1-dichloro-2-methyl-3-chloromethylcyclopropane, 20439-54-7.

Acknowledgment.—Spectral data were obtained and largely interpreted by Dr. F. J. Impastato and Dr. D. W. Imhoff. Elemental analyses were conducted by Mr. W. J. Easley.

Bicyclobutyl Derivatives. V. Syntheses of Conjugated Perhalogenated Diolefins[1]

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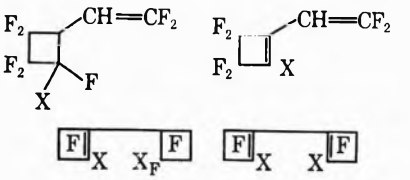
Received December 17, 1968

The cycloaddition of 1,1,4,4-tetrafluorobutadiene-1,3 to CF_2=CFCl and CF_2=CCl_2, respectively, led to the formation of the following perhalogenated derivatives which have been examined and characterized.

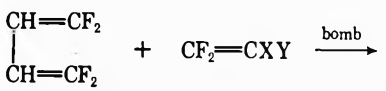


X = Cl or F

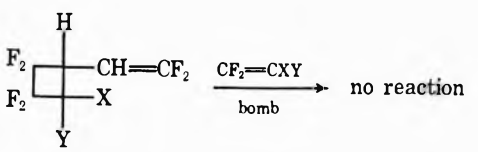
This paper reports the cycloaddition of 1,1,4,4-tetrafluorobutadiene-1,3 to CF_2=CFCl and CF_2=CCl_2 leading to perhalogenated "dibox" compounds.[3]

Results and Discussion

The thermal cycloaddition of 1,1,4,4-tetrafluorobutadiene-1,3 (I) with excess tetrahaloethylenes has led to the 1:1 adducts, 1-(β,β-difluorovinyl)-2,2-dihalo-3,3,4,4-tetrafluorocyclobutanes (IIa and b, 60–90%). No 1:2 diadducts were detected even in the presence of a large excess of tetrahaloethylene. The vinyl cyclobutane



I

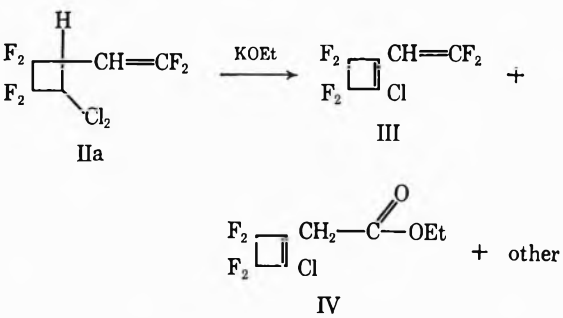


IIa, X = Y = Cl
b, X = F, Y = Cl

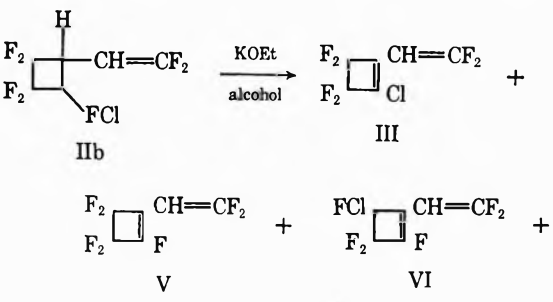
adducts are stable, colorless liquids. They have been characterized by microanalysis, H and ^{19}F nmr spectra, infrared spectra, and mass spectra.

The observed resistance of IIa and IIb to further cycloaddition reactions implied the requirement of a diene intermediate in these highly halogenated systems. Dehydrohalogenation of IIa or IIb would lead to more reactive vinylcyclobutenes.

Several classical dehydrohalogenation media were tested on this system with limited success. Ethanolic potassium hydroxide reacts exothermically with IIa to



give 1-(β,β-difluorovinyl)-2-chloro-3,3,4,4-tetrafluorocyclobutene (III, 45%) and a complex mixture of ether substitution products. The ester IV (18%) apparently stems from base-catalyzed hydrolysis of one or more product ethers. Potassium ethoxide converts IIb into a mixture of three possible dienes, III, V, and VI, along with a very complex mixture of ethers. The three vinylcyclobutenes were characterized by their infrared and mass spectra and by microanalysis. They are colorless liquids which polymerize to waxy solids within several hours at room temperature. Potassium hydroxide in mineral oil successfully dehydrohalogenates IIa to III (35%) and IIb to III (10%), V (25%), and VI



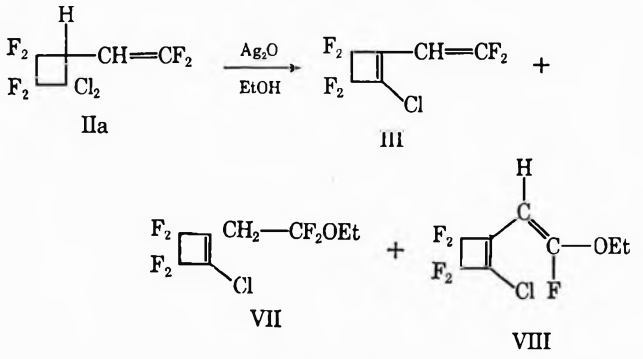
(1) Previous papers in this series: (a) J. D. Park and W. C. Frank, *J. Org. Chem.*, **29**, 1445 (1964); (b) *ibid.*, **32**, 1333 (1967); (c) *ibid.*, **32**, 1336 (1967); (d) *ibid.*, **32**, 1340 (1967).

(2) This paper represents parts of Ph.D. Theses submitted to the Graduate School, University of Colorado, Boulder, Colo., by S. K. Choi, 1969, and by H. E. Romine, 1968.

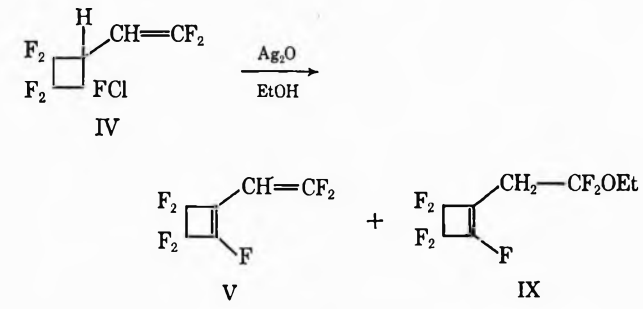
(3) "Dibox" is a trivial name used to designate dicyclobutene.

(15%) at elevated temperature, but the reaction is very exothermic once initiated and extensive polymerization frequently destroys the product. Triethylamine reacts violently with IIa or IIb in an inert solvent at −78°, giving only tars.

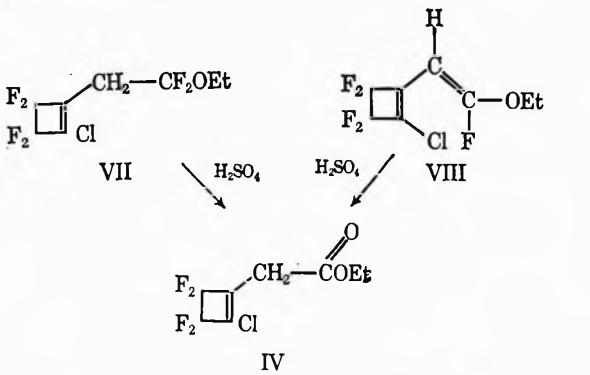
Dehydrohalogenation is best accomplished in this system through the use of silver oxide in 95% ethanol. Compound IIa reacts to give III (60%), a stable liquid VII (20%), and a white waxy solid VIII (15%).



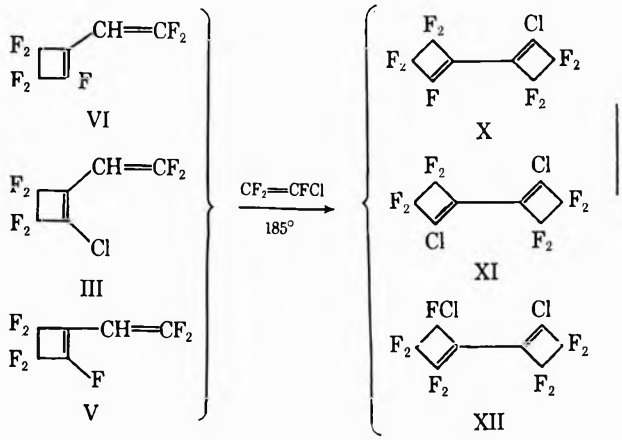
Similar to the reactions of IIa, IIb is converted to V (77%) and IX (7%) on treatment with silver oxide. IX was characterized through its mass and infrared spectra. XIII is a colorless liquid which liberates HF and darkens on standing. No dehydrofluorination products are observed in these mild silver oxide reactions, and the desired vinyl cyclobutenes are consistently prepared in good yield.



The fluorocarbon ethers VII and VIII are converted quantitatively to 1-carbethoxymethyl-2-chloro-3,3,4,4-tetrafluorocyclobutene (IV) on treatment with oleum.



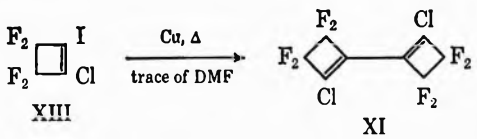
Problems in preparing and storing pure vinylcyclobutenes in quantities exceeding several grams made further codimerization studies difficult. In order to establish the reactivity of these compounds, a mixed sample of IIb, III, V, and VI was treated with a twenty-fold excess of chlorotrifluoroethylene in an autoclave at 185°. Compound IIb has been shown to be inert under these reaction conditions and therefore serves as a standard against which the reactivity of the other materials can be measured. Work-up revealed 40–50% reaction of each diene and the development of three products. Preparative gas chromatography afforded 2-chlorononafluoro(bi-1,1′-cyclobut-1-enyl) (X), a pungent, colorless liquid, the related 2,2′-dichlorooctafluoro derivative (XI), and 2,4′-dichlorooctafluoro(bi-1,1′-cyclobut-1-enyl) (XII) as the three reaction products in a 4:5:6 ratio.



The simplicity of the product mixture allows an analysis of the course of the reaction. Product X could have resulted from addition of chlorotrifluoroethylene to III followed by dehydrochlorination or addition to V followed by dehydrofluorination. However, dehydrochlorination products from the adducts of chlorotrifluoroethylene with V or VI are not observed, while all products in their observed distribution can be accounted for assuming thermal dehydrofluorination from each of the required adducts. Evidence for presence of the unreacted adducts could not be found, but some polymeric material was noted in the reaction mixture.

Further work on codimerizations was rendered superfluous by the development of two alternative syntheses of dicyclobutenes incorporating coupling reactions.

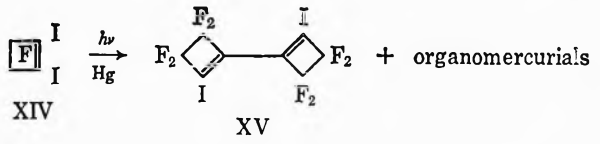
Recent studies in this laboratory[4,5] outlining the preparation of vinyliodocyclobutenes by halogen exchange reactions has promoted an interest in the chemistry of these novel fluorocarbons. It was consequently discovered that 1-iodo-2-chloro-3,3,4,4-tetrafluorocyclobutene couples to form XI when passed over hot copper turnings. The presence of a trace of dimethylformamide is necessary to initiate the radical reaction.



While yields vary from 30 to 60% with considerable decomposition, this one-step synthesis is convenient for small-scale laboratory preparations. The reaction is general of polyfluorinated vinyliodocycloalkenes, as will be discussed further in a forthcoming paper.[6]

(4) G. G. J. Moore, Ph.D. Thesis, University of Colorado, 1965.
(5) R. J. McMurtry, Ph.D. Thesis, University of Colorado, 1965.
(6) J. D. Park and S. K. Choi, to be published.

Photochemically initiated radical reactions of 1,2-diiodo-3,3,4,4-tetrafluorocyclobutene (XIV) have been observed to give 2,2′-diiodooctafluoro(bi-1,1′-cyclobut-1-enyl) (XV), a white crystalline solid, in 16% yield.



XIV XV

The major product (57%) of this mercury-sensitized reaction is a green organometallic species which was not sufficiently stable to permit characterization.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary apparatus and are corrected; boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord. Proton nuclear magnetic resonance spectra were run on a Varian A-60 or A-60A spectrometer using tetramethylsilane as an internal reference. Fluorine nuclear magnetic resonance spectra were run on a Varian HA-100 spectrometer using $CFCl_3$ (F-11) as an internal reference. Chemical shifts are recorded as parts per million on the δ scale, with coupling constants as cycles per second. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Mass spectra were obtained from an Atlas CH-4 mass spectrometer and were measured at 70 eV.

Synthesis of 1-(β,β-Difluorovinyl)-3,3,4,4-tetrafluoro-2,2-dichlorocyclobutane (IIa).—A 500-ml stainless steel autoclave was charged with 67.8 g (0.54 mol) of 1,1,4,4-tetrafluorobutadiene, 225 g (1.70 mol) of 1,1-dichloro-2,2-difluoroethylene, and 2 ml of *d*-limonene. The mixture was brought to 220° in a shaker during 2 hr and maintained at that temperature for 36 hr. After cooling, the dark liquid contents were collected and fractionally distilled to give 126.7 g (91%) of the adduct IIa: bp 105–107° (628 mm); $n^{26}D$ 1.3784; d^{26} 1.59; ir 3100 and 2990 (C—H) and 1750 cm^{-1} (C=C); nmr ($CFCl_3$) δ 4.48 (m, 1, C=C—**H**) and 3.94 (m, 1, C—**H**); mass spectrum *m/e* 258 (2 Cl), 238 (2 Cl), 222 (1 Cl), and 160 (1 Cl).

Anal. Calcd for $C_6H_2Cl_2F_6$: C, 27.8; H, 0.8; Cl, 27.4; F, 44.0. Found: C, 27.71; H, 0.76; Cl, 27.47; F, 44.02.

Synthesis of 1-(β,β-Difluorovinyl)-2,3,3,4,4-pentafluoro-2-chlorocyclobutane (IIb).—A 500-ml stainless steel autoclave was charged with 60.1 g (0.48 mol) of 1,1,4,4-tetrafluorobutadiene, 225 g (1.94 mol) of chlorotrifluoroethylene, and 3 ml of *d*-limonene. The mixture was heated in a shaker to 260° during 8 hr and maintained at that temperature for 18 hr. After cooling, a light orange liquid was collected from the bomb which on fractional distillation gave 67.8 g (58%) of 1-(β,β-difluorovinyl)-2,3,3,4,4-pentafluoro-2-chlorocyclobutane (IIb); bp 75–78° (630 mm); $n^{26}D$ 1.3358; d^{26} 1.63; ir 3120 and 2990 (C—H) and 1750 cm^{-1} (C=C); nmr ($CFCl_3$) δ 4.47 (m, 1, C=C—**H**) and 3.88 (m, 1, C—**H**); mass spectrum *m/e* 242 (1 Cl), 223 (1 Cl), 207, 203 (1 Cl), 188, and 187.

Anal. Calcd for $C_6H_2ClF_7$: C, 29.7; H, 0.83; Cl, 14.6; F, 54.9. Found: C, 29.51; H, 0.93; Cl, 13.53; F, 54.77.

Dehydrohalogenation of 1-(β,β-Difluorovinyl)-3,3,4,4-tetrafluoro-2,2-dichlorocyclobutane (IIa). A. Reaction with Potassium Ethoxide.—A solution of 5.18 g (0.02 mol) of IIa in 10 ml of 95% ethanol in a flask was cooled to 0° prior to the dropwise addition of a solution of 1.7 g (0.03 mol) of potassium hydroxide with rapid stirring. Following an additional 6 hr of stirring at 25°, the mixture was quenched with water and the crude product isolated. Preparative gas chromatography (6 ft × 0.5 in. column packed with 15% SE-30 on 30–60 mesh Chromosorb W-HMDS at 200°) yielded 1-(β,β-difluorovinyl)-3,3,4,4-tetrafluoro-2-chlorocyclobutene (III, 45%) and 1-carbethoxymethyl-3,3,4,4-tetrafluoro-2-chlorocyclobutene (IV, 18%) along with 20% recovered IIa. Compound VII is a colorless, readily polymerized liquid: $n^{27}D$ 1.3897; d^{27} 1.64; ir 3100 (C—H) and 1720 and 1630 cm^{-1} (C=C); mass spectrum *m/e* 222 (1 Cl), 203 (1 Cl), and 187.

Anal. Calcd for C_6HClF_6: C, 32.4; H, 0.5; Cl, 15.9; F, 51.2. Found: C, 32.16; H, 0.51; Cl, 16.39; F, 52.66.

Compound IV is a stable colorless liquid: $n^{28}D$ 1.3968; d^{28} 1.40; ir 3030 (C—H), 1760 (C=O) and 1670 cm^{-1} (C=C); nmr ($CFCl_3$) δ 4.52 (d, 1, J_{HF} = 31.5 cps, —CH=CFOEt), 4.12 (q, 2, J_{HH} = 7.0 cps, —OCH_2CH_3) and 1.43 (t, 3, J_{HH} = 7.0 cps, —OCH_2CH_3); mass spectrum fragments at *m/e* 201 (1 Cl), 173 (1 Cl), 154 (1 Cl), 123 (1 Cl), and 119.

B. Reaction with Potassium Hydroxide in Mineral Oil.—To a mixture of 10 ml of light mineral oil and 2.8 g (0.05 mol) of KOH was added with stirring 8.15 g (0.031 mol) of IIa during 1 hr. A very exothermic and apparently autocatalytic reaction ensued with refluxing, discoloration, and polymerization. Following 16 hr of stirring at 25°, vacuum distillation gave III (35%) and recovered IIa (25%).

C. Reaction with Silver Oxide in 95% Ethanol.—A solution of 5.18 g (0.02 mol) of IIa in 10 ml of 95% ethanol was added with rapid stirring to a suspension of 2.32 g (0.01 mol) of Ag_2O in 10 ml of 95% ethanol during 10 min. Stirring was continued for 16 hr or until AgCl formation and mild heat evolution ceased. The pale yellow oil which separated on quenching with water was water washed and dried (Na_2SO_4). Preparative gas chromatography (6 ft × 0.5 in. column packed with 15% SE-30 on 30–60 mesh Chromosorb W-HMDS at 180°) gave recovered IIa (25%), the diene III (45%), and two new ethers, VII (15%) and VIII (12%). Compound VII has been identified as 1-(2,2-difluoro-2-ethoxy)ethyl-3,3,4,4-tetrafluoro-2-chlorocyclobutene: $n^{26}D$ 1.3777; d^{25} 1.46; ir 3070 (C—H) and 1670 cm^{-1} (C=C); ^1H nmr ($CFCl_3$) δ 3.97 (q, 2, J_{HH} = 7.0 cps, —O—CH_2—), 2.98 (t, 2, J_{HF} = 9.5 cps, C—CH_2—C), and 1.27 (t, 3, J_{HH} = 7.0 cps, —CH_2—CH_3); ^{19}F nmr ($CFCl_3$) δ 117.8 (m, 1, —CF_2—CF_2—C—Cl), 116.3 (m, 1, —CF_2—CF_2—C—Cl), and 114.1 (broad s, 1, —CF_2—OEt); molar refraction calcd, 42.17, and obsvd, 42.23. Compound VIII has been identified as 1-(*cis*-α-hydro-β-ethoxy-β-fluoro)-vinyl-3,3,4,4-tetrafluoro-2-chlorocyclobutene: mp 38.1–39.7°; ir 3050 (C—H) and 1695 and 1640 cm^{-1} (C=C); ^1H nmr ($CFCl_3$) δ 4.52 (d, 1, J_{HF} = 31.5 cps, —CH = CFOEt), 4.12 (q, 2, J_{HH} = 7.0 cps, —O—CH_2—CH_3), and 1.43 (t, 3, J_{HH} = 7.0 cps, —O—CH_2—CH_3); ^{19}F nmr ($CFCl_3$) δ 118.3 (m, 1, —CF_2—CF_2—C—Cl) and 115.2 (m, 1, —CF_2—CF_2—C—Cl). The vinylic F was not scanned. Although the presence of VIII in a single isomeric form lacks explanation, a careful analysis of the product mixture confirmed the absence of the other isomer.

Dehydrohalogenation of 1-(β,β-Difluorovinyl)-2,3,3,4,4-pentafluoro-2-chlorocyclobutane (IIb). A. Reaction with Potassium Ethoxide.—To a solution of 2.8 g (0.05 mol) of KOH in 15 ml of 95% ethanol was added during 90 min with stirring, 8.05 g (0.033 mol) of IIb. The mixture was kept below 50° with intermittent cooling in an ice bath. Stirring at ambient was continued until the fluorocarbon was consumed (90 min) while the mixture progressed from yellow to milky brown. The product was quenched, water washed, and finally dried (Na_2SO_4). Preparative gas chromatography (6 ft × 0.5 in. column packed with 15% SE-30 on 30–60 mesh Chromosorb W-HMDS at 200 and 260°) gave III (10%) and the new dienes V (12%) and VI (8%) along with a very complex mixture of by-products (70%). Compound V is the desired 1-(β,β-difluorovinyl)-2,3,3,4,4-pentafluorocyclobutene: $n^{27}D$ 1.3453; d^{27} 1.62; ir 3150 (C—H) and 1750 and 1700 cm^{-1} (C=C); ^1H nmr ($CFCl_3$) δ 4.96 (d, 1, J_{HF} (*trans*) = 25.0 cps); ^{19}F nmr ($CFCl_3$) δ 117.4 (m, 2, —CF_2—CF_2—C—F), 116.9 (m, 2, —CF_2—CF_2—C—F), 114.6 (m, 1, —CF_2—CF_2—C—F), 73.6 (m, 1, —C=C<$^{H}_{F}$), and 68.4 (m, 1, —C=C<$^{H}_{F}$); mass spectrum *m/e* 206, 187, 156, and 137.

Anal. Calcd for C_6HF_7: C, 35.0; H, 0.5; F, 64.5. Found: C, 33.03; H, 0.49; F, 64.01.

Compound VI has been identified as 1-(β,β-difluorovinyl)-2,3,3,4-tetrafluoro-4-chlorocyclobutene: $n^{27}D$ 1.3884; d^{27} 1.66; ir 3130 (C—H) and 1750 and 1700 cm^{-1} (C=C); mass spectrum *m/e* 222 (1 Cl), 203 (1 Cl), and 187.

Anal. Calcd for C_6HClF_6: C, 32.4; H, 0.5; Cl, 15.9; F, 51.2. Found: C, 31.31; H, 0.52; Cl, 15.65; F, 52.35.

B. Reaction with Potassium Hydroxide in Mineral Oil.—To a stirred mixture of 2.8 g (0.05 mol) of KOH in 10 ml of light mineral oil was added during 90 min 8.10 g (0.033 mol) of IIb. A very exothermic reaction ensued and a water bath was required to keep the mixture below 120°. Stirring at 75° was continued for 8 hr, after which vacuum stripping gave 4.3 g of crude product. Chromatographic analysis and separation (10 ft ×

0.25 in. column packed with 10% SE-30 on Chromosorb W at 160°) provided III (10%), V (25%), and VI (15%), identified by comparison with authentic samples prepared in the previous experiment.

C. Reaction with Silver Oxide in 95% Ethanol.—A solution of 48.4 g (0.2 mol) of IIb in 100 ml of 95% ethanol was added during 80 min to a stirred suspension of 23.2 g (0.1 mol) of Ag_2O in 100 ml of 95% ethanol. A mild exothermic reaction occurred with considerable AgCl formation during the addition and for the subsequent 16 hr of stirring at ambient. Quenching with water followed by a water wash and drying (Na_2SO_4) gave a pale yellow liquid. Chromatographic analysis (6 ft × 0.5 in. column packed with 15% SE-30 on 30–60 mesh Chromosorb W-HMDS at 160°) gave 30% recovered IIb, the desired diene, V (55%), and a new ether, IX (5%). Compound IX is identified as 1-(2,2-difluoro-2-ethoxy)ethyl-2,3,3,4,4-pentafluorocyclobutene: $n^{25}D$ 1.3713; d^{25} 1.43; ir 3070 (C—H) and 1740 cm^{-1} (C=C); mass spectrum *m/e* 252, 233, 232, 224, 223, and 204.

Sulfuric Acid Hydrolysis of 1-(*cis*-α-Hydro-β-ethoxy-β-fluorovinyl-3,3,4,4-tetrafluoro-2-chlorocyclobutene (VII).—A mixture of 2.1 g (0.0085 mol) of VII and 5.0 ml of concentrated H_2SO_4 was prepared in a test tube and agitated until the cessation of gas evolution (15 min). The dark liquid was quenched carefully with ice water to give a dark oily product. Preparative gas chromatography (6 ft × 0.5 in. column packed with 15% SE-30 on 30–60 Chromosorb W-HMDS at 175°) provided IX (94%) identical with the sample prepared earlier by basic hydrolysis.

Sulfuric Acid Hydrolysis of 1-(2,2-difluoro-2-ethoxy)ethyl-3,3,4,4-tetrafluoro-2-chlorocyclobutene (VII).—In a manner analogous to the preceding reaction, 2.2 g (0.0086 mol) of VII was agitated with 5.0 ml of concentrated H_2SO_4 and the mixture quenched to give a dark oil. A 94% yield of IV was obtained on preparative chromatography of the mixture as described above.

Codimerization of Mixed Vinyl cyclobutenes with Chlorotrifluoroethylene.—A stainless steel autoclave was charged with 3.0 ml of *d*-limonene, 210 g (1.81 mol) of chlorotrifluoroethylene and 27.3 g of mixed cyclic fluorocarbons consisting of VI (30%), III (25%), 2,2,3,3-tetrafluorocyclobutene (20%), and VIb (25%) as an inert standard. The mixture was heated at 185° for 42 hr in a shaker at autogenous pressure to give a light yellow liquid. Fractional distillation to remove the 1,2-dichloro-1,2,3,3,4,4-hexafluorocyclobutane gave 24.6 g of crude liquid product. Comparative analytical gas chromatography (6 ft × 0.13 in. column packed with 10% UC W-98 on 80–100 mesh Chromosorb W at 120 and 200°; 6-ft × 0.13-in. column packed with 10% Carbowax 20 M on 80–100 mesh Chromosorb P at 140°; and a 10 ft × 0.25 in. column packed with 15% Ucon on 60–80 mesh firebrick R at 140°) indicated the presence of VI (15%), III (15%), V (10%), and IIb (25%) plus the three products, X (8%), XI (10%), and XII (12%). Vacuum fractionation of the product followed by preparative gas chromatography (6 ft × 0.50 in. column packed with 15% SE-30 on 30–60 mesh Chromosorb W-HMDS at 160°) permitted isolation of the products. Compound X is 2-chlorononafluoro(bi-1,1′-cyclobut-1-enyl): $n^{26}D$ 1.3721; d^{26} 1.75; ir 1740, 1670, and 1610 cm^{-1} (unsymmetrical conjugated diene); ^{19}F nmr ($CFCl_3$) δ 117.5 (m, 2, —CF_2—CF_2—CF=), 116.5 (m, 2,—CF_2—CF_2—CCl=), 115 (m, 1, —CF_2—CF_2—CF=), 114.7 (m, 2, —CF_2—CF_2—CCl), and 114.2 (m, 2, —CF_2—CF_2—CF=); mass spectrum *m/e* 302 (1 Cl), 283 (1 Cl), 267, 233 (1 Cl), and 217.

Anal. Calcd for C_8F_9Cl: C, 31.7; Cl, 11.7. Found: C, 31.4; Cl, 12.43.

Compound XI is 2,2′-dichlorooctafluoro-(bi-1,1′-cyclobut-1-enyl): mp 67.8–69.1°; ir 1560 cm^{-1} (C=C); ^{19}F nmr ($CFCl_3$) δ 116.3 (m, 1, —CF_2—CF_2—CCl=) and 112.8 (m, 1, —CF_2—CF_2—CCl=); mass spectrum *m/e* 318 (2 Cl), 299 (2 Cl), 283 (1 Cl), 248 (2 Cl), and 247.

Anal. Calcd for $C_8F_8Cl_2$: C, 30.0; F, 47.7; Cl, 22.2. Found: C, 29.84; F, 47.88; Cl, 21.67.

Compound XII is 2,4′-dichlorooctafluoro(bi-1,1′-cyclobut-1-enyl): mp 58.4–59.9°; ir 1590 and 1550 cm^{-1} (unsymmetrical conjugated diene); mass spectrum *m/e* 318 (2 Cl), 299 (2 Cl), 283 (2 Cl), 248 (2 Cl), and 247. It is distinguished from XI by mixture melting point depression and by its infrared spectrum.

Careful analysis of the product mixture indicated only traces of higher boiling adducts and no perfluoro(bi-1,1′-cyclobut-1-enyl).

Coupling of 1-Iodo-2-chloro-3,3,4,4-tetrafluorocyclobutene (XIII) over Copper in a Hot Tube.—A 1-in.-i.d. Pyrex tube was packed with alternating 3-in. bands of fine copper turnings and copper along a 12-in. length and fitted with a condenser and dropping funnel at the top and a flask at the bottom before being suspended vertically in a tube furnace. The tube was heated to 180° and 46 g (0.16 mol) of XIII containing ~1% dimethylformamide was added dropwise at a rate of 2.0 ml per hr during 10 hr. After an additional 6 hr of heating, 13.5 g (53%) of white crystalline XI identical with that prepared previously was collected from the receiver flask.

Photochemical Reaction of 1,2-diiodo-3,3,4,4-tetrafluorocyclobutene (XIV) over Mercury.—A stirred mixture of 7.5 g (0.019 mol) of XIII and 42.6 g (0.113 mol) of mercury in a quartz vessel was irradiated by 13 clear mercury arc sources in a Rayonette photochemical reactor for 24 hr. Filtration of the mixture gave mercuric iodide, recovered mercury, 10 g of a dense green solid, and 4.2 g of colorless liquid. The unidentified green solid is unstable with respect to mercury and could not be purified for analysis. It is insoluble in water, ethanol, acetone, carbon tetrachloride, hexane, and diethyl ether. The liquid fraction was separated by gas chromatography (6 ft × 0.5 in. column packed with 15% SE-30 on 30–60 mesh Chromosorb W-HMDS at 200°) to give 2.0 g of recovered XIV and 2.2 g (32%) of 2,2′-diiodooctafluoro(bi-1,1′-cyclobut-1-enyl) (XV): mp 145.2–146.7°; ir 1520 cm^{-1} (C=C); mass spectrum *m/e* 502, 483, 375, and 325.

Anal. Calcd for $C_8F_8I_2$: C, 19.1; F, 30.3; I, 50.5. Found: C, 18.85; F, 30.91; I, 50.02.

Registry No.—IIa, 20290-60-2; IIb, 20290-61-3; III, 20290-62-4; IV, 20238-10-2; V, 20290-63-5; VI, 20290-64-6; VII, 20238-35-1; VIII, 20238-36-2; IX, 20238-11-3; X, 20290-65-7; XI, 20290-66-8; XII, 20238-12-4; XV, 20238-13-5.

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A Stereospecific 1,2 Cycloaddition of Trifluoroethylene with Vinyl Chloride. Nuclear Magnetic Resonance Spectrum of 1-Chloro-2,3,3-trifluorocyclobutane

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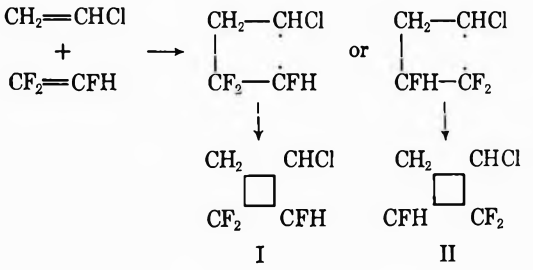
Trifluoroethylene and vinyl chloride have been shown to undergo a stereospecific 1,2 cycloaddition under thermal conditions to give 1-chloro-2,3,3-trifluorocyclobutane with the 1-chlorine and 2-fluorine *trans* to each other.

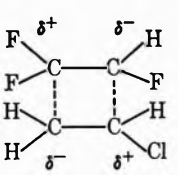
In general, only ethylenes of the type $CF_2{=}CX_2$ (where X = halogens) react readily with themselves or with allenes, ketenes, or activated alkenes, dienes, or alkynes to undergo 1,2 cycloadditions to yield cyclobutanes.[2] These reactions have been reported to give roughly equal amounts of *cis* and *trans* isomers where this possibility exists.[2]

Trifluoroethylene has been shown to undergo no reaction with itself when heated in a sealed tube at 180° for 30 hr.[3]

The thermal high pressure reaction of trifluoroethylene with vinyl chloride was studied in order to ascertain if the cyclic dimer 1-chloro-2,3,3-trifluorocyclobutane could be obtained, in analogy to the thermal codimerizations of 1-halo-1,2,2-trifluoroethylenes with 1,1-dihalo-2,2-difluoroethylenes. Two possible cyclobutanes (I and II) might be formed as depicted below.



Two factors favor the formation of the first isomer, I. First, $-\dot{C}FH$ is probably a more stable radical than either $-CH_2\cdot$ or $-CF_2\cdot$, since the predominant peak in the mass spectrum of the product of the reaction is $[CFH{=}CHCl]^{+\cdot}$. All $[CF_2{=}CX_2]^{+\cdot}$ fragments appear in rather low abundance. Second, the relative polarities of the two reacting olefins will favor the transition state leading to the isomer I. Further, one



might expect the *trans* form of I (1-chlorine and 2-fluorine *trans* to each other) to predominate because of steric considerations.

(1) This paper represents part of a Ph.D. Thesis submitted by R. O. Michael to the Graduate School, University of Colorado, 1968.

(2) J. D. Roberts and C. M. Sharts, *Org. Reactions*, **12**, 1 (1962).

(3) J. D. Park, H. V. Holler, and J. R. Lacher, *J. Org. Chem.*, **25**, 990 (1960).

Results

Trifluoroethylene and vinyl chloride were heated at 230° for 6 days. Vapor phase chromatography on three different columns (SE-30, Ucon, and Carbowax 20M) all indicated the product to be better than 95% pure and to consist of a single sharp peak. The infrared spectrum showed no significant absorption in the double-bond region, 1600–1800 cm^{-1}, indicating that the product is saturated.

The presence of structure I was indicated by potassium hydroxide induced dehydrohalogenation, which gave about a 68% yield of 2,3,3-trifluorocyclobutene.

The mass spectrum and nmr results proved the presence of structure I. The mass spectrum contained peaks expected from the cleavage of I into the four possible ethylene type fragment ions. The base peak was due to $[CFH{=}CHCl]^{+\cdot}$, which could only come from I and not II.

The nmr spectrum shows the presence of three symmetrical fluorine multiplets and four symmetrical proton multiplets from one isomer of I. The spectrum is nearly first order. The chemical shift between H_Y and H_Z is only 75 Hz and $J_{H_Y,H_Z} = -14.21$ Hz, resulting in second-order perturbations in the spectra of these two nuclei. Each nucleus is split into 64 lines from coupling to the other 6 nuclei. Many of these transition frequencies were accidentally degenerate, but it was always possible to pick out the 64 peaks for each nucleus by considering the amplitude of the degenerate lines. An iterative nmr computer program[4] was used to determine the best values of the nmr parameters using 156 of the 448 transition frequencies, including 54 lines from H_Y and H_Z. The rms error between calculated and observed frequencies was 0.10 Hz, and the probable errors of the parameters is under 0.05 Hz. The signs of all the vicinal and cross-ring coupling constants were determined relative to the signs of the geminal coupling constants using homonuclear spin tickling.[5] Other experiments have shown that J_{FF} (*gem*) and J_{HF} (*gem*) are positive[6,7] and J_{HH} (*gem*) is negative.[8] The results are given in Table I.

The J_{HH} couplings between the CF_CH_W and CH_YH_Z group, J_{WY} and J_{WZ}, are −1.43 and 1.85 Hz. The dihedral angle dependence of vicinal J_{HH} is well known,[9]

(4) LAOCN3 by A. A. Bothner-By and S. Castellano, Quantum Chemistry Program Exchange, Indiana University, Bloomington, Ind.

(5) R. Freeman and W. A. Anderson, *J. Chem. Phys.*, **37**, 2053 (1962).

(6) E. L. Mackor and C. MacLean, *ibid.*, **44**, 65 (1966).

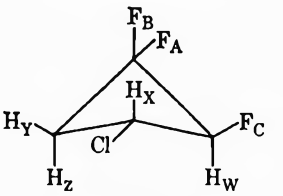
(7) D. F. Evans, S. L. Manatt, and D. D. Elleman, *J. Amer. Chem. Soc.*, **85**, 238 (1963).

(8) I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967).

(9) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1965); *J. Chem. Phys.*, **30**, 11 (1959).

TABLE I

NMR PARAMETERS FOR 1-CHLORO-2,3,3-TRIFLUOROCYCLOBUTANE[a]



Chemical shifts (ppm)	
Fluorine[b]	Hydrogen[c]
δ_A 93.72	δ_W 4.98
δ_B 124.64	δ_X 4.12
δ_C 188.76	δ_Y 2.97
	δ_Z 2.33

Coupling constants (Hz)		
J_{FF}	J_{HF}	J_{HH}
J_{AB} (*gem*) = 210.19	J_{AW} (27°) = 7.81	J_{WX} (136°) = 6.11
J_{AC} (81°) = 0.93	J_{AX} (ea) = 2.70	J_{WY} (ae) = −1.43
J_{BC} (27°) = −3.69	J_{AY} (81°) = 2.49	J_{WZ} (aa) = 1.85
	J_{AZ} (27°) = 9.16	J_{XY} (27°) = 9.70
	J_{BW} (136°) = 8.17	J_{XZ} (136°) = 9.00
	J_{BX} (aa) = 3.45	J_{YZ} (*gem*) = −14.25
	J_{BY} (27°) = 15.99	
	J_{BZ} (136°) = 20.02	
	J_{CW} (*gem*) = 50.95	
	J_{CX} (27°) = 14.70	
	J_{CY} (ee) = 11.58	
	J_{CZ} (ea) = −3.32	

[a] Approximate dihedral angles are given for the vicinal couplings (see discussion) assuming the puckering angle of the cyclobutane ring is 27°,[10] and the cross ring couplings are labelled according to their stereochemistry, axial (a) or equatorial (e). [b] Upfield from $CFCl_3$. [c] Downfield from tetramethylsilane.

and these values are not consistent with the dihedral angles of the two vicinal couplings, differing by about 109°. Thus, the nmr shows that CFH and CH_2 cannot be vicinal as in II.

Discussion

Comparison of the vicinal J_{HF} couplings between the CH_2 and CF_2 groups with those observed by Lambert and Roberts[10] in other cyclobutanes strongly suggests that the chlorine and adjacent fluorine are both *trans* and equatorial in the isomer of I formed in the reaction. Lambert and Roberts[10] showed that 1,1-difluoro-2,2-dichloro-3-deuterio-3-phenylcyclobutane (III) consists predominantly of one conformer with the phenyl group equatorial, whereas 1,1-difluoro-3-bromo-3-phenylcyclobutane (IV) approximately equal populations of equatorial and axial conformers. In the former case, they found that the vicinal couplings between the CH_2 and CF_2 groups were 1.75, 8.57, 12.59, and 20.52 Hz, which corresponded to dihedral angles of approximately 80, 27, 27, and 136°, respectively. In IV the vicinal J_{HF} values were 8.90, 10.60, 12.45, 12.52 Hz;[5] the couplings are all averaged to about 12 Hz owing to interconversion between the two possible conformers. We find in I that the vicinal couplings between the CF_2 and CH_2 groups are 2.49, 9.16, 15.99, and 20.02 Hz. Consequently, I probably exists predominantly in one conformer. Since vicinal J_{HF} values follow approximately the same dihedral angle dependence as vicinal J_{HH} values,[10,11] the 2.49 Hz coupling is assigned to that between the equatorial H_Y and equatorial F_A. We would expect from simple steric arguments that the chlorine and F_C are both equatorial. This prediction is substantiated by the absence of small vicinal couplings to the protons in the CH_XCl and CH_WF_C groups. If H_W were equatorial, then the vicinal coupling to the equatorial F_A should be smaller than the observed 7.81 Hz. Similarly, the vicinal coupling of H_X to the equatorial H_Y is 9.70 Hz. The above arguments enabled the assignment of the stereochemistry of all the couplings in I given in Table I. To the best of our knowledge, this is the first determination of the signs of the J_{HF} cross-ring couplings in a cyclobutane. The cross-ring J_{HF} equatorial–equatorial coupling is much larger than the axial–axial coupling (11.58 and 3.45 Hz, respectively). Nmr studies on several other substituted cyclobutanes are necessary before it is possible to generalize these results. The large variations in the vicinal J_{HF} couplings with electronegativity, C–C bond length, and H–C–C–F bond angle at constant dihedral angle observed by Williamson, *et al.*,[11] suggest that cross-ring couplings should also vary considerably with molecular structure.

The cross-ring J_{HH} values are consistent with other studies which have shown that *trans* cross-ring couplings are negative whereas *cis* cross ring couplings vary from −0.5 to 2.3 Hz.[8] We obtained −1.43 and 1.85, respectively. As expected from previous measurements of vicinal J_{HH} and J_{HF} in saturated systems, the signs of all these couplings are positive.[8,12] The results of Williamson, *et al.*[11], mentioned above show that the

(10) J. B. Lambert and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 3884, 3891 (1965).

(11) K. L. Williamson, Y. L. Hsu, F. H. Hall, S. Swager, and M. S. Coulter, *ibid.*, **90**, 6717 (1968).

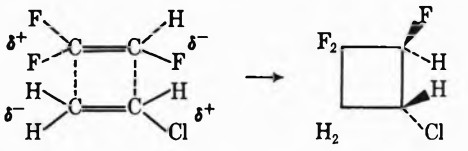
(12) L. D. Hall and J. F. Manville, *Chem. Ind.* (London), 468 (1967).

large variation of the 27° vicinal J_{HF} in the CH_2CF_2 group observed by us in I (9.16 and 15.77 Hz) and by Lambert and Roberts[10] in III (8.57 and 12.59 Hz) is probably due to small differences in C–C–F bond angles between axial and equatorial fluorines.

This is also the first determination of vicinal J_{FF} in a CF_2–CFH grouping in a cyclobutane ring. The opposite signs for the two vicinal couplings is expected from analogy to previous results for cyclobutenes and cyclobutanes.[13-15]

Conclusions

The interpretation of the nmr spectrum of 1-chloro-2,3,3-trifluorocyclobutane shows that the trifluoroethylene and vinyl chloride undergo a stereospecific 1,2 cycloaddition. Two explanations are possible for formation of only the *trans* isomer: (1) that it is an equilibrium reaction in which the most stable isomer predominates; (2) that it has an ionic rather than a diradical or a four-centered intermediate and that only the most electrostatically stable configuration of reactants leads to products.



Experimental Section

Infrared spectra were taken on a Perkin-Elmer Infracord. Nuclear magnetic resonance spectra were taken on a Varian HA-100 analytical spectrometer. Product analysis and fine scale preparations were carried out on an Aerograph Autoprep Model A-700, using a Texas Instruments Inc. Servariter model recorder. Refractive indices were taken on a Bausch & Lomb refractometer. Mass spectra were taken on a CEC 21 103C mass spectrometer equipped with an all glass heated (150°) inlet system. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn.

Codimerization of Trifluoroethylene with Vinyl Chloride.—Following the procedure of Park, Lacher, and Holler,[3] about 472 g of trifluoroethylene and 433 g of vinyl chloride were transferred into a sealed 1.5-l. autoclave containing 3 ml of *d*-limonene (added to prevent polymerization). The autoclave was heated to 230° for about 6 days. Upon cooling, 445 g of gaseous material and 284 g of a black liquid were obtained. Distillation of the liquid in a 3-ft glass helix packed column yielded 34.2 g (3.8% of theory) of 1-chloro-2,3,3-trifluorocyclobutane; bp 73–76° (627 mm); $n^{27}D$ 1.3683; d^{27} 1.3648. Molar refractivity: calcd, 23.76; found, 23.76.

Anal. Calcd for $C_4H_4ClF_3$: C, 33.24; H, 2.79; F, 39.44; Cl, 24.53. Found: C, 33.21; H, 2.77; F, 39.52; Cl, 24.73.

Tetramethylsilane and trichlorofluoromethane were added to the next liquid as internal reference lock signals for the nmr spectra. The sample was distilled *in vacuo* to remove oxygen.

Reaction of 1-Chloro-2,3,3-trifluorocyclobutane with Potassium Hydroxide.—Following the procedure of Park, Lacher, and Holler,[3] about 9.5 g of 1-chloro-2,3,3-trifluorocyclobutane was added dropwise over about 3 hr to a suspension of 18 g of potassium hydroxide suspended in 27 ml of heavy white mineral oil at room temperature in a 50-ml three-neck flask equipped with a stirrer and reflux condenser. After 44 hr, about 4.8 g (68% of theory) of a volatile product was obtained whose infrared spectrum was identical with that of known 2,3,3-trifluorocyclobutene. About 0.1 g each of *t*-butylpyrocatechol and diphenylamine was placed in the reaction flask and the gas trap to prevent polymerization of the cyclobutene. Catechol may be used in place of *t*-butylpyrocatechol.

Acknowledgments.—The authors wish to express their appreciation to the 3M Co., St. Paul, Minn., for their support of this work through a grant-in-aid.

Registry No.—Trifluoroethylene, 359-11-5; vinyl chloride, 75-01-4; 1-chloro-2,3,3-trifluorocyclobutane (*trans*), 20445-03-8.

(13) R. A. Newmark, *Chem. Commun.*, 1123 (1968).
(14) R. K. Harris and R. Ditchfield, *Spectrochim. Acta A*, **24**, 2089 (1968).
(15) R. E. Ernst, *Mol. Phys.*, in press.

Reactions of Dehydroacetic Acid and Related Pyrones with Secondary Amines

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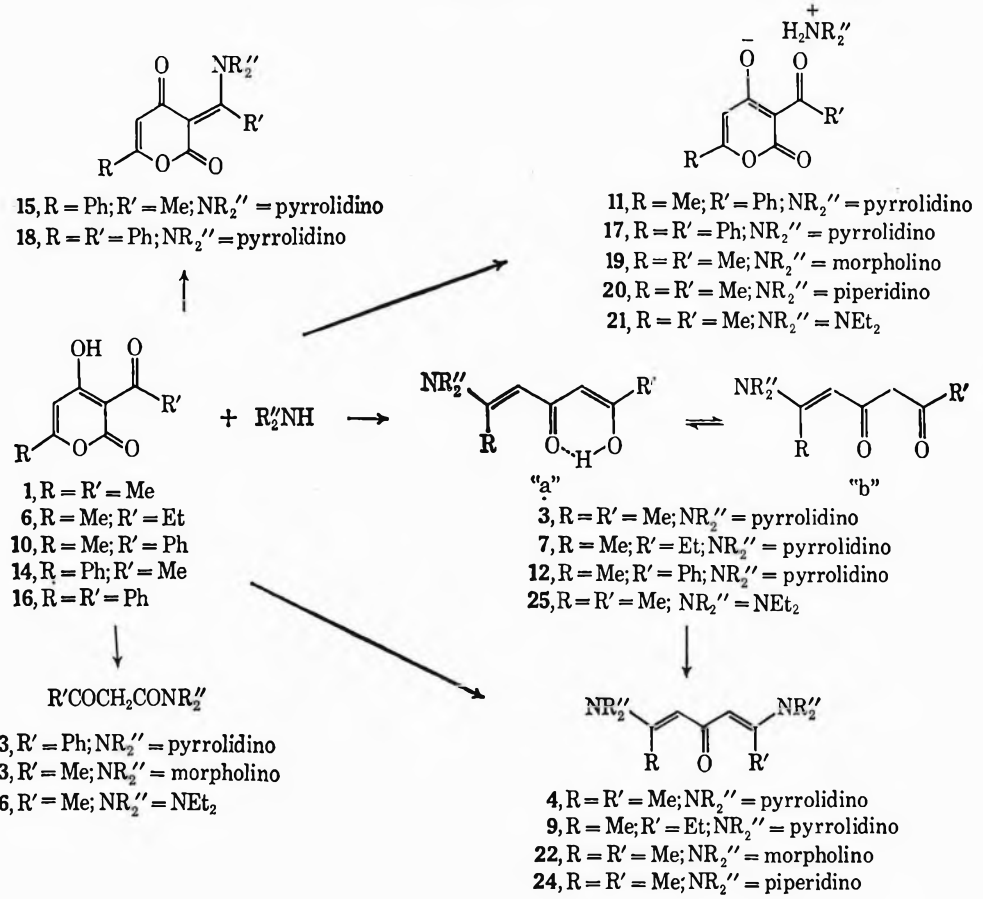
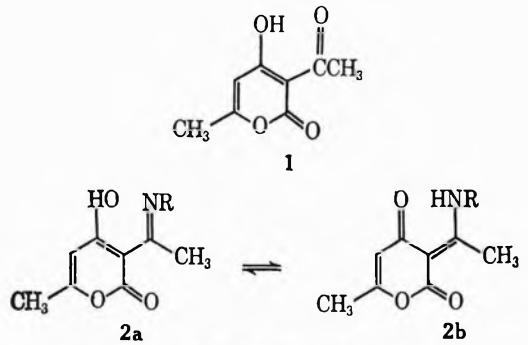
A study of the reactions of dehydroacetic acid (1) and related pyrones with secondary amines has been undertaken. Pyrrolidine reacts readily with dehydroacetic acid (1), 3-propionyl-4-hydroxy-6-methyl-2-pyrone (6), and 3-benzoyl-4-hydroxy-6-methyl-2-pyrone (10) to yield **3**, **7**, and **12**, the respective products of nucleophilic attack at the 6 position of the pyrone, followed by ring opening and decarboxylation; with 3-acetyl-4-hydroxy-6-phenyl-2-pyrone (14) and dehydrobenzoylacetic acid (16), it gives in each case the product of condensation at the carbonyl of the side chain. Reaction of enediones **3** and **7** with pyrrolidine gives the corresponding dienones **4** and **9** which could also be obtained directly from dehydroacetic acid (1) and 3-propionyl-4-hydroxy-6-methyl-2-pyrone (6) and excess pyrrolidine. Enedione **12**, however, gives **13**, the pyrrolidinamide of benzoylacetic acid, when treated with pyrrolidine. When morpholine and diethylamine are employed as amines, a more complex reaction produces in the case of dehydroacetic acid (1) not only enediones and dienones but also acetoacetamides formed by attack at the 2 position of the pyrone. Mechanisms for these various transformations are discussed.

A primary or secondary amine could conceivably attack dehydroacetic acid (1) at any of four possible sites: the carbonyl of the acetyl side chain at the 3 position, the carbon atom terminating the conjugated carbon chain at the 6 position, the lactone carbonyl at the 2 position, and the carbon atom at the 4 position (the carbon of a potential carbonyl group). Actually, primary aliphatic and aromatic amines were shown to react preferentially and exclusively with the carbonyl of the acetyl side chain at the 3 position to form the Schiff

SCHEME I



base **2a**, which probably exists in the tautomeric form **2b**.[1-6]



We recently undertook a study of the reactions of dehydroacetic acid (**1**) and related pyrones with various secondary amines. Of primary interest was whether attack at the carbonyl of the acetyl side chain at the 3 position is also a general reaction of secondary amines or whether secondary amines show a preference for reaction at one or more of the other reactive sites of this tetrafunctional molecule.

Dehydroacetic acid (**1**) reacted with 1 equiv of pyrrolidine in toluene at 50° to afford a crystalline compound with the empirical formula $C_{11}H_{17}NO_2$. This compound gave a strong enol test with ethanolic ferric chloride. Its infrared spectrum in KBr exhibited broad weak absorption in the 4-μ region and strong absorption at 6.1, 6.35, and 6.45 μ. The solution infrared spectrum in chloroform displayed an additional band at 5.85 μ. This evidence suggested that the compound had the tautomeric structure **3a** $\rightleftharpoons$ **3b** (Scheme I).[7] Furthermore, the absence of the band at 5.85 μ in the spectrum in KBr indicates that this compound, as a solid, exists entirely in the enol form **3a**. The 100-MHz nmr spectrum of a freshly prepared solution of **3a** $\rightleftharpoons$ **3b** in deuterated benzene showed four different methyl resonances occurring at δ 1.85, 2.15, 2.35, and 2.40 ppm and absorption for three different vinyl hydrogens at δ 4.58, 4.84, and 5.32 ppm. The singlets at 1.85 and 2.15 ppm are readily assigned to the enol and keto methyl groups of **3a** and **3b**, respectively,[8] and those at 2.35 and 2.40 ppm to the 1-methyl groups of **3b** and **3a**, respectively.

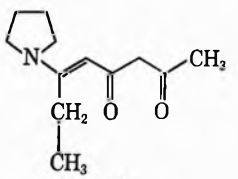
The vinyl resonances at 4.58 and 4.84 ppm can be assigned to the C-3 vinyl protons of **3a** and **3b**, respectively, the vinyl resonance at low field being due to the C-5 vinyl proton of **3a**. The two other signals in the spectrum at δ 3.43 and 17.62 ppm can be assigned to the 5-methylene group of **3b** and to the enol proton resonance of **3a**. Integrated peak areas are consistent with these assignments and indicate that enedione **3** exists to the extent of approximately 80% in the enol form

(1) S. Iguchi, K. Hisatsune, M. Himeno, and S. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **7**, 323 (1959).
(2) S. Garratt, *J. Org. Chem.*, **28**, 1886 (1963).
(3) D. Cook, *Can. J. Chem.*, **41**, 1435 (1963).
(4) J. D. Edwards, J. E. Page, and M. Pianka, *J. Chem. Soc.*, 5200 (1964).
(5) R. N. Schut, W. G. Strycker, and T. M. H. Liu, *J. Org. Chem.*, **28**, 3046 (1963).
(6) D. R. Gupta and R. S. Gupta, *J. Indian Chem. Soc.*, **42**, 421 (1965).
(7) Although, for simplicity, only one enolic form is shown, other tautomeric forms, although less likely, cannot be entirely excluded.
(8) *Cf.* the spectrum of acetylacetone. L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1959, p 70.

3a under these conditions. A spectrum of the same sample recorded 3 hr later showed a significant reduction in the enol content. Integrated peak area ratios indicated that the tautomeric mixture now contained 70% enol **3a**.

When enedione **3** was treated with an excess of pyrrolidine in refluxing toluene, it was converted into 2,6-bis-(N-pyrrolidino)hepta-2,5-dien-4-one (**4**) in 87% yield. Similarly, reaction of dehydroacetic acid (**1**) with an excess of pyrrolidine in refluxing benzene or toluene led directly to dienone **4** in 98% yield (Scheme I). Under these conditions, none of the intermediate enedione accumulated. The structure of dienone **4** was supported by infrared and nmr spectra and elemental analysis, and was confirmed by independent synthesis which involved reaction of 2,6-dimethyl-4-pyrone (**5**) with an excess of pyrrolidine in refluxing toluene.[9]

Two mechanisms for the conversion of dehydroacetic acid (**1**) to enedione **3** are worthy of consideration. The route preferred by us involves nucleophilic attack by pyrrolidine at the 6 position of the pyrone followed by opening of the pyrone ring and decarboxylation to yield enedione **3**.[10] The alternative pathway involves condensation of pyrrolidine with the carbonyl of the acetyl side chain at the 3 position. The pyrone ring would then be opened by nucleophilic attack of HO^- at the 6 position. Subsequent decarboxylation would yield enedione **3**. Evidence that the reaction of dehydroacetic acid (**1**) with pyrrolidine involved initial attack of pyrrolidine at the 6 position of the pyrone and not at the carbonyl of the acetyl side chain was obtained from a study of the reaction of 3-propionyl-4-hydroxy-6-methyl-2-pyrone (**6**) with pyrrolidine. In this case, reaction of pyrrolidine at the 6 position of the pyrone would give rise to enedione **7**, while initial reaction of pyrrolidine at the carbonyl of the propionyl side chain would lead to enedione **8**. Actually, 3-propionyl-4-hydroxy-6-methyl-2-pyrone (**6**) was found to react with an equivalent amount of pyrrolidine in toluene at 50° to form enedione **7** in 75% yield. That the product from this reaction was **7** and not enedione **8** follows from the nmr spectrum. The spectrum of a freshly prepared solution of enedione **7** in deuterated benzene showed the following features: two overlapping triplets centered at δ 1.00 and 1.08 ppm which can be assigned to the 8-methyl groups in **7b** and **7a**, respectively;[11] two quartets centered at δ 2.17 and 2.53 ppm produced by the 7-methylene groups in **7a** and **7b**; two singlets at δ 2.38 and 2.44 ppm caused by the 1-methyl groups of **7b** and **7a**; a singlet at 3.42 ppm which can be assigned to the 5-methylene group of keto form **7b**; three singlets at δ 4.63, 4.86, and 5.34 ppm produced by the C-3 vinyl protons of **7a** and **7b** and the C-5 vinyl proton of **7a**; and a broad resonance signal at δ 17.55 ppm caused by the hydroxyl group of enol **7a**. Integrated peak areas support these assignments and indicate that enedione **7** consists of a mixture of 84% **7a** and 16% **7b** under the conditions in which the spectrum was recorded. Significant in the spectrum was the absence of methyl resonance lines in the region of 1.85–2.15 ppm. Enedione **3**, on the other hand, showed keto and enol methyl resonance lines at 2.15 and 1.85 ppm, respectively, and we would expect the keto and enol methyl of enedione **8** and its enol to resonate at similar chemical shifts. The absence of methyl resonance lines in the region of 1.85–2.15 ppm of the spectrum clearly excludes structure **8**; it establishes unequivocally that in the reaction of pyrrolidine with **6** and by analogy with **1** initial attack of pyrrolidine occurs at the 6 position of the pyrone.



8

Enedione **7** was readily transformed into dienone **9** by heating with an excess of pyrrolidine in toluene. Dienone **9** could also be obtained directly, in 63% yield, by treating pyrone **6** with an excess of pyrrolidine in refluxing toluene. The structural assignment of **9** was supported by elemental analysis and infrared and nmr spectra.

The reaction of 3-benzoyl-4-hydroxy-6-methyl-2-pyrone (**10**) (Scheme I) with pyrrolidine was also investigated. Treatment of pyrone **10** with 1 equiv of pyrrolidine in toluene at 50° afforded the salt **11** in 96% yield.

Reaction of **10** with an excess of pyrrolidine in refluxing toluene produced enedione **12** in 73% yield. The nmr spectrum of a freshly prepared solution of **12** in deuterated benzene indicated that **12** consisted of a mixture containing 85% enol tautomer **12a** and 15% keto tautomer **12b**. A spectrum of the same solution recorded 3 hr later showed no change in the composition of the tautomeric mixture.

When enedione **12** was treated with an excess of pyrrolidine in refluxing toluene, it was partially converted into **13**. The structure of **13** follows from its infrared and nmr spectra and elemental analysis. The nmr spectrum indicated that **13** consisted of a 1:1 keto–enol mixture in deuteriochloroform solution.

Next, the reaction of pyrrolidine with several 3-acyl-4-hydroxy-6-phenyl-2-pyrones was examined. Treatment of 3-acetyl-4-hydroxy-6-phenyl-2-pyrone (**14**) (Scheme I) with an equivalent amount of pyrrolidine in toluene at 50–60° yielded a crystalline compound, $C_{17}H_{17}NO_3$, indicating a 1:1 condensation with loss of one molecule of water. The ultraviolet spectrum was similar to that of pyrone **14** [λ_{max}^{MeOH} 220 mμ (log ϵ 4.18) and 354 (4.19)]. The infrared spectrum displayed strong bands at 5.9, 6.1, 6.32, 6.4, and 6.66 μ, and the compound was readily converted back into pyrone **14** in dilute hydrochloric acid. On the basis of this evidence, structure **15** was assigned to the product. The structure of **15** was further supported by the nmr spectrum in which the vinylic CH produced a signal at 6.36 ppm and the methyl group gave a singlet at 2.65 ppm.

Reaction of dehydrobenzoylacetic acid (**16**) with 1 equiv of pyrrolidine under similar conditions afforded pyrrolidinium dehydrobenzoylacetate (**17**) in 98% yield. When the condensation of **16** with pyrrolidine

(9) 2,6-Bis(N-pyrrolidino)hepta-2,5-dien-4-one has also been prepared in these laboratories from 2,4,6-heptanetrione and pyrrolidine by R. A. Langdale-Smith and D. T. Manning, unpublished work.

(10) Cleavage of 2-pyrones at the 6 position has been observed with cyanide ion and with complex metal hydrides under certain conditions: G. Vogel, *Chem. Ind.* (London), 268, 1829 (1962); *J. Org. Chem.*, **30**, 203 (1965).

(11) The nmr signal for the enol methyl in the related 3,5-heptanedione is also found at lower field than the signal for the keto methyl (see Experimental Section).

was carried out in refluxing toluene with an excess of pyrrolidine, a mixture of **17** and **18** was obtained. The yields were 60 and 11%, respectively. The structure of **18** follows from elemental analysis, ultraviolet, infrared and nmr spectra and hydrolysis back to dehydrobenzoylacetic acid (**16**) in dilute hydrochloric acid. We found that it was possible to convert the highly insoluble **17** into **18** by refluxing **17** in ethanol or 2-propanol.

Finally, the reactions of dehydroacetic acid (**1**) with morpholine, piperidine, and diethylamine were investigated. In contrast to the reaction of **1** with 1 equiv of pyrrolidine in toluene at 50°, which led to enedione **3**, treatment of **1** with an equivalent amount of either morpholine, piperidine or diethylamine under similar conditions gave the corresponding salts **19**–**21** (Scheme I).

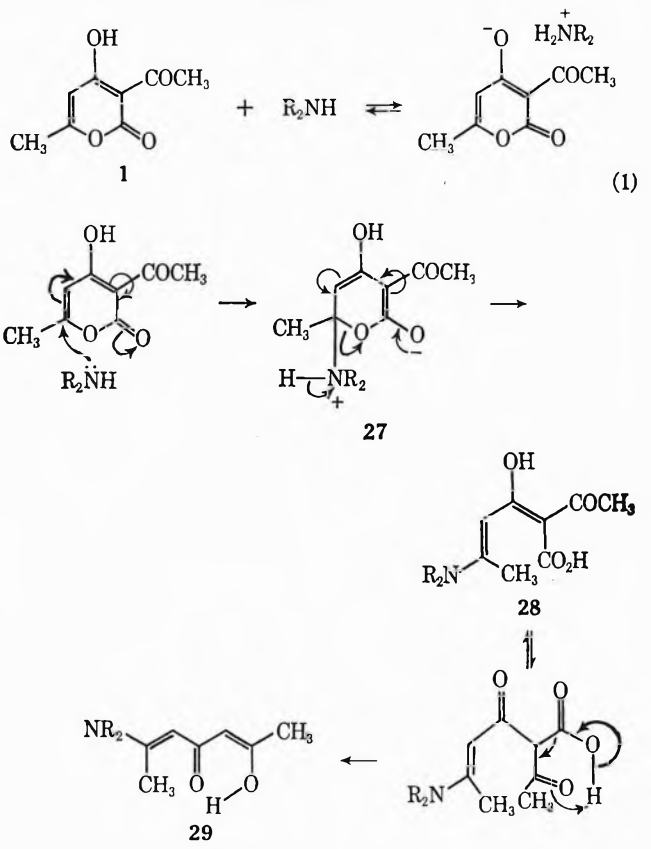
When dehydroacetic acid (**1**) was treated with an excess of morpholine in refluxing benzene, a mixture of dienone **22** and 4-acetoacetylmorpholine (**23**) was obtained. The yields were 26 and 33%, respectively. The structural assignments of **22** and **23** were substantiated by infrared and nmr spectra and elemental analysis. The structure of **23** was further confirmed by comparison of its infrared spectrum and a mixture-melting-point determination with an authentic specimen of **23** prepared by acetoacetylating morpholine with diketene.

Reaction of **1** with an excess of piperidine in benzene at 60° led to a mixture from which the only pure product isolated was 2,6-bis(N-piperidino)hepta-2,5-dien-4-one (**24**) (Scheme I). Considerable difficulty was experienced in isolating **24** owing to its apparent instability in the crude state. Treatment of **1** with an excess of the more hindered diethylamine in refluxing benzene furnished diethylammonium dehydroacetate (**21**) in 48% yield and an oil which could not be induced to crystallize. The nmr spectrum of the crude oil was examined prior to distillation and indicated that it consisted essentially of the tautomeric mixture **25a** $\rightleftharpoons$ **25b**. Distillation of the oil, however, resulted in the separation of a third compound identified as **26** by comparison of its infrared and nmr spectra with those of an authentic sample of **26** prepared from ethyl acetoacetate and diethylamine by the method of Utzinger[12] (Scheme I). Enedione **25** decomposed during attempted distillation and purification has not been possible.

Several examples of the reactions of both 3-acyl-4-hydroxy-6-methyl-2-pyrones and 3-acyl-4-hydroxy-6-phenyl-2-pyrones with pyrrolidine have been presented in this paper. In addition, the reactions of dehydroacetic acid (**1**) with morpholine, piperidine, and diethylamine have been described. Four different modes of attack were possible in each case. The products isolated from the reactions of the 3-acyl-4-hydroxy-6-methyl-2-pyrones **1**, **6**, and **10** with pyrrolidine were the result of initial attack of pyrrolidine at only the 6 position of the pyrone, while the products isolated from the reactions of the 3-acyl-4-hydroxy-6-phenyl-2-pyrones **14** and **16** with pyrrolidine were the result of attack at the carbonyl of the acyl side chain in the 3 position. On the other hand, the products isolated from the reactions of dehydroacetic acid (**1**) with morpholine and diethylamine were the result of attack of amine at the 6 and the 2 or 4 positions.

The first step in the reactions of dehydroacetic acid and related acylpyrones with secondary amines appears to be a simple acid–base reaction which results in salt formation (eq 1) (Scheme II). The solubility of these

SCHEME II



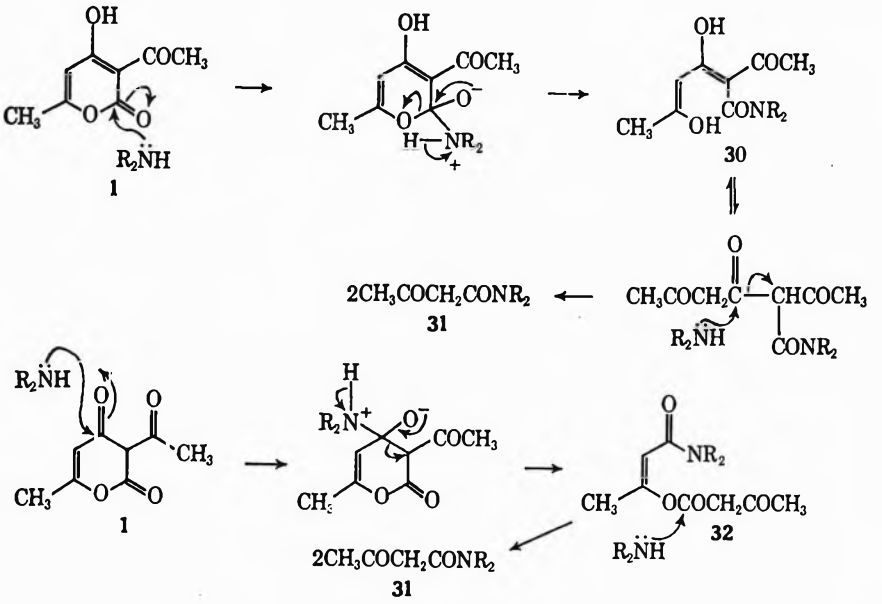
salts plays an important role in the reactions of acylpyrones with 1 equiv of amine. The low solubility of morpholinium, piperidinium and diethylammonium dehydroacetate, pyrrolidinium dehydrobenzoylacetate, and the pyrrolidinium salt of pyrone **10** results in the precipitation of these salts from solution and in effect protects the pyrone nucleus from attack. On the other hand, when the acylpyrones **1** and **6** are treated with an equivalent amount of pyrrolidine, no salt precipitation occurs and reaction proceeds presumably by dissociation of the salt into acylpyrone and free amine which then attacks the pyrone nucleus. Salt solubility becomes unimportant in reactions with excess amine since it has been observed experimentally that acylpyrone–amine salts are readily soluble in a benzene– or toluene–amine medium.

The mechanism for opening of the pyrone ring at the 6 position undoubtedly involves nucleophilic attack by the amine on the carbon atom at the 6 position to afford as an intermediate the resonance-stabilized carbanion **27**. Subsequently, **27** breaks down with expulsion of the carboxylate group to give the rather unstable β-keto acid **28**, which then undergoes facile decarboxylation to give the enol **29**.

A plausible mechanism for the formation of amides of acetoacetic acid from the reactions of dehydroacetic acid with secondary amines involves nucleophilic attack by the amine on the carbon of the lactone carbonyl at the 2 position to give the amide of α,γ-diacetylacetoacetic acid (**30**) (Scheme III). **30** is then cleaved by reaction with amine at the carbon of the β-carbonyl to afford the observed amide of acetoacetic acid (**31**).

(12) G. E. Utzinger, *Helv. Chim. Acta*, **35**, 1359 (1952).

SCHEME III

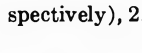
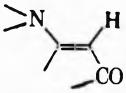


An alternative mechanism involves nucleophilic attack by pyrrolidine on the carbon atom at the 4 position to form **32**. Attack of amine at the ester carbonyl would then give the observed amide of acetoacetic acid (**31**).

The lack of reactivity of the carbonyl of the side chain in dehydroacetic acid (**1**) toward pyrrolidine is totally unexpected and could not have been predicted *a priori* in view of the affinity shown by this group for reaction with primary amines.[1-6] On the other hand, the analog **14**, which carries a phenyl substituent in the 6 position, reacts preferentially at the carbonyl of the acetyl side chain and not at the 6 position. Presumably, the steric effect of the 6-phenyl substituent in **14** is responsible for the decreased reactivity of the 6 position in **14** in comparison with **1**. The same argument applies to the reaction of dehydrobenzoylacetic acid (**16**) with pyrrolidine leading to **18**, where attack occurs preferentially at the carbonyl of the benzoyl side chain owing to the unfavorable steric situation at the 6 position.

Experimental Section

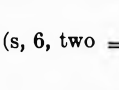
All melting points are uncorrected and were taken with a Mel-Temp capillary melting point apparatus. Infrared spectra were determined with either Baird-Atomic Models AB-2 and 4-55 or Perkin-Elmer Model 21 spectrophotometers using potassium bromide pellets of the compounds. The nmr spectra were determined at either 60 or 100 MHz with Varian Associates A-60 and HA-100 spectrometers. Chemical shifts are expressed in parts per million (ppm) downfield from an internal tetramethylsilane standard. Nmr peak multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), qr (quartet), and m (multiplet). The ultraviolet spectra were obtained with a Cary recording spectrophotometer, Model 14. The microanalyses were performed by Union Carbide Corp. Analytical Department, South Charleston, W. Va. Dehydroacetic acid (**1**) was the commercial product of Union Carbide Corp. 3-Benzoyl-4-hydroxy-6-methyl-2-pyrone (**10**), mp 108–110°, was prepared from 4-benzoyloxy-6-methyl-2-pyrone by Fries rearrangement with aluminum chloride. 3-Acetyl-4-hydroxy-6-phenyl-2-pyrone (**14**), mp 169–171°, was obtained by acetylating 6-phenyl-4-hydroxy-2-pyrone with acetic anhydride in the presence of sulfuric acid. Dehydrobenzoylacetic acid (**16**) was prepared from ethyl benzoylacetate by the method of Arndt.[13] The preparation of pyrones **10** and **14** has been described elsewhere.[14]

Reaction of Dehydroacetic Acid (1) with One Equivalent of Pyrrolidine.—Pyrrolidine (18 g, 0.25 mol) was added dropwise during 20 min to a stirred solution of dehydroacetic acid (42 g, 0.25 mol) in 100 ml of toluene at 50°. The reaction was mildly exothermic and the temperature rose to 55°. After the addition was complete the mixture was allowed to stand at room temperature for 40 hr. The precipitated solid (27.2 g, mp 103–106°) was collected by filtration and crystallized from benzene–cyclohexane mixture to give 20.4 g of enedione **3**, mp 110–112°. The toluene mother liquor was evaporated to dryness under reduced pressure, and the resulting semisolid residue was triturated with ether. The solid (14.8 g, mp 82–89°) which separated was collected and crystallized from benzene–cyclohexane mixture to give a second crop of **3** (11.5 g, mp 109–110°). The yield of combined recrystallized enedione **3** (31.9 g) was 65.5%. An additional crystallization from benzene–cyclohexane mixture furnished an analytical sample, mp 110–112°. Enedione **3** gave an intense green color with ethanolic ferric chloride: ir (KBr) 3.38 (CH_3 and CH_2), 3.54 (NCH_2), 4 (weak, broad, chelated OH), 6.1 (strong, C=C), 6.35 and 6.45 (very strong, chelated conjugated C=O and C=C), 7.27 (CCH_3), 7.52, 8.75, 9.70 and 12.37 μ (RR'C=CHR''). The solution ir ($CHCl_3$) shows an additional band at 5.85 μ (C=O); nmr (benzene-d_6) δ 1.05–1.35 (m, 4, CH_2CH_2), 1.85 and 2.15 (two s, 3, =C(OH)CH_3 and -$COCH_3$, respectively), 2.35 and 2.40 (two s, 3, ), 2.50–2.80 (m, 4, CH_2NCH_2), 3.43 (s, 0.4, $COCH_2CO$), 4.58 and 4.84 (two s, 1, ), 5.32 (s, 0.8, -CH=C(OH)-), and 17.62 (broad s, 0.8, intramolecularly chelated OH).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.93; H, 9.04; N, 7.27.

Reaction of Enedione 3 with Pyrrolidine.—A stirred mixture of enedione **3** (19.5 g, 0.1 mol) and pyrrolidine (14.2 g, 0.2 mol) in 90 ml of toluene was heated under reflux for 2 hr, water being removed with a Dean–Stark trap. Filtration of the cold solution afforded 21.5 g (87%) of 2,6-bis(N-pyrrolidino)hepta-2,5-dien-4-one (**4**), mp 205–210° dec. An analytical sample recrystallized from methanol had mp 210–215° dec; ir (KBr) 3.2 (=CH), 3.35 (CH_3 and CH_2), 3.48 (NCH_2), 6.16 (C=C), 6.55 (strong, conjugated C=O and C=C), 6.75, 6.84 (C=C), 7.06, 7.5,

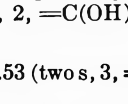
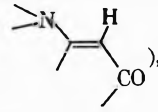
(13) F. Arndt, B. Eistert, H. Scholz, and E. Aron, *Ber.*, **69**, 2373 (1936).
(14) E. Marcus, J. F. Stephen, and J. K. Chan, *J. Heterocycl. Chem.*, **6**, 13 (1969).

9.1, 9.7, 10.85, 10.94 and 12.37 μ; nmr ($CDCl_3$) δ 1.90 (m, 8, two CH_2CH_2), 2.54 (s, 6, two ), 3.28 (m, 8, two CH_2NCH_2) and 4.91 (s, 2, =CHCOCH=).

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.59; H, 9.88; N, 11.12.

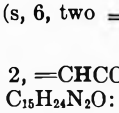
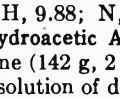
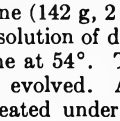
Reaction of Dehydroacetic Acid (1) with an Excess of Pyrrolidine.—Pyrrolidine (142 g, 2 mol) was added dropwise during 20 min to a stirred solution of dehydroacetic acid (84 g, 0.5 mol) in 300 ml of benzene at 54°. The temperature rose to 72° and carbon dioxide was evolved. After the addition was complete the mixture was heated under reflux for 2 hr. After cooling 115.9 g of dienone **4**, mp 211–215° dec, was collected. Concentration of the benzene filtrate furnished a second crop of 4.6 g, mp 209–215° dec. The yield was 97%. A sample of the above dienone showed no depression in melting point on admixture with a sample of dienone **4** obtained from the reaction of enedione **3** with pyrrolidine.

2,6-Bis(N-pyrrolidino)hepta-2,5-dien-4-one (4) from 2,6-Dimethyl-4-pyrone (5).—A mixture of 2,6-dimethyl-4-pyrone (31 g, 0.25 mol), pyrrolidine (71 g, 1 mol), and 100 ml of toluene was stirred and refluxed under a water separator for 25 hr. Filtration of the cold mixture gave 31.4 g (51%) of **4**, mp 200–208° dec. A single crystallization from methanol furnished 25 g of pure **4**, mp 211–215° dec.

Reaction of 3-Propionyl-4-hydroxy-6-methyl-2-pyrone (6) with One Equivalent of Pyrrolidine.—A stirred solution of pyrone **6** (18.2 g, 0.1 mol) in 60 ml of toluene at 50° was treated dropwise during 15 min with pyrrolidine (7.2 g, 0.1 mol). After the addition was complete the mixture was allowed to stand overnight at ambient temperature. The toluene was evaporated under reduced pressure, and the solid residue of 21.8 g was dissolved in 300 ml of ether. Concentration of the ether solution *in vacuo* furnished 12.6 g of enedione **7**, mp 64–70°. Further concentration of the ether afforded a second crop of 2.9 g, mp 55–62°. The yield of the combined crops (15.5 g) was 74%. Two crystallizations from ether at 0° gave an analytical sample, mp 82–86°. Enedione **7** gave an intense green color with ethanolic ferric chloride: ir (KBr) 3.4 (CH_3 and CH_2), 3.53 (NCH_2), 4 (weak, broad, chelated OH), 6.15 (C=C), 6.5 (very strong, broad, chelated conjugated C=O and C=C), 7.06, 7.5, 8.25, 8.75, 9.3, 9.9, 10.65 and 12.2 μ (RR'C=CHR''). The solution ir spectrum ($CHCl_3$) shows an additional band at 5.85 μ (C=O); nmr (benzene-d_6) δ overlapping 1.00 (t) and 1.08 (t) (3, $COCH_2CH_3$ and $=C(OH)CH_2CH_3$, respectively), 1.25–1.50 (m, 4, CH_2CH_2), 2.17 and 2.53 (two qr, 2, $=C(OH)CH_2CH_3$ and $COCH_2CH_3$, respectively), 2.38 and 2.53 (two s, 3, ), overlapping qr at 2.53, ~2.65–2.90 (m, 4, CH_2NCH_2), 3.42 (s, 0.32, $COCH_2CO$), 4.63 and 4.86 (two s, 1, ), 5.34 (s, 0.84, -CH=C(OH)-), and 17.55 (broad s, 0.84, intramolecularly chelated OH).

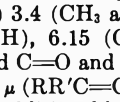
Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.60; H, 9.50; N, 6.74.

3,5-Heptanedione.—3,5-Heptanedione was prepared from ethyl propionate and methyl ethyl ketone in the presence of sodamide as described by Hauser:[15] nmr (benzene-d_6) δ overlapping 0.89 (t) and 0.97 (t) (6, $COCH_2CH_3$ and $=C(OH)CH_2CH_3$, respectively), overlapping 2.08 (qr) and 2.18 (qr) (4, $=C(OH)$-CH_2CH_3 and $COCH_2CH_3$, respectively), 3.16 (s, 0.3 $COCH_2CO$), 5.26 (s, 0.85, -CH=C(OH)-), and 15.7 (broad s, 0.85, intramolecularly chelated OH).

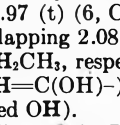
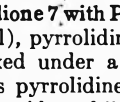
Reaction of Enedione 7 with Pyrrolidine.—A mixture of enedione **7** (5.2 g, 0.025 mol), pyrrolidine (3.5 g, 0.05 mol), and 25 ml of toluene was refluxed under a water separator for 1 hr. The toluene and excess pyrrolidine were evaporated under reduced pressure, and the residue of 7.5 g was crystallized from toluene to give 3.5 g (49%) of 2,6-bis(N-pyrrolidino)octa-2,5-dien-4-one (**9**), mp 154–156°. An analytical sample recrystallized from toluene had mp 154–156°; ir (KBr) 3.25 (=CH), 3.4 (CH_3 and CH_2), 3.53 ($N-CH_2$), 6.16 (C=C), 6.53 (strong, broad, conjugated C=O and C=C), 6.75, 6.85, 7.05, 7.45, 8.9, 9.03, 9.7, 10.75 and 12.45 μ; nmr ($CDCl_3$) δ 1.19 (t, 3, CH_2CH_3), 1.90 (m, 8, two CH_2CH_2), 2.51 (s, 3, ), overlapping 3.10 (qr) and 3.17–3.50 (m) (10,  and two CH_2NCH_2), 4.85 (s, 1, ) and 4.93 (s, 1,).

Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68. Found: C, 72.85; H, 10.04; N, 10.72.

Reaction of 3-Propionyl-4-hydroxy-6-methyl-2-pyrone (6) with an Excess of Pyrrolidine.—A solution of pyrone **6** (9.1 g, 0.05 mol) in 30 ml of toluene was treated with pyrrolidine (14.2 g, 0.2 mol), and the mixture was refluxed under a water separator. After 2 hr the solution was cooled and the crystals of 2,6-bis(N-pyrrolidino)octa-2,5-dien-4-one (8.3 g, 63%), mp 151–153°, which formed were collected. Recrystallization from toluene gave 6.2 g of dienone **9**, mp 154–156°. A mixture melting point with a sample of **9** prepared from enedione **7** and pyrrolidine was not depressed.

Reaction of 3-Benzoyl-4-hydroxy-6-methyl-2-pyrone (10) with One Equivalent of Pyrrolidine.—Pyrrolidine (3.55 g, 0.05 mol) was added dropwise during 15 min to a stirred solution of **10** (11.5 g, 0.05 mol) in 50 ml of toluene at 50°. The temperature rose to 56° and the salt precipitated from solution. After the addition was complete the mixture was stirred at room temperature for 2 hr. The precipitated salt (14.4 g, 96%), mp 155–156°, was filtered off and washed with toluene. An analytical sample recrystallized from ethanol had mp 155–156°; ir (KBr) 3.35, 3.6, 3.75, 3.85, 4.05 (NH_2^+), 5.95 (strong, lactone C=O), 6.90 (strong, conjugated C=O), 6.26, 6.37, 6.55 (C=C and NH_2^+), 7.25 (CCH_3), 12.88, 13.81 and 14.12 μ (CH, monosubstituted phenyl); nmr (D_2O with acetone as internal standard) δ 1.70–2.00 (m, 4, CH_2CH_2), 2.13 (d, 3, ), 3.00–3.25 (m, 4, CH_2NCH_2), 5.77 (d, 1,) and 7.25–7.80 (m, 5, C_6H_5).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.59; H, 6.30; N, 4.58.

Reaction of 3-Benzoyl-4-hydroxy-6-methyl-2-pyrone (10) with an Excess of Pyrrolidine.—A stirred solution of pyrone **10** (11.5 g, 0.05 mol) in 50 ml of toluene at 50° was treated dropwise during 14 min with pyrrolidine (14.2 g, 0.2 mol). After the addition was complete the mixture was stirred and refluxed for 10 min. The toluene and excess pyrrolidine were removed *in vacuo* to give a yellow solid which was washed with 100 ml of ether and filtered to give 11.9 g of material, mp 135–137°. Crystallization of this solid from benzene–cyclohexane mixture afforded 9.4 g (73%) of enedione **12**: mp 140–142°; ir (KBr) 3.28 (=CH), 3.35 (CH_3), 3.48 (NCH_2), 4.0 (weak, broad, chelated OH), 6.45 (broad, strong, chelated conjugated C=O and C=C), 6.68 (aromatic C=C), 7.22 (CCH_3), 8.53, 8.73 (CN), 12.25, 12.73 (RR'C=CHR''), 13.15 and 14.4 μ (CH, monosubstituted phenyl). The solution ir spectrum ($CHCl_3$) shows additional bands at 5.95 (C=O) and 6.15 μ (C=C); nmr (benzene-d_6) δ 1.05–1.30 (m, 4, CH_2CH_2), 2.27 and 2.42 (two s, 3, ), 2.50–2.76 (m, 4, CH_2NCH_2), 4.06 (s, 0.3, $COCH_2CO$), 4.76 and 5.09 (two s, 1, ), 6.14 (s, 0.85, -CH=C(OH)-), 7.19 (broad s) and 7.80–8.10 (m, 5, C_6H_5) and 18.4 (broad s, 0.85, intramolecularly chelated OH).

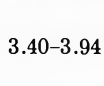
Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.89; H, 7.45; N, 5.40.

Reaction of Enedione 12 with Pyrrolidine.—A mixture of enedione **12** (8.6 g, 0.3 mol) and pyrrolidine (4.73 g, 0.06 mol) in

(15) J. T. Adams and C. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1220 (1944).

50 ml of toluene was refluxed under a water separator for 2 hr. The toluene and excess pyrrolidine were removed under reduced pressure, and the resulting oil was dissolved in 100 ml of ether. On standing for several hours at 0° the solution deposited 4.2 g of unchanged enedione **12**, mp 136–138°, which was collected by filtration. The ether filtrate was evaporated to dryness *in vacuo* to give 4.5 g of an oil. This oil was dissolved in the minimum amount of ether required for solution and the solution stored at −78° overnight. The solid of 2 g, mp 44–54°, which separated was collected. The nmr spectrum of this material indicated that it was a mixture which contained 6 mol % of enedione **12** and 94 mol % of the pyrrolidinamide of benzoylacetic acid (**13**). Recrystallization from ether at 0° afforded pure **13**: 1.6 g (22%); mp 63–66°; ir (liquid film) 3.27 (aromatic CH), 3.37 (CH_2), 3.47 (NCH_2), 3.7–4.6 (weak, broad, chelated OH), 5.92 (benzoyl C=O), 6.15 (amide C=O and aromatic C=C), 6.77 (CH_2 and aromatic C=C), 7.35 (CN), 13.1 and 14.55 μ (CH, monosubstituted phenyl); nmr ($CDCl_3$) δ 1.64–2.12 (m, 4, CH_2CH_2), 3.10–3.70 (m, 4, CH_2NCH_2), 4.0 (s, 1, $COCH_2CO$), 5.62 (s, 0.5, -CH=C(OH)-), 7.15–7.57, 7.62–7.83 and 7.90–8.05 (m, 5, C_6H_5) and 15.28 (s, 0.5, intramolecularly chelated OH).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.89; H, 7.09; N, 6.42.

Reaction of 3-Acetyl-4-hydroxy-6-phenyl-2-pyrone (14) with One Equivalent of Pyrrolidine.—Pyrrolidine (3.55 g, 0.05 mol) was added dropwise during 10 min to a stirred solution of pyrone **14** (11.5 g, 0.05 mol) in 120 ml of toluene at 50°. After the addition was complete the mixture was heated at 50–60° for 4 hr. Most of the toluene was evaporated under reduced pressure and cyclohexane was added to the residue. On standing the solution deposited 13.9 g of solid, mp 90–103°. Recrystallization from benzene–cyclohexane mixture furnished 10.2 g of **15**, mp 101–105°. A sample dried overnight at 60° *in vacuo* had mp 152–156°; $\lambda_{max}^{CH_3OH}$ 220 mμ (log ϵ 4.18) and 354 (4.19); ir (KBr) 3.25 (=CH), 3.34 (CH_3 and CH_2), 3.45 (NCH_2), 5.9 (strong, lactone C=O), 6.1 (conjugated C=O), 6.32, 6.4, 6.66 (C=C), 7.15, 7.26 (CCH_3), 8.17 (lactone COC), 13.0 (RR'C=CHR''), 14.1 and 14.5 μ (CH, monosubstituted phenyl); nmr ($CDCl_3$) δ 2.05 (t, 4, CH_2CH_2), 2.65 (s, 3, ), 3.40–3.94 (m, 4, CH_2NCH_2), 6.36 (s, 1, ), 7.20–7.56 and 7.68–7.93 (m, 5, C_6H_5).

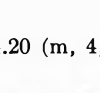
Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 73.64; H, 6.18; N, 4.33.

Treatment of **15** with picric acid in ethanol gave the picrate, mp 214–216° dec.

Anal. Calcd for $C_{23}H_{20}N_4O_{10}$: C, 53.91; H, 3.93; N, 10.93. Found: C, 53.79; H, 4.00; N, 10.66.

Reaction of Dehydrobenzoylacetic Acid (16) with One Equivalent of Pyrrolidine.—A stirred suspension of **16** (14.6 g, 0.05 mol) in 100 ml of toluene at 50° was treated dropwise during 19 min with pyrrolidine (3.55 g, 0.05 mol). After the addition was completed the mixture was heated at 50–60° for 2 hr. The precipitated **17**, 17.7 g (98%), mp 160–161°, was collected by filtration. An analytical sample recrystallized from ethanol had mp 164–166°; ir (KBr) 3.32, 3.63 (NH_2^+), 6.0 (conjugated lactone C=O), 6.1 (conjugated C=O), 6.21 (C=C), 6.3, 6.68 (aromatic C=C), 6.55, 7.88 (lactone COC), 12.36 (RR'C=CHR''), 12.95, 13.99 and 14.8 μ (CH, monosubstituted phenyl); nmr ($CDCl_3$) δ 1.55–2.00 (m, 4, CH_2CH_2), 2.78–3.10 (m, 4, CH_2NCH_2), 6.44 (s, 1, ) and 7.20–8.15 (m, 12, NH_2^+ and two C_6H_5).

Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.40; H, 5.84; N, 3.88.

Reaction of Dehydrobenzoylacetic Acid (16) with an Excess of Pyrrolidine.—A stirred solution of dehydrobenzoylacetic acid (14.6 g, 0.05 mol) in 100 ml of boiling toluene was treated with pyrrolidine (14.2 g, 0.2 mol). The mixture was then stirred and refluxed for 5 min. The solid of 9.3 g, mp 163–165°, which had separated was collected by filtration. The toluene mother liquor was concentrated *in vacuo* to about 50 ml when a second crop of 1.5 g, mp 163–165°, precipitated from solution. A mixture melting point with authentic pyrrolidinium dehydrobenzoylacetate was not depressed. The yield was 59.5%. The toluene solution was evaporated to dryness, and the residue thus obtained was recrystallized from benzene to give 1.9 g (11%) of **18**, mp 196–199° dec. A second crystallization from benzene afforded an analytical sample: mp 200–202° dec; $\lambda_{max}^{CH_3OH}$ 275 mμ (log ϵ = 3.93) and 358 (3.89); ir (KBr) 3.25 (=CH), 3.36 (CH_2), 3.46 (NCH_2), 5.95 (strong, conjugated lactone C=O), 6.12 (strong, C=C and conjugated C=O), 6.31 6.39 (C=CN), 8.10 (lactone COC), 12.97, 13.20, 14.15 and 14.5 μ (CH, monosubstituted phenyl); nmr ($CDCl_3$) δ 1.73–2.28 (m, 4, CH_2CH_2), 3.50–4.20 (m, 4, CH_2NCH_2), 6.30 (s, 1, ), 7.18–7.53 and 7.62–7.85 (m, 10, two C_6H_5).

Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.55; N, 4.06. Found: C, 76.35; H, 5.35; N, 4.00.

Conversion of 17 into 18.—A solution of **17** (34.8 g, 0.096 mol) in 300 ml of 2-propanol was heated under reflux for 25 hr. The 2-propanol was removed under reduced pressure, and the residue was extracted with 250 ml of boiling benzene. The insoluble solid of 18.3 g, mp 172–184° dec (a mixture of **17** and **18**), was collected by filtration. Evaporation of the filtrate afforded 12.4 g of **18**, mp 196–198° dec.

Morpholinium Dehydroacetate (19).—A stirred solution of dehydroacetic acid (21 g, 0.125 mol) in 75 ml of toluene at 53° was treated during 10 min with morpholine (11.5 g, 0.125 mol). The temperature rose to 65°; after the addition was complete the mixture was stirred at room temperature for 2 hr. The precipitated solid 30.7 g (96%), mp 114–115° dec, was filtered off. An analytical sample recrystallized from ethyl acetate had mp 114–115° dec; ir (KBr) 3.45–3.75 and 4.0–4.2 (strong, broad, NH_2^+), 5.85 (strong, lactone C=O), 6.05 (strong, conjugated C=O), 6.2 (C=C and NH_2^+), 9.0 (lactone COC) and 12.78 μ (RR'C=CHR''); nmr (D_2O with acetone as internal standard) δ 2.15 (d, 3, ), 2.49 (s, 3, $COCH_3$), 3.24–3.50 (m, 4, CH_2NCH_2), 3.90–4.17 (m, 4, CH_2OCH_2) and 5.76 (d, 1, ).

Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.80; H, 6.65; N, 5.52.

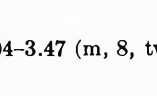
Piperidinium Dehydroacetate (20).—Under the same conditions used for **19**, dehydroacetic acid (21 g, 0.125 mol) and piperidine (10.65 g, 0.125 mol) furnished 30.7 g (97%) of **20**, mp 132–133° dec. Recrystallization from toluene furnished an analytical sample: mp 129–130° dec; ir (KBr) 3.45, 3.65, 3.81, 3.96 and 4.14 (components of a broad band, NH_2^+), 5.94 (strong, lactone C=O), 6.03 (strong, conjugated C=O), 6.25 (NH_2^+ and C=C), 6.55 (C=C), 7.27 (CCH_3) and 12.85 μ (RR'C=CHR''); nmr (D_2O with acetone as internal standard) δ 1.50–2.00 (m, 6, $CH_2CH_2CH_2$), 2.13 (d, 3, ), 2.50 (s, 3, $COCH_3$), 3.08–3.45 (m, 4, CH_2NCH_2) and 5.78 (d, 1, ).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.72; H, 7.46; N, 5.50.

Diethylammonium Dehydroacetate (21).—Under the same conditions used for **19**, dehydroacetic acid (16.8 g, 0.1 mol) and diethylamine (7.3 g, 0.1 mol) gave 22.2 g (92%) of **21**, mp 106–109° dec. Recrystallization from ethyl acetate afforded an analytical sample, mp 106–109° dec; ir (KBr) 3.35, 3.48 (CH_3 and CH_2), 4.0 (strong, NH_2^+), 5.93 (strong, lactone C=O), 6.04 (strong, conjugated C=O), 6.15, 6.33 (C=C), 6.55, 6.65 and 8.6 μ; nmr (D_2O with acetone as internal standard) δ 1.25 (t, 6, two NCH_2CH_3), 2.06 (d, 3, ), 2.43 (s, 3, $COCH_3$), 3.06 (qr, 4, two NCH_2CH_3) and 5.70 (d, 1,).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.44; H, 7.83; N, 5.39.

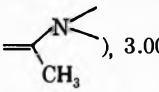
Reaction of Dehydroacetic Acid (1) with an Excess of Morpholine.—Morpholine (87 g, 1 mol) was added dropwise during 22 min to a stirred solution of dehydroacetic acid (42 g, 0.25 mol) in

150 ml of benzene at 54°. The reaction was mildly exothermic, the temperature rose to 61°, and after about one-third of the morpholine had been added morpholinium dehydroacetate precipitated from solution. When the addition was complete the mixture was heated under reflux for 4 hr and then allowed to stand overnight at room temperature. The benzene and excess morpholine were evaporated *in vacuo*, and the resulting oil was dissolved in 300 ml of ether. The ethereal solution was cooled to −78° and after standing for several hours at this temperature deposited 18.5 g (26.4%) of **22**, mp 140–163° dec. An analytical sample of dienone **22** prepared by recrystallization from benzene–hexane mixture had mp 169–175° dec; ir (KBr) 3.3 (=CH), 3.38 (CH_3), 3.55 (OCH_2 and NCH_2), 6.15 (C=C), 6.35–6.55 (broad, strong, conjugated C=O and C=C), 7.0, 8.0, 8.88, 9.03 (ether COC), 10.0, 11.03, 12.05 and 14.5 μ; nmr ($CDCl_3$) δ 2.49 (s, 6, two ), 3.04–3.47 (m, 8, two CH_2NCH_2), 3.50–3.83 (m, 8, two CH_2OCH_2) and 5.23 (s, 2, =CHCOCH=).

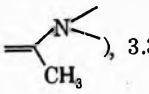
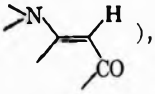
Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.49; H, 8.59; N, 10.11.

The original mother liquor was concentrated *in vacuo*. Crystallization of the oil thus obtained from ethyl ether–benzene–petroleum ether (bp 60–70°) mixture gave pale yellow needles of 4-acetoacetylmorpholine (12.2 g, mp 56–60°). A further crystallization from benzene–petroleum ether (bp 60–70°) mixture furnished 7.9 g of **23** as colorless needles, mp 69–71°. An additional portion of **23** was obtained by evaporating the ethyl ether–benzene–petroleum ether (bp 60–70°) mother liquor to dryness and distilling the residue at 1 mm. Crystallization of the distillate, 4 g, bp 150–160°, from benzene–petroleum ether (bp 60–70°) mixture gave 2.1 g of **23**, mp 62–66°. The yield of combined crude material (14.2 g) was 33.5%. **23** gave a violet color with ethanolic ferric chloride. A mixture melting point with an authentic sample of **23** prepared from morpholine and diketene showed no depression.

Preparation of 4-Acetoacetylmorpholine (23).—Diketene (84 g, 1 mol) was added dropwise with stirring during 1.25 hr to morpholine (109 g, 1.25 mol). During the addition the temperature was kept below 50° by use of an ice bath. After the addition was complete the mixture was allowed to stand at ambient temperature for 2.5 hr. Excess morpholine was evaporated and the residue was distilled under reduced pressure to give 118.8 g (69.5%) of **23** as a colorless liquid, bp 150–165° (2–3 mm), which solidified on cooling. Recrystallization from benzene–petroleum ether (bp 60–70°) mixture gave fine colorless needles of **23**, mp 68–70° (lit.[16] mp 71°).

Reaction of Dehydroacetic Acid (1) with an Excess of Piperidine.—A stirred solution of dehydroacetic acid (42 g, 0.25 mol) in 150 ml of benzene at 54° was treated dropwise during 20 min with piperidine (85 g, 1 mol). During the addition the temperature rose to 60°; after the addition was completed the mixture was maintained at 60° for 4 hr. The benzene and excess piperidine were removed under reduced pressure, and the resulting oil was dissolved in 100 ml of ether. On standing 21 g of a white solid, mp 70–95° dec, precipitated from solution. This material was extremely sensitive to heat and has not been identified. The ether mother liquor was evaporated to small volume, and petroleum ether (bp 60–70°) was added to the cloud point. On standing for several days at −78° the solution deposited 6.3 g (9.1%) of 2,6-bis(N-piperidino)hepta-2,5-dien-4-one (**24**), mp 82–85°. Recrystallization from benzene–petroleum ether (bp 60–70°) mixture at 0° afforded an analytical sample: mp 85–87°; ir (KBr) 3.25 (=CH), 3.43 (CH_3 and CH_2), 3.6 (NCH_2), 6.48 (strong, broad, conjugated C=O and C=C), 7.25, 7.33, 9.05 and 12.28 μ (RR'C=CHR''); nmr ($CDCl_3$) δ 1.58 (broad s, 12, two $CH_2CH_2CH_2$), 2.50 (s, 6, two ), 3.00–3.50 (m, 8, two CH_2NCH_2) and 5.20 (s, 2, =CHCOCH=).

Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.86; H, 10.21; N, 10.14. Found: C, 73.69; H, 10.26; N, 9.78.

Reaction of Dehydroacetic Acid (1) with an Excess of Diethylamine.—Diethylamine (29.2 g, 0.4 mol) was added dropwise over a period of 15 min to a stirred solution of **1** (16.8 g, 0.1 mol) in 40 ml of benzene at 50°. During the addition the temperature rose to 65° and diethylammonium dehydroacetate (**21**) precipitated from solution. After the addition was complete the mixture was stirred and refluxed for 7 hr. The benzene and excess diethylamine were evaporated under reduced pressure, and the resulting oil of 22.3 g was dissolved in 30 ml of ether. On standing the solution deposited 11.5 g (47.7%) of **21**, mp 108–110° dec. The mother liquor was concentrated *in vacuo* and afforded 10.8 g of **25** as an oil: ir (neat) 3.36 (CH_3), 3.44 (CH_3 and CH_2), 4.0 (broad, weak, chelated OH), 5.86 (C=O), 6.15, 6.47 (C=C and conjugated C=O), 7.22 (CCH_3), 7.35 ($COCH_3$), 8.74, 9.54 and 12.35 μ (RR'C=CHR''); nmr ($CDCl_3$) δ 1.15 (t, 6, two NCH_2CH_3), 1.85 and 2.16 (two, s, 3, $=C(OH)CH_3$ and $COCH_3$), 2.5 (d, 3, ), 3.3 (qr, 5.2, CH_2NCH_2 and $COCH_2CO$), 4.68 and 5.00 (two s, 0.7, ), and 5.13 (s, 0.3, –CH=C(OH)–).

The spectrum also showed weak lines at 1.2, 1.35, 2.0, 2.06, 2.2, 2.3, 2.5, and 5.52. The oil was distilled under reduced pressure and afforded 1.5 g (5%) of the diethylamide of acetoacetic acid (**26**), bp 100° (2 mm), identified by comparison of its infrared and nmr spectra with those of an authentic specimen prepared from ethyl acetoacetate and diethylamine by the method of Utzinger.[12]

Registry No.—**3b**, 20103-86-0; **4**, 20103-87-1; **7b**, 20103-88-2; **9**, 20103-89-3; **11**, 20103-90-6; **12b**, 20103-91-7; **13**, 20103-92-8; **15**, 20103-93-9; **15** picrate, 20103-94-0; **17**, 20103-95-1; **18**, 20103-96-2; **19**, 20103-97-3; **20**, 20103-98-4; **21**, 20103-99-5; **22**, 20104-00-1; **24**, 20104-01-2.

Acknowledgment.—Thanks are extended to Mr. W. H. Joyce and Mr. C. B. Strow of Union Carbide Corp. for interpretations of infrared and nmr spectra.

(16) P. Couturier, P. Blanc, and S. Frajdenrajch, *Bull. Soc. Chim. Fr.*, 594 (1962).

Preparation of Bicyclic Enamines and Their Reaction with Sulfene

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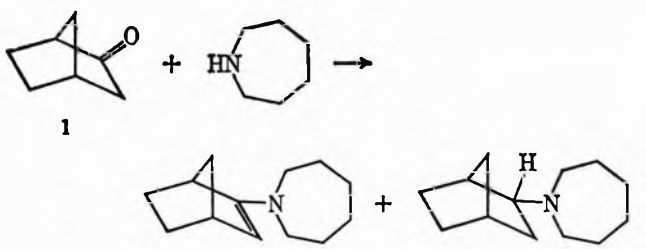
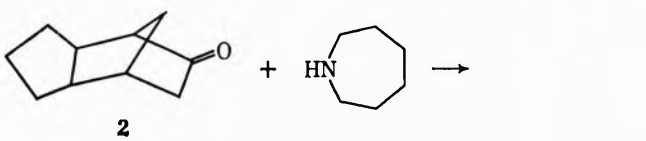
The uncatalyzed reactions of norbornanone and *exo*-tricyclo[5.2.1.$0^{2,6}$]decan-8-one with a variety of secondary amines have been studied and have been found to yield, in addition to the expected enamines, small amounts of the corresponding saturated amines. The α,β-unsaturated amines form ternary iminium salts with strong acid and are readily reduced with 90% formic acid. Addition of sulfene afforded, in stereoselective fashion, single cycloadducts which are probably the result of *exo* addition.

Recently, it was reported that the *p*-toluenesulfonic acid catalyzed reactions of norbornanone (**1**) and *exo*-tricyclo[5.2.1.$0^{2,6}$] decan-8-one (**2**) with hexamethylenimine in refluxing xylene produce, in each case, a mixture of the corresponding enamines **3a** and **4a** and the

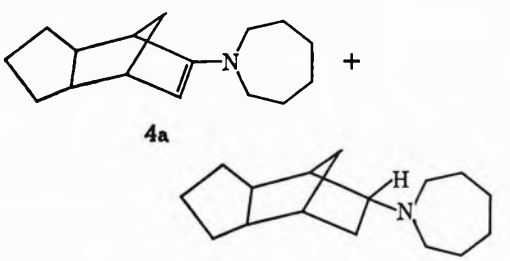


1

3a **5a**



2

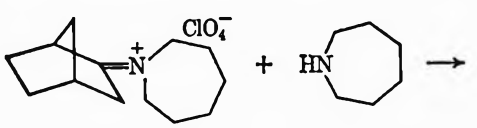


4a

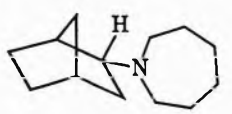
6a

saturated amines **5a** and **6a**. In addition, the authors report that the *p*-toluenesulfonic acid catalyzed reaction of norbornanone (**1**) with morpholine produces enamine **3b** and no saturated amine, and that the reaction of norbornanone (**1**) with hexamethylenimine in the absence of added catalyst gives **3a** and no saturated amine.[1-3]

The authors believe that the saturated amines **5a** and **6a** are formed by reduction of the corresponding enamines **3a** and **4a** with hexamethylenimine since they were able to reduce N-2-bicyclo[2.2.1]heptylidenehexamethyleniminium perchlorate (**7a**) to **5a**, in 60% yield,



7a

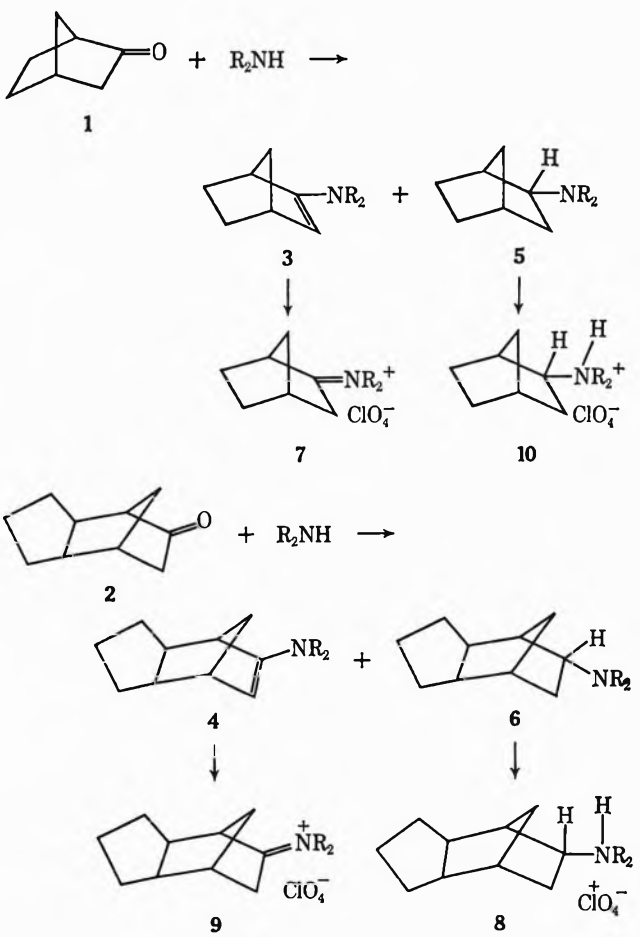


5a

with an excess of hexamethylenimine.[2,3] In view of the facile reduction of enamine **3a** to saturated amine **5a** with hexamethylenimine, the observation by Cook, *et al.*, that formic acid fails to reduce **3a** and the corresponding pyrrolidine enamine **3c** is surprising.[1,2] Interest in bicyclic and tricyclic enamines as intermediates for other studies led us to investigate the reactions of norbornanone (**1**) and *exo*-tricyclo[5.2.1.$0^{2,6}$]decan-8-one (**2**) with a variety of secondary amines, and we report here the results of this investigation.

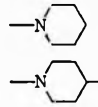
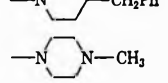
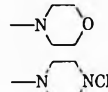
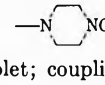
Prolonged reflux of a mixture of norbornanone (**1**) and excess secondary amine in toluene, in the absence of added catalyst, afforded the bicyclic enamines **3a–f** (Table I, Scheme I). Reaction of *exo*-tricyclo[5.2.1.$0^{2,6}$]dec-

SCHEME I



(1) A. G. Cook, *J. Amer. Chem. Soc.*, **85**, 648 (1963).
(2) A. G. Cook, W. C. Meyer, K. E. Ungrodt, and R. H. Mueller. *J. Org. Chem.*, **31**, 14 (1966).
(3) A. G. Cook and C. R. Schulz, *ibid.*, **32**, 473 (1967).

TABLE I

Compd	$-NR_2$	Reaction solvent	Moles of R_2NH per mole of ketone	Reaction time, days	Yield, %	Yield, % saturated amine	Bp, °C (mm)	ν_{max}^{film}, cm^{-1}, H, NR_2	δ_{CDCl_3}, ppm[a] H, NR_2
Enamines Derived from Norbornanone									
3a		Toluene	1.5	5	48	8	83 (0.5)	1600	4.27 d (J = 3)
3b		Toluene	1.5	14	61	1	91–106 (2)	1600	4.60 d (J = 3)
3c		Benzene	3	14	72	3	66–68 (2)	1600	4.13 d (J = 3)
3d		Toluene	1.5	21	70	2	73–76 (2)	1600	4.48 d (J = 3)
3e		Toluene	1.5	14	65	5	151–157 (2)	1600	4.52 d (J = 3)
3f		Toluene	1.5	13	85	1	62–64 (2)	1600	4.52 d (J = 3)
Enamines Derived from *exo*-Tricyclo[5.2.1.$0^{2,6}$]decan-8-one									
4a		Toluene	1.5	8	39	7	103–115 (0.2)	1600	4.25 d (J = 3)
4b		Toluene	1.5	21	22	12	114–120 (2)	1600	4.65 d (J = 3)
4c		Toluene	1.5	10	55	0.3	103–107 (0.5)	1600	4.60 d (J = 3)

[a] d, doublet; coupling constants (J) in cycles per second.

an-8-one (**2**) with hexamethylenimine, morpholine, and N-methylpiperazine under similar conditions furnished the corresponding tricyclic enamines **4a–c**. In addition to α,β-unsaturated amines, the reactions of **1** and **2** with secondary amine yielded in all cases investigated small amounts of by-product. These by-products were detected by gas–liquid partition chromatography and they showed identical retention times with authentic samples of the corresponding saturated amines prepared by formic acid reduction of the corresponding enamines. On this basis, they have been formulated as such. In seeking further support for our formulation of the by-products as saturated amines, we hydrolyzed the product mixture resulting from the reaction of **2** with morpholine and obtained the saturated amine **6b** which was converted into its perchlorate salt **8b**. This proved to be identical with authentic **8b** made from pure **6b** which had beeh obtained by reduction of enamine **4b** with formic acid.

Bicyclic and tricyclic enamines **3a–f** and **4a–c** are colorless liquids (**4b** and **4c** are solids at 0°) which are extremely sensitive to air and moisture. However, they can be stored for prolonged periods without appreciable decomposition in a nitrogen atomsphere at 0°. The infrared spectra of the α,β-unsaturated amines exhibit a strong C=C stretching band at 1600 cm^{-1} and not at 1685 cm^{-1} as had been reported previously.[2] In our opinion the 1685-cm^{-1} band reported by Cook, *et al.*, for **3a**, **3b**, and **4a** arises from an impurity.[4] The nmr spectra (in $CDCl_3$) show the vinyl hydrogen signal as a doublet; the splitting is presumably due to interaction with the bridgehead hydrogen. With perchloric acid C^{β} protonation occurs to give the ternary iminium salts **7a–e** and **9a–b** (Table II). All of these have been characterized by elemental analyses and by the strong infrared absorption band in the region of 1672–1709 cm^{-1} indicative of $>C{=}\overset{+}{N}<$. In addition, they are identical with respect to melting point and infrared spectra with those prepared by Cook, *et al.*, from the reactions of norbornanone (**1**) and *exo*-tricyclo[5.2.-1.$0^{2,6}$]decan-8-one (**2**) with the corresponding secondary amine perchlorate salts.[2]

In spite of reports to the contrary,[1,2] we find that bicyclic enamines **3a–f** and the tricyclic enamines **4a–c** react vigorously with 90% formic acid[5,6] with evolution of carbon dioxide to afford the saturated amines **5a–f** and **6a–c**, respectively (Table III). Structures **5a–f** and **6a–c** were supported by elemental analyses and infrared and nmr spectra. Gas chromatographic analysis of the saturated amines demonstrated that a single isomer was present, indicating that the reduction is stereospecific. The saturated amines were further characterized by converting them to their perchlorate salts

(4) Dr. Cook kindly furnished us with a copy of the infrared spectrum of the crude product derived from the *p*-toluenesulfonic acid catalyzed reaction of norbornanone with morpholine in refluxing xylene. Comparison of this spectrum with the infrared spectrum of 2-N-morpholinobicyclo[2.2.1]-hept-2-ene prepared by us revealed that, with the exception of minor intensity differences at 1370, 1167, 1147, 1039, and 1030 cm^{-1}, and the presence of additional weak bands at 3278, 1685, 893, and 877 cm^{-1} in Dr. Cook's spectrum, the spectra were identical. We must therefore conclude that the 1685-cm^{-1} band originates from an impurity.

(5) F. L. de Benneville and J. H. Macartney, *J. Amer. Chem. Soc.*, **72**, 3073 (1950).

(6) P. L. de Benneville, U. S. Patent 2,578,787 (1951).

TABLE II

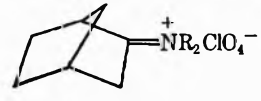
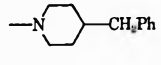
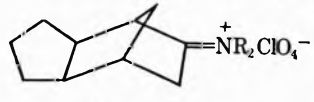
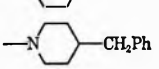
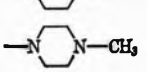
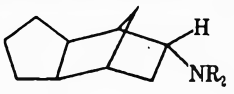
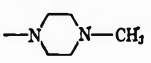
Compd	–NR₂	Solvent for crystallization	Mp, °C	ν_{max}^{KBr}, cm⁻¹, >C=N<	Formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Calcd, % N	Found, % C	Found, % H	Found, % Cl	Found, % N
Ternary Iminium Salts of Bicyclic Enamines													
7a		Ethanol	302–304 dec	1672	$C_{13}H_{22}ClNO_4$	53.51	7.60	12.15	4.80	53.23	7.73	11.85	4.95
7b		Ethanol	250–253 dec	1694	$C_{11}H_{18}ClNO_5$	47.23	6.49	12.68	5.01	47.07	6.53	12.38	5.15
7c		Ethanol	226–227	1709	$C_{11}H_{18}ClNO_4$	50.10	6.88	13.45	5.31	50.22	6.93	13.59	5.36
7d		Ethanol	293–295 dec	1694	$C_{12}H_{20}ClNO_4$	51.89	7.26	12.77	5.04	51.84	7.34	12.69	5.18
7e		Methanol	172–175	1681	$C_{19}H_{26}ClNO_4$	62.03	7.13	9.64	3.81	61.94	7.32	9.70	3.54
Ternary Iminium Salts of Tricyclic Enamines													
9a		Methanol	210–213	1678	$C_{16}H_{26}ClNO_4$	57.91	7.90	10.68	4.22	57.72	7.80	11.00	4.01
9b		Ethanol	152–154	1694	$C_{14}H_{22}ClNO_5$	52.58	6.94	11.09	4.38	52.20	7.00	11.01	4.48

TABLE III

Compd	$-NR_2$	Bp, °C (mm)	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
				2-Aminobicyclo[2.2.1]heptanes						
										
5a		88 (1.5)	72	$C_{13}H_{23}N$	80.76	11.99	7.25	80.52	12.12	7.10
5b		70–72 (0.5)	66	$C_{11}H_{19}NO$	72.88	10.57	7.73	73.06	10.56	7.85
5c		64 (0.5)	76	$C_{11}H_{19}N$	79.94	11.59	8.48	79.95	11.33	8.51
5d		79 (1.5)	59	$C_{12}H_{21}N$	80.38	11.81	7.81	80.68	11.73	7.89
5e		183–185 (0.5)	77	$C_{19}H_{27}N$	84.70	10.10	5.20	84.50	10.30	5.12
5f		86–87 (3)	79	$C_{12}H_{22}N_2$	74.17	11.41	14.42	73.87	11.25	14.21
				8-Amino-*exo*-tricyclo[5.2.1.$0^{2,6}$]decanes						
										
6a		96–97 (1)	74	$C_{16}H_{27}N$	82.34	11.66	6.00	82.48	11.96	5.85
6b		97–98 (1.5)	67	$C_{14}H_{23}NO$	75.97	10.47	6.33	75.70	10.70	6.23
6c		90 (0.5)	77	$C_{15}H_{26}N_2$	76.86	11.18	11.95	77.23	11.18	11.87

10a–f and **8a–c** (Table IV). Leonard and Sauers[7] have shown that the first step in the formic acid reduction of an enamine is the formation of a ternary iminium formate followed by nucleophilic attack of the hydride of the formate anion at the α carbon of the original enamine grouping. In the formic acid reduction of the above bicyclic and tricyclic enamines, attack by the hydride of the formate anion would be expected to take place from the less hindered side of the molecule, the *exo* side, to give the *endo*-amino isomer.[8,9] Comparison of the physical properties of the saturated amines **5a** and **6a** with those of *endo*-2-N-hexamethyleniminobicyclo-[2.2.1]heptane and *endo*-8-N-hexamethylenimino-*exo*-tricyclo[5.2.1.$0^{2,6}$]decane produced by the lithium aluminum hydride reduction[3] of the iminium salts **7a** and **9a** showed that they were identical. Therefore, saturated amines produced by formic acid reduction of bicyclic and tricyclic enamines are indeed *endo* isomers. Several enamines, **3b**, **3e**, and **3f**, were also reduced catalytically over a 5% palladium-on-carbon catalyst at 50 psi, and it was found that catalytic hydrogenation is also stereospecific and gives rise to the *endo* isomer.

As mentioned earlier, the *p*-toluenesulfonic acid catalyzed reaction of norbornanone (1) with hexamethylenimine is reported as producing a mixture of enamine **3a** and saturated amine **5a** in approximately equal amounts, while the reaction of norbornanone (1) with morpholine under similar conditions produces only enamine **3b**.[2,3] Repetition of this latter reaction gave, in our hands, a mixture of enamine **3b** and saturated amine **5b** in a 1:2 ratio. In view of the significantly larger amounts of saturated amine produced in these acid-catalyzed reactions, it would appear that, in spite of the long reaction times involved, the uncatalyzed reaction is the preferred method for the preparation of these and other bicyclic and tricyclic enamines.

Sulfene chemistry has received a great deal of attention in recent years, and the ability of sulfene to add to electron-rich double bonds has been well documented.[10]

Paquette[11] examined the cycloaddition of sulfene to a variety of enamines derived from 5-norbornene-2-carboxaldehyde and observed that this cycloaddition is stereoselective and gives adducts which are the result of *exo* addition to the enamine double bond. We were interested in preparing the sulfene adducts of the various bicyclic and tricyclic enamines described above; such a study also offered a further opportunity of examining the stereoselectivity of sulfene addition to a bicyclic moiety.

Addition of 1 equiv of methanesulfonyl chloride to an equimolar mixture of the appropriate bicyclic enamine **3a–f** and triethylamine in dioxane or tetrahydrofuran at 5–10° afforded crystalline adducts which have been formulated, on the basis of infrared and nmr spectra and elemental analyses, as the tricyclic aminothietane diox-

(7) N. J. Leonard and R. R. Sauers, *J. Amer. Chem. Soc.*, **79**, 6210 (1957).

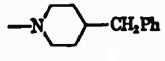
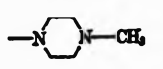
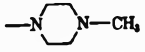
(8) S. Beckmann and R. Mezger, *Chem. Ber.*, **89**, 2738 (1956).

(9) For a comprehensive discussion of *exo* and *endo* addition to various norbornane derivatives, see J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, Chapter 3.

(10) For recent reviews on sulfene chemistry, see T. J. Wallace, *Quart. Rev.* (London), **20**, 67 (1966); G. Opitz, *Angew. Chem. Intern. Ed. Engl.*, **6**, 107 (1967).

(11) L. A. Paquette, *J. Org. Chem.*, **29**, 2851 (1964).

TABLE IV

Compd	-NR₂	Solvent for crystallization	Mp, °C	ν_{max}^{KBr}, cm⁻¹, +HNR₂	Formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Calcd, % N	Found, % C	Found, % H	Found, % Cl	Found, % N
Perchlorate Salts of 2-Aminobicyclo[2.2.1]heptanes													
10a		Ethanol	303–314 dec	3134[b]	$C_{12}H_{22}ClNO_4$	53.14	8.23	12.07	4.77	53.05	8.43	11.95	4.89
10b		Ethanol	213–214	2439 2564 2631	$C_{11}H_{20}ClNO_5$	46.89	7.16	12.59	4.97	46.71	7.27	12.38	5.08
10c		Ethanol–ether	178–180	2500 2625 2681	$C_{11}H_{20}ClNO_4$	49.71	7.59	13.34	5.27	49.42	7.53	13.27	5.15
10d		Ethanol	270–283 dec	2551 2688	$C_{12}H_{22}ClNO_4$	51.51	7.93	12.67	5.01	51.33	7.81	12.70	4.76
10e		Ethanol	190–193	2584 2688	$C_{19}H_{28}ClNO_4$	61.86	7.65	9.34	3.79	61.86	7.75	9.69	3.44
10f		Methanol	265–271 dec	2469 2564 2667	$C_{12}H_{24}Cl_2N_2O_8$	36.14	6.12	17.94	7.09	36.23	6.21	17.62	7.06
Perchlorate Salts of 8-Amino-*exo*-tricyclo[5.2.1.0^{2,6}]decanes													
8a		Methanol	232–234	3125[b]	$C_{16}H_{28}ClNO_4$	57.56	8.45	10.62	4.20	57.30	8.48	10.81	4.24
8b		Ethanol	237–239	3125[b]	$C_{14}H_{24}ClNO_5$	52.25	7.52	11.02	4.35	52.23	7.48	11.01	4.04
8c[a]		Ethanol	243–244 dec	2439 2564 2631	$C_{15}H_{28}Cl_2N_2O_8$	41.39	6.48	16.29	6.44	41.40	6.50	16.08	6.24

[a] Diperchlorate salt. [b] Spectrum obtained in Nujol.

TABLE V

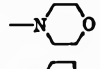
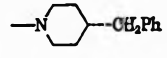
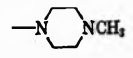
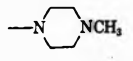
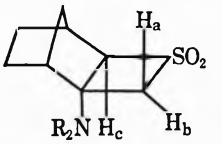
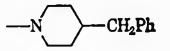
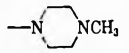
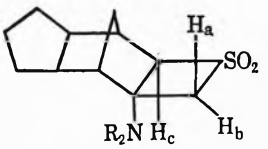
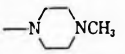
Compd	–NR₂	Yield, %	Mp, °C	Solvent for reaction	Solvent for crystallization	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
5-Amino-3-thiatricyclo[4.2.1.0^{2,5}]nonane 3,3-Dioxides														
11a		41	99–100	Tetrahydrofuran	Methanol	$C_{14}H_{23}NO_2S$	62.42	8.60	5.20	11.90	62.17	8.75	5.12	11.53
11b		67	161–164	Dioxane	Methanol	$C_{12}H_{19}NO_3S$	56.02	7.44	5.44	12.46	55.81	7.33	5.41	12.46
11c		48	103–106	Tetrahydrofuran	Methanol	$C_{12}H_{19}NO_2S$	59.72	7.93	5.80	13.28	59.46	7.95	5.70	13.22
11d		32	99–101	Dioxane	Methanol	$C_{13}H_{21}NO_2S$	61.14	8.29	5.49	12.55	60.90	8.40	5.46	12.57
11e		50	96–100	Tetrahydrofuran	Methanol	$C_{20}H_{27}NO_2S$	69.52	7.88	4.05	9.28	69.36	7.96	3.99	9.29
11f		54	132–136	Tetrahydrofuran	Methanol	$C_{13}H_{22}N_2O_2S$	57.74	8.20	10.36	11.86	57.66	8.35	10.11	11.63
11-Amino-9-thiatetracyclo[5.4.1.0^{2,6}.0^{8,11}]dodecane 9,9-Dioxides														
12a		29	105–106	Tetrahydrofuran	Petroleum ether (bp 60–70°)	$C_{17}H_{27}NO_2S$	65.98	8.80	4.53	10.36	65.75	8.71	4.45	10.13
12b		61	175–178	Tetrahydrofuran	Methanol	$C_{15}H_{23}NO_3S$	60.58	7.79	4.71	10.78	60.49	7.76	4.63	10.72
12c		47	152–154	Tetrahydrofuran	Cyclohexane	$C_{16}H_{26}N_2O_2S$	61.90	8.44	9.03	10.33	61.81	8.60	9.09	10.31

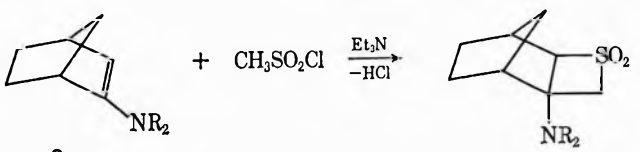
TABLE VI

Nuclear Magnetic Resonance Spectra

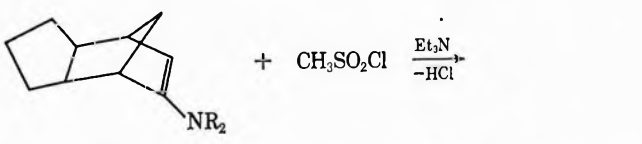
Compd	-NR₂	Chemical shifts in δ units[a] H_a	H_b	H_c
				
11a		3.75, J_{AB} = 14	4.13, J_{cb} = 3	3.95 (m), $J_{ac} < 1$
11b		3.64, J_{AB} = 14	4.36, J_{cb} = 3	4.0 (m), J_{ac} = 1
11c		3.66, J_{AB} = 14	4.20, J_{cb} = 3	3.91 (m), J_{ac} = 1
11d		3.53, J_{AB} = 14	4.29, J_{cb} = 3	3.98 (m), J_{ac} = 1
11e		3.48, J_{AB} = 14	4.22, J_{cb} = 3	3.92 (m), $J_{ac} < 1$
11f		3.61, J_{AB} = 14	4.31, J_{cb} = 3	3.96 (m), $J_{ac} < 1$
				
12a		3.62, J_{AB} = 14	4.05, J_{cb} = 3	3.85 (m), $J_{ac} < 1$
12b		3.54, J_{AB} = 14	4.28, J_{cb} = 3	3.90 (m), J_{ac} = 1
12c		3.54, J_{AB} = 14	4.23, J_{cb} = 3	3.90 (m), J_{ac} = 1

[a] m, multiplet; coupling constants (J) in cycles per second.

ides **11a–f** (Table V). Under similar conditions, the tricyclic enamines **4a–c** reacted with sulfene to yield the corresponding tetracyclic aminothietane dioxides **12a–c**



3 **11**



4 **12**

(Table V). Examination of the nmr spectra of the adducts (Table VI) reveals that the nonequivalent methylene hydrogens (H_a, H_b) adjacent to the sulfone group appear as an AB quartet and that each peak of the AB quartet is additionally split into a doublet. The coupling constant (J_{AB} = 14 cps) is in good agreement with the coupling constants expected for geminal protons. The pair of doublets at lower field was assigned to H_b, since H_b is subject to substantial deshielding from the proximate amino group, while H_a is effectively removed from the area of strong deshielding and therefore resonates at higher field. Based on these assignments, the splitting of the pair of AB lines at lower field can be attributed to a *cis*-1,3-transannular interaction with H_c, while the splitting of the upfield pair is due to a *trans*-1,3-transannular interaction of H_a with H_c. The tertiary hydrogen H_c appears as a multiplet which is not well enough resolved to permit a detailed analysis. Furthermore, in view of the complexity of the spectrum at higher field, it has not been possible to establish whether H_c is coupling with a bridgehead or bridge methylene proton of the norbornane system. Consequently, although attack of sulfene from the *exo* side is to be expected,[9] confirmation of *exo* addition based on nmr data has not been possible.

The cycloaddition of sulfene to bicyclic and tricyclic enamines derived from norbornanone (**1**) and *exo*-tricyclo[5.2.1.$0^{2,6}$]decan-8-one (**2**) appears to be stereoselective inasmuch as only single adducts were obtained. However, in view of the low yields of adducts isolated, mention should be made of the possibility that only the major isomer was isolated and that the minor isomer, if indeed any was formed, was lost during work-up.

Experimental Section

All melting points and boiling points are uncorrected, and melting points were taken with a Mel-Temp capillary melting point apparatus. Infrared spectra were determined with Baird-Atomic Models 4-55 and AB-2 and Perkin-Elmer Model 21 spectrometers

with potassium bromide pellets or Nujol mulls of the solids, and neat samples of the liquids. Nmr spectra were obtained from Varian A-60 and HA-100 spectrometers using tetramethylsilane as internal standard and $CDCl_3$ as solvent. Elemental analyses were performed by Union Carbide European Research Associates, Brussels, Belgium. Norbornanone was obtained from Aldrich Chemical Co. *exo*-Tricyclo[5.2.1.$0^{2,6}$]decan-8-one was derived from dicyclopentadiene in three steps, by a procedure similar to that described in the literature.[12,13] Toluene and benzene were dried over sodium. The secondary amines employed were dried over potassium hydroxide and freshly distilled prior to use.

General Procedure for Enamine Formation.—A solution of norbornanone (55 g, 0.5 mol) and secondary amine (1.5 mol) in 300 ml of toluene was refluxed for 14 days, under a 3-ft column packed with glass helices and topped with a water separator. The solution was concentrated *in vacuo*. The residue was distilled through a 6-in. column packed with glass helices at reduced pressure to give the enamine which was analyzed by vapor phase chromatography. The analytical gas chromatography was performed on an F & M Model 720 dual column chromatograph with helium as carrier gas, on a 12 ft × 0.25 in. column of poly(*m*-phenyl ether) (5% suspended on Chromosorb G, DMCS treated), at a flow rate of 60 ml/min, and at a column temperature of 200°. The relative areas of enamine and saturated amine were measured by a disk integrator, and in converting to weight ratios it has been assumed that area per cent = weight per cent. For the analyses of enamines **3e** and **3f** a 5 ft × 0.25 in. column packed with 10% phenyl diethanolamine succinate on Anakrom was used.

General Procedure for Iminium Perchlorate Salt Formation.—A solution of enamine (0.01 mol) in 15 ml of ethanol was treated with a solution of 70% perchloric acid (1.44 g) in 5 ml of ethanol. The salt crystallized from solution during the addition and was recrystallized to constant melting point from ethanol.

General Procedure for Formic Acid Reduction.—90% Formic acid (5.1 g) was added dropwise to the enamine (0.1 mol) at room temperature with vigorous stirring. After a short induction period, the addition was accompanied by a vigorous evolution of carbon dioxide, and the temperature rose to 60° and was maintained at 50–60° by external cooling. After the addition was completed the mixture was stirred and heated at 60–70° for 1–2 hr. The mixture was poured into dilute hydrochloric acid and extracted with ether. The aqueous solution was made basic with sodium hydroxide and extracted with ether. Distillation of the dried ether extract furnished the saturated amine.

General Procedure for the Catalytic Hydrogenation of Bicyclic and Tricyclic Enamines.—A solution of enamine (0.1 mol) in 100 ml of ethanol was hydrogenated over 1.0 g of a 5% Pd/C catalyst in a Parr apparatus at an initial pressure of 50 psi. After hydrogen uptake ceased, the catalyst was removed by filtration. After evaporation of the ethanol the residue was distilled through an 8-in. Vigreux column under reduced pressure to give pure saturated amine.

General Procedure for Perchlorate Salt Formation of Saturated Amines.—A solution of 70% perchloric acid (1.44 g) in 5 ml of ethanol was added dropwise to a solution of saturated amine (0.01 mol) in 10 ml of ethanol. When the addition was completed the salt was precipitated by addition of excess ether and recrystallized from ethanol.

General Procedure for Reaction of Methanesulfonyl Chloride with Bicyclic and Tricyclic Enamines.—A solution of methanesulfonyl chloride (13.8 g, 0.12 mol) in 20 ml of dry purified tetrahydrofuran was added dropwise during 1 hr to a stirred mixture of enamine (0.1 mol) and triethylamine (12.1 g, 0.12 mol) in 100 ml of tetrahydrofuran at 5° under a nitrogen atmosphere. During the addition the temperature was maintained at 5–10° by use of an ice bath. When the addition was completed the mixture was allowed to stand overnight at ambient temperature. The precipitated triethylamine hydrochloride was separated by filtration and washed with tetrahydrofuran and a little ether. The combined filtrates were evaporated under reduced pressure, and the resulting solid or semisolid was purified by crystallization.

Registry No.—**3a**, 20238-04-4; **3b**, 5024-92-0; **3c**, 20238-06-6; **3d**, 20238-07-7; **3e**, 20238-08-8; **3f**, 20238-09-9; **4a**, 20238-33-9; **4b**, 20238-34-0; **4c**, 20238-37-3; **5a**, 20238-38-4; **5b**, 20238-39-5; **5c**, 20238-40-8; **5d**, 20238-41-9; **5e**, 20238-42-0; **5f**, 20238-43-1; **6a**, 20238-44-2; **6b**, 20238-45-3; **6c**, 20238-46-4; **7a**, 5024-72-6; **7b**, 5024-76-0; **7c**, 5024-78-2; **7d**, 5024-77-1; **7e**, 20238-27-1; **8a**, 20290-68-0; **8b**, 20238-47-5; **8c**, 20238-48-6; **9a**, 6200-89-1; **9b**, 20238-50-0; **10a**, 20238-51-1; **10b**, 20238-52-2; **10c**, 20238-53-3; **10d**, 20238-54-4; **10e**, 20238-55-5; **10f**, 20238-56-6; **11a**, 20238-28-2; **11b**, 20238-29-3; **11c**, 20238-30-6; **11d**, 20238-31-7; **11e**, 20238-32-8; **11f**, 20290-67-9; **12a**, 20238-01-1; **12b**, 20238-02-2; **12c**, 20238-03-3.

Acknowledgment.—The authors wish to express thanks to Messrs. H. L. Joyce and C. B. Strow of Union Carbide Corp. for interpretations of infrared and nmr spectra.

(12) H. A. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, **67**, 723 (1945).
(13) P. D. Bartlett and A. Schneider, *ibid.*, **68**, 6 (1946).

α-Methoxy-α-trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and Amines[1]

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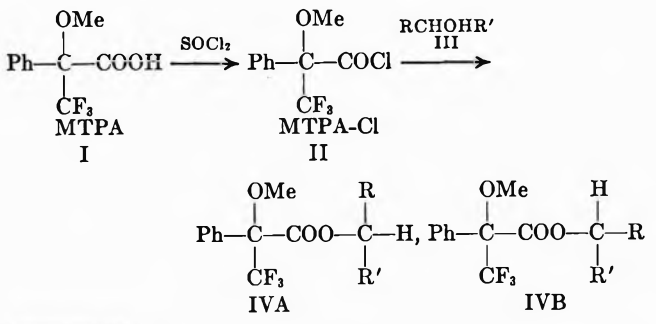
Diastereomeric esters and amides have been prepared from α-methoxy-α-trifluoromethylphenylacetyl chloride and various secondary alcohols and amines. The nmr spectra of the *R,R* and *S,S vs.* the *R,S* and *S,R* diastereomers show significantly different chemical shifts: 0.03–0.13 ppm in the proton region and 0.11–0.71 ppm in the fluorine region. By measuring the intensities of the nmr signals of the diastereomerically situated groups of esters and amides prepared from this enantiomerically pure reagent, satisfactory determinations of the enantiomeric composition of a number of alcohols and amines have been made. The use of the α-methoxy-α-trifluoromethylphenylacetyl derivative offers the distinct advantage, over other reagents having only proton resonances, that determinations of enantiomeric composition based upon fluorine resonances are usually more reliable, since the fluorine signals are simple and in an uncongested region. This is a absolute method, independent of optical rotation; accurate determinations can be made on 20-mg samples. Thus this reagent extends the application of this nmr technique. Furthermore, the reagent shows complete stability to racemization under prolonged reaction conditions. A practical synthesis and convenient resolution of the reagent have been developed.

Recent developments in methods for the determination of enantiomeric composition (optical purity) have been reviewed by Mislow and Raban.[2] Our interest in this problem is dictated by continuing studies on the asymmetric reduction of ketones with the necessity of determining the enantiomeric composition of the resulting chiral alcohols on relatively small samples.[3] In a previous paper[4] we reported on the applications and limitations of a series of mono-α-substituted phenylacetic acids for the nuclear magnetic resonance (nmr) and gas–liquid partition chromatographic (glpc) determination of enantiomeric composition.[5] The reagents previously studied do not give satisfactory results with hindered secondary carbinols because of epimerization at the α-carbon center of the acid moiety.[4,5] In addition, when nmr was used as the technique for quantitative measurement of diastereomer ratios, serious restrictions were often encountered owing to the overlapping of proton signals. In earlier studies on the determination of enantiomeric composition of partially active carbinols by glpc and nmr, it was recognized that α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, I) might be ideally suited for this purpose.[5] This reagent can react *via* its acid chloride (II) with chiral alcohols (III) to give a mixture of



diastereomeric esters (IVA and IVB) whose nmr spectrum can be used for quantitative analysis of the enantiomeric composition of the chiral alcohol from which it was made.

The advantages of this reagent for the determination of enantiomeric composition of a chiral alcohol are: (a) the generally excellent separation of both proton and fluorine nmr signals of the diastereomers IVA and IVB; (b) the presence of the trifluoromethyl group permitting the use of fluorine nmr, which occurs in an uncongested region of the spectrum; (c) its marked stability toward racemization even under severe conditions of acidity, basicity, and temperature; (d) its relative ease of preparation and resolution; (e) its inherent volatility which allows lower molecular weight derivatives to be purified, as well as analyzed, by glpc; (f) its versatility, *i.e.*, it may be used for determination of enantiomeric composition of primary and secondary amines as well as carbinols.

It should be re-emphasized[2,4] that this method is absolute and does not require that the carbinol or amine be previously resolved. Furthermore, the accuracy of the determination of enantiomeric composition by this method is not dependent in any way on the magnitude of the optical rotation; and yet one can calculate the maximum optical rotation from the rotation of a partially active sample and its enantiomeric composition as determined by this technique.

The nmr spectrum (Figure 1) of N-4-methyl-2-pentyl-α-methoxy-α-trifluoromethylphenylacetamide prepared from racemic materials, illustrates the advantage of using the signals from the trifluoromethyl group over those from the protons of an MTPA ester for nmr determination of enantiomeric composition. The signals for the isopropyl group, as well as for the α-methyl group, occur as two sets of doublets, one for the *R,S/S,R* enantiomeric pair and another for the *R,R/S,S* enantiomeric pair. Quite obviously, any

(1) We acknowledge with gratitude the support of this work by the U. S. Public Health Service (NIH GM 5248) and the National Science Foundation (GP 6738).

(2) M. Raban and K. Mislow, "Topics in Stereochemistry," Vol. II, N. L. Allinger and E. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967, p 199.

(3) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.*, **29**, 37 (1964).

(4) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **90**, 3732 (1968).

(5) (a) K. Mislow and M. Raban, *Tetrahedron Lett.*, 4249 (1965). (b) M. Raban and K. Mislow, *ibid.*, 3961 (1966). (c) J. Jacobus, M. Raban, and K. Mislow, *J. Org. Chem.*, **33**, 1142 (1968). (d) D. J. Sandman, K. Mislow, W. P. Giddings, J. Dirlam, and G. C. Hanson, *J. Amer. Chem. Soc.*, **90**, 4877 (1968). (e) D. J. Sandman and K. Mislow, *J. Org. Chem.*, **33**, 2924 (1968). (f) D. M. Feigl and H. S. Mosher, *Chem. Commun.*, 615 (1965). (g) D. W. Dull, Ph.D. Thesis, Stanford University, 1967.

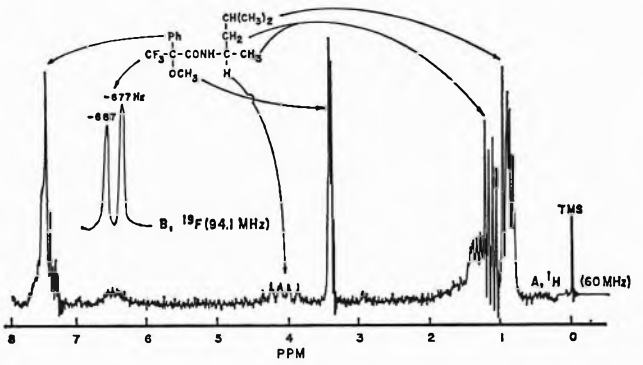


Figure 1.—The nmr spectrum of N-4-methyl-2-pentyl-α-methoxy-α-trifluoromethylphenylacetamide from racemic materials: (A) 60 MHz, ^{1}H, $CDCl_3$ solvent, TMS; (B) 94.1 MHz, ^{19}F, $CDCl_3$ solvent with trifluoroacetic acid internal standard.

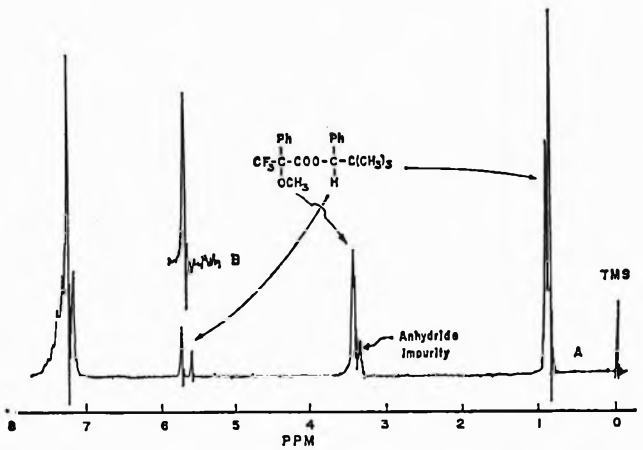


Figure 2.—(A) The 60-MHz proton nmr spectrum of diastereomeric esters from racemic phenyl-*t*-butylcarbinol and racemic α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA Cl). The anhydride impurity is absent when distilled MTPA Cl is used. (B) The α-carbinyl hydrogen signal of the single diastereomer from pure (+)-phenyl-*t*-butylcarbinol and MTPA Cl from pure (+) acid.

attempt at obtaining the relative proportions of these diastereomers by integration of proton signals would lead to very inaccurate results because of signal overlapping and perturbation. On the other hand, the fluorine nmr spectrum taken at 94.1 MHz is uncomplicated and shows a separation of 10 Hz for the signals for the two diastereomeric pairs, so that the relative areas of these signals can be obtained with reasonable accuracy by integration. It is of interest to note that the ^{19}F signals are broadened because of long range coupling with the protons of the methoxy group, and that the fluorine signals for the two diastereomeric pairs are not of the same intensity, although racemic materials were used in the synthesis (Figure 1).

When (*R*)-(+)-phenyl-*t*-butyl-carbinol, (*R*-III, R = phenyl, R′ = *t*-butyl, the pure isomer as measured by optical rotation) was treated with enantiomerically pure MPTA Cl (II), the signal for the α hydrogen of the carbinol moiety in the resulting ester IV was a singlet (Figure 2B), as was also the signal for the *t*-butyl group. However, when racemic phenyl-*t*-butyl-carbinol, *RS*-III, was treated with racemic acid chloride, *RS*-II, the spectrum (Figure 2A) for the resulting mixture of diastereomeric ester pairs (*R,R*-IV + *S,S*-IV *vs.* *R,S*-IV + *S,R*-IV) showed grossly unequal signals for the respective α and *t*-butyl protons. The inequality of these signals is a consequence of the different rate of reaction of the reagent *R*-II with carbinol *R*-III to yield *R,R*-IV as compared to the rate of reaction of *R*-II with *S*-III to give *R,S*-IV. As has been discussed,[2] the rate of reaction of *S*-II with *S*-III to give *S,S*-IV, and of *S*-II with *R*-III to give *S,R*-IV will differ by exactly the same amount. We have observed that this difference may be quite large, especially when dealing with hindered carbinols. As has been pointed out,[2] therefore, when this reaction is being employed for the accurate determination of enantiomeric composition, it is imperative that (a) the reaction be quantitative with respect to the substrate (such as III) and (b) the reagent (such as II) be enantiomerically pure.

The nmr data for a number of esters and amides of MTPA are collected in Table I. The chemical shift differences between diastereotopic[6] protons was 0.03–0.13 ppm, while the range for the signals from the diastereotopic α-trifluoromethyl groups was 0.11–0.71 ppm. Such differences permitted precise integrations of the fluorine signals, but comparable precision in measuring the signals from the diastereotopic proton was not always possible because of overlapping or perturbation. When practical, though, the determinations were done for the sake of convenience by using the proton spectra.

Although these studies have been primarily with secondary carbinols, the chemical shift differences were substantial for the signals from both the diastereotopic methyl and trifluoromethyl groups of the ester from the tertiary alcohol methylphenyltrifluoromethylcarbinol.[5g,7] Thus this method should be generally applicable to those tertiary alcohols which are chiral at the carbinol center.

Furthermore, the chemical shift differences of the signals for the diastereotopic α hydrogens in the MTPA ester of neopentyl alcohol in benzene solvent differ by 0.15 ppm compared with 0.10 ppm for the analogous signals for the *o*-methylmandelate ester.[5a] However, this method will not always be applicable. Although the chemical shift differences were about 0.08 ppm for the diastereotopic hydrogens in the esters of benzyl and *o*-chlorobenzyl alcohols, the center bands were separated by only 2.4 Hz at 100 MHz; analysts of a sample which was not 100% deuterated would be virtually impossible. We have also made use of the reagent to confirm the enantiomeric purity of a sample of optically active neopentylamine-1-*d*.[8]

This method is much simpler than that used by Guthrie and Cram.[9] Two special examples will illustrate the utility of this method. A study was made some years ago of the asymmetric reduction of methyl *t*-butyl ketone by the Grignard reagent from the three (+)-1-halo-2-methylbutanes.[10] The synthetic yield of reduction product from the iodo compound was very low; the optical rotation and therefore the extent of asymmetric synthesis could not be determined. The crucial fraction from this reaction had

(6) For the definition of this terminology, see M. Raban and K. Mislow, "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967, pp 1–37.
(7) G. A. Olah and C. V. Pittman, *J. Amer. Chem. Soc.*, **88**, 3310 (1966).
(8) G. Solladié, Stanford University, results to be published.
(9) R. D. Guthrie and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 5288 (1967).
(10) W. M. Foley, F. J. Welch, E. M. La Combe, and H. S. Mosher, *ibid.*, **81**, 2779 (1959).

been saved; it was purified by glpc, and the enantiomeric composition of the methyl-*t*-butylcarbinol determined, by conversion to the MTPA ester, to be 7.5% e.e.[11] as compared with 13.4% e.e. and 11.7% e.e. respectively for the carbinols obtained by reduction with the chloro and bromo Grignard reagents.

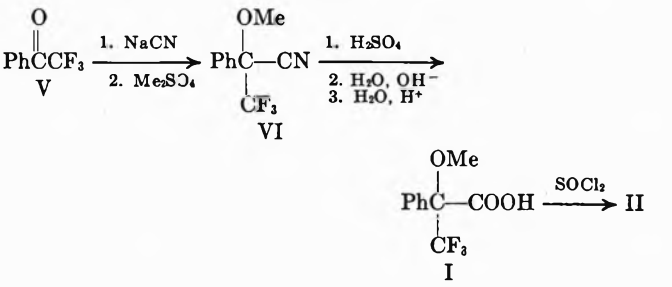
The resolution and determination of maximum rotation for methyltrifluoromethylcarbinol has presented difficulties. The initially reported resolution[12] gave material of $[\alpha]^{25}D$ −2.6° (neat). Analysis by glpc of the *o*-methylmandelate esters[5d,13] gave a calculated value of $[\alpha]^{27}D$ −5.6° (neat) for the pure enantiomer. This value was subsequently revised[14] to $[\alpha]^{25}D$ −5.8° (neat) based on a combination of further resolution and glpc analysis *via* the *o*-methylmandelates. It now seems certain that some racemization of the *o*-methylmandeloyl moiety had taken place during the preparation of the diastereomeric esters, thereby leading to a calculated value which was high. Formation of the (+)- and (−)-MTPA esters of partially active methyltrifluoromethylcarbinol and analysis of their nmr spectra and gas chromatograms gave maximum rotation values of $[\alpha]^{24}D$ −5.15 ± 0.09° and −5.07 ± 0.08° (neat) respectively. Preparative glpc resolution of the mixture of diastereomeric esters made from pure (−)-MTPA and racemic methyltrifluoromethylcarbinol gave a recovered (−) ester which contained 1.5 ± 0.5% of the other diastereomer. Lithium aluminum hydride reduction of this ester regenerated methyltrifluoromethylcarbinol, $\alpha^{25}D$ −6.19° (neat). Correcting for the amount of (+) enantiomer present gives a value of $\alpha^{24}D$ −6.39°, $\alpha^{25}D$ −5.07 ± 0.09° (neat, d_4^{25} 1.263) for the totation of the pure enantiomer. These limits of error include the uncertainty in determining the signal areas, the optical rotation, and the density.

A study of the data in Table I shows certain relationships between chemical shifts and configuration within closely related series. However, in general it seems premature to speculate on these relationships with the limited data available. One conclusion, which applies to the diastereomeric esters of the aliphatic alcohols so far studied, is as follows: when the signal(s) from the R group attached to the carbinol carbon on one isomer (IVA) is shifted downfield with respect to the signal(s) for this same R group in the other diastereomer (IV B), the reverse will be true for the signal(s) from the R′ group; *i.e.*, when the signals for the R group are shielded, those for the R′ group will be relatively deshielded.

Table II compares the enantiomeric composition (% e.e.) of a number of compounds determined by optical rotation and by the nmr method. The agreement, which is at worst within 1%, confirms the reliability of MTPA as a general reagent for the determination of enantiomeric composition of alcohols and amines. The accuracy of the method can be improved in specific cases by careful standardization of procedures and especially by the use of multiple-scanning summation techniques.

The recommended procedure for the preparation of the diastereomeric derivatives, either esters or amides, is described in the experimental section. Since treatment of the acid, I, with thionyl chloride can give some acid anhydride, which is very much less reactive than the acid chloride II, it is recommended that the acid chloride be vacuum distilled before use. It can be stored in sealed vials and used as needed. Generally a full molar excess of the acid chloride was taken if undistilled material was employed; this is unnecessary when the distilled acid chloride is used, since it has been observed that 0.2 molar excess, and in one case 0.02 molar excess, was sufficient to achieve complete reaction. Analytical determinations were routinely conducted starting with 0.1 to 0.2 mmol of carbinol, *i.e.*, about 20 mg of an alcohol such as phenyl-*t*-butylcarbinol, although initial experiments were carried out on larger amounts.

Racemic α-methoxy-α-trifluoromethylphenylacetic acid[15] (MTPA) was made from phenyl trifluoromethyl ketone[16] (I) by cyanide addition in 1,2-dimethoxyethane (glyme) solvent followed by methylation with dimethylsulfate to give VI, which was distilled and then hydrolyzed in two stages without isolation of the intermediate amide to give MTPA in high over-all yield. This procedure is preferable to hydrolysis of the cyanohydrin to give α-hydroxy-α-trifluoromethylphenylacetic acid followed by resolution and then methylation.[15]



The acid (I) is readily resolved *via* crystallization of the α-phenylethylamine salts from ethanol. Using both isomers of the resolving agent, 70% of the acid may be obtained in either the enantiomerically pure (+) or (−) form. The optically active distilled acid chloride (II) is formed in nearly quantitative yield by refluxing with excess thionyl chloride for 50 hr.

Pirkle and Beare[17] have concluded that (−)-methyl α-hydroxy-α-trifluoromethylphenylacetate has the absolute *R* configuration based upon correlation of its nmr chemical shift in (−)-1-naphthylethylamine with those of (*R*)-(−)-methyl mandelate, (*R*)-(−)-methyl atrolactate, and (*R*)-(+)-methyl α-hydroxy-α-trichloromethylphenylacetate. Since α-hydroxy-α-trifluoromethylphenylacetic acid [(+) in methanol and water, (−) in chloroform] is converted to (−)-methyl α-hydroxy-α-trifluoromethylphenylacetate (neat) and (+)-methyl α-methoxy-α-trifluoromethylphenylacetate (neat), which is converted into (+)-α-methoxy-α-trifluoromethylphenylacetic acid, it follows that all of these have the *R* configuration based on this evidence. Preliminary circular dichroism studies[18] are

(11) Per cent enantiomeric excess (% e.e.) by definition is the per cent excess of the preponderant enantiomer over the racemate.

(12) J. W. Crawford, *J. Chem. Soc.*, 4280 (1965).

(13) D. M. Feigl, Ph.D. Thesis, Stanford University, 1965.

(14) J. W. Crawford, *J. Chem. Soc.*, 2322 (1967).

(15) D. L. Dull and H. S. Mosher, *J. Amer. Chem. Soc.*, **89**, 4230 (1967).

(16) K. T. Dishart and R. Levine, *ibid.*, **78**, 2268 (1956); also commercially available.

(17) W. H. Pirkle and S. D. Beare, *Tetrahedron Lett.*, 2579 (1968). There is a typographical error on page 258; the symbol with formula 2 should be *R*-(−).

(18) W. Voetler and E. Bunnenberg, private communication.

TABLE I

NMR CHEMICAL SHIFTS OF DIASTEREOMERIC ESTERS AND AMIDES OF (+)-α-METHOXY-α-TRIFLUOROMETHYLPHENYLACETIC ACID[a]

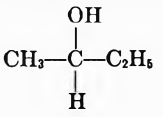
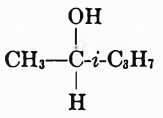
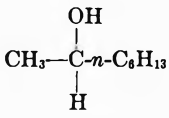
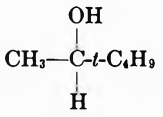
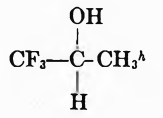
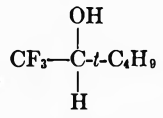
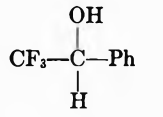
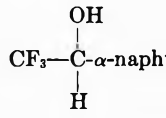
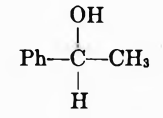
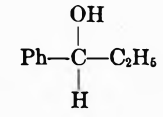
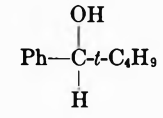
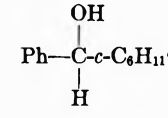
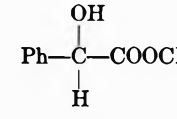
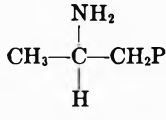
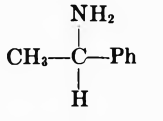
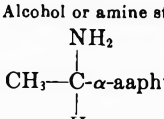
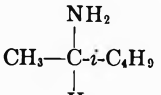
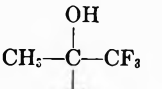
Alcohol or amine structure	Registry no.	Configuration,[b] *R* or *S*	Chemical shifts of diastereomers in Hz downfield of TMS or TFA[c] CF₃	OCH₃	H	CH₃	Other
	20445-05-0	*R* (−)	539	214[d]	306	73	56[e]
	20445-06-1	*S* (+)	532	216	306	79	48
	20445-07-2	*R* (−)	581	212[d]	299.5	72.3	55.5[f]
	20445-08-3	*S* (+)	565	214	299.5	77	51
	20445-09-4	*R* (−)	576	213	278	...	...
	20445-10-7	*S* (+)	546	213	278	...	...
	20445-11-8	*R* (−)	601	211[d]	292.3	71.2	53.8[g]
	20445-12-9	*S* (+)	581	214	294.3	75.3	51
	20445-13-0	*R* (+)	422	212	328	82.5	−240[i]
	20445-14-1	*S* (−)	395	209	328	89.5	−265
	20445-15-2	...	600	216	318	...	53[g]
		...	600	210	320	...	58
	20445-16-3	*S* (+)	551	208	381.2	...	−1106[i,j]
	20445-45-2	*R* (−)	501	216	376.8	...	−1086
	20445-17-4	...	562	208	...	...	100[i]
		...	495	219	...	...	117
	20445-18-5	...	547	213	366	96.5	...
		...	499	208	369	93	...
	20445-19-6	...	537	206	356.2	...	48.7[e]
		...	501	211	351.5	...	54
	20445-20-9	*R* (+)[k]	670	209[d]	345.5	...	53[g]
	20445-21-0	*S* (−)	623	210	337.5	...	56
	20445-22-1	*S* (−)[k]	−682[i]	210	336	...	...
	20445-23-2	*R* (+)	−648	205	342	...	...
	20455-46-3	*S* (+)	270	213	368	...	227[m]
	20455-47-4	*R* (−)	263	222	368	...	227
	20445-24-3	*R* (−)	695	192	260	66	...
	20445-25-4	*S* (+)	648	195	260	70	...
	20445-26-5	*R* (+)	710	198	308	83.7	...
	20445-27-6	*S* (−)	687	201	308	87.6	...

TABLE I (*Continued*)

Alcohol or amine structure	Registry no.	Configuartion,[b] R or S	Chemical shifts of diastereomers in Hz downfield of TMS or TFA[c] CF₃	OCH₃	H	CF₃	Other
	20445-28-7	(+)	739	195	359	98.5	...
		(−)	695	197	359	101.5	...
	20445-29-8	...	687	204	248	66.0	...
		...	677	204	248	69.5	...
	20445-30-1	...	575	212	...	131	−462[i]
		...	535	216	...	132.5	−462

[a] See Experimental Section for details of experimental conditions. If an entry is preceeded by a (−), it indicates that the signal was upfield from the TFA standard rather than downfield. The values refer to 94.1 MHz, ^{19}F and 60 MHz, ^{1}H nmr. [b] The configuration and/or sign of rotation of the alcohol or amine used for preparation of the ester or amide is indicated. No entry indicates that racemic alcohol or amine was used. [c] The diastereomer with furthest downfield α-CF_3 signal is listed first. Where identical values are given for both diastereomers, the differences in chemical shifts was 0.2 Hz or less or the coupling pattern was so complex that small differences which existed could not be determined by direct inspection of the spectra. [d] The assignment of the signals to the appropriate diastereomers was ambiguous and may be reversed. [e] The terminal methyl proton signal of the ethyl group. [f] The terminal methyl proton signal of the isopropyl group. [g] The proton signal of the *t*-butyl group. [h] Carbon tetrachloride solvent used instead of deuteriochloroform. [i] The fluorine signal of the carbinyl trifluoromethyl group. [j] External trifluoroacetic acid standard. [k] See ref 20. [l] c-C_6H_{11} represents the cyclohexyl group. [m] The methyl proton signal of the carbomethoxy group.

TABLE II

COMPARISON OF ENANTIOMERIC COMPOSITION DETERMINED BY OPTICAL ROTATION AND NMR ANALYSIS OF DIASTEREOMERIC MTPA DERIVATIVES

Alcohol or amine Structure	Mmoles	Per cent enantiomeric excess[a,b] Optical Rotation	Nmr of MTPA derivative A-60, ^{1}H	HA-100, ^{19}F
$CH_3CH(OH)C_2H_5$	0.23	82.4	82.0	...
$CH_3CH(OH)$-*n*-C_6H_{11}	2.3	96.1	...	96.5
$CH_3CH(OH)$-*i*-C_3H_7	4.6	95.5	95.0	...
	5.7	95.5	95.0	95.3
$CH_3CH(OH)$-*t*-C_4H_9	0.35	7.8	7.5	...
$CH_3CH(OH)CF_3$	0.48	75.8[e]	75	...
	0.36	97[e]	98	...
$PhCH(OH)CF_3$	5.6	45.2	45.5	...
	0.15	45.2	44.9	...
PhCH(OH)-c-C_6H_{11}	0.26	78.5	77.5	79.0
PhCH(OH)-*t*-C_4H_9	6.7	100	100[d]	...
	0.14	100	100[d]	...
$PhCH(OH)COOCH_3$	0.12	67.1	67.0	67.3
$PhCH(NH_2)CH_3$	25	100	100[d]	100
	0.43	42.2	42.4	...
$PhCH_2CH(NH_2)CH_3$	16	100	100[d]	100
	0.22	100	100[d]	100
PhCH(NH_2)-α-Naph	5.8	36.4[c]	35.0	36.0

[a] By definition, per cent enantiomeric excess (% e.e.) equals the per cent of the predominant isomer in excess of the racemate. [b] Proton resonance determined on Varian Associates A-60 spectrometer and ^{19}F resonance determined either on Varian Associates DP-60 (56.4 MHz) or HA-100 (94.1 MHz) spectrometers under conditions given in the Experimental Section. The precision of all determinations was better than ±1%. [c] Composition of the enantiomer mixture was determined by quantitative mixing of the two pure enantiomers. [d] Signals for only one diastereomer observed. [e] Rotation of pure enantiomer based on $\alpha^{24}D$ −6.39° (neat, l = 1) obtained by preparative glpc resolution of the MTPA ester followed by lithium aluminum hydride regeneration.

also best interpreted in terms of the *R*-(+) configuration for (+)-MTPA. However, our experience with aberrant ORD curves for these same derivatives[15] makes it seem at least possible that the same factors which render the ORD data unreliable for establishing the configuration in this particular series might also be operating in these other methods. Therefore we prefer to leave the question of the absolute configuration of the MTPA reagent open until chemical proof, such as that obtained for the secondary trifluoromethylcarbinols,[19] has been obtained.

Experimental Section

Nmr Measurements.—The proton nmr spectra were obtained at 36° on a Varian Associates A-60 spectrometer using, except where otherwise specified, deuteriochloroform solvent and approximately 3% tetramethylsilane (TMS) as an internal standard. The fluorine nmr spectra were obtained with Varian HA-100 (94.1 MHz) and DP-60 (54.6 MHz) spectrometers using a solvent mixture of 80% deuteriochloroform and approximately 20% trifluoroacetic acid (TFA) by volume as an internal standard added immediately prior to making the determination. The precise chemical shift was dependent upon the amount of TFA added; therefore, the values in Table I have been recorded only to the nearest hertz, for fluorine. Although we experienced few difficulties with the potentially destructive trifluoroacetic acid as an internal standard, it might be preferable to use it as an external standard, or to substitute another neutral standard in certain cases. However, the TFA has a significant effect on the chemical shift differences. Thus the α-CF_3 signals are shifted upfield, when the TFA is external, from the position when the TFA is internal. The chemical shift differences between diastereomers are larger when internal TFA is used. The difference for the α-CF_3 signals for the diastereomeric 2-butyl esters (Table I, example 1) is 7 Hz when TFA is internal and 1-2 Hz when external. Determinations of diastereomer ratios were usually based on machine integrals; accurate values were dependent upon very careful machine tuning, although this was less critical for the determinations using the fluorine signals where large chemical shift differences were observed. When proton signals were resolved, measuring relative peak heights gave answers which corresponded to those obtained by machine integration. This procedure was much simpler and was used when it was established that it was reliable in a specific case. The glpc separations and analyses were performed with a Varian Aerograph A-90-P3 instrument using a 30 ft × 3/8 in., 30% STAP column on 60/80 DMGS-W support.

Alcohols and Amines.—Racemic trifluoromethyl-*t*-butylcarbinol,[20] phenyltrifluoromethylcarbinol[20] α-naphthyltrifluoromethylcarbinol[21] were made by lithium aluminum hydride reduction of

(19) H. Peters and H. S. Mosher, *J. Org. Chem.*, **33**, 4245 (1968).
(20) D. M. Feigl and H. S. Mosher, *ibid*, **33**, 4242 (1968).
(21) W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **89**, 5485 (1967).

the corresponding ketones. Methylphenyltrifluoromethylcarbinol[7] was made in 89% yield by the action of phenylmagnesium bromide on methyltrifluoromethyl ketone. Other carbinols and both isomers of α-phenylethylamine (Norse Chemical Corporation), α-(1-naphthyl)ethylamine (Aldrich Chemical Co.), and α-benzylethylamine (Mann Research Laboratories) were commercially available. Partially active (+)-phenyltrifluoromethylcarbinol,[20] phenylcyclohexylcarbinol,[22] phenylethylcarbinol,[7] and phenyl-*t*-butylcarbinol[20] were obtained by asymmetric reduction of the corresponding ketones. Optically active methylethylcarbinol,[23] methylisopropylcarbinol,[24] and methyl-*n*-hexylcarbinol[25] were obtained by classical resolutions.

(+)-α-Methoxy-α-trifluoromethylphenylacetic Acid (MTPA) (I).—Phenyl trifluoromethyl ketone (159 g, 0.915 mol, Columbia Organic Chemicals Co.), powdered sodium cyanide (77 g, 1.57 mol) and 1,2-dimethoxyethane (glyme, 400 ml, freshly distilled, bp 85°) were mixed at room temperature and stirred for 1.5 hr. The temperature initially rose to about 40°. Dimethyl sulfate (150 g, 1.12 mol) was added dropwise over a 5-hr period at such a rate that the temperature did not exceed about 60°. Pentane (200 ml) was added to the cooled reaction mixture, the precipitated salts were removed by filtration, the solvent was evaporated, and the residue was distilled to give α-methoxy-α-trifluoromethylphenylacetonitrile (192 g, 97.5% yield, bp 85–89° (20 mm); 39–40° (2 mm), Water (50 ml) was carefully added to a mixture of the nitrile (192 g) and concentrated sulfuric acid (600 ml). After heating the two-layer mixture on the steam bath for 2 hr with occasional shaking, it became homogeneous. It was heated for an additional 4 hr. The hydrolysis mixture was cooled and extracted with a total of 1 l. of a 3:1 mixture of ether–benzene in three portions. The solvent was evaporated to give a dark residue which was vigorously refluxed with sodium hydroxide (120 g in 400 ml of water) for 3 hr. The cooled mixture was extracted with ether (2 25-ml portions from which 18.7 g, 11% yield of amide was recovered upon evaporation) and the aqueous layer acidified with sulfuric acid. The acidified layer was extracted with a 3:1 ether–benzene mixture and the extracts were dried ($MgSO_4$), the solvent evaporated, and the residue was distilled to give MTPA (131.7 g, 63% yield), bp 105–110° (1 mm).

Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.28; H, 3.87. Found: C, 51.24; H, 4.03.

Resolution of α-Methoxy-α-trifluoromethylphenylacetic Acid.—Racemic MTPA (87.3 g), (+)-α-phenylethylamine (45.0 g, $\alpha^{25}D$ 37.34°, neat, l = 1) and ethanol (300 ml) were mixed. The salt which formed immediately was dissolved by heating on the steam bath, and the solution was insulated and allowed to cool slowly without being disturbed for 48 hr. The salt was collected by filtration, washed with a minimum of cold ethanol, and recrystallized twice from ethanol to give 29.0 g, mp 195–198°, $[\alpha]^{26}D$ 59.1 ± 1.1° (*c* 1.32, EtOH). Reprocessing solids from the filtrate gave an additional 14.5 g, $[\alpha]^{19}D$ 62.5 ± 1.6° (c 1.23, EtOH). These combined crystals were decomposed with dilute hydrochloric acid and the regenerated acid extracted with ether. The extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue distilled to give the (+) was acid, 28.6 g, bp 116–118° (1.5 mm), $[\alpha]^{25}D$ 68.5 ± 1.3° (*c* 1.49, CH_3OH). The more soluble salt fractions were decomposed in the usual manner and the isolated acid treated with (−)-α-phenylethylamine (30 g, $[\alpha]^{25}D$ −36.34°, neat l = 1) in ethanol (230 ml). Processing the salt as above gave a total of 55.4 g, $\alpha^{28}D$ −60° ± 2° (*c* 1, EtOH) which was decomposed as above to give 34.7 g, bp 115–117° (1.5 mm), $[\alpha]^{24}D$ −71.8 ± 0.6° (*c* 3.28, CH_3OH). The total recovery on the resolution was 72%.

α-Methoxy-α-trifluoromethylphenylacetyl Chloride (II).—(+)-MPTA (41.0 g), thionyl chloride (75 ml, distilled practical grade) and sodium chloride (0.5 g) were refluxed together for 50 hr. After excess thionyl chloride was removed by vacuum evaporation, the residue was distilled to give 43.8 g, 90% yield, bp 54–56° (1 mm), $[\alpha]^{24}D$ 129.0 ± 0.2 (*c* 5.17, CCl_4), $\alpha^{25}D$ −10.0 ± 0.1° (neat, l = 1). Shorter reaction times result in a second higher-boiling product, bp 130–155° (1 mm), which was identified as the anhydride.

2,2,2-Trifluoroacetophenone Cyanohydrin.—The following procedure was used when the cyanohydrin was isolated. A solution of 81.6 g (1.23 mol) of potassium cyanide in 300 ml of water and 60 ml of ethanol in a 2-l flask was kept between 0 and 5° while 216 g (1.22 mol) of 2,2,2-trifluoroacetophenone (Peninsular Chemical Research) was added dropwise with stirring over a period of 40 min. A solution of 72 ml of 96% sulfuric acid and 180 ml of water was added with maintenance of the temperature below 10°. After the mixture had warmed to room temperature, it was extracted with ether. After drying ($MgSO_4$), the ether was evaporated to give a solid residue which was recrystallized from hexane: 208.7 g (83% yield); mp 75–77°; ir ν_{max}^{KBr} 3380, 1450, 1260, 1210, 1175, 1125, 1010, 930, 760, 740, and 695 cm^{-1}.

Anal. Calcd for $C_9H_6F_3NO$: C, 53.73; H, 3.06; N, 6.96. Found: C, 53.45; H, 2.85; N, 6.79.

α-Hydroxy-α-trifluoromethylphenylacetamide.—2,2,2-Trifluoroacetophenone cyanohydrin (138 g, 0.68 mol) was dissolved in 96% sulfuric acid (1.5 l) at room temperature. After 15 min, the solution was poured onto ice and the product extracted with ether. The extract was washed with water, dried ($MgSO_4$), and the ether removed to give, after recrystsllization from hexane–benzene, 134.6 g (83% yield) of the amide: mp 102–103°; ir ν_{max}^{KBr} 3530, 3400, 3200, 1700, 1570, 1260, 1190, 1170, 980, 950, 750, and 700 cm^{-1}.

Anal. Calcd for $C_9H_8F_3NO_2$: C, 49.32; H, 3.67. Found: C, 49.40; H, 3.73.

α-Hydroxy-α-trifluoromethylphenylacetic Acid.—A solution of α-hydroxy-α-trifluoromethylphenylacetamide (107.5 g) in water (700 ml) containing potassium hydroxide (132 g) was refluxed for 4.5 hr. The amide is acidic enough so that it dissolves in the base, and the progress of the hydrolysis was followed by noting ammonia evolution. The cooled solution was poured onto ice and hydrochloric acid. The product was extracted with ether, dried ($MgSO_4$), and recrystallized from benzene: 92.5 g (85%); mp 110.5–111.5°; ir ν_{max}^{KBr} 3400, 3060, 1740, 1210, 1180, 1120, 1000, 950, and 700 cm^{-1}.

Anal. Calcd for $C_9H_7F_3O_3$: C, 49.10; H, 3.20. Found: C, 49.35; H, 3.25.

Alternatively, the acid can be obtained by direct hydrolysis of the nitrile by heating it with 12 times its volume of concentrated hydrochloric acid for 4 hr at 110° in a Carius tube: yield 84%.

Resolution of α-Hydroxy-α-trifluoromethylphenylacetic Acid with (+)-α-(1-Naphthyl)ethylamine.—A mixture of 22.0 g (0.1 mol) of racemic α-hydroxy-α-trifluoromethylphenylactic acid and 17.2 g (0.1 mol) of (+)-α-(1-naphthyl)ethylamine (Aldrich Chemical Co.), $\alpha^{20}D$ 81.35° (neat, l = 1) in 80 ml of 6:1 benzene-ethanol was prepared. Heat was evolved and the salts precipitated immediately. Two recrystallizations of this material from the same solvent system gave 7.5 g of salt, $[\alpha]^{22}D$ 15.5 ±1.2° (*c* 1.68, ethanol). In a trial resolution, material with this rotation remained unchanged on further recrystallization. Decomposition of this fraction with dilute hydrochloric acid and recrystallization of the product from hexane–benzene gave, in three fractions, 4.09 g, mp 123–124°. All fractions had $[\alpha]^{20}D$ −22.5 ± 0.7° (*c* 2.70, chloroform), $[\alpha]^{20}D$ 31.1 ± 0.7° (*c* 2.76, water) within experimental error, indicating that the initial product was probably stereochemically homogeneous. Concentration of the mother liquors gave two additional salt fractions of 3.09 g, $[\alpha]^{23}D$ 14.3 ± 0.6° (*c* 2.93, ethanol), and 12.6 g, $[\alpha]^{22}D$ 0.0° (c 5.5, ethanol). Decomposition of these fractions gave, after recrystallization, 1.0 g, $[\alpha]^{20}D$ −23.2 ± 0.7° (*c* 2.93, chloroform), and 5.4 g, $[\alpha]^{22}D$ 8.8 ± 0.6° (*c* 3.62, chloroform). Decomposition of the remaining salt fractions gave, after recrystallization, 4.3 g, $[\alpha]^{19}D$ 9.3 ± 0.3° (*c* 3.56, chloroform).

A subsequent exploratory resolution with (−)-α-phenylethylamine in methylene chloride was also successful.

Methyl α-Hydroxy-α-trifluoromethylphenylacetate.—A solution of the α-hydroxy acid (92.5 g) in methanol (350 ml) was saturated with dry hydrogen chloride and refluxed for 3 hr; the esterification mixture was cooled, resaturated, refluxed for an additional 2.5 hr, and allowed to stand at room temperature overnight. After distilling the methanol, the residue was taken up in ether, washed with saturated salt solution and sodium bicarbonate, dried ($MgSO_4$), and the product distilled: 82.7 g (84%); bp 86–92° (2–3 mm); ir ν_{max}^{film} 3470, 1745, 1450, 1435, 1300, 1235, 1170, 1125, 1075, 1000, 955, 800, 770, 735, and 710 cm^{-1}.

Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.28; H, 3.87. Found: C, 51.22; H, 4.02.

(22) R. McLeod, F. J. Welch, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960).

(23) A. W. Ingersoll, *Org. Reactions*, **2**, 403 (1944).

(24) Pickard and Kenyon, *J. Chem. Soc.*, **101**, 620 (1912).

(25) R. L. Shriner and J. H. Young, *J. Amer. Chem. Soc.*, **52**, 3332 (1930).

(+)-α-Hydroxy-α-trifluoromethylphenylacetic acid, $[\alpha]^{19}D$ 9.3° ($CHCl_3$, 40% enantiomerically pure), gave methyl ester (83% yield), $\alpha^{19}D$ 6.90 ± 0.06° (neat, l = 1).

Methyl α-Methoxy-α-trifluoromethylphenylacetate.—A mixture of the α-hydroxy ester (82.7 g), dry silver oxide (98.7 g), methyl iodide (550 g), Dreirite (94 g), and glass beads was stirred vigorously under reflux for 50 hr. The reaction mixture was filtered, the solid was extracted with ether, and the extracts and filtrate were distilled to give 78.5 g, bp 93–96° (4 mm).

Anal. Calcd for $C_{11}H_{11}F_3O_3$: C, 53.22; H, 4.46. Found: C, 53.33; H, 4.60.

Optically active acid, $[\alpha]^{22}D$ 8.8° ($CHCl_3$, 39.1% enantiomerically pure), was converted in 90% yield into (−)-methyl α-methoxy-α-trifluoromethylphenylacetate, $\alpha^{20}D$ −48.64 ± 0.04° (neat, l = 1), $[\alpha]^{21}D$ −37.5 ± 0.02° (c 4.48, acetone).

Racemic methyl ester methyl ether was hydrolyzed by refluxing with a 1:3:16 mixture by weight of potassium hydroxide, ethanol, and water for 45 min to give α-methoxy-α-trifluoromethylphenylacetic acid identical with that obtained by the direct procedure. There was no racemization of the optically active methyl ester methyl ether under the same conditions.

Preparation of Esters and Amides of MTPA.—The synthesis of N′-α-(1-naphthyl)ethyl-α-methoxy-α-trifluoromethylphenylacetamide will illustrate the procedure for the preparation of both esters and amides in gram quantities when only the undistilled acid chloride was available. The synthesis of phenyltrifluoromethylcarbinyl α-methoxy-α-trifluoromethylphenylacetate will illustrate the procedure, used for the preparation of milligram amounts, which is recommended as a general procedure for use in determining the enantiomeric composition of either alcohols or amines. Purification of the final product, if required, can be done either by preparative glpc, by column chromatography on silica gel using benzene solvent, or by preparative tlc. Separation of diastereomers can take place by these methods, and care must be exercised that both isomers are completely collected. All key compounds gave satisfactory analyses, and all compounds gave spectra consistent with their assigned structures, taking into consideration nmr nonequivalence of diastereotopic groups.

N-α′-(1-Naphthyl)ethyl-α-methoxy-α-trifluoromethylphenylacetamide.—A sample of partially active (−)-α-naphthylethylamine, 1.09 g, $[\alpha]^{24}D$ −37.32° (c 7, EtOH), was added to a mixtur of undistilled MTPA Cl (prepared by refluxing 3.7 g of (−)-MTPA and excess thionyl chloride for 5 hr and then removing the excess thionyl chloride *in vacuo*) dissolved in carbon tetrachloride (17 ml) and pyridine (5 ml). The mixture was refluxed for 90 min and the crude product (2.6 g) isolated by acidifying, extracting, washing with base, drying, and evaporating the solvent. A sample was removed for nmr analysis (Table I) and the remainder recrystallized from hexane–benzene.

Anal. Calcd for $C_{22}H_{20}NF_3O_2$: C, 68.23; H, 5.17; N, 3.62. Found: C, 68.35; H, 5.32; N, 3.60.

Before recrystallization of the product, both nmr and ir spectra showed that acid anhydride was present (*cf.* Figure 2A).

Phenyltrifluoromethylcarbinyl α-Methoxy-α-trifluoromethylphenylacetate.—Phenyltrifluoromethylcarbinol [0.0262 g, 0.148 mmol, $\alpha^{25}D$ 18.51° (neat, l = 1)] and distilled (+)-MTPA Cl (0.0379 g, 0.15 mmol) were mixed with carbon tetrachloride (5 drops) and dry pyridine (5 drops) and allowed to stand in a stoppered flask for 12 hr. Water (1 ml) was added and the reaction mixture transferred to a separatory funnel with ether (20 ml). The ether solution, after washing successively with dilute hydrochloric acid, saturated sodium carbonate solution, and water, was dried ($MgSO_4$), filtered, evaporated, and the residue was dissolved in deuteriochloroform for nmr analysis. A larger sample prepared by the same procedure was purified by glc (retention times of the diastereomers 20.0 and 21.8 min, 220°, helium flow rate 94 cm³/min).

Anal. Calcd for $C_{18}H_{14}O_3F_6$: C, 55.11; H, 3.59. Found: C, 55.34; H, 3.70.

Methylphenyltrifluoromethylcarbinyl α-Methoxy-α-trifluoromethylphenyl Acetate.—When the general procedure was applied to the tertiary alcohol, methylphenyltrifluoromethylcarbinol,[7] the yield was negligible but was 20% when refluxed for 14 hr in excess pyridine. The ester was purified by glpc; the diastereomers had retention times of 20.6 and 22.2 min on a 5-ft × 0.25-in., 20% silicone M rubber column at 155° and a helium flow rate of 64 ml/min.

Methyl-*t*-butylcarbinyl-α-Methoxy α-trifluoromethylphenylacetate.—Methyl-*t*-butylcarbinol (0.036 g, $\alpha^{25}D$ 0.49 ± 0.02° (neat, l = 1), obtained from the asymmetric reduction of methyl *t*-butyl ketone by Grignard reagent from (+)-1-iodo-2-methylbutane,[10] distilled MTPA Cl (0.111 g, from pure (+) acid), and pyridine (0.5 ml) were allowed to stand for 1 hr. Water was added to the cooled mixture which was then extracted with ether. The ether extract was washed successively with dilute hydrochloric acid and dilute sodium carbonate solution, dried ($MgSO_4$), and evaporated to give a residual oil. This oil was analyzed by nmr as reported in Table II.

Methyltrifluoromethylcarbinyl α-Methoxy-α-trifluoromethylphenylacetate.—A sample of methyltrifluoromethylcarbinol (0.0554 g, $\alpha^{19}D$ −4.85° (neat, l = 1) was treated with distilled MPTA-Cl (0.1815 g, prepared from pure (+) acid) and pyridine (0.5 ml) for one hour. Water was added and the mixture extracted with ether (20 ml). The ether extract was washed with dilute hydrochloric acid, sodium carbonate solution, and water, and dried ($MgSO_4$). The residue on evaporation was analyzed both by glpc and nmr as reported in Table II.

Preparative Glpc Resolution of Methyltrifluoromethylcarbinol.—(−)-MTPA (100% e.e.) was converted to the distilled acid chloride. This (−)-MTPA-Cl (12.6 g, 100% e.e. as analyzed by nmr of the (+)-α-phenylethylamide), methyltrifluoromethylcarbinol (6.9 g, Columbia Organic Chemical Company), and carbon tetrachloride (5 ml) were mixed with resulting spontaneous cooling. The solution was cooled to −70°, and dry pyridine (5 ml) was added. The reaction mixture was warmed to room temperature and then heated 1 hr at 100°, cooled, and diluted with ether. The ether extract was washed with dilute hydrochloric acid, dilute sodium carbonate, and water, dried ($MgSO_4$), and distilled to give 9.1 g, bp 71–72° (1 mm). A series of injections of 0.1-ml samples with separate collection of the diastereomers (retention times 48 and 54 min respectively, 30 ft × 3/8 in. STAP column at 150° helium flow rate 55 ml/min) gave the predominant isomer (3.41 g) which by glpc analysis was shown to include 1.5 ± 0.5% of its diastereomer. This mixture was reduced by lithium aluminum hydride in dibutyl ether. The dibutyl ether solution of the product obtained by working up the mixture was distilled and the distillate purified by glpc (SE-30 column 20 ft × 3/8 in., 103°, helium flow rate 58 ml/min, retention time 9.8 min). The glpc purified carbinol was subjected to a vacuum transfer (to preclude the presence of impurities resulting from any "bleeding" of the column) to give (−)-methyltrifluoromethylcarbinol [0.87 g, $\alpha^{25}D$ −6.19 ± 0.02° (neat, l = 1), corrected for e.e., $\alpha^{25}D$ −6.39 ± 0.09°]. This material showed no significant impurities when analyzed on SE-30, STAP, Carbowax 20M-TPA, and 4000 columns. This carbinol (0.0431 g) was reconverted to the MTPA ester using distilled MTPA-Cl 100% e.e. Analysis by both nmr and glpc gave a 99.0:1.0 ± 0.5 diastereomer ratio, thereby confirming the activity of the carbinol and proving that no racemization had taken place during these transformations. The major uncertainty in both determinations is in the base line for the minor component; there cannot be less than 1.0% of the minor component but there might be a maximum of 2.0%.

Registry No.—2,2,2-Trifluoroacetophenone cyanohydrin, 20445-04-9; (+)-I, 20445-31-2; (−)-I, 17257-71-5; II, 20445-33-4; α-hydroxy-α-trifluoromethylphenylacetamide, 20445-34-5; α-hydroxy-α-trifluoromethylphenylacetic acid, 20445-35-6; methyl α-hydroxy-α-trifluoromethylphenylacetate, 20445-36-7; methyl α-methoxy-α-trifluoromethylphenylacetate, 20445-37-8.

The Oxidation of Oxygen-Labeled Phenylacetic Anhydride by Pyridine N-Oxide. The Relative Nucleophilicities of Pyridine and Pyridine N-Oxide[1a]

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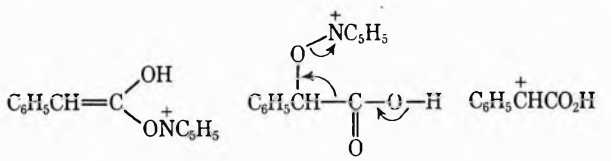
The reaction of pyridine N-oxide with phenylacetic anhydride, uniformly labeled with ^{18}O, produces unlabeled benzaldehyde, indicating that the oxygen atom of the product is derived from the amine oxide. When this reaction is conducted in a large excess of pyridine, the ratio of benzaldehyde to N-benzylpyridinium ion produced is 0.12–0.23, indicating that pyridine N-oxide is substantially more nucleophilic than pyridine toward the intermediate. By the use of competition experiments, it was determined that the ratios of nucleophilic attack of pyridine to that of the N-oxide on methyl iodide, benzhydryl bromide, and *p*-methoxybenzhydryl bromide are 8–15, 5.7, and 3.8, respectively. It is concluded that attack by pyridine N-oxide becomes relatively more favorable as the positive charge on the electrophile increases. This implies that the carbon atom of the intermediate which is to become bonded to the N-oxide group in the oxidative decarboxylation bears a high positive charge. It is suggested that the α-carboxybenzyl cation (**3**) or its conjugate base is the intermediate which is directly attacked by pyridine N-oxide.

The oxidation of phenylacetic anhydride by pyridine N-oxide produces benzaldehyde and proceeds with the given stoichiometry.[2-5] The suggestion has been

$$(C_6H_5CH_2CO)_2O + 2C_5H_5NO \longrightarrow C_6H_5CHO + 2C_5H_5N + CO_2 + C_6H_5CH_2CO_2H$$

made[2,4,5] that the reaction involves acylation of pyridine N-oxide followed by nucleophilic displacement of pyridine by a second pyridine N-oxide molecule from the enol (**1**) (or the corresponding enolate) of the acylation product to produce the cation (**2**) (or the corresponding carboxylate species). Loss of a proton, carbon dioxide, and pyridine from **2** would lead to the major observed products.[6] The attack of pyridine N-oxide on **1** could be S_N2' or S_N1' in nature; in the latter case, the cation **3** or its conjugate base would be an intermediate.



1 **2** **3**

Some such electrophilic intermediate has been trapped by acetic acid and by pyridine, each utilized as a solvent.[5] In the latter case, it has now been found that a significant quantity of benzaldehyde (0.05–0.10 mol per mole of carbon dioxide generated) is produced in addition to the N-benzylpyridinium ion, **4** (0.43 mol per mole of carbon dioxide), which is thought to be formed by the known[7] decarboxylation shown. It is

$$C_6H_5\underset{\underset{+NC_5H_5}{|}}{CHCOOH} \longrightarrow \underset{\mathbf{4}}{C_6H_5CH_2\overset{+}{N}C_5H_5} + CO_2$$

very likely that even more benzaldehyde than that isolated is produced in the reaction since this product is known to be partially destroyed under similar conditions even in the absence of excess pyridine, probably by a Perkin-type condensation with phenylacetic anhydride.[8] In view of the large molar excess (49:1) of pyridine over pyridine N-oxide in this experiment, the considerable degree of capture of the intermediate by pyridine N-oxide would require the latter to be substantially more nucleophilic than pyridine toward the electrophilic intermediate in order for the above mechanism to be acceptable. Such a nucleophilicity order is *a priori* unexpected since pyridine is almost 10^5 times more basic than pyridine N-oxide.[9a] Of course, nucleophilicity does not always correlate well with basicity[10] but we have found (see below) that pyridine is more nucleophilic than pyridine N-oxide toward several substrates and it therefore became necessary to consider the possibility of a mechanistic alternative in which a direct competitive attack of the nucleophiles on the benzylic carbon atom is not required.

One such mechanism, which seems reasonable in a solution containing phenylacetic anhydride and pyridine, involves acylation of the hydroxyl group of **1** prior to the loss of pyridine. The acyloxy group would be expected to stabilize the positive charge of **3** to yield the cation **5**. Attack of pyridine at the partially positive carbon atom or at the carbonyl group might be reversible whereas attack by pyridine N-oxide might lead irreversibly to product **6**, which upon hydrolysis or loss of an anhydride molecule would yield benzaldehyde (only the attack at the carbonyl group is shown in Scheme I).

In order to distinguish between the attack of pyridine N-oxide directly on the α position as required by all previously suggested mechanisms[2-5] and any other mechanism such as the one outlined above, the reaction of pyridine N-oxide with phenylacetic anhydride which was uniformly labeled with ^{18}O (1.4%) was performed. The anhydride was prepared by hydrolysis of phenylacetonitrile with water enriched to the extent of 1.4%

(1) (a) We wish to thank the donors of the Petroleum Research Fund, Administered by the American Chemical Society, for support of this work. (b) NASA Predoctoral Fellow.

(2) T. Cohen and J. H. Fager, Abstracts, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, p 36 C; T. Cohen, I. H. Song, and J. H. Fager, *Tetrahedron Lett.*, 237 (1965).

(3) C. Rüchardt, S. Eichler, and O. Krätz, *ibid.*, 233 (1965); C. Rüchardt and O. Krätz, *ibid.*, 5915 (1966).

(4) T. Koenig, *ibid.*, 3127 (1965); 2751 (1967).

(5) T. Cohen, I. H. Song, J. H. Fager, and G. L. Deets, *J. Amer. Chem. Soc.*, **89**, 4968 (1967).

(6) T. Cohen and I. H. Song, *J. Org. Chem.*, **31**, 3058 (1966).

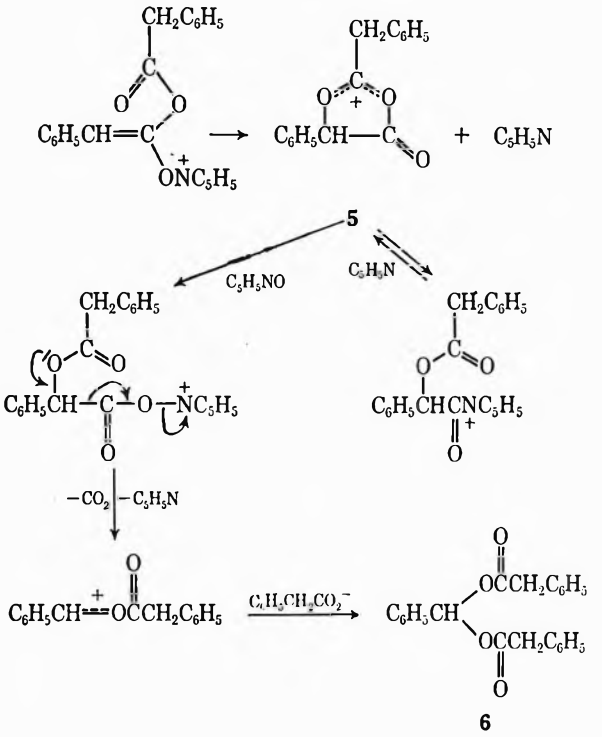
(7) T. Cohen and I. H. Song, *J. Amer. Chem. Soc.*, **87**, 3780 (1965).

(8) T. Cohen and J. H. Fager, *ibid.*, **87**, 5701 (1965).

(9) (a) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., New York, N. Y., 1967, p 97; (b) p 153.

(10) R. Gompper, *Angew. Chem. Intern. Ed. Engl.*, **3**, 560 (1964), and references cited there.

SCHEME I



with ^{18}O. Since commercial samples of such water are also highly enriched with deuterium, it became necessary to convert it into protium water in order to avoid the introduction of deuterium into the benzylic position during the hydrolysis; this would seriously complicate the mass spectrometric analysis of the benzaldehyde produced. The exchange was accomplished very effectively by extended ebullition of the enriched water with hydrogen sulfide.

The resulting benzaldehyde, which was analyzed on the LKB 9000 combined gas chromatograph–mass spectrometer equipped with an accelerating voltage alternator, was found to contain 0.23% ^{18}O, the same as that found for unlabeled benzaldehyde. It is thus clear that pyridine N-oxide does indeed attack the carbon atom which is originally α to the carboxylic acid function as suggested earlier.[2-5]

In order to determine whether a mechanism involving attack of pyridine N-oxide on the α-carbon atom is consistent with the finding that pyridine N-oxide is more nucleophilic than pyridine toward the intermediate, a study of the comparative nucleophilicities of these two bases was undertaken next. An equimolar mixture of the two nucleophiles was allowed to react with each of the following substrates: methyl iodide, benzhydryl bromide, and *p*-methoxybenzhydryl bromide. Methyl iodide was chosen as the prototype of an SN2 substrate; the reaction in this case was performed in acetonitrile since this solvent, unlike several others, allowed a resolution of the nmr peaks used for the product analysis (see below). The experiments with the other two substrates were performed in dimethylformamide in order to maximize the SN1 contribution.

In the case of methyl iodide, the products were N-methylpyridinium iodide and N-methoxypyridinium iodide. Control tests showed that the former is stable under the reaction conditions but that the latter is slowly converted into the former by the action of pyridine. However, without carrying out an extensive kinetic investigation, it is possible with a knowledge of the approximate rate of this conversion to arrive at a minimum (8) and a maximum (15) figure for the ratio of attack of pyridine to that of pyridine N-oxide (see Table I).

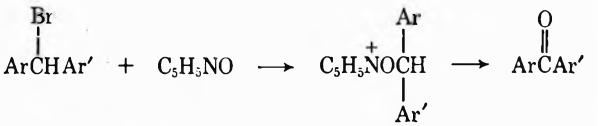
TABLE I

RATIO OF ATTACK OF PYRIDINE TO THAT OF PYRIDINE N-OXIDE ON ALKYL HALIDES

RX	Pyridine attack/ pyridine N-oxide attack	Total yield, %
CH_3I	8–15,[a,b] 9–15[a,c]	*d*
$(C_6H_5)_2CHBr$[e]	5.5, 6.0	97
CH_3O–$C_6H_4(C_6H_5)CHBr$[f]	3.7, 3.9	93

[a] See Experimental Section for method of calculation of minimum and maximum values. [b] Thirteen millimoles of each nucleophile and 11 mmol of methyl iodide in 10 ml of acetonitrile. [c] Thirty-four millimoles of each nucleophile and 8.5 mmol of methyl iodide in 20 ml of acetonitrile. [d] Not determined. [e] Fifty-seven millimoles of each nucleophile and 50 mmol of alkyl halide in 45 ml of DMF. Results are for duplicate experiments. [f] Twenty-five millimoles of each nucleophile and 22 mmol of alkyl halide in 25 ml of DMF. Results are for duplicate experiments.

Attack of pyridine on either of the benzhydryl bromides (7) produces the corresponding N-benzhydrylpyridinium bromide which is stable under the reaction conditions and which was gravimetrically determined as the picrate. Attack of pyridine N-oxide on either bromide produces the unstable salt 8 which, as expected,[11] is rapidly converted into the corresponding benzophenone (9); the latter was determined by gas chromatography.



The results in the table indicate that as the SN1 character of the displacement increases the nucleophilicity of the pyridine N-oxide increases relative to that of pyridine.[12] This is quite understandable on the basis of current knowledge of nucleophilicity, particularly with regard to ambident anions,[10] and of the structure of pyridine N-oxide, the oxygen atom of which has a substantially greater negative charge than the nitrogen atom of pyridine.[9b] A fairly good analogy would be the competition between oxygen and nitrogen attack in the displacement of bromide ion from substituted benzyl bromides by nitrite ion, supplied as the silver salt. The ratio of attack of the formally neutral nitrogen atom to that of the negatively charged oxygen atom decreases from 5.3 to 0.64 in proceeding from the *p*-nitro to the *p*-methoxy substituent.[13] The increased ability of the negative oxygen atom to attack as the positive charge on the target carbon atom is increased is presumably a result of favorable electrostatic interactions in the transition state.

From an extrapolation of the results in Table I, it seems likely that a very high positive charge on the car-

(11) W. Feely, W. L. Lehn, and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957).

(12) Strictly speaking, the ratios of nucleophilic attack in the table are not relative nucleophilicities since a large excess of the nucleophiles was not used. The actual nucleophilicity ratios and also the spread between the two benzhydryl cases would be expected to be somewhat larger.

(13) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

bon atom which is to become bonded to the N-oxide function would be required in order for pyridine N-oxide to be substantially more nucleophilic than pyridine toward the intermediate. Thus, attack of pyridine N-oxide on the cation **3** (or possibly its conjugate base), rather than directly on the enol **1**, is probably indicated. This conclusion is consistent with, but not demanded by, the kinetic study of Koenig[4] which shows that the reaction rate is dependent on the first power of the concentration of pyridine N-oxide.[14]

Further evidence for the intermediate **3** is being sought and the synthetic implications of such cations are under investigation.

Experimental Section

^{18}O-Enriched Phenylacetic Anhydride.—All glassware used throughout the ^{18}O experimental work was oven dried overnight at 180°.

^{18}O-Enriched sodium phenylacetate was prepared as follows. To a solution of 18.9 g (1.05 mol) of ^{18}O-enriched protium water (see below) and 82 ml of absolute ethanol in a flask equipped with a condenser and magnetic stirrer was added piece by piece 8.0 g (0.35 g-atom) of freshly cleaned metallic sodium. Then 41 g (0.35 mol) of phenylacetonitrile, which had been dried over 3-A molecular sieve, was added and the solution was stirred and heated at reflux (78°) for 68 hr. Throughout this period the reaction solution was swept with dry nitrogen to remove ammonia. Evaporation of the solvent left a white solid. The crude solid was dissolved in 200 ml of water and the basic solution extracted with ether to clearness. Evaporation of the water yielded 56.2 g (97%) of pure white material after being dried in a vacuum desiccator ($CaSO_4$).

To a suspension of 10.0 g (0.0633 mol) of ^{18}O-enriched sodium phenylacetate and 40 ml of acetonitrile (refluxed over calcium hydride overnight and distilled at 81°) was added dropwise and with stirring a solution of 6.02 g (0.0317 mol) of pure *p*-toluenesulfonyl chloride in 20 ml of acetonitrile. The reaction mixture was heated at reflux (81°) for 2.5 hr. Evaporation of the solvent left a white solid which was added to 150 ml of ether and the suspension filtered. The solid salt was further washed with ether (three 20-ml portions) and the combined filtrates were washed with 50 ml of 10% sodium carbonate and two 25-ml portions of water. Evaporation of the ether afforded the crude pale yellow product. The material was then dissolved in a minimum amount of ether. Cooling in powdered Dry Ice gave a white crystalline solid which was removed by filtration and dried in a vacuum desiccator ($CaSO_4$) to yield 5.3 g (66%) of pure product, mp 72.0–72.5° (lit.[8] mp 72.5–73.0°).

Analysis of ^{18}O-Enriched Phenylacetic Anhydride.—To determine the per cent enrichment of the labeled anhydride, a derivative, ^{18}O-enriched N,N-diethylphenylacetamide, was prepared by adding 100 mg of the labeled anhydride to 3 ml of diethylamine and heating at reflux for 1 hr. Isotopic analysis, performed on the LKB 9000 combined gas chromatograph–mass spectrometer equipped with an accelerating voltage alternator (Carbowax 20M column at 235°), indicated 1.4 atom % ^{18}O enrichment.

Reaction of ^{18}O-Enriched Phenylacetic Anhydride with Pyridine N-Oxide.—It is essential that anhydrous conditions prevail throughout this reaction. To the extent that water is present, any enriched benzaldehyde produced would be diluted by a hydration–dehydration exchange reaction. The pyridine N-oxide was freshly distilled at 125–130° (0.4 mm). Benzene was refluxed over calcium hydride overnight and distilled (80°) into a 3-A molecular sieve. The pyridine N-oxide, ^{18}O-enriched phenylacetic anhydride, benzene, balance, and appropriate equipment were placed in a glove bag containing phosphorus pentoxide as a desiccant. The bag was filled with nitrogen and then pumped down, the cycle being repeated four times. All weighings and transfers were performed in the dry bag. The flasks were securely stoppered before bringing them out. The reaction was performed in duplicate. Both flasks contained 1.12 g (0.0118 mol) of pyridine N-oxide, 1.50 g (0.0059 mol) of ^{18}O-enriched phenylacetic anhydride, and approximately 35 ml of benzene. The flasks were equipped with dry reflux condensers and the reaction solutions were heated at reflux over nitrogen (dried by passing through Drierite) for 24 hr. After being cooled to room temperature, the flasks were stoppered, sealed with Teflon tape, and stored in a desiccator ($CaSO_4$).

Analysis of Benzaldehyde for ^{18}O-Enrichment.—Combined gas chromatograph–mass spectrometer analysis (Carbowax 20M column at 130°) of the product benzaldehyde indicated an ^{18}O content of 0.23 atom %. An authentic sample of unlabeled benzaldehyde was found to contain 0.2 atom % ^{18}O.

Normalization of ^{18}O-Enriched Deuterium Oxide.—The 1.6 atom % ^{18}O-enriched deuterium oxide was obtained from Bio-Rad Laboratories. Baker CP grade (99.6%) hydrogen sulfide was used. The molecular sieve pellets (3 A,[15] Linde) were activated by drying in an oven at 180° for a minimum of 2 days. The exchange system was assembled as follows. Hydrogen sulfide was passed through a pancake-type single-stage regulator into the activated molecular sieve, then through a three-way stopcock and gas dispersion tube of porosity C into the labeled heavy water. Finally, it was allowed to exit through a spiral condenser and a one-way exit valve. The three-way stopcock, connecting the entrance of the gas dispersion tube to the exit of the condenser, served as a pressure-equalizing system to prevent the labeled water from backing up into the frit and tubing whenever ebullition of hydrogen sulfide was ceased. All line connections in the Tygon tubing were sealed with Teflon tape. The dispersion tube and condenser were likewise sealed onto the flask containing the water. At no time was the system exposed to air. Tubing connectors allowed the molecular sieve to be replaced with freshly activated sieve at least once a week. An ice–water bath was maintained at all times during ebullition to prevent loss of water vapor to the passing hydrogen sulfide. Initially, the temperature was held at 5–6° (deuterium oxide freezes at 4°). After 4 days of exchange, the flask could be immersed in ice without freezing. Thereafter the temperature was held at 1–5°. Through 88 g (4.4 mol) of the ^{18}O-enriched deuterium oxide, 3.9 pounds (53 mol) of dry hydrogen sulfide was slowly bubbled for approximately 660 hr. The water remained clear throughout the exchange. Virtually no free sulfur appeared. After completion of the ebullition, the system was disconnected and the normalized ^{18}O-enriched water was heated at reflux for 2 hr in order to remove dissolved hydrogen sulfide. The labeled water was then distilled at 100°. A recovery of 61.0 g (77%) was obtained. The absence of deuterium in the water was indicated by the lack of deuterium incorporation into the benzaldehyde product of the above reaction; this was clear from the mass spectrogram.

Reactivity of Pyridine and Pyridine N-Oxide toward Methyl Iodide. A.—A solution of 1.25 g (0.013 mol) of pyridine N-oxide, 1.06 g (0.013 mol) of pyridine, and 1.54 g (0.011 mol) of methyl iodide in 10 ml of acetonitrile was stirred for 1 hr at room temperature. The solution was then diluted with acetonitrile[16] and analyzed by comparing the areas of the N-methyl and N-methoxy signals on a Varian A-60 nmr spectrometer. This analysis indicated the presence of 6.2% of N-methoxypyridinium iodide and 93.8% of N-methylpyridinium iodide. However, the control reaction described below showed that under conditions similar to those in this reaction 45% of N-methoxypyridinium iodide is converted into N-methylpyridiniun iodide. This figure is an absolute maximum since (1) the pyridine concentration in the control was greater than that in the reaction itself at all times and (2) in the control, N-methoxypyridinium ion was exposed to the pyridine during the whole hour, whereas in the reaction this ion is generated at an unknown rate as the reaction progresses. A maximum ratio of pyridine attack to that of pyridine N-oxide (93.8/6.2 = 15) can be calculated assuming such slow formation of N-methoxypyridinium iodide that essentially none of it is attacked by pyridine. A minimum value (89/11 = 8) can be calculated assuming that all of the salt produced was exposed to pyridine during the whole hour.

B.—A solution of 3.20 g (0.0337 mol) of pyridine N-oxide, 2.73 g (0.034 mol) of pyridine, and 1.20 g (0.0085 mol) of methyl iodide

(14) If the enolization is rate determining rather than an equilibrium step, this dependence on pyridine N-oxide concentration would be found regardless of the S_Ni' or S_N2' nature of the attack of pyridine N-oxide on the enol **1**.

(15) Selective adsorption of water from hydrogen sulfide occurs with a 3-A molecular sieve. With 4-A or greater hydrogen sulfide itself is absorbed.

(16) Such dilution was necessary in order to separate the N-OMe and N-Me signals.

in 20 ml of acetonitrile was allowed to react as described above. The yields of N-methoxypyridinium iodide and N-methylpyridinium iodide were 6 and 94%, respectively. The maximum and minimum ratios are calculated to be 15 and 9, respectively.

C. Control Tests.—A solution of 0.308 g (0.0013 mol) of N-methoxypyridinium iodide and 1.03 g (0.013 g mol) of pyridine in 7.15 ml of acetonitrile was stirred for 1 hr, at room temperature. At the end of this period the nmr spectrum showed that 45% of the N-methoxypyridinium ion had been converted into the N-methylpyridinium ion. This experiment indicates that the rate of attack of pyridine on the methyl group of the methoxy compound is sufficiently slow so that this mechanism can not account for the much greater apparent nucleophilicity of pyridine. However, this conclusion would be invalid if the iodide ion displaced the O-methyl group, since the concentration of iodide ion in the control test was considerably below that in the competition reaction. The resulting methyl iodide could then methylate pyridine.

Therefore, another test was performed in order to determine whether methylation of the pyridine N-oxide is reversible under the reaction conditions. A solution of 0.320 g (0.00138 mol) of N-trideuteriomethoxypyridinium iodide and 0.184 g (0.00138 mol) of undeuterated methyl iodide in 3.25 ml of acetonitrile was stirred at room temperature for 1 hr. The nmr spectrum indicated that exchange of the methyl groups is negligible.

Another control test showed that N-methylpyridinium iodide is stable toward pyridine N-oxide under the reaction conditions.

Reaction of Pyridine N-Oxide and Benzhydryl Bromide.—Equivalent quantities of pyridine N-oxide and benzhydryl bromide were dissolved in benzene and the solution heated at reflux for 2 hr. Comparison of glpc retention times with those of an authentic sample of benzophenone indicated the presence of this ketone in the reaction mixture.

Reactivity of Pyridine and Pyridine N-Oxide toward Benzhydryl Bromide.—To a solution of 5.417 g (0.0569 mol) of pyridine N-oxide and 4.500 g (0.0569 mol) of pyridine in 45 ml of dimethylformamide (dried over calcium sulfate and distilled under reduced pressure at 60°) was added 12.4 g (0.050 mol) of benzhydryl bromide, which had been purified by recrystallization from hexane. The solution was heated at 80° for 2 hr. Gas chromatograph comparison with an authentic sample indicated that benzophenone was present: Carbowax 20M column at 237°, retention time 12.6 min; Hi-Eff-8BP column at 210°, retention time 14.0 min. By glpc examination the yield of benzophenone was calculated to be 15%. The N-benzhydrylpyridinium bromide product was analyzed as the picrate which was prepared as follows. An aliquot (11.81 g) of the reaction solution was made basic with concentrated ammonium hydroxide. The resulting cloudy solution was extracted with three 10-ml portions of ether. The aqueous solution was then treated with 50 ml of basic ammonium picrate solution and stored in a refrigerator for 3 hr. The yellow crystalline picrate was collected in a Büchner funnel and 100 ml more of ammonium picrate solution was added to the filtrate which was then stored in a refrigerator for 3 hr. The additional picrate was similarly collected and washed with ice water. Treating the filtrate with ammonium picrate solution produced no more precipitate. The product was oven dried at 90° until a constant weight was obtained to yield 3.46 g (82%), mp 171–171.5° (lit.[17] mp 172°). In a duplicate run, the yields were 14% benzophenone and 84% N-benzhydrylpyridinium picrate.

A control test showed that N-benzhydrylpyridinium bromide is stable toward pyridine N-oxide under the reaction conditions.

(17) A. E. Chichibabin, *J. Russ. Phys. Chem. Soc.*, **34**, 133 (1902).

4-Methoxybenzhydryl Bromide.—4-Methoxybenzophenone was prepared in 87% yield by the method of Gattermann, *et al.*[18] The ketone was reduced to 4-methoxybenzhydrol as follows. To a slurry of 2.70 g (0.071 mol) of lithium aluminum hydride and 150 ml of anhydrous ether in a flask equipped with a reflux condenser and magnetic stirrer was added a solution of 30.0 g (0.142 mol) of 4-methoxybenzophenone in 150 ml of anhydrous ether at such a rate as to maintain gentle reflux (addition time, 20 min). The gray slurry was stirred overnight. Excess lithium aluminum hydride was destroyed by slowly adding water through an addition funnel until all hydrogen evolution ceased. The resulting gel was poured onto ice and acidified with 10% aqueous hydrogen chloride. After separation of the ether layer the aqueous layer was extracted to clearness with ether. The combined extract was washed with saturated sodium carbonate solution, water, and dried over Drierite. The solution was concentrated on a rotatory evaporator to approximately 150 ml and stored in a freezer overnight. The white crystalline product was collected on a sintered-glass funnel and air dried to yield 24.5 g (81%), mp 65–66° (lit.[19] mp 65–66°). Recrystallization from hexane afforded white silky needles, mp 66.5–67.0°. An ir spectrum showed an O–H band present at 2.75 μ (s) and no carbonyl band at 5.90 μ.

To a solution of 11.0 g (0.047 mol) of the pure alcohol in 125 ml of spectroscopic grade chloroform was added 10 g of calcium sulfate. Dry hydrogen bromide gas was bubbled through a gas dispersion tube into the solution for 20 min. The light orange solution was flushed with nitrogen and filtered, and the filtrate stripped to yield a deep red oil. The oil was extracted with hot hexane. Concentration and cooling of the extract afforded the product as white crystals rapidly turning to light pink. An ir spectrum showed no O–H band present at 2.75–3.00 μ and no carbonyl band at 5.90 μ. The yield was 9.8 g (75%).

Reactivity of Pyridine and Pyridine N-Oxide toward 4-Methoxybenzhydryl Bromide.—To a solution of 2.34 g (0.0246 mol) of pyridine N-oxide and 1.95 g (0.0246 mol) of pyridine in 25 ml of purified dimethylformamide was added 6.21 g (0.0224 mol) of 4-methoxybenzhydryl bromide. The solution was heated at 80° for 2 hr. Gas chromatographic comparison with an authentic sample indicated that 4-methoxybenzophenone was present: OV-17 column at 210°, retention time 15.7 min. By glpc examination the yield of 4-methoxybenzophenone was calculated to be 20%. The N-(4-methoxybenzhydryl)pyridinium bromide was analyzed as the picrate as in the above procedure. The yield was 73%. The picrate, recrystallized from benzene, melted at 141–141.5°.

Anal. Calcd for $C_{25}H_{20}N_4O_8$: C, 59.52; H, 4.00. Found: C, 59.32, 59.22; H, 4.01, 4.09.

A duplicate reaction yielded 19% 4-methoxybenzophenone and 75% N-(4-methoxybenzhydryl)pyridinium picrate.

Registry No.—Phenylacetic anhydride, 1555-80-2; pyridine N-oxide, 694-59-7; pyridine, 110-86-1; N-(4-methoxybenzhydryl)pyridinium picrate, 20104-04-5.

Acknowledgments.—We wish to thank the National Institutes of Health for providing the LKB 9000 combined gas chromatograph–mass spectrometer which was used for the isotopic analyses. We also thank Mr. John Naworal for recording the mass spectra.

(18) L. Gattermann, R. Ehrhardt, and H. Maisch, *Ber.*, **23**, 1199 (1890).
(19) R. F. Tietz and W. E. McEwen, *J. Amer. Chem. Soc.*, **77**, 4007 (1955).

Model Reactions for the Metabolism of Thyroxine. I. Nonenzymic Cleavage of the Diphenyl Ether Linkage of 3′-Hydroxythyropropionic Acid

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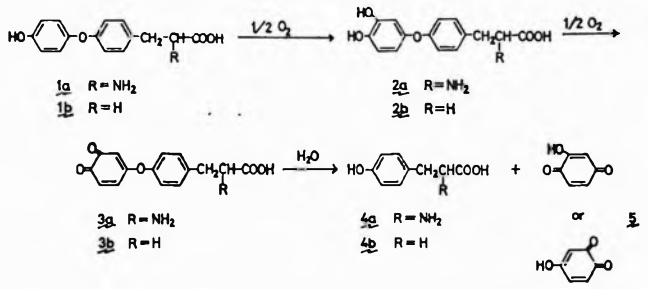
In connection with the hypothetical catabolic pathway by which thyroxine is converted into 3′-hydroxy-3,5,5′-triiodothyronine which in turn cleaves at the diphenyl ether linkage to form 3,5-diiodotyrosine, nonenzymic autoxidations of 3′-hydroxythyropropionic acid and of related compounds were carried out under various conditions. A facile cleavage of the diphenyl ether linkage of 3′-hydroxythyropropionic acid occurred at pH 7.6 and above and phloretic acid was formed in nearly quantitative yield. Chemical and electron spin resonance spectroscopic evidence indicates that in this reaction an initially formed semiquinone radical is converted, probably *via* an *o*-quinone, into the semiquinone radical of 1,2,4-trihydroxybenzene and phloretic acid.

Rupture of the diphenyl ether linkage of thyroxine (T_4)[2] is one of the possible pathways in the metabolism of T_4. Various investigators have found that the formation of 3,5-diiodotyrosine (DIT)[2] and other reaction products in the enzymic degradation of T_4 *in vitro* is always accompanied by deiodination. (For a review of earlier work see Rall, *et al.*;[3] for a more recent report see Björkstén.[4]) Lissitzky, *et al.*,[5,6] postulated a mechanism for the oxidation of thyronine by polyphenol oxidase as shown in Scheme I. They

SCHEME I



reported that aerobic incubation of thyronine (**1a**) with a polyphenol oxidase resulted in the formation of 3′-hydroxythyronine (**2a**) and tyrosine (**4a**) in addition to hydroxybenzoquinone (**5**) which was detected spectroscopically as its phenazine derivative. It is reasonable to assume an analogous pathway in the enzymic degradation of T_4 to DIT. In such a hypothetical pathway the first step would be an oxidative deiodination at the 3′ position. The 3′-hydroxy-3,5,5′-triiodothyronine thus formed would be oxidized to an *o*-quinone which then undergoes hydrolytic splitting at the diphenyl ether linkage to give diiodotyrosine and hydroxybenzoquinone (**5**). However, 3′-hydroxy-3,5,5′-triiodothyronine, an intermediate in this scheme, has so far neither been detected nor synthesized.

(1) Recipient of U. S. Public Health Service Grant AM 07955 from the National Institute of Arthritis and Metabolic Diseases.

(2) Abbreviations used: T_4, thyroxine; DIT, 3,5-diiodotyrosine; HTP, 3′-hydroxythyropropionic acid; THB, 1,2,4-trihydroxybenzene; hfsc, hyperfine splitting constant(s).

(3) J. E. Rall, J. Robbins, and C. G. Lewallen in "The Hormones," Vol. V, G. Pincus, K. V. Thimann, and E. B. Astwood, Ed., Academic Press, New York, N. Y., 1964, p 249.

(4) F. Björkstén, *Acta Chem. Scand.*, **20**, 1438 (1966).

(5) S. Lissitzky and S. Bouchilloux, *Bull. Soc. Chim. Biol.*, **39**, 133, 1215 (1957).

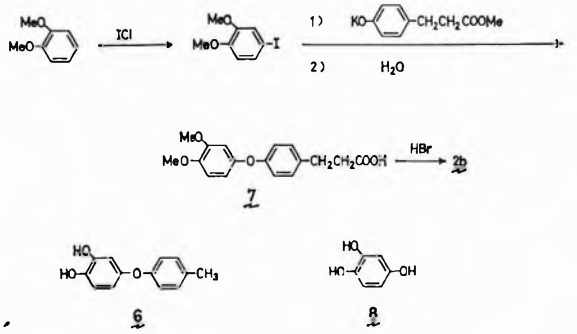
(6) S. Lissitzky, M-T. Bénévent, J. Nunez, C. Jacquemin, and J. Roche, *C. R. Soc. Biol.*, **154**, 267 (1960).

As part of a program to elucidate the nature of the reaction which involves cleavage of the diphenyl ether linkage of T_4, we investigated the nonenzymic autoxidation of 3′-hydroxythyropropionic acid (HTP)[2] (**2b**) and related catechols as simple models for the hypothetical intermediate, 3′-hydroxy-3,5,5′-triiodothyronine. Exposure of nearly neutral or alkaline aqueous solutions of HTP to air at room temperature resulted in the splitting of the molecule at the diphenyl ether bridge and the formation of phloretic acid (**4b**) in nearly quantitative yield. The nature of various free-radical intermediates formed in the course of this autoxidation was established by esr spectroscopy in conjunction with oxygen uptake experiments. The characterization of these intermediates made it possible to derive a mechanism for the autoxidative degradation of HTP.

Results

Synthesis of HTP.—HTP (**2b**) was synthesized from veratrole in 30% over-all yield as summarized in Scheme II. Iodination of veratrole with ICl gave 4-iodoveratrole in 67% yield. The acid **7** was obtained in 51.5% yield by condensation of 4-iodoveratrole with the potassium salt of methyl 3-(4-hydroxyphenyl)propionate, followed by alkaline hydrolysis. Demethylation of **7** with hydrobromic acid gave HTP in 58% yield. The catechol **6** was synthesized in a similar manner (see Experimental Section).

SCHEME II



Autoxidation of Catechols.—When a solution of HTP (**2b**) in sodium phosphate buffer (pH 7.6) was allowed to stand in an open container at room temperature, the reaction mixture turned orange-brown and after 3 days

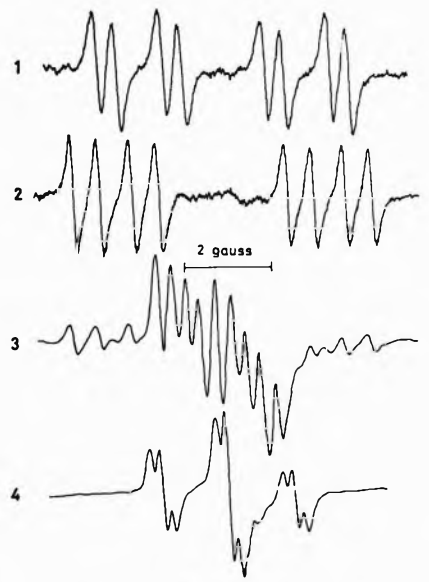


Figure 1.—Esr signals: signal 1, signal of the semiquinone radical **10** (see Scheme III), first signal observed at pH 9.6 in the autoxidation of HTP, g = 2.0039, a_3 = 1.53, a_5 = 3.96, a_6 = 0.43 G (numbering of the semiquinone ring protons according to Stone and Waters[7]); signal 2, signal of the semiquinone radical **13** of THB (see Scheme III) observed at pH >9.5 in the autoxidation of THB and also at pH 12 in the autoxidation of HTP, a_3 = 1.34, a_5 = 4.85, a_6 = 0.61; signals 3 and 4; unidentified signals observed at pH 12 in the autoxidation of HTB and/or THB.

no starting material could be detected by tlc. The reaction mixture, after acidification with HCl, was extracted with ether. The ether extract was chromatographed on a column of silica gel. Phloretic acid (**4b**) was isolated in 96% yield by eluting the column with $CHCl_3$–actone (9:1). The yield of **4b** under various experimental conditions is shown in Table I.

TABLE I

AUTOXIDATION OF HTP AT VARIOUS pH VALUES

pH	Autoxidation period, hr[a]	Temp, °C	Yield of phloretic acid (4c), %[b]
7.6	68	25	96
10.0	19	25	100
12.0	1	25	94

[a] Time required for complete disappearance of HTP. [b] The yield was determined by vpc of the trimethylsilyl derivative.

Extraction of the aqueous layer which remained after the above-mentioned ether extraction with 1-butanol gave substances which were identical with the products of the autoxidation of THB[2] (**8**) as shown by tlc and paper electrophoretic analysis. The autoxidation of THB was carried out in the same manner as that of HTP. These results suggest that **8** is formed when the diphenyl ether linkage is cleaved in the course of the autoxidation of HTP. The intermediary formation of **8** or of an oxidation product of **8** such as the semiquinone **13** is also supported by the esr studies reported below.

In the autoxidation of 1,2-dihydroxy-4-toluoxybenzene under similar conditions, diphenyl ether cleavage was also observed. *p*-Cresol was one of the reaction products.

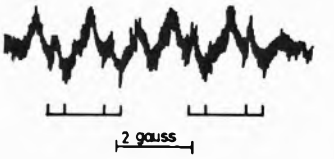


Figure 2.—Esr signal observed in the autoxidation of HTP (7×10^{-3} M) in 0.1 M phosphate buffer, pH 7.6. A time-averaging computer (404 scannings) was used to compensate for the low radical concentration at this pH.

At pH 12, autoxidation of HTP was completed after less than 1 hr, when 0.43 mol of oxygen had been taken up per mole of HTP.

Esr Studies.—Esr studies were carried out in order to obtain information on intermediates in the autoxidation of HTP. When a 1.4×10^{-3} to 1.1×10^{-2} M solution of HTP in 0.1 M phosphate buffer was circulated in the presence of air through an esr cell at pH 7.6, no signal was observed. When the pH was raised to 9.6 a pair of quartets (Figure 1, signal 1) could be observed. Signal 1 is similar to that of the semiquinone radical **13** (signal 2) obtained in the autoxidation of THB, but the hfsc[2] and the behavior of the two radicals are different. In the autoxidation of HTP at pH 7.6, the rate of reaction is very slow (see above) and the radical concentration consequently so low that no signal could be observed directly. However, when a time-averaging computer (404 scannings) was used, a pair of quartets (Figure 2) could be detected. Although the double quartet signal was somewhat deformed (additional absorption between the two quartets), its hfsc coincide well with those of signal 1. (At pH 9–10 signal 1 deformed slowly and assumed the same shape as the signal shown in Figure 2.)

When the pH of a 1.1×10^{-2} M solution of HTP was raised from 9.6 to 12.0, signal 1 changed to signal 3 which is a composite signal. One of its components (the peripheral part of the signal) is identical with signal 2, which was obtained when a solution of THB in 0.1 M phosphate buffer (pH >9.5) was circulated through an esr cell in the presence of air but without oxygen bubbling. The hfsc of signal 2 are nearly identical with those reported by Stone and Waters[7] for the semiquinone radical **13** of THB. Signal 2 was quite stable at pH 9–10, but on raising the pH to 12, it changed to a composite signal consisting of signals 2 and 4. When oxygen was then bubbled through the solution, signal 2 disappeared and only signal 4 remained. The life time of radical 4 is short and within several minutes of oxygen-bubbling signal 4 changed further to signal 3 (less the peripheral quartet).

Discussion

The radical giving rise to signal 1 (Figure 1) should be the semiquinone radical **10** of HTP, judging from its hfsc which resemble those of the semiquinone radical **13** of THB (signal 2). The facts that signal 1 could be observed in the autoxidation of HTP not only at a high pH, but also at pH 7.6, and that the autoxidation products are essentially the same at pH 7.6 and at 12.0 (Table I) indicate that the phenolic hydroxyls of HTP are partly dissociated at pH 7.6 and that the formation

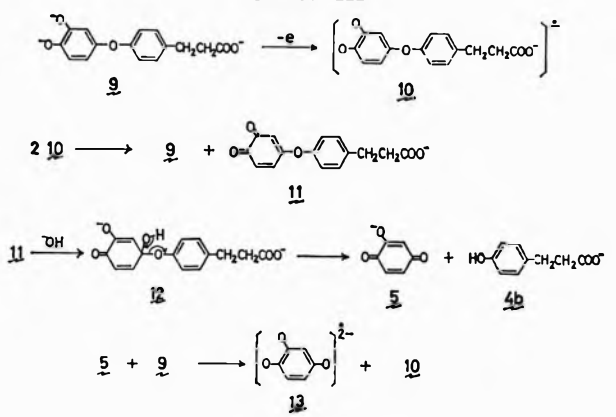
(7) T. J. Stone and W. A. Waters, *J. Chem. Soc.*, 1488 (1965).

of the semiquinone radical **10** of HTP must be the initial step in the autoxidation of HTP. This conclusion is supported by oxygen uptake experiments which show that 0.4–0.5 mol of O_2 is consumed per mole of HTP.

Another important observation made in the course of the esr experiments is the appearance of the signal of the semiquinone radical **13** of THB in the autoxidation of HTP. The identity of signal 2 observed in the autoxidation of HTP with signal 2 observed in the autoxidation under similar conditions of THB was proven by comparison of their shapes and hfsc and also by the identical behavior of those radicals on raising the pH to 12. This converted both signals into signal 3. The fleeting intermediary appearance of signal 4 was observed only in the case of THB and not in that of HTP. This is certainly due to the short life time of the radical 4. The nature of the free radicals giving rise to signals 3 and 4 remains to be elucidated. Furthermore, the butanol-soluble products from the autoxidation of HTP at pH 7.6 were essentially the same as those obtained from THB under similar conditions. The appearance of the semiquinone radical **13** of THB when HTP is autoxidized strongly supports Lissitzky's hypothetical mechanism for the enzymic degradation of thyronine (**1a**) (Scheme I) according to which thyronine is split at the diphenyl ether bridge to form hydroxybenzoquinone (**5**). Since the diphenyl ether linkage of T_4 can be ruptured chemically,[8] photolytically,[9] and enzymically,[4-6,10-12] it is reasonable to suspect a similar mode of breakdown of T_4 *in vivo*. In a recent investigation, however, Pittman and Chambers, Jr.,[13] found that in the rat the major excretion products arising from administered T_4 still had an intact diphenyl ether structure.

A plausible mechanism for the autoxidation of HTP, which is a model for the enzymic degradation of thyronine, can be derived from our findings. This hypothetical mechanism is shown in Scheme III.

SCHEME III



According to this scheme, the first step in the autoxidation of HTP is the formation of the semiquinone radical **10** from HTP in its dissociated form (**9**) by electron transfer involving a molecule of oxygen. Semiquinones are well known to undergo a disproportionation process. Thus **10** is converted back into **9** and into a quinone **11**. Alternatively further oxidation of **10** to **11** by oxygen is also possible, although less plausible. Nucleophilic attack of the quinone **11** by a hydroxyl anion causes cleavage of the ether linkage. Thus hydroxybenzoquinone (**5**) and phloretic acid (**4b**) are formed *via* the intermediate **12**. Electron transfer between HTP (**9**) and hydroxybenzoquinone (**5**) thus formed gives rise to the semiquinone radicals **10** and **13**, the latter of which is certainly more stable because of a more favored electron delocalization and can therefore be detected by esr as a component of signal 3.

In order to ascertain the intermediary formation of the *o*-quinone **11**, attempts were made to synthesize **11**. Treatment of thyropropionic acid with Fremy's salt yielded a red pigment which could not be isolated in pure form but which showed spectral properties which are in agreement with those expected for **11**. A solution of this pigment in phosphate buffer (pH 7.6) yielded phloretic acid (**4b**) on standing at room temperature. This finding also supports the above mechanism.

Another conceivable mechanism for the diphenyl ether cleavage in the autoxidation of HTP is "quinol ether equilibration."[14] This mechanism can, however, be ruled out by the nearly quantitative yield of phloretic acid.

Experimental Section

Spectra.—Nmr spectra were determined with a JMN-3H-60 recording spectrometer. Tetramethylsilane was used as an internal standard. Esr spectra were determined as described previously.[15,16] Ir spectra (Nujol mulls or KBr disks) were recorded with a Nihon Bunko Model IR-S spectrometer.

Chromatograms.—For vapor phase chromatography (vpc), columns (150 cm, 3.0-mm i.d.) packed with silicon DC 550 were used. The carrier gas was helium. The substances to be analyzed were injected after being converted into their trimethylsilyl derivatives by means of O,N-bis(trimethylsilyl)acetamide. For thin layer chromatography (tlc) silica gel covered glass plates containing a fluorescent indicator were used. Spots became visible in short-wave ultraviolet light or in iodine vapor.

Preparation of Starting Materials. 4-Iodoveratrole.—Iodine monochloride (16.3 g, 0.1 mol) was added dropwise during 15 min to a stirred ice-cooled solution of 13.8 g (0.1 mol) of veratrole in 10 ml of acetic acid. Stirring was continued for another 6 hr at room temperature. After the addition of 15 g of sodium carbonate, the reaction mixture was extracted with ether and the ether extract washed with water, dried (Na_2SO_4), and evaporated. Distillation of the oily residue gave 17.6 g (67%) of 4-iodoveratrole, bp 120–124° (5 mm) [lit.[17] bp 150–170° (7 mm)]. Authentic 4-iodoveratrole synthesized from 4-nitroveratrole by a known procedure[18] showed identical behavior in vpc.

1,2-Dihydroxy-4-toluoxybenzene (**6**).—A stirred mixture of the potassium salt of *p*-cresol prepared from 16.4 g (0.15 mol) of *p*-cresol and 4.0 g (0.15 g-atom) of potassium in dry benzene, 20 g (76 mmol) of 4-iodoveratrole, and 1 g of active copper[19] was heated at 150–180° for 4 hr. After cooling, the reaction mixture was extracted with ether and the ether extract washed with a dilute aqueous NaOH solution and with water, dried (Na_2SO_4), and evaporated *in vacuo*. Two successive distillations of the residue

(8) S. Lissitzky and M. Roques, *Bull. Soc. Chim. Biol.*, **39**, 521 (1957).
(9) S. Lissitzky, M-T. Bénévent, and M. Roques, *Biochim. Biophys. Acta*, **51**, 407 (1961).
(10) L. G. Plaskett, *Biochem. J.*, **78**, 652 (1961).
(11) J. Wynn and R. Gibbs, *J. Biol. Chem.*, **237**, 3499 (1962).
(12) J. Roche, J. Nunez, and C. Jacquemin, *Biochim. Biophys. Acta*, **64**, 475 (1962).
(13) C. S. Pittman and J. B. Chambers, Jr., *Endocrinology*, **84**, 705 (1969).
(14) G. D. Cooper, H. S. Blanchard, G. F. Endres, and H. Finkbeiner, *J. Amer. Chem. Soc.*, **87**, 3996 (1965).
(15) T. Matsuura, H. Kon, and H. J. Cahnmann, *J. Org. Chem.*, **29**, 3058 (1964).
(16) A. Nishinaga, H. Kon, H. J. Cahnmann, and T. Matsuura, *ibid.*, **33**, 157 (1968).
(17) C. Seer and E. Karl, *Monatsh.*, **34**, 647 (1913).
(18) D. Cardwell and R. Robinson, *J. Chem. Soc.*, **107**, 256 (1915).
(19) R. Q. Brewster and R. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1950, p 446.

gave 11.7 g of 1,2-dimethoxy-4-toluoxybenzene, bp 178–184° (9 mm). A solution of 5 g (20.4 mmol) of this distillate in 20 ml of 48% hydrobromic acid and 60 ml of acetic acid was refluxed for 2 hr under nitrogen. Acetic and hydrobromic acid were removed by evaporation *in vacuo*. Successive distillation at 10^{-3} mm (bath temperature 150°) and crystallization from benzene–isooctane of the residue gave 2.2 g (31%) of **6**, mp 94–97°.

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.18; H, 5.83. Found: C, 72.21; H, 5.59.

3-[4-(3,4-Dimethoxyphenoxy)phenyl]propionic Acid (7).—The potassium salt of methyl 3-[4-hydroxyphenyl]propionate was prepared from 36.0 g (0.2 mol) of the free phenol[20] and 7.82 g (0.2 g-atom) of potassium in absolute methanol. After complete evaporation of the methanol, 60 g (0.22 mol) of 4-iodoveratrole and 1 g of active copper[19] was added and the mixture heated in an oil bath (150–160°) for 4 hr. After cooling, the mixture was extracted with ether and the ether extract washed with water, with a dilute NaOH solution, and again with water, dried (Na_2SO_4), and evaporated *in vacuo*. The oily residue was dissolved in 400 ml of 10% alcoholic KOH and the solution heated on a boiling water bath for 30 min. The reaction mixture was evaporated *in vacuo*, the residue dissolved in water, and the solution washed with ether, then acidified under ice cooling with concentrated hydrochloric acid. The precipitate formed was dried and crystallized from benzene–petroleum ether to give 31.3 g (51.5%) of **7** as colorless needles: mp 101–104°; nmr ($CDCl_3$) δ 2.77 (m, 4, CH_2CH_2), A_2B_2 pattern, 3.81 (s, 3, OCH_3), 3.84 (s, 3, COH_3), 6.85 (m, 7, aromatic), 10.8 (broad s, 1, COOH), disappears on addition of D_2O.

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.29; H, 5.68.

3-[4-(3,4-Dihydroxyphenoxy)phenyl]propionic Acid (HPT) (2b).—A solution of 5 g (1.7 mmol) of **7** in 100 ml of 48% hydrobromic acid and 100 ml of acetic acid was refluxed for 2.5 hr under nitrogen. The reaction mixture was evaporated *in vacuo* and acetic acid was completely removed by repeated addition and evaporation of water. The oily residue was extracted with ether and the ether extract washed with water, dried (Na_2SO_4), and evaporated to give a syrup which solidified on standing in a refrigerator. Recrystallization from benzene containing a few drops of acetic acid gave 2.5 g (58%) of **2b** as colorless needles: mp 117–118°; nmr [$(CD_3)_2CO$] δ 2.72 (m, 4, CH_2CH_2), A_2B_2 pattern, 6.77 (m, 7, aromatic), 7.85 (broad s, 2, OH), 9.7 (very broad s, 1, COOH), signals of OH and COOH disappear on addition of D_2O.

Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.59, H, 5.49.

3-[4-(4-Hydroxyphenoxy)phenyl]propionic Acid (1b).—The potassium salt of methyl 3-[4-hydroxyphenyl]propionate was prepared from 36.0 g (0.2 mol) of the free phenol as described above. After complete evaporation of the methanol, 52 g (0.22 mol) of 4-iodoanisole[21] and 1 g of active copper[19] was added and the mixture heated in an oil bath (150–180°) for 5 hr. After cooling, the mixture was shaken with water and ether. The ether layer was washed with ice-cooled dilute aqueous NaOH and water, then dried (Na_2SO_4) and evaporated. The residue was dissolved in 400 ml of 10% alcoholic KOH and heated at 70° for 30 min. The reaction mixture was evaporated and the residue dissolved in water. The aqueous solution was washed with ether, then acidified with dilute HCl to give 23.0 g of 3-[4-(4-methoxyphenoxy)phenyl]propionic acid as a colorless precipitate. A solution of the precipitate in a mixture of 200 ml of acetic acid and 200 ml of 48% hydrobromic acid was refluxed for 4 hr under nitrogen. The reaction mixture was evaporated and acetic and hydrobromic acid were removed by repeated addition and evaporation of water. The crystalline residue gave, after recrystallization from water, 15.2 g (30%) of **1b** as colorless crystals, mp 160–162° (lit. mp 162–163°,[22] 162°,[23] 175°[24]).

Oxygen Uptake Experiments.—Oxygen uptake was measured in a previously described apparatus.[25] A solution (1.82×10^{-3} *M*) of 200 mg of HTP in 400 ml of either 0.2 *M* sodium phosphate buffer (pH 7.6) or 0.2 *M* boric acid–NaOH (pH 7.7) or 0.3 *M* NaOH (pH ~12) was stirred under oxygen at 17°.

Autoxidation of HTP (2b) and of 1,2,4-Trihydroxybenzene (THB) (8).—A solution of 2 g (7.3 mmol) of HTP in 1 l. of 0.067 *M* sodium phosphate buffer (pH 7.6) was stirred magnetically at room temperature in an open container, until no starting material was detectable by tlc (3 days). The course of the reaction was followed by removing 1-ml aliquots from time to time and extracting them with ether after acidification (HCl, congo red). The extract was then analyzed by tlc. When starting material could no longer be detected the reaction mixture was acidified with HCl. (In some experiments the reaction mixture was treated with sodium borohydride and then worked up in the same manner. The tlc patterns obtained with or without borohydride treatment were identical.) The acidified mixture (A) was extracted with ether and the ether layer washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue (2.16 g) which showed one major and several minor tlc spots was chromatographed on a silica gel column (60 g). Elution with chloroform–acetone (9:1) gave 1.16 g (96%) of phloretic acid (**4b**) (mixture melting point and ir spectrum). Subsequent elution with chloroform–acetone (85:15) yielded a minor product (146 mg). Its methylation with diazomethane gave 120 mg of a methylated product as a syrup which was not a uniform compound, but whose nmr spectrum indicates that it consisted mainly of methylated HTP or a closely related compound. The acidified solution (A), after extraction with ether, was further extracted with 1-butanol. The butanol extract was evaporated to dryness, the residue extracted with ether, and the ether extract washed with water, dried (Na_2SO_4), and evaporated. The residue (108 mg) showed at least four tlc spots. Attempts to separate the mixture by preparative tlc were not successful. Paper electrophoresis at pH 6.15 (pyridine–acetic acid–water, 10:1:78) and tlc gave patterns which were identical with those obtained with an autoxidized solution of THB. The autoxidation of THB was carried out in the same manner as described for HTP. The autoxidation of HTP was also carried out under other conditions (higher pH and lower temperatures). In each case the tlc pattern was virtually identical with that obtained in the autoxidation of HTP at pH 7.6 and room temperature.

Autoxidation of 1,2-Dihydroxy-4-toluoxybenzene (6).—A solution of 2 g (0.01 mol) of **6** in 1 l. of sodium phosphate buffer (0.067 *M*, pH 7.7) was stirred in an open container at room temperature until no starting material was detectable by tlc (3 days). The reaction mixture was acidified and extracted with ether and the ether washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a column of silica gel (50 g). Elution with chloroform gave 80 mg of *p*-cresol (ir and tlc). Further elution with chloroform–acetone (9:1) gave 700 mg of a powdery product. Attempts to purify it were unsuccessful, ir (KBr) 3450 and 3350 cm^{-1} (OH), no C=O band. The aqueous layer obtained in the above-mentioned extraction with ether, was further extracted with 1-butanol. The butanol extract, upon evaporation *in vacuo*, gave a few milligrams of an oily residue, whose tlc and paper electrophoretic patterns showed similarities to those obtained with the autoxidation products of THB (**8**).

Oxidation of 3-[4-(4-Hydroxyphenoxy)phenyl]propionic Acid (1b) with Fremy's salt.—To an ice-cooled stirred solution of 774 mg (3 mmol) of **1b**, synthesized as described above, in 60 ml of acetone was added over a period of 50 min 2.1 g of Fremy's salt (potassium nitrosodisulfonate) dissolved in 145 ml of 0.06 *M* KH_2PO_4. The mixture was then diluted with 100 ml of water and stirred for 20 min under ice cooling. The reaction mixture, after addition of another 100 ml of water, was extracted with chloroform (20 ml). The residue obtained upon drying (Na_2SO_4) and evaporating the chloroform extract was dissolved in absolute ether. When the solution was cooled to −70°, a red precipitate formed: uv ($CHCl_3$) 336 mμ (log ϵ 4.04, based on quinone **11**); ir (Nujol) no OH band, 1660 and 1640 cm^{-1} (C=O).

The red precipitate was dissolved in phosphate buffer (pH 7.6) and the solution allowed to stand at room temperature for 3 hr. The reaction mixture was then acidified and repeatedly extracted with ether. Analysis of the ether extract by tlc revealed the presence of phloretic acid (**4b**) together with other unidentified products.

Formation of Radicals.—In order to observe stable radicals formed in the autoxidation of HTP, solutions of HTP (1.4×10^{-3} to 1.1×10^{-2} *M*) were prepared by adding HTP to 0.1 *M*

(20) E. Fischer and O. Nouri, *Ber.*, **50**, 614 (1917).

(21) H. R. Frank, P. E. Fanta, and D. S. Tarbell, *J. Amer. Chem. Soc.*, **70**, 2314 (1948).

(22) A. Nishinaga and T. Matsuura, *J. Org. Chem.*, **29**, 1812 (1964).

(23) L. Petit and N. P. Buu-Hoi, *ibid.*, **26**, 3832 (1961).

(24) R. I. Meltzer, S. Farber, E. Merrill, and A. Caro, *ibid.*, **26**, 1413 (1961).

(25) A. Nishinaga, H. J. Cahnmann, H. Kon, and T. Matsuura, *Biochemistry*, **7**, 388 (1968).

sodium phosphate buffer (pH 7.6–9.6) in an open container at room temperature. Immediately after the addition, circulation (~140 ml/min) of the straw-colored solution through an esr cell was started and the signals were recorded. The pH was kept at the desired value by the occasional addition of 1 *M* NaOH. In some cases oxygen or nitrogen was bubbled through the reaction mixture. Stable radicals formed in the autoxidation of THB were observed in a similar manner.

Registry No.—Thyroxine, 51-48-9; **2b**, 20224-53-7; **6**, 20224-54-8; **7**, 20224-55-9; **10**, 12349-50-7; **13**, 12349-49-4.

The Kinetics of the Decarboxylative Dehydration of β-Anisyl-β-hydroxy-α-phenylpropionic Acid[1,2]

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The decarboxylative dehydrations of *erythro*- and *threo*-β-anisyl-β-hydroxy-α-phenylpropionic acids proceed at different rates in dilute aqueous sulfuric acid solution. Both stereoisomers give *trans*-4-methoxystilbene. The diastereoisomers are interconverted at a rate which is slower than decarboxylation in dilute sulfuric acid solution, but at a rate more rapid than decarboxylation in more acidic medium. These facts are interpreted in terms of generation of a dipolar ion which loses carbon dioxide more rapidly than it reacts with water.

The behavior of β-hydroxy acids under a variety of circumstances has been studied in these laboratories; in addition to studies of the mechanism of acid-catalyzed dehydration[4,5] many features of the decarboxylative dehydration have been elucidated.[6-8] The reaction shows a particularly modest increase in rate with increasing acidity of the medium;[6] a plot of log *k* *vs.* H_0 typically has a slope of 0.4–0.6. It was shown that there are circumstances in which racemization (*e.g.*, of β-hydroxy-β-arylbutyric acids) is no more rapid than decarboxylation. This situation applies at low acidities. At higher acidities racemization was much more rapid than any other reaction of the β-hydroxy acids. It was also shown[1] that both diastereoisomers of α-methyl-β-hydroxy-β-(*p*-tolyl)propionic acid gives *trans*-*p*-propenyltoluene. In order to examine the kinetic features of decarboxylative dehydration more thoroughly, particularly in relation to the stereochemistry of the process, we have sought a compound which would be more suitable than β-anisyl-β-hydroxybutyric acid. For this purpose we have chosen to examine the kinetic behavior of the two diastereoisomers of β-anisyl-β-hydroxy-α-phenylpropionic acid (**1**). Ultraviolet spectra are distinctive for the four possible products, both *cis*- and *trans*-α-phenyl-*p*-methoxycinnamic acids, which could result from simple acid-catalyzed dehydration, as well as *cis*- and *trans*-4-methoxystilbenes, which could result from decarboxylative dehydration. These differences in spectra thus make it easy to follow the course of the reaction of **1** in detail.

A mixture of the two isomers of **1** was prepared by an Ivanov reaction and separated by chromatography over alumina. The *threo* configuration is assigned to the predominant isomer (mp 151–152°) on the basis of the following arguments. Zimmerman and Traxler[9] have unambiguously determined the configuration of the two diastereoisomers of α,β-diphenyl-β-hydroxypropionic acid (**2**) by a direct chemical method. More recently Canciell, *et al.*,[10] have shown that it is generally true that *threo* isomers of compounds such as **2** show a larger coupling constant between the α and β hydrogens than do the *erythro* isomers. Coupling constants very similar to those reported for *threo* **2** and *erythro* **2** were observed for the two diastereoisomers of **1**.

In fairly dilute sulfuric acid at 65° *threo* **1** and *erythro* **1** separately showed excellent first-order kinetics as followed by the appearance of the spectrum of *trans*-4-methoxystilbene. *threo* **1** reacted more rapidly than *erythro* **1**. These observations show that there is not rapid interconversion of the two diastereoisomers.

In 0.8 *M* sulfuric acid, the exclusive product is *trans*-4-methoxystilbene from both isomers. Control experiments showed that there is essentially none of the substituted cinnamic acid formed by simple dehydration, and that less than 1% of the *cis*-4-methoxystilbene is formed. Thus, the decomposition of both stereoisomers of **1** gives the same *trans* olefin, an observation which is completely in accord with the previous stereochemical results obtained in the study of α-methyl-β-hydroxy-β-(*p*-tolyl)propionic acid.[1]

When the kinetic studies were carried out at 65° in more concentrated sulfuric acid medium (about 1 *M*) the usual first-order plot was no longer linear, but showed some curvature. For *threo* **1** a plot of (log [*threo* **1**]) *vs.* time was slightly concave upward.

The lack of simple first-order behavior shows up more clearly in our kinetic measurements at 44°. Under these conditions and working in more concentrated sulfuric acid media, neither isomer showed simple first-order behavior. For *threo* **1** the plot of (log [*threo* **1**]) *vs.* time is concave upward initially and becomes linear only after about 50% reaction. For *erythro* **1** the corresponding plot is slightly concave downward, again becoming linear after approximately 50% reaction. Moreover, the limiting slope for the later stages of reac-

(1) Previous paper: D. S. Noyce and S. K. Brauman, *J. Amer. Chem. Soc.*, **90**, 5218 (1968).

(2) Supported in part by grants from the National Science Foundation (G 13125, GP 1572, and GP 6133X).

(3) Dow Chemical Co. Graduate Fellow in Chemistry, 1964–1965.

(4) D. S. Noyce, P. A. King, C. A. Lane, and W. L. Reed, *J. Amer. Chem. Soc.*, **84**, 1638 (1962).

(5) D. S. Noyce and R. A. Heller, *ibid.*, **87**, 4325 (1965).

(6) D. S. Noyce, L. Gortler, M. J. Jorgenson, F. B. Kirby, and E. C. McGoran, *ibid.*, **87**, 4329 (1965).

(7) D. S. Noyce, S. K. Brauman, and F. B. Kirby, *ibid.*, **87**, 4335 (1965).

(8) D. S. Noyce, L. M. Gortler, F. B. Kirby, and M. D. Schiavelli, *ibid.*, **89**, 6944 (1967).

(9) H. E. Zimmerman and M. D. Traxler, *ibid.*, **79**, 1920 (1957).

(10) J. Canciell, J. Basselier, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1906 (1963).

tion for both isomers stabilizes at the same value. Further information regarding analysis of these observations is given in the Experimental Section.

Experimental Section[11]

β-Anisyl-β-hydroxy-α-phenylpropionic Acid (1).—A mixture of the *threo* and *erythro* isomers was obtained by an Ivanov reaction.[12] To the Ivanov reagent prepared from 46 g (0.29 mol) of sodium phenylacetate and isopropylmagnesium chloride was added 39.5 g (0.29 mol) of *p*-anisaldehyde in 200 ml of ether. Vigorous stirring and slow addition were helpful in preventing the formation of an awkward, thick, gummy mass. After heating for an additional 8 hr, the reaction mixture was hydrolyzed by pouring onto ice and a 6 *N* HCl aqueous acetone solution. Work-up in the usual fashion afforded a mixture of crude acids. Chromatography on Baker alumina first removed a substantial amount of unreacted phenylacetic acid. Continued elution with 1:1 ether–petroleum ether (bp 30–60°) afforded 6 g (7.7%) of *erythro* acid, followed by 25.4 g (32%) of *threo* acid. The *erythro* acid was purified by three crystallizations from ethyl acetate–petroleum ether (bp 30–60°), mp 169–170°.

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92; neut equiv, 272. Found: C, 70.70; H, 6.04; neut equiv, 274.

The *threo* acid was similarly purified, mp 151–152°.

Anal. Found: C, 70.62; H, 5.94; neut equiv, 274.

Ivano and Nicolov[12] reported a single isomer, mp 136.5° dec, while Blicke and Cox[13] reported an acid of mp 168–170° on extensive crystallization of material originally melting at 139–140°.

Methyl *erythro*-β-anisyl-β-hydroxy-α-phenylpropionate was prepared by esterification of the *erythro* acid with diazomethane. Recrystallization from ethyl acetate–petroleum ether (bp 30–60°) and sublimation gave material of mp 88.5–89.5°.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.37; H, 6.46.

Similarly **methyl *threo*-β-anisyl-β-hydroxy-α-phenylpropionate** was prepared, mp 95–96°.

Anal. Found: C, 71.48; H, 6.52.

A small sample of *cis*-α-phenyl-*p*-methoxycinnamic acid was prepared by irradiation of *trans*-α-phenyl-*p*-methoxycinnamic acid. Recrystallization of the crude acid mixture from benzene gave recovered *trans* acid. From the mother liquors the *cis* acid was obtained, and purified by crystallization from benzene, mp 124–125° (lit.[14] mp 123°).

Kinetic Procedures.—The rate of decarboxylation was determined by measuring the increase of absorption at 315 mμ with a Beckman DU spectrophotometer using 10-cm cells. Stock solutions of the hydroxy acid were prepared in dioxane, and diluted with sulfuric acid of the requisite concentration, so that the final solution contained 5% dioxane and was $\sim 5 \times 10^{-7}$ *M* in hydroxy acid. At these very low concentrations, special precautions to avoid photochemical isomerization were taken.

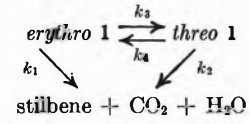
Product Studies.—*cis*-4-Methoxystilbene is relatively stable under the decarboxylation conditions.[15] The rate of isomerization of *cis*-4-methoxystilbene (extrapolated to 64% in 0.8 *M* sulfuric acid) is 6.8×10^{-6} sec^{-1}. Under these same conditions the rate of decarboxylation of the *erythro* acid is 7×10^{-4} sec^{-1}. The ratio of decarboxylation to isomerization rates is therefore 108. Further *cis*-4-methoxystilbene is recovered almost completely unchanged under the conditions of the following experiment.

Separate samples of the *erythro* and *threo* acids were heated at 65° for 45 min in 1.5 *M* sulfuric acid, and the products of the reaction examined carefully. These conditions are sufficient to cause almost complete decarboxylation. The aqueous solutions were extracted with pentane, and the pentane extracts washed carefully with 10% sodium bicarbonate solutions. From the pentane extracts upon evaporation, the residue was taken up in a measured quantity of 95% ethanol, and the uv spectrum then recorded (Cary Model 14 spectrophotometer). In each case the spectrum was superimposable on that of an authentic sample of *trans*-4-methoxystilbene. Thus, the *trans* isomer is the exclusive product of decarboxylative dehydration.

Simple dehydration of the β-anisyl-β-hydroxy-α-phenylpropionic acids was shown to be an insignificant competing reaction, even in relatively concentrated mineral acid solutions as shown by the following experiment. A sample of the *erythro* acid (0.1 g) was heated at 64.7° for 5 hr in 250 ml of 0.8 *M* sulfuric acid (5% dioxane added). The resulting suspension was extracted with chloroform, and the neutral and acidic material separated. The neutral material was *trans*-4-methoxystilbene (as above). The bicarbonate extracts were carefully acidified (cold) to a pH of 2, and extracted with chloroform. The layer was dried, concentrated, and the spectrum determined. From the absorbance at 306 mμ, the maximum amount of α-phenyl-*p*-methoxycinnamic acid formed was determined; less than 0.8% of substituted cinnamic acids was formed.

Analog Computer Simulation of Kinetic Pattern.—The complex behavior of two substances, E and T, which may be interconverted, both of which give a third compound, irreversibly, was simulated by employing a Pace analog computer.[16] The results were registered on an X–Y recorder, and were compared with the experimentally found data. The experimental apparent percentage reaction was plotted against time on a scale such that 95% reaction was presented over the full time scale.

In the scheme (eq 1) the ratio k_3/k_4 was constrained to a value of 2, and k_1 and k_2 were varied over a reasonable range of values.



(1)

The conditions which would give concentration *vs.* time values to match the experimentally observed situations were sought. To be particularly noted is that the observed rate behavior at 44° in 2–4.5 *M* acid could be very satisfactorily reproduced, including initial rates, and also the ultimate, and similar rates for both isomers after 50–70% reaction. As an example of the results obtained, the data in Table I show the range of acceptable values under one set of conditions.

TABLE I

H_2SO_4, *M*	H_0	Starting isomer	k_2/k_1	k_3/k_1	Final rate, sec^{-1}
2.49	−0.93	*threo*	5 ± 1	3.5 ± 1	4.2×10^{-4}

Epimerization Studies.—It was necessary to use an indirect method for determining the ratio of *threo* to *erythro* isomer at equilibrium inasmuch as the acids were unstable in dilute sulfuric acid. It seemed that the methyl esters would provide reasonable models. Approximately 0.10 g of the methyl ester of one pure diastereoisomer or a mixture of esters of known composition was dissolved in 50 ml of dioxane, and diluted to 5 l. with 1 *M* sulfuric acid. After being kept at 44° for 5 hr, the reaction mixture was poured over ice, saturated with salt, and extracted thoroughly with ether. The combined ether extracts were washed with Na_2CO_3, dried over $MgSO_4$, concentrated, and the remaining esters dissolved in pyridine. The nmr spectrum of the pyridine solution was determined and the ratio of the two isomers determined from multiple scans. The ester methyl peaks are well separated in pyridine solution, that for the *erythro* isomer being 6 cycles to higher field than the peak for the *threo* isomer. Approaching the equilibrium from both sides gave an equilibrium value of *threo*/*erythro* of 2.02 ± 0.09.

Activation Parameters.—Values for the activation parameters for the decarboxylative dehydration of both *erythro* 1 and *threo* 1 can be calculated at $H_0 = 0$ from the rates of the two isomers at 64° and the mathematically separated rates at 43.72° (with a short extrapolation needed). Using the value of 8.9×10^{-5} sec^{-1} for the final observed rate at 43.72° ($H_0 = 0$), the activation parameters listed in Table II are obtained. It should be noted that the nature of the separation of the rates in the fashion described here precludes obtaining high precision in the energy

(11) Analyses are by the Microanalytical laboratory, Department of Chemistry, University of California, Berkeley. Melting points are uncorrected; nmr spectra were determined at 60 Mc with a Varian A-60 spectrometer.

(12) D. Ivanov and N. I. Nicolov, *Bull. Soc. Chim. Fr.*, **51**, 1325 (1932).

(13) F. F. Blicke and R. H. Cox, *J. Amer. Chem. Soc.*, **77**, 5401 (1955).

(14) Y. de Schuttenbach, *Ann.*, **6**, 77 (1936).

(15) D. S. Noyce, D. R. Hartter, and F. B. Miles, *J. Amer. Chem. Soc.*, **90**, 4633 (1968).

(16) We wish to express our appreciation to Professor E. Grens of the Department of Chemical Engineering, University of California, for counsel in the use of the analog computer, and for making these facilities available to us.

TABLE II

ACTIVATION PARAMETERS FOR THE DECARBOXYLATIVE DEHYDRATION OF β-ANISYL-β-HYDROXY-α-PHENYLPROPIONIC ACID

erythro			threo		
k_1, sec^{-1} [a]	E_a, kcal	$\Delta S^{\pm}$, eu	k_2, sec^{-1} [a]	E_a, kcal	$\Delta S^{\pm}$, eu
2.97×10^{-5}	34	+26	1.19×10^{-4}	31	+19

[a] At 44°, $H_0 = 0$.

of activation, and particularly in the apparent entropy of activation. Nevertheless, the entropy of activation is strikingly positive.

Results and Discussion

The results of kinetic measurements at two temperatures and in media of varied sulfuric acid concentration are given in Tables III, IV, and V. These kinetic results are best discussed in separate sections dealing with rate behavior of the two diastereoisomers of **1** in various concentrations of mineral acid.

TABLE III

DECARBOXYLATIVE DEHYDRATION OF *threo*-β-ANISYL-β-HYDROXY-α-PHENYLPROPIONIC ACID IN 5% AQUEOUS DIOXANE–H_2SO_4, T = 64.21°

H_2SO_4, M	H_0 [a]	$10^4k_{initial}$, sec^{-1}	10^4k_{final}, sec^{-1}
0.03076	1.80	1.07	Same
0.050	1.58	1.70	Same
0.05974	1.50	2.00	Same
0.100	1.25	3.73	Same
0.1364	1.09	3.73	Same
0.200	0.89	6.28	Same
0.294	0.67	7.82	Same
0.322	0.62	8.50	Same
0.408	0.49	10.2	Same
0.459	0.42	12.8	
0.7504	0.12	16.9	15.6
0.7734	0.10	17.4	14.1
1.070	−0.11	23.6	19.6
1.614	−0.42	34.0	29.6

[a] H_0 was measured at 64°.

TABLE IV

DECARBOXYLATIVE DEHYDRATION OF *erythro*-β-ANISYL-β-HYDROXY-α-PHENYLPROPIONIC ACID IN 5% AQUEOUS DIOXANE–H_2SO_4, T = 64.21°

H_2SO_4, M	H_0 [a]	$10^4k_{initial}$, sec^{-1}	10^4k_{final}, sec^{-1}
0.03148	1.79	0.302	Same
0.07985	1.36	0.765	Same
0.100	1.25	0.910	Same
0.100	1.25	0.955	Same
0.200	0.89	1.72	Same
0.2652	0.73	2.11	Same
0.3288	0.61	2.50	Same
0.4673	0.41	3.82	Same
0.550	0.31	5.05	
0.5875	0.27	5.16	5.37
0.6998	0.17	5.75	6.43
0.8316	0.06	7.00	7.36
1.538	−0.37	13.8	19.9

[a] H_0 was measured at 64°.

At *low* concentration of mineral acid (<0.5 M) both the *threo* isomer and the *erythro* isomer give excellent pseudo-first-order kinetics. Moreover, the rates for the two isomers are distinctly different, with the *threo* isomer

TABLE V

DECARBOXYLATIVE DEHYDRATION OF *erythro*- AND *threo*-β-ANISYL-β-HYDROXY-α-PHENYLPROPIONIC ACID IN 5% AQUEOUS DIOXANE–H_2SO_4, T = 43.72°

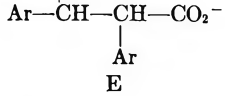
H_2SO_4, M	H_0 [a]	Isomer [b]	10^4k_{final}, sec^{-1} [c]
1.097	−0.30	T	1.84
1.994	−0.69	E	2.78
2.49	−0.93	E	4.36
2.49	−0.93	T	4.20
3.29	−1.31	T	8.63
3.29	−1.31	T	8.82
3.49	−1.41	E	10.2
4.39	−1.85	E	20.6
4.39	−1.85	T	18.9
4.39	−1.85	T	20.1
4.58	−1.95	T	22.9
4.58	−1.95	T	23.6

[a] H^0 was measured at 44°. [b] *T*, *threo* isomer; E, *erythro* isomer. [c] The error in the rate constant is about ±5%.

reacting about four times more rapidly than the *erythro* isomer. These detailed kinetic observations supplement and substantiate the stereochemical observations of Noyce and Brauman[1] which showed that there was no interconversion of the two epimers of α-methyl-β-hydroxy-β-*p*-tolylpropionic acid in weakly acidic solution.

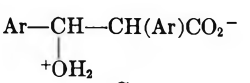
Concurrently, however, both stereoisomers of **1** give *trans*-4-methoxystilbene as the nearly exclusive product. The product-forming step thus takes place from a common intermediate, but this product-forming step cannot be the rate-limiting process. Acceptable species for the product forming intermediate are severely limited. A β-lactone is excluded.[17] The carbonium ion formed by acid-catalyzed loss of water from the hydroxy acid is excluded by the manner on which the reaction rate varies with mineral acid concentration.

An attractive and acceptable intermediate is the dipolar ion E, recognizing that the stereochemical differ-



E

ence between the two epimers is removed as soon as the dipolar ion is symmetrically solvated. A further restriction is that the dipolar ion E loses carbon dioxide more rapidly than it reacts with water to generate the zwitterion C, else equilibration would precede decar-



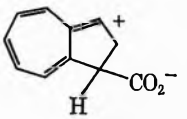
C

boxylation. Equilibration prior to decarboxylation is excluded by the kinetic behavior at low concentrations of mineral acid.

The pH rate profile for a reaction proceeding through the zwitterion C and dipolar ion E should be independent of pH in the region where we have made measurements, except for salt effects. At this juncture the recent observations of Longridge and Long[18] are partic-

(17) D. S. Noyce and E. G. Banitt, *J. Org. Chem.*, **31**, 4043 (1966).
(18) J. L. Longridge and F. A. Long, *J. Amer. Chem. Soc.*, **90**, 3092 (1968).

ularly germane. They showed that the decarboxylation of azulene-1-carboxylic acid proceeds through a zwitterion F, analogous to E. Further they demon-



F

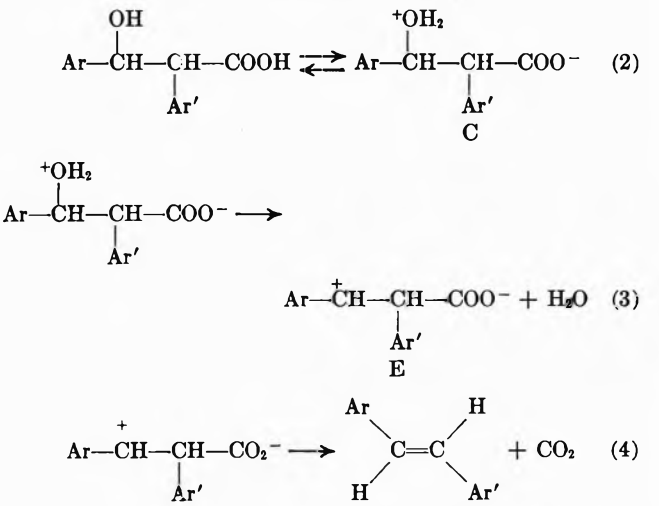
strated that the decarboxylation rate of F is subject to a very pronounced positive salt effect, with rates in 5 *M* salt which are nearly ten times the rates in 0.5 *M* salt. In sulfuric acid they noted that the rate increase in more concentrated acid closely paralleled these salt effects, and that, therefore, the increasing rates in more concentrated mineral acid are the result of a salt effect, not an additional acid-catalyzed reaction pathway.

Returning to a consideration of our data, we therefore conclude that the mechanistic scheme proposed earlier[1] is completely satisfactory to explain the kinetic data obtained in the investigation. Decarboxylation proceeds from a zwitterion C by rate-limiting loss of water to give E irreversibly, followed by very rapid loss of CO_2 to give *trans*-4-methoxystilbene.

In *higher* concentrations of sulfuric acid (0.5–4.0 *M*) the total rate of decarboxylation shows a modest increase in rate due to the salt effect, but not due to an acid-catalyzed reaction. Concomitantly, the acid-catalyzed interconversion of the *threo* and *erythro* isomers become relatively more rapid and more important. This leads to some difficulties in the kinetic measurements as decarboxylation is now proceeding from a variable mixture of the two stereoisomers. For example, in 4.39 *M* sulfuric acid at 44° (Table V), the measured rate constant near the end of a run is the same starting with either isomer, indicating that equilibration was almost complete.

Detailed analysis shows that this interpretation will fit the data. By assuming reasonable values for the rate of acid-catalyzed epimerization, and for the composition of an equilibrium mixture of the two epimers, it was possible to reproduce the observed rates of decarboxylation for the runs in more concentrated sulfuric acid solutions with compounds curves generated by an analog computer.

Thus the decarboxylative–dehydration reaction proceeds by the following mechanism (eq 2–4).



The close relationship between this mechanism and other similar situations should be pointed out. Shiner and Martin[19] have shown that the decomposition of glycidic esters proceeds by way of a zwitterion analogous to C and the parallel with the steps in the present mechanism can be essentially complete, by including a dipolar ion analogous to E. The similarity to the results of Longridge and Long[18] on the decarboxylation of azulene-1-carboxylic acid, has already been mentioned. In addition a parallelism may be noted to the decarboxylative debromination studied by Cristol and Norris[20] and by Grovenstein and Lee.[21] Recently several studies of the decarboxylation of substituted anthranilic and of salicylic acids have been carried out and the mechanistic parallelism is evident.[22–24]

Registry No.—1 (*erythro*), 20445-40-3; 1 (*threo*), 20414-13-5; 1 (*erythro*-methyl ester), 20414-14-6; 1 (*threo*-methyl ester), 20445-41-4.

(19) V. J. Shiner, Jr. and B. Martin, *J. Amer. Chem. Soc.*, **84**, 4824 (1962).
(20) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 632, 2645 (1953).
(21) E. Grovenstein and D. E. Lee, *ibid.*, **75**, 2639 (1953).
(22) A. V. Willi, C. M. Won, and P. Vilk, *J. Phys. Chem.*, **72**, 3142 (1968); A. V. Willi, *Helv. Chim. Acta*, **43**, 644 (1960); A. V. Willi, *Trans. Faraday Soc.*, **55**, 433 (1959).
(23) G. E. Dunn, P. Leggate, and I. E. Scheffler, *Can. J. Chem.*, **43**, 3080 (1965).
(24) J. M. Los, R. F. Rekker, and C. H. T. Tonsbeek, *Rec. Trav. Chim. Pays-Bas*, **86**, 622 (1967).

The Preparation and Chemistry of the Isomeric Monomethyl Derivatives of Perthiocyanic Acid

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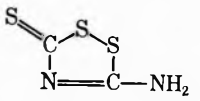
Received November 26, 1968

The disodium salt (**5**) of perthiocyanic acid (3,5-dimercapto-1,2,4-thiadiazole) is known to react with 2 mol of an alkylating agent to give dialkyl perthiocyanates. In this study, the course of the monoalkylation of **5** was investigated. The reaction of **5** with 1 mol of methyl iodide gave 27% dimethyl perthiocyanate and 28% 3-methylmercapto-5-mercapto-1,2,4-thiadiazole (**8**); the 5-methyl isomer was not detected. The reaction of **8** with other alkylating agents gave a series of "mixed" perthiocyanates, *e.g.*, 3-methylmercapto-5-benzylmercapto-1,2,4-thiadiazole. The reaction of 3-imino-5-methylmercapto-1,2,4-dithiazole with hydroxide ion resulted both in ring opening and rearrangement to give the salts of S-methyl cyanodithioimidocarbonate and the 5-methyl isomer, 3-mercapto-5-methylmercapto-1,2,4-thiadiazole. The evidence for these products comes from the subsequent methylation of the salts which gave 84% dimethyl cyanodithioimidocarbonate and 7% dimethyl perthiocyanate.

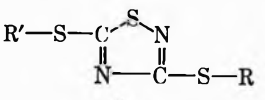
The addition of concentrated hydrochloric acid to an aqueous ammonium thiocyanate solution gives 3-amino-5-thione-1,2,4-dithiazole (**1**), commonly known as isoperthiocyanic acid.[2-5] Earlier work[6,7] with **1** demonstrated or suggested the reaction sequence



1

shown in Scheme I. The scheme shown was confirmed (*cf.* Experimental Section), as was the interrelationship of **1**, the cyanodithioimidocarbonate dianion (**2**), and the perthiocyanate dianion (**5**).

Various derivatives (**6**) of **5** were prepared by treating it with 2 equiv of an alkylating agent.[6,8] However, the reaction of **5** with 1 equiv of an alkylating agent has not been studied. It can lead to two isomers, and further reaction with another alkylating agent would result in novel "mixed" perthiocyanates (**7**, R ≠ R′).

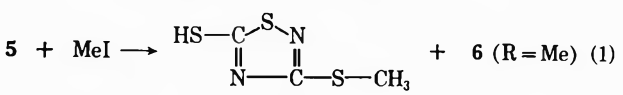


7

In this study the preparation and chemistry of monomethylated perthiocyanates were investigated.

Results and Discussion

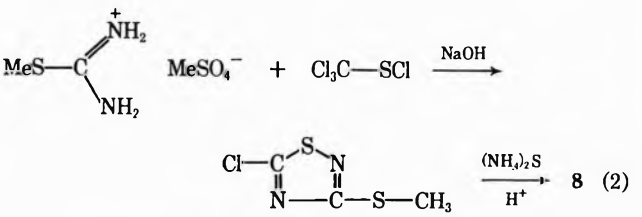
3-Methyl Isomer.—The reaction (eq 1) of sodium perthiocyanate (**5**) with 1 equiv of methyl iodide



8 (1)

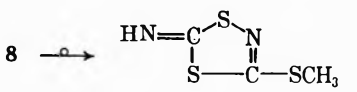
gave a 28% yield of 3-methylmercapto-5-mercapto-1,2,-4-thiadiazole (**8**) and a 27% yield of dimethyl perthiocyanate (**6**, R = Me). The latter compound arose from further methylation of **8**. One factor responsible for the poor material balance was the difficulty in separating **8** from isoperthiocyanic acid (**1**).[9]

The structure of **8** was proven by synthesizing the same compound by the method (eq 2) of Goerdeler and Sperling.[10]



(2)

The possibility of a rearrangement (eq 3), analogous



(3)

to that of **4** to **1**, was ruled out based on the following evidence. The infrared spectrum of **8** shows weak SH absorption at 2560 cm^{-1} and 2670 cm^{-1}. Compound **8** dissolved in 10% aqueous sodium hydroxide without deposition of sulfur. The reaction of **8** with diazomethane gave an 88% yield of dimethyl perthiocyanate (**6**, R = Me). Isoperthiocyanic acid (**1**) gave gummy material, which could not be purified under the same conditions. Thus, the preparation of **6** (R = Me) from **8** under neutral conditions, the smooth formation of the sodium salt of **8**, and the infrared spectrum all indicate that structure **8** is stable and retains the 1,2,4-thiadiazole arrangement.

Various derivatives of **8** were prepared by treating the sodium salt with the appropriate alkylating agent in THF (Table I).

5-Methyl Isomer.—We were unable to isolate or find evidence for the 5-methyl isomer (**7**, R = H; R′ = Me) from the reaction of **5** with 1 equiv of methyl iodide (eq 1). Thus, alternate routes to this compound were investigated.

(1) Geigy Chemical Co., Ardsley, N. Y. 10502

(2) (a) A. Wöhler, *Ann. Phys.*, **69**, 273 (1821); (b) P. Klason, *J. Prakt. Chem.*, (2) **38**, 366 (1888).

(3) L. L. Bambas, "The Chemistry of Heterocyclic Compounds," Vol. 4, Interscience Publishers, Inc., New York, N. Y., 1952, p 35.

(4) A. Hordvik, *Acta Chem. Scand.*, **15**, 1186 (1961).

(5) H. J. Emeléus, A. Haas and N. Sheppard, *J. Chem. Soc.*, 3165 (1963).

(6) A. Hantzsch and M. Wolvekamp, *Ann.*, **331**, 265 (1904).

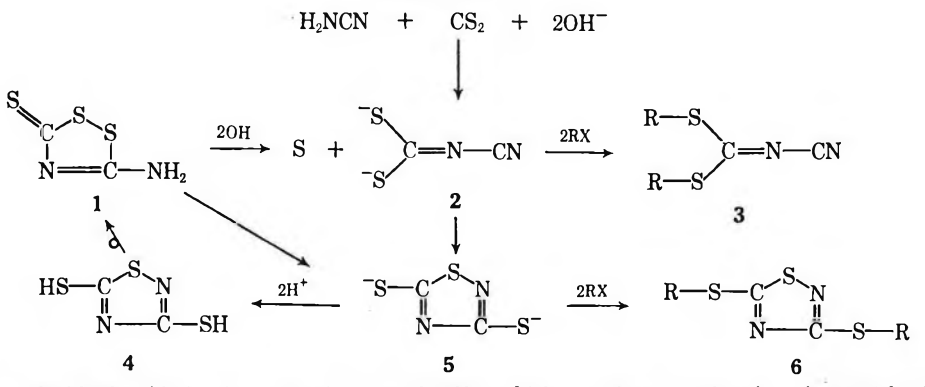
(7) E. Söderback, *Acta Chem. Scand.*, **1**, 529 (1947).

(8) W. H. Hill, U. S. Patent 2,521,570 (1950); E. W. Bousquet, U. S. Patent 2,285,410 (1942).

(9) Isoperthiocyanic acid was obtained from unreacted **5** on acidification.

(10) J. Goerdeler and G. Sperling, *Ber.*, **90**, 892 (1957).

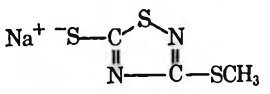
SCHEME I[a]



[a] Treating **1** with 2 mol of hydroxide ion in water gives **2** and sulfur which on subsequent heating gives **5**.[2b,6] Compound **2** can be prepared from cyanamid as shown,[6] and further reaction with sulfur gives **5** (*cf.* Experimental Section). Compound **5** can also be obtained directly from **1** and hydroxide ion in ethanol or ethanol–water[4-7] (*cf.* Experimental Section). The acidification of **5** gives the unstable perthiocyanic acid[4,7] which rearranges to **1**.

TABLE I

PREPARATION OF "MIXED" PERTHIOCYANATES

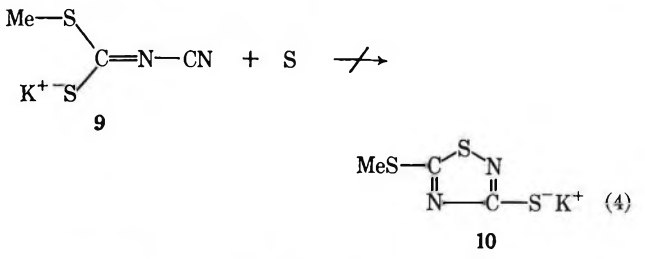


+ R'X ⟶ **7** (R = Me)

R'	Yield of 7, %
Benzyl	71
2,4-Dinitrophenyl	94
Triphenyltin	99
s-Triazinyl[a]	53

[a] This reaction was run using 3 mol of the sodium salt and 1 mol of cyanuric chloride to give the trisubstituted thiocyanurate.

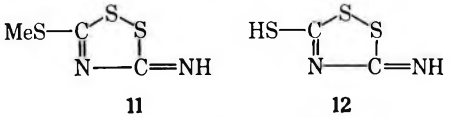
Addition of Sulfur to S-Methyl Potassium Cyanodithioimidocarbonate (9).—The preparation of the 5-methyl isomer *via* the addition of sulfur to **9** (eq 4) was investigated in view of the successful



(4)

addition of sulfur to **2** (*cf.* Experimental Section) and the preparation of 3-chloro-5-methyl-mercapto-1,2,4-thiadiazole from chlorine and **9**.[11] However, no significant amount of sulfur was absorbed under conditions identical with the reaction of **2** with sulfur. Also, neither raising the temperature nor changing the solvent to dimethylformamide increased the reactivity.

Rearrangement of 3-Imino-5-methylmercapto-1,2,4-Dithiazole (11).—The reported preparation[12] of salts of **11** provided a second approach to the 5-methyl isomer. A tautomer (**12**) of isoperthiocyanic acid



is analogous to **11**, and suggested that **11** would undergo a similar rearrangement (eq 5) as that shown

$$11 + OH^- \longrightarrow 10 + H_2O \quad (5)$$

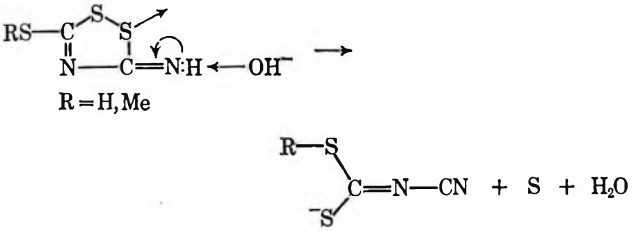
in Scheme I (**1** → **5**). However, the addition of the hydroiodide of **11** to 2 mol of potassium hydroxide in an ethanol–water solution precipitated an 85% yield of sulfur based on eq 6. The sulfur was removed by

$$11 + OH^- \longrightarrow 9 + S + H_2O \quad (6)$$

filtration, and 1 mol of dimethyl sulfate was added to the filtrate. Thus, the subsequent methylation of the filtrate would give dimethyl cyanodithioimidocarbonate (**3**, R = Me) and dimethyl perthiocyanate (**6**, R = Me), diagnostic of **9** and the desired 5-methyl isomer (**10**), respectively. Indeed, after 18 hr at room temperature, gas chromatographic analysis showed an 84% yield of **3** (R = Me) and a 7% yield of **6** (R = Me).

Based on the above correlation between the yield of sulfur and **3**, and the demonstrated addition of sulfur to the cyanodithioimidocarbonate anion (**3**) to form the perthiocyanate anion (**5**), it would be reasonable to suggest that **10** arose from the readdition of the sulfur in solution to **9** (eq 4). However, the demonstrated inertness of sulfur to **9** would indicate that an alternate mechanism is operative.[13]

Finally, the similar reactivity of isoperthiocyanic acid (**1**) and 3-imino-5-methylmercapto-1,2,4-dithiazole (**11**) towards hydroxide ion suggests a similar reaction path for the ring-opening reaction. A mechanism, based on proton abstraction from the exocyclic imino hydrogen, is proposed. Alternate mechanisms, involving the tautomeric hydrogen atom, can be



(11) R. J. Timmons and L. S. Wittenbrook, *J. Org. Chem.*, **32**, 1566 (1967).

(12) R. E. Allen, R. S. Shelton, and M. G. Van Campen, Jr., *J. Amer. Chem. Soc.*, **76**, 1158 (1954).

(13) A referee suggested that **9** arises from **10** and that **10** is an intermediate in the formation of **9** from **11**. This is certainly a possibility, but does not appear to be the case in the analogous transformations involving **1**, **2**, and **5** (Scheme I). Thus, there is no evidence for the formation of **2** from **5**, but **5** can be prepared from **2**.

written for isoperthiocyanic acid (R = H), but are not possible for the methyl derivative (**11**).

Experimental Section

The infrared spectra were determined in Nujol on an IR-8 Beckman spectrophotometer. Gas chromatographic analyses were carried out on an F & M 720 gas chromatograph using a silicone DC 550 column programmed from 120 to 270° at 15 deg min^{-1}.

Preparation of Potassium Perthiocyanate from Dipotassium Cyanodithioimidocarbonate (2)[6] and Sulfur.—To 12.0 g (0.062 mol) of **2** dissolved in 100 ml of a 50% ethanol–water solution was added 1.98 g (0.062 mol) of sulfur. The sulfur dissolved after stirring for 2 hr at room temperature. The solution was filtered and divided in half.

(a) **Methylation to Dimethyl Perthiocyanate.**—To one-half of the solution was added 8.81 g (0.062 mol) of methyl iodide. After 5 hr at room temperature, the reaction mixture was poured onto ice. The white solid was filtered and air dried to give 4.10 g (80%) of dimethyl perthiocyanate, mp 36–38° (lit.[6] mp 42°), mmp with an analytical sample, no depression. The ir spectra of the two samples were identical.

(b) **Acidification to Isoperthiocyanic Acid (1).**—The other half of the solution was acidified with 6 *N* HCl to give 4.20 g (90%) of **1**, mp 202° dec, mmp with an analytical sample of **1**, no depression. The ir spectra of the two samples were identical.

5 and Methyl Iodide.—To a solution of 106.6 g (2.66 mol) of sodium hydroxide in 200 ml of water and 800 ml of ethanol was added in portions 200.0 g (1.33 mol) of isoperthiocyanic acid. After solution, 193.0 g (1.33 mol) of methyl iodide was added dropwise, the temperature being kept between 15–25°. The reaction was stirred at room temperature for 24 hr and then poured onto ice. The resulting solid was filtered and air dried to give 62.5 g (27%) of dimethyl perthiocyanate, mp 35–39° (lit.[6] mp 42°), mmp with an authentic sample, no depression. The ir spectra of the 2 samples were identical. The filtrate was acidified dropwise with concentrated HCl; a yellow solid precipitated which was filtered and air dried to give 140.0 g, mp 120–140° (cloudy). Recrystallization from 1500 ml of ethyl acetate gave 61.3 g (28%) of 3-methylmercapto-5-mercapto-1,2,4-thiadiazole (**8**), mp 146–150 dec. An additional recrystallization from acetonitrile gave an analytically pure sample, mp 149–150 dec (lit.[10] mp 150–151° dec), mmp with an analytial sample of **8** prepared by the method of Goerdeler and Sperling, no depression. The ir spectra of the two samples were identical.

Anal. Calcd for $C_3H_4N_2S_3$: N, 17.1; S, 58.6. Found: N, 17.0; S, 58.4.

3-Methylmercapto-5-mercapto-1,2,4-thiadiazole (8) was prepared following the procedure of Goerdeler and Sperling,[10] mp 149–150° dec (lit.[10] mp 150–151° dec); **8** dissolved smoothly in 10% aqueous NaOH and was recovered unchanged on acidification with HCl.

Anal. Calcd for $C_3H_4N_2S_3$: N, 17.1; S, 58.6. Found: N, 17.0; S, 58.6.

8 and Diazomethane.—An ethereal solution of diazomethane was prepared using 21.5 g (0.10 mol) of N-methyl-N-nitroso-*p*-toluenesulfonamide. To a solution of 5.00 g (0.031 mol) of **8** in 25 ml of tetrahydrofuran (THF) was added the diazomethane solution. The reaction was allowed to proceed at room temperature until gas evolution ceased. The solvents were allowed to evaporate, and the residue was poured over ice. The mixture was cooled until the product became crystalline. It was filtered and air dried to give 4.80 g (88%) of dimethyl perthiocyanate (**6**, R = Me), mp 30–39°. The ir spectrum was identical with an authentic sample of **6**. Recrystallization from ethanol–water gave 3.01 g, mp 36–39°, mmp with an analytical sample of **6**, no depression.

3-Methylmercapto-5-benzylmercapto-1,2,4-thiadiazole.—The sodium salt of **8** was prepared by adding 22.0 g (0.13 mol) of **8** to a solution of 5.36 g (0.13 mol) of sodium hydroxide in 20 ml of water and 80 ml of methanol. The resulting solution was stripped to dryness. The residue (0.13 mol of the sodium salt) was dissolved in 200 ml of THF, and to it was added a solution of 22.9 g (0.13 mol) of benzyl bromide in 100 ml of THF. Within a few minutes, sodium bromide started to precipitate; after 20 hr at room temperature, the reaction mixture was filtered. The residue amounted to 12.9 g (94%) of sodium bromide. The filtrate was stipped to dryness, leaving 32.2 g of an orange liquid. Distillation gave 3.40 g of a forerun, bp 98–110° (0.50 mm), followed by 23.8 g (71%) of pure 3-methylmercapto-5-benzylmercapto,1,2,4 thiadiazole, bp 148–150° (0.35 mm), $n^{30}D$ 1.6552.

Anal. Calcd for $C_{10}H_{10}N_2S_3$: N, 11.0; S, 37.8. Found: N, 10.8; S, 37.8.

3-Methylmercapto-5-(2′,4′-dinitrophenylmercapto)-1,2,4-thiadiazole.—To a solution of 18.6 g (0.10 mol) of the sodium salt of **8** in 100 ml of THF was added a solution of 20.2 g (0.10 mol) of 1-chloro-2,4-dinitrobenzene in 100 ml of THF. After 19 hr at room temperature (sodium chloride precipitated as the reaction proceeded), the reaction mixture was filtered. The residue amounted to 5.00 g (86%) of sodium chloride. The filtrate was poured over ice to give a yellow solid; the solid was washed free of chloride with water and dried to give 31.0 g (94%) of 3-methylmercapto-5-(2′,4′-dinitrophenylmercapto)-1,2,4-thiadiazole, mp 114–116°. Recrystallization from carbon tetrachloride gave an analytical sample, mp 117–118°.

Anal. Calcd for $C_9H_6N_4O_4S_3$: C, 32.8; H, 1.8; N, 16.9; S, 28.9. Found: C, 32.7; H, 1.8; N, 17.0; S, 28.9.

3-Methylmercapto-5-triphenyltinmercapto-1,2,4-thiadiazole.—To a solution of 0.061 mol of the sodium salt in 100 ml of THF was added a solution of 23.5 g (0.061 mol) of triphenyltin chloride in 75 ml of THF. As the reaction proceeded, sodium chloride precipitated. After 17 hr at room temperature, the reaction mixture was filtered. The residue amounted to 3.30 g (93%) of sodium chloride. The filtrate was stripped to dryness; the residue was triturated with an ethanol–water solution to give 31.0 g (99%) of 3-methylmercapto-5-triphenyltinmercapto-1,2,4-thiadiazole, mp 72–76°. Recrystallization from 95% ethanol gave an analytical sample, mp 75–76°.

Anal. Calcd for $C_{21}H_{18}N_2S_3Sn$: N, 5.5; S, 18.7; Sn, 23.1. Found: N, 5.4; S, 18.6; Sn, 23.0.

Tris(3-methylmercapto-1,2,4-thiadiazole-5)-trithiocyanurate.—To 0.12 mol of the sodium salt dissolved in 100 ml of THF was added 7.26 g (0.04 mol) of cyanuric chloride dissolved in 50 ml of THF. Immediate precipitation occurred, and the temperature rose to 45°. After 1 hr at reflux, the reaction was allowed to stand at room temperature overnight and then filtered. The residue was washed with THF and water and dried (16.5 g). Washing the crude product with boiling dioxane and acetonitrile gave 12.0 g (53%) of tris(3-methylmercapto-1,2,4-thiadiazole-5)-trithiocyanurate, mp 252–254°.

Anal. Calcd for $C_{12}H_9N_9S_9$: C, 25.4; H, 1.6; N, 22.2; S, 50.7; Cl, 0.0. Found: C, 25.7; H, 1.6; N, 21.9; S, 50.1; Cl, 0.1.

3-Imino-5-methylmercapto-1,2,4-dithiazole Hydriodide (11) and Hydroxide Ion.—To 3.12 g (0.050 mol) of potassium hydroxide dissolved in 100 ml of a 50% ethanol–water solution was added 7.33 g (0.025 mol) of 3-imino-5-methylmercapto-1,2,4-dithiazole hydroiodide.[12] The mixture was stirred at room temperature for 2 hr and then filtered. The residue amounted to 0.68 g of sulfur, mp 90–105°; recrystallization from dimethylformamide gave 0.20 g, mp 117–119°, mmp with authentic sulfur, no depression.

To the filtrate was added 3.16 g (0.025 mol) of dimethyl sulfate. After 18 hr at room temperature, the solution was poured into water and extracted with ether. Drying the ether extract ($MgSO_4$) and then stripping the solvent left 3.40 g of a pale yellow solid. Gc analysis showed 84% dimethyl cyanodithioimidocarbonate and 7% dimethyl perthiocyanate.

Registry No.—**8**, 20069-40-3; 3-methylmercapto-5-benzylmercapto-1,2,4-thiadiazole, 20429-49-6; 3-methylmercapto-5-(2′,4′-dinitrophenylmercapto)-1,2,4-thiadiazole, 20429-50-9; 3-methylmercapto-5-triphenyltinmercapto-1,2,4-thiadiazole, 20429-51-0; Tris-(3-methylmercapto-1,2,4-thiadiazole-5)trithiocyanurate, 20429-52-1.

Acknowledgment.—The author is indebted to Mr. Ivor Simmons, Mr. Patrick Branigan, and their respective staffs for the instrumental and elemental analyses, respectively.

The Kinetics and Mechanisms of the Oxidation of Methanol and of α-Phenylethanol by Peroxydisulfate Ion[1]

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The oxidation of methanol by aqueous peroxydisulfate ion has been found to proceed *via* two distinct paths, one in the presence of oxygen (path A), the other in its absence (path B). The reaction path in absence of oxygen was found to be catalyzed by Cu(II) ion and inhibited by the oxidation product, formaldehyde. When copper catalysis and formaldehyde inhibition are minimized the observed rate law is rate = $k[S_2O_8^{2-}]^{3/2}$. A radical-chain mechanism consistent with the observed rate law and stoichiometry is presented. A value of k for the oxidation of methanol-d_3 was determined. The isotope effect is shown to be reasonable with respect to the proposed mechanism. Additional steps are presented to explain the formaldehyde inhibition. Rate and stoichiometric data are also presented for the peroxydisulfate oxidation of α-phenylethanol.

The kinetics of the oxidation of methanol by aqueous peroxydisulfate ion have been reinvestigated. Previous investigators[2-7] had proposed that the oxidation proceeds by a radical-chain mechanism. They were unable to suggest a mechanism consistent with their observed rate dependence (three-halves on peroxydisulfate and one-half on methanol) without involving a bimolecular initiation step between peroxydisulfate and methanol. Kolthoff,[2] however, using allyl acetate as a radical trapping agent, had shown that a bimolecular step does not contribute to chain initiation. This investigation was undertaken to clarify this situation and to investigate further other factors (such as the reported effects of trace metals and oxygen) affecting the peroxydisulfate oxidation of alcohols.

Experimental Section

Materials.—All chemicals not described below were reagent grade. The solvent in all cases was unbuffered; the pH varied from approximately 3.5 to 2 in the runs with methanol. Unless indicated otherwise, all experiments involving methanol were performed using distilled water. Deionized water, prepared by passing distilled water through a Barnsted mixed-bed ion-exchange column, was used for the experiments with α-phenylethanol.

Baker and Adamson reagent grade potassium peroxydisulfate was recrystallized from deionized water either once or twice before use. Spectral grade methyl alcohol (Fisher Analyzed Reagent No. A-408) was used in the majority of experiments. A few runs were carried out with reagent grade methanol distilled from calcium oxide; no differences were found between the rate constants obtained with the two grades of alcohol. Methanol-free formaldehyde was prepared by the method of Ledbury and Blair.[8] The aqueous formaldehyde solution was analyzed for per cent formaldehyde. This value, coupled with the measured index of refraction of the solution, was then applied to a ternary phase diagram[9] for the system methanol–formaldehyde–water. For a typical preparation which was 25%, w/w, in formaldehyde with $n^{18}D$ 1.3593, the indicated percentage of methanol is 0 ± 2. Allyl acetate, purchased from the Aldrich Chemical Co., was freshly distilled before use, bp 101.5–102°.

Methanol-d_3 (>99% isotopic purity claimed by supplier) was purchased from Merck Sharp and Dohme of Canada, lot no. AP 569, and used without further purification. Mass spectral and infrared analyses showed its isotopic purity to be 96% or greater.

K & K Laboratories α-phenylethanol was fractionally distilled before use, bp 89–90° (12 mm), $n^{20}D$ 1.5213. Tlc on 0.5-mm-thick silica gel plates in 4:1 v/v benzene–ethyl acetate gave only one spot with an R_f value of 0.41.

Techniques.—Kinetics were followed on a Beckman DK-1 recording spectrophotometer. A thermostated cell holder through which water or ethylene glycol was circulated from a constant-temperature bath enabled temperatures within the cell compartment to be maintained to ±0.5°. Matched ground-glass stoppered silica cells of 1.0-cm path length were used.

Peroxydisulfate ion absorbs in a broad ascending curve from approximately 300 mμ out to beyond 200 mμ.[10] This fact in conjunction with the nonabsorbing character of methanol and formaldehyde in this region of the spectrum allowed the loss of peroxydisulfate ion to be followed with full-scale deflection over a wide range of concentrations. In the case of α-phenylethanol, kinetics were monitored by following the increase in absorption due to the product acetophenone (log $E_{max}^{55°}$ 4.074, λ_{max} 244 mμ). In all cases the reference solution was of the same composition as the reaction mixture, with the omission of peroxydisulfate. Previous work[7] and preliminary experiments showed that for the concentrations of peroxide employed the spectrophotometer light source does not induce the photochemical decomposition of peroxydisulfate.

Rate constants were calculated either from plots of $1/(A_t - A_\infty)^{1/2}$ *vs.* time, where A_t is absorbance at time t and A_∞ is absorbance at time infinity (ten half-lives) or directly from spectrophotometric traces. A_∞ was not usually zero; it varied from zero by ±0.03 units owing to slight cuvette imbalance and/or instrument drift. Rate constants calculated for duplicate runs usually agreed to ±8%. Initial rate constants varied by ±20%; in these cases at least seven determinations were made and an average taken.

Three different procedures were employed for initiating the reactions depending upon the desired degree of oxygen exclusion. When the exclusion of air was not required, the procedure was to allow the peroxydisulfate solution to attain temperature in the cell in the spectrophotometer. Alcohol and/or other additives were then introduced directly into the cell with a hypodermic syringe or micropipet, and the solution was mixed by shaking; this procedure usually required from 10 to 20 sec. In those runs which were carried out in order to determine initial rate constants, it was desirable to reduce the amount of air present in the reaction mixture. In these cases deaeration was accomplished by bubbling a stream of prepurified nitrogen, for approximately 0.5 hr, through a peroxydisulfate solution in an external vessel fitted with a rubber stopper drilled to pass a small pipet. The solution was then brought to temperature and pipeted into the spectrophotometer cell where other reactants were added in the manner described above. An apparatus was designed for the purpose of carrying out a number of runs in an environment as free from oxygen as possible. This apparatus and the method of initiating the reaction were similar to that previously described.[7] In the experiments involving allyl acetate, the production of

(1) Abstracted from the Ph.D. Thesis of J. E. McIsaac, Jr., Brown University, 1968. A preliminary account of this work has been published: J. O. Edwards, A. R. Gallopo, and J. E. McIsaac, Jr., *J. Amer. Chem. Soc.*, **88**, 3891 (1966).

(2) I. M. Kolthoff, E. J. Meehan, and E. M. Carr, *ibid.*, **75**, 1439 (1953).

(3) P. D. Bartlett and J. D. Cotman, *ibid.*, **71**, 1419 (1949).

(4) L. R. Subbaraman and M. Santappa, *Curr. Sci.*, **33**, 208 (1964).

(5) L. R. Subbaraman and M. Santappa, *Proc. Indian Acad. Sci.*, **64**, 345 (1966).

(6) L. R. Subbaraman and M. Santappa, *Z. Phys. Chem.*, **48**, 163 (1966).

(7) D. L. Ball, M. M. Crutchfield, and J. O. Edwards, *J. Org. Chem.*, **25**, 1599 (1960).

(8) W. Ledbury and E. Blair, *J. Chem. Soc.*, 26 (1925).

(9) J. F. Walker, "Formaldehyde," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1953, p 484.

(10) L. J. Heidt, J. B. Mann, and H. R. Schneider, *J. Amer. Chem. Soc.* **70**, 3011 (1948).

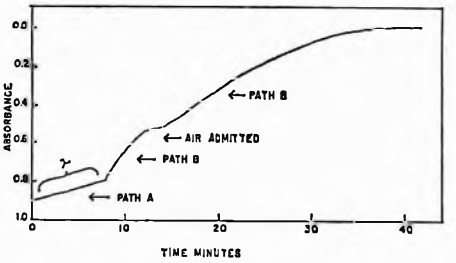

Figure 1.—Typical trace of absorbance *vs.* time at 231 mμ showing path A, path B, and the length of path A, τ.

polyallyl acetate precluded the use of a spectrophotometric technique. The method employed was iodometric analysis of unreacted peroxydisulfate.[11]

Yields.—Yields of formaldehyde were determined by sealing the reactants in 5-ml glass ampoules and submerging the ampoules in a thermostated bath for the required length of time, after which they were analyzed by the method of Romijin.[12] The yields of acid produced during the course of the reaction were determined similarly except that aliquots were titrated with 0.1 *N* NaOH using an automatic titrator, a Radiometer titragraph, type SBR2C. The remaining solution was analyzed spectrophotometrically for the concentration of unreacted peroxydisulfate.

Results

Methanol Oxidation.—The oxidation of methanol was found to proceed *via* two distinct reaction paths. When the oxidation is initiated in a stoppered spectrophotometer cell with reactants initially at equilibrium with the atmosphere, a relatively slow reaction is first observed; after several minutes, however, the reaction rate increases dramatically. If a small amount of air is introduced into the cuvette, the rapid reaction is immediately quenched and the rate of loss of peroxydisulfate returns to approximately the initially observed value. Again, after a short time a sharp rate increase is observed.

Figure 1 illustrates these dramatic changes. The slower portion of the reaction will be designated as path A, the fast portion as path B, and the length of path A will be τ; this nomenclature is the same as that chosen by Ball, *et al.*, who observed these same general characteristics in the peroxydisulfate oxidation of 2-propanol.[7] The rapid change in the slopes of plots of absorbance *vs.* time, from path A to path B, probably coincides with the complete consumption of dissolved oxygen in the system. Inhibition of peroxydisulfate oxidations involving organic reductants by oxygen is is well documented.[4-7,13,14] Attempts to eliminate completely the A portion of the reaction by degassing all reactants with oxygen-free nitrogen and carrying out the reactions in a nitrogen atmosphere were unsuccessful. τ could only be shortened by slightly more than a factor of one-half, to 3.5 min, under conditions for which without degassings, τ averaged 8 min. This is reasonable since oxygen is continually produced by the peroxydisulfate oxidation of water.[15] Some oxygen would then always be present at the initiation of the

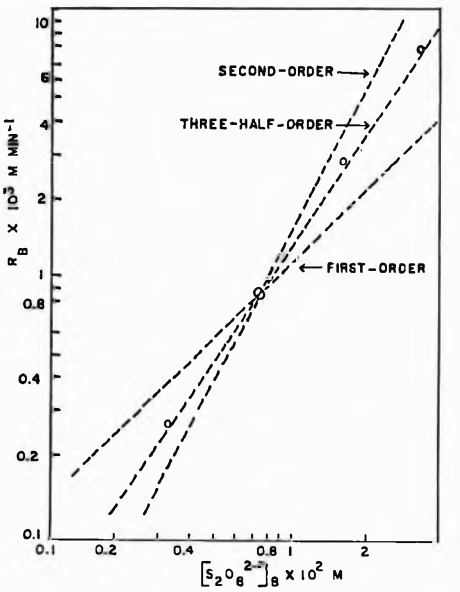

Figure 2.—Demonstrating the kinetic dependence of path B on the concentration of $S_2O_8^{2-}$ at the commencement of path B: $T = 70°$; $[CH_3OH]_0 = 0.78\ M$; R_B = initial rate of loss of $S_2O_8^{2-}$.

alcohol oxidation. No significant difference was observed in the shape of the three-halves-order plot or the value of the rate constant obtained under nitrogen as compared to the results found by the technique usually employed.

For the purposes of the presentation of tabular and graphical data, initial reactant concentrations, indicated by the subscript zero, are those at the beginning of path A. The subscripts A and B will also be used when it is necessary to differentiate between initial reactant concentrations for the two paths.

Stoichiometry.—The previously observed stoichiometry (when $[CH_3OH]_0 \geq 1\ M$) given by eq 1 was re-

$$S_2O_8^{2-} + CH_3OH \longrightarrow CH_2O + 2H^+ + 2SO_4^{2-} \quad (1)$$

$$CH_2O + H_2O \rightleftharpoons CH_2(OH)_2 \quad (2)$$

affirmed; see Table I. Equation 2 is included to demonstrate the hydration equilibrium of formaldehyde; under the conditions of our experiments formaldehyde is present at >99% as the hydrate.[16]

Table I
Yield of Formaldehyde as a Function of Methanol Concentration and Temperature[a,b]

$[CH_3OH]_0$, *M*	Temp, °C 60	70	80
1.5	101.0	101.8	102.7
1.1	100.4	101.0	99.4
0.78	96.4	98.0	100.8
0.39	93.7	95.6	98.1
0.20	88.6	91.0	87.0

[a] Yields of H_2CO in per cent, based on $K_2S_2O_8$ lost at initial $K_2S_2O_8$ concentrations of approximately $8.5 \times 10^{-3}\ M$, assuming the stoichiometry of eq 1. [b] Yields >100% are due to interference by methanol in the analytical method at concentrations of methanol >0.8 *M*.

Rate Law. Path B.—The rate of loss of peroxydisulfate ion for path B was found to be proportional to the

(11) I. M. Kolthoff and E. M. Carr, *Anal. Chem.*, **25**, 298 (1953).
(12) I. M. Kolthoff and N. H. Furman, "Volumetric Analysis," Vol. 2, John Wiley & Sons, Inc., New York, N. Y., 1929, p 444.
(13) A. R. Gallopo, Ph.D. Thesis, Brown University, 1967.
(14) H. N. Po and T. L. Allen, *J. Amer. Chem. Soc.*, **90**, 1127 (1968); E. Ben-Zvi and T. L. Allen, *ibid.*, **83**, 4352 (1961); A. J. Kalb and T. L. Allen, *ibid.*, **86**, 5107 (1964).
(15) I. M. Kolthoff and J. K. Miller, *J. Amer. Chem. Soc.*, **73**, 3055 (1951).
(16) R. P. Bell and A. O. McDougall, *Trans. Faraday Soc.*, **56**, 1281 (1960).

three-halves power of the concentration of the peroxide. The kinetic dependence of the reaction on peroxydisulfate was determined in two ways—by varying the concentration of peroxide and observing the change in initial rate (see Figure 2) and from the linearity of integrated three-halves-order rate plots at ratios of peroxide–alcohol greater than 100. As this ratio falls below 100, the plots exhibit slight curvature during the initial portion of path B (see Figure 3). This initial deviation was observed by both Bartlett and Cotman[3] and Kolthoff, *et al.*,[2] but it was not further considered by them.

The curvature of integrated rate plots at the lowest alcohol concentrations, together with the decrease in the yields of formaldehyde under these conditions suggested that the product aldehyde was itself being oxidized and inhibiting the methanol oxidation. Indeed this was found to be the case, as is indicated by the data of Table II. The first five entries of Table II demonstrate the dependence of the rate constant obtained from integrated plots on methanol concentration; the middle three entries show the change in the initial rate constant as a function of alcohol concentration; the variation in rate constant as a function of the concentrations of both methanol and added formaldehyde are shown in the last six entries.

TABLE II

RATE CONSTANTS AS A FUNCTION OF METHANOL AND FORMALDEHYDE CONCENTRATIONS[a]

$[CH_3OH]_0$, M	$[CH_2(OH)_2]_0 \times 10^3$ M	$k^{3/2}$, $M^{-1/2}$ min^{-1}
1.5	0.0	1.62[b]
1.1	0.0	1.53[b]
0.78	0.0	1.41[b]
0.39	0.0	1.08[b]
0.20	0.0	0.97[b]
1.5	0.0	1.55[c]
0.79	0.0	1.49[c]
0.20	0.0	1.38[c]
1.6	7.7	1.27[b]
1.5	4.7	1.25[b]
1.5	16.6	1.06[b]
1.5	33.1	0.86[b]
0.80	7.7	1.00[b]
0.40	7.7	0.82[b]

[a] $[S_2O_8^{2-}]_0 \cong 8 \times 10^{-3}$ M, $T = 70°$. [b] Obtained from integrated rate plots; in the presence of added CH_2O some plots exhibited very soft sigmoidal shapes. [c] Obtained from initial rates.

The initial rate constants agree quite well with those calculated from integrated rate plots at 1.5 and 0.78 M alcohol. The value of the initial constant at the lowest methanol concentration is considerably larger than the corresponding value obtained from the integrated plots. The smaller value of the initial rate constant at 0.20 M alcohol may be due to some interference by formaldehyde, even under conditions where its concentration has been significantly reduced.

The data are consistent with a zero-order dependence of the rate on the concentration of methanol. The experimentally determined rate law for the B portion of the reaction for the concentration range explored is then

$$\frac{-d[S_2O_8^{2-}]}{dt} = k[S_2O_8^{2-}]^{3/2} \quad (3)$$

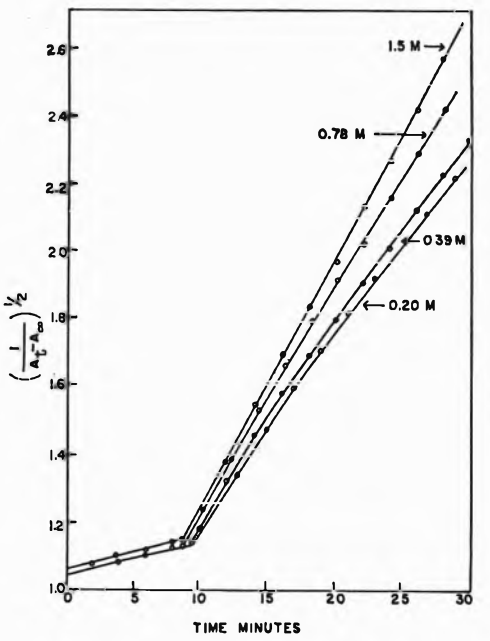

Figure 3.—Integrated rate plots for four methanol concentrations: $[S_2O_8^{2-}]_0 \cong 8 \times 10^{-3}$ M; $T = 70°$.

Deuterium Isotope Effect.—In order to gain further insight into the details of the path B mechanism, the effect of replacing the three α hydrogens of methanol with deuterium was investigated. The value of the initial three-halves-order rate constant at 70° and 0.80 M methanol-d_3 is 1.19 ± 0.03. This value in conjunction with that found for the protium compound at 0.79 M alcohol gives 1.25 ± 0.1 for the ratio k_H/k_D.

Activation Energy.—The Arrhenius activation parameters for path B were obtained in the interval 60–80°. Table III lists the values of the rate constant as a function of temperature. The values at the three highest temperatures were obtained from integrated rate plots. The preceding work has shown that at the concentrations of peroxydisulfate and methanol used in these runs, the aldehyde formed during the reaction does not affect the kinetics. However, at 60° the integrated plots exhibited an initial curvature analogous to that observed at lower alcohol concentrations and 70°. Thus, the 60° value was obtained from initial rates. A possible rationale concerning this observation will be considered in the discussion. The Arrhenius activation parameters are $A = 9.5 \times 10^{12}$ $M^{-1/2}$ sec^{-1} and $E_a = 23 \pm 1$ kcal mol^{-1}.

TABLE III

TEMPERATURE DEPENDENCE OF PATH A AND OF PATH B[a]

Temp, °C	$k^{3/2}$, $M^{-1/2}$ min^{-1}	R_A[b] $\times 10^4$ M min^{-1}	τ, min
60	0.57	0.42	29.5
70	1.62	1.17	7.1
75	2.58	2.25	4.1
80	3.82	3.7	2.6

[a] $[S_2O_8^{2-}]_0 \cong 8 \times 10^{-3}$ M, $[CH_3OH]_0 = 1.5$ M. [b] R_A = initial rate of path A.

Mechanism of Formaldehyde Inhibition.—Formaldehyde is itself capable of being oxidized by peroxydisulfate to yield formic acid.[17] The stoichiometry is given by eq 4. Equation 4 predicts that 3 mol of

$$S_2O_8^{2-} + CH_2(OH)_2 \longrightarrow HCOOH + 2H^+ + 2SO_4^{2-} \quad (4)$$

(17) L. R. Subbaraman and M. Santappa, *Z. Phys. Chem.*, **48**, 172 (1966).

strong acid should be produced for each mole of peroxide consumed. It was found that for an initial peroxide concentration of 8.2×10^{-3} *M* and an equivalent concentration of formaldehyde, 86.5% of the theoretical amount of acid was formed; with a tenfold excess of formaldehyde the acid yield was 101%.

The foregoing data clearly indicate that aldehyde inhibition must involve the simultaneous oxidation of methanol and formaldehyde. If this is so, then at the lowest alcohol concentration an excess of titratable acid, formic acid, should be produced in addition to the 2 equiv of HSO_4^- predicted by eq 1. Table IV is a summary of the data obtained for the concentration of strong acid produced during the course of two experiments—one at a high alcohol concentration where the yield of formaldehyde has been found to be 100%, the other at a much lower concentration where only 82.5% of the total theoretical yield of aldehyde is produced. At 1.5 *M* alcohol only 2 mol of acid are produced, during and up to the completion of the reaction for each mole of peroxydisulfate consumed. These data also confirm the stoichiometry of the reaction with respect to acid production. At 0.10 *M* methanol, however, there is an increasing amount of acid produced with time over and above the stoichiometric quantity of eq 1. This "excess" acid is attributed to the oxidation of formaldehyde. Based on the 82.5% yield of H_2CO at 0.1 *M* alcohol, and assuming that the deficit of 17.5% is caused by the reaction of one-half of this deficit, or 8.75% of the initial peroxide with formaldehyde, the calculated excess concentration of acid at infinite time is 7.2×10^{-4} *M*. The excess found, 8.2×10^{-4} *M*, is in good agreement.

Table IV

Comparison of the Total Acid Produced with Peroxydisulfate Lost as the Reaction Proceeds[a]

$[CH_3OH]_0$, *M*	$[S_2O_8^{2-}]$ lost $\times 10^3$ *M*	$[H^+]/2$ gained $\times 10^3$ *M*	$\Delta \times 10^3$, *M*[b]
1.5	1.28	1.20	−0.08
1.5	4.25	4.28	+0.03
1.5	6.94	6.85	−0.09
1.5	8.52	8.48	−0.04
0.10	0.64	0.76	+0.12
0.10	2.37	2.66	+0.29
0.10	5.36	5.69	+0.33
0.10	8.19	8.60	+0.41

[a] $T = 70°$. [b] $\Delta = [H^+]/2$ gained $- [S_2O_8^{2-}]$ lost.

Effect of Additives.—The effect of a number of additives upon both paths of the reaction was investigated. These additives included Cu^{2+} and the disodium salt of ethylenediaminetetracetic acid (EDTA). The results of these experiments are listed in Table V. Also included therein are observations on the effects of solvent and purity of the potassium peroxydisulfate (as indicated by the number of recrystallizations from deionized water) employed in the kinetic runs.

The data indicate that under the conditions of our experiments up to 10^{-5} *M* Cu^{2+} can be tolerated without significant kinetic consequences to path B. Above 10^{-5} *M*, Cu^{2+} produces an increase in the rate of path B. Not only was a rate increase observed, but the kinetic dependence changed to first order in peroxydisulfate. This behavior contrasts sharply with the effect of Cu^{2+} on the path B oxidation of 2-propanol[7] where no effect of copper was found. A catalytic effect of Cu^{2+} was, however, also observed on path B by Gallopo for the system peroxydisulfate–ethanol.[13] A stoichiometric and kinetic study of the effect of Cu^{2+} on this system is reported in ref 13.

Table V

Effect of Additives, Solvent, and the Number of Recrystallizations of $K_2S_2O_8$[a]

$[CH_3OH]_0$, *M*	Additive	Conditions[b,c]	$R_A \times 10^4$,[f] *M* min^{-1}	τ, min	k_{obsd}
1.5	None	D, 1	1.17	7.1	1.62[d]
0.78	None	D, 1	1.29	8.1	1.42[d]
1.5	None	DI, 2	1.06	9.3	1.37[d]
0.78	N_2	D, 1	Not measurable	3.5	1.50[d]
1.5	1×10^{-5} EDTA	DI, 2	0.81[g]	11.3	1.37[d]
0.78	1×10^{-5} EDTA	D, 2	1.32	8.9	1.38[d]
1.5	1×10^{-5} EDTA	D, 2	1.17	8.9	1.44[d]
1.5	1×10^{-4} EDTA	D, 2	0.054	11.5	1.26[d]
1.5	1×10^{-5} Cu^{2+}	D, 2	1.27	8.0	1.72[d]
1.5	5×10^{-5} Cu^{2+}	D, 2	1.36	8.0	1.23[e]
1.5	1×10^{-4} Cu^{2+}	D, 2	1.42	7.5	1.84[e]

[a] $[S_2O_8^{2-}]_0 \cong 8 \times 10^{-3}$ *M*, $T = 70°$. [b] D = distilled water, DI = deionized water. [c] Number of recrystallizations of $K_2S_2O_8$ from DI water. [d] Obtained from integrated three-halves-order plots; units are $M^{-1/2}$ min^{-1}. [e] Obtained from integrated first-order plots; units are min^{-1}. [f] Obtained from traces of absorbance *vs.* time; R_A = initial rate of path A. [g] Value for one run; duplicate exhibited no change of absorbance with time.

EDTA was added to several reaction mixtures for which the solvent was either distilled or deionized water. In the presence of 10^{-5} *M* EDTA, the rate constants and the rate plots do not differ, within experimental error, from the behavior observed in the absence of EDTA. At 10^{-4} *M* EDTA the value of the rate constant is low, but the plots from which it was calculated exhibit initial curvature similar to that found in the case of aldehyde inhibition. Ball, *et al.*,[7] found that EDTA can react slowly with peroxydisulfate alone. The slight rate reduction may be due to a specific effect of EDTA itself, rather than to its ability to chelate trace metal ions.

Path A.—A study of path A was not the major purpose of this investigation, and, while the results do not permit firm mechanistic postulations, they are informative and agree generally with observations reported for 2-propanol[7] and ethanol.[13] The following data were obtained on solutions initially at equilibrium with air at room temperature. There was negligible space above solutions in the stoppered cuvettes and at the temperatures employed the rate of solution of additional oxygen is not thought to be important. Thus, τ may be considered an approximate measure of the original concentration of dissolved oxygen and $1/\tau$ is then proportional to the rate of oxygen consumption. The values of R_A and τ are probably of no greater accuracy than ±20%; deviations of this magnitude were found in duplicate runs.

The rate of path A appears to be independent of oxygen concentration. Although oxygen is necessary for path A to be observed, spectrophotometric traces are linear for the full length of *A*.[18] By varying the initial concentration of peroxydisulfate and methanol, path A was found to be independent of alcohol concentration, but not independent of peroxide. Log–log plots of the data of Table VI, for $[S_2O_8^{2-}]_A$ *vs.* R_A and τ have slopes of 0.81 and 0.86, respectively. Ar-

(18) The traces are nonlinear for the first 1 or 2 min, during which time thermal equilibrium was established within the thermostated cell compartment following the mixing of reactants.

rhenius plots of R_A and τ data from Table III give apparent activation energies of 26 and 29 ± 2 kcal mol^{-1}. The larger value obtained from the τ data is as would be expected since temperature change would affect not only the rate of loss of oxygen but also its solubility.

The effects of additives upon path A are summarized in Table V. The only dramatic effect discernible is that of EDTA at 10^{-4} M in distilled water or 10^{-5} M EDTA in deionized water with twice recrystallized $K_2S_2O_8$. The comparatively small value of R_A at 10^{-4} M EDTA is difficult to interpret, as indicated in the discussion of the effects of additives on path B; it may be due to inhibition of the reaction by EDTA itself. The first-order rate constant calculated from R_A is 6.5 × 10^{-4} min^{-1} which is over two times slower than the rate constant for the thermal decomposition alone,[15] 1.45 × 10^{-3} min^{-1}. The effect of 10^{-5} M EDTA in deionized water with twice recrystallized $K_2S_2O_8$ may be real and due to reduced concentrations of trace metal ions. In a duplicate run under these conditions, however, there was no measurable change in absorbance during the entire course of A. With 10^{-5} M EDTA in distilled water there was no effect on either R_A or τ. These observations can be rationalized by assuming that path A is subject to trace metal catalysis; this is consistent with the reported effects of trace metals on the path A oxidation of 2-propanol[7] and ethanol.[13] When metal ion catalysis is eliminated, any inhibiting effect of EDTA itself would be more noticeable on a slower uncatalyzed path.[19]

TABLE VI

EFFECT OF VARIATION OF REACTANT CONCENTRATIONS ON PATH A AT 70°

$[CH_3OH]_0$, M	$[S_2O_8^{2-}]_A$ × 10^3 M	R_A × 10^4 M min^{-1} [a]	τ, min
1.5	8.0	1.17	7.1
0.78	8.0	1.29	8.1
0.39	8.0	1.25	8.6
0.78	4.7	0.92	12.6
0.78	16.0	2.01	4.1
0.78	32.0	3.34	2.6

[a] R_A = initial rate of path A.

The lack of any appreciable effect of added Cu^{2+} in conjunction with the EDTA data indicate that the concentrations at which trace metal ions are able to catalyze path A must be extremely low and such catalysis must reach a limiting value at very small metal ion concentrations. Although Cu^{2+} is probably not the only catalytic ion present it has been found to be a very effective catalyst in peroxydisulfate oxidations.[7,13,14,20]

Oxidation of α-Phenylethanol.—Approximately 1 mol of acetophenone was formed for each mole of peroxydisulfate consumed. Based on the initial peroxide concentration under nitrogen and at 65–70° an 84% yield of the 2,4-dinitrophenylhydrazone of acetophenone was isolated. Spectrophotometrically determined yields ranged from 86 to 99%. All of the experiments listed in Table VII were conducted under nitrogen and pseudo-zero-order conditions at 10^{-4} M $K_2S_2O_8$ using deionized water. The data of Table VII are consistent with the following rate law for the production of acetophenone.

TABLE VII

DEMONSTRATING THE DEPENDENCE OF THE THREE-HALVES-ORDER RATE CONSTANT ON REACTANT CONCENTRATIONS FOR THE OXIDATION OF α-PHENYLETHANOL[a]

$[S_2O_8^{2-}]_0$ × 10^4 M	$[C_6H_5CHOHCH_3]_0$ × 10^3 M	$k^{3/2}$ $M^{-1/2}$ min^{-1}
1.8	3.7	0.32
5.0	3.6	0.28
7.8	3.6	0.29
9.5	3.6	0.27
4.9	0.64	0.32
4.9	1.1	0.34
4.9	1.8	0.31
4.9	2.4	0.34
		Av 0.31 ± 0.02

[a] T = 55°, under nitrogen in deionized water.

$$\frac{d[C_6H_5COCH_3]}{dt} = k[S_2O_8^{2-}][C_6H_5CHOHCH_3]^{1/2} \quad (5)$$

Discussion

The oxidations reported herein clearly must proceed by a free-radical-chain mechanism initiated by the thermal decomposition of peroxydisulfate ion to two sulfate radical ions. Evidence supporting this statement is listed below.

(a) Peroxydisulfate ion has been shown to decompose in aqueous solution by a nonchain radical process.[15,21] It is well-known and widely used initiator of vinyl polymerizations.

(b) The oxidation of methanol is inhibited by oxygen and the oxidation of α-phenylethanol appears to be influenced by oxygen.[1] Oxygen inhibition of radical reactions involving organic compounds is a well-known phenomenon.

(c) The rates of these oxidations are a sensitive function of experimental conditions. The presence of oxygen, of trace metal ions, and of additives such as Cu^{2+} and formaldehyde have marked effects on rates. Such sensitivity is characteristic of radical reactions.

(d) The observed fractional dependence of rates on reactant concentrations is common for radical reactions.

(e) The deiodination of aryl iodides in methanolic sodium methoxide, which is postulated to occur *via* a free-radical mechanism, has been successfully initiated with $K_2S_2O_8$.[22]

(f) Allyl acetate and diphenylpicrylhydrazyl reduce the rate of loss of peroxydisulfate ion in the presence of alcohols to the rate of its decomposition in pure water.[2,13,21,23] Based on Kothoff and Miller's[15] values for the rate constant for the oxidation of water by $S_2O_8^{2-}$ the calculated chain lengths are, for methanol at 70° and 8 × 10^{-3} M $S_2O_8^{2-}$, 100, and, for α-phenylethanol at 55° 1.8 × 10^{-4} M $S_2O_8^{2-}$ and 3.6 × 10^{-3} M $C_6H_5CHOHCH_3$, 130.

Postulated Mechanisms.—The proposed mechanism for the path B oxidation of methanol for the case of negligibly small concentrations of $H_2C(OH)_2$, *i.e.*, during

(19) Products of EDTA interference might absorb in the ultraviolet and cause the rate of change of absorbance to decrease to values less than those expected from the thermal decomposition of peroxydisulfate alone.

(20) Gallopo[13] has concluded that the following metal ions, present at a concentration of 10^{-5} M, as well as Cu(II), are probably capable of catalyzing the ethanol reaction: Ni(II), Fe(II), Cr(III), Hg(II), Sn(II), Sn(III), and Ti(II).

(21) C. E. H. Bawn and D. Magerison, *Trans. Faraday Soc.*, **51**, 925 (1955).

(22) J. F. Bunnett and Carl C. Wamser, *J. Amer. Chem. Soc.*, **89**, 6712 (1967).

(23) K. B. Wiberg, *ibid.*, **81**, 252 (1959).

the initial portion of path B or when the concentration of methanol is in 100-fold or greater excess over the initial concentration of $S_2O_8^{2-}$, is,

$$S_2O_8^{2-} \xrightarrow{k_1} 2\,SO_4\cdot^- \quad (6)$$

$$SO_4\cdot^- + CH_3OH \xrightarrow{k_2} \dot{C}H_2OH + H^+ + SO_4^{2-} \quad (7)$$

$$CH_2OH + S_2O_8^{2-} \xrightarrow{k_3} CH_2O + H^+ + SO_4^{2-} + SO_4\cdot^- \quad (8)$$

$$\dot{C}H_2OH + \dot{C}H_2OH \xrightarrow{k_4} HOCH_2CH_2OH \quad (9)$$

$$CH_2O + H_2O \rightleftharpoons CH_2(OH)_2 \quad (2)$$

Assuming steady-state conditions for long chains these steps lead to the rate law

$$-\frac{d[S_2O_8^{2-}]}{dt} = k_3\left(\frac{k_1}{k_4}\right)^{1/2}[S_2O_8^{2-}]^{3/2}$$

This rate law agrees with our experimental results where $k = k_3(k_1/k_4)^{1/2}$.

The k_2 step probably involves abstraction of an α hydrogen from methanol and not the hydrogen bound to oxygen. Several pieces of evidence point to this conclusion: (a) esr spectra of radicals produced by hydrogen abstraction from alcohols by hydroxyl radicals have been shown to be consistent with removal of an α hydrogen;[24] (b) isotopic labeling experiments have provided evidence that attack by hydrogen atoms on hydroxylic hydrogens of alcohols does not readily occur;[25,26] (c) radical abstraction of α hydrogens should be approximately 9 kcal mol^{-1} more exothermic than hydrogen abstraction from the OH group of an alcohol.[27] The k_3 step explains the increased rate of loss of peroxydisulfate observed in the presence of alcohol compared with the rate of the water reaction. The chain termination reaction, k_4, is the only step consistent with the observed kinetics and proposed radical intermediates. The two organic radicals may either dimerize to ethylene glycol or disproportionate to methanol and formaldehyde. Photolysis experiments[28] on mixtures of water–hydrogen peroxide and the alcohols, methanol, ethanol, and 2-propanol, have shown that hydroxymethyl radicals prefer dimerization to disproportionation. Dimerization is also consistent with our kinetic deuterium isotope effect (*vide infra*).

An alternative mechanism involving HO· radicals is also reasonable. In our case such a mechanism would be kinetically indistinguishable from that proposed above. Recent work by Dogliotti and Hayon[29] on the flash photolysis of aqueous solutions of peroxydisulfate containing methanol, ethanol, and 2-propanol indicates that for the pH range 1–4.8 the sulfate radical ion reacts directly with alcohol by α-hydrogen abstraction.

The measured activation energy is also consistent with the proposed mechanism. The energy of activation, assuming all steps follow an Arrhenius temperature dependence, would be given by $E_a = E_3 + {}^1/_2(E_1 - E_4)$. E_1 has a value of approximately 33.5 kcal mol^{-1}.[15] E_4, the activation energy for the reaction of two radicals, should be very small;[30] for the purpose of this approximate calculation it is assumed that $E_4 = 0$. These values, together with the experimental value of E_a (23 kcal mol^{-1}), give $E_3 = 6.2$ kcal mol^{-1}; this is a reasonable value for the reaction of a radical and a molecule.[31]

The observed deuterium isotope effect provides further support for the proposed mechanism. The derived rate constant $k_3(k_1/k_4)^{1/2}$ does not contain k_2, the rate constant for abstraction of hydrogen by the sulfate radical ion. This leads to the prediction that the observed rate constant should be insensitive to deuterium substitution at the α carbon, *e.g.*, a primary isotope effect. The value of k_H/k_D of 1.25 ± 0.1 is of the magnitude expected for a secondary isotope effect on k_3 or an *inverse* secondary α-isotope effect on k_4.[32] Seltzer[33] has found that $k_H/k_D = 1.12$–1.15 per deuterium atom for radical-forming ractions. Since k_4 enters into the rate constant as $(1/k_4)^{1/2}$ the measured value of the rate constant for methanol-d_3 is predicted to be decreased by a factor of $(1/1.12^4)^{1/2}$ to $(1/1.15^4)^{1/2}$.[34–36] These ratios lead to values of 1.25–1.32 for k_H/k_D.

Mechanism of Formaldehyde Inhibition.—Formaldehyde inhibition is postulated to occur by steps analogous to those proposed above. In the inhibition

$$CH_2(OH)_2 + SO_4\cdot^- \xrightarrow{k_5} \dot{C}H(OH)_2 + SO_4^{2-} \quad (10)$$

$$\dot{C}H(OH)_2 + S_2O_8^{2-} \xrightarrow{k_6} HCOOH + H^+ + SO_4^{2-} + SO_4\cdot^- \quad (11)$$

$$\dot{C}H(OH)_2 + \dot{C}H_2OH \xrightarrow{k_7} \text{products} \quad (12)$$

mechanism k_5 and k_6 are added to the steps for path B oxidation of methanol and the k_4 step is replaced by k_7. Aldehyde inhibition is attributed to a more rapid reaction of the sulfate radical ion with aldehyde than with alcohol and a subsequent decrease in chain length as the termination step k_7 becomes operative.

When the steady-state approximation is applied to the sequence of steps 6–8 and 10–12, assuming long chains, eq 13 is obtained. According to eq 13 the

$$\frac{-d[S_2O_8^{2-}]}{dt} = \left(\frac{k_1k_3k_6}{k_7}\right)^{1/2}[S_2O_8^{2-}]^{3/2} \times \left[\left(\frac{k_2[CH_3OH]}{k_5[CH_2(OH)_2]}\right)^{1/2} + \left(\frac{k_5[CH_2(OH)_2]}{k_2[CH_3OH]}\right)^{1/2}\right] \quad (13)$$

initial three-halves-order rate constant for path B in the presence of added formaldehyde should be a function of the ratio of methanol to formaldehyde. A plot of $k_{3/2}([CH_3OH]_B/[CH_2(OH)_2]_B)$ *vs.* $[CH_3OH]_B/[CH_2(OH)_2]_B$ should be linear. The points of Figure 3 fit a straight line (correlation coefficient = 0.994) and are

(24) M. C. R. Symons and M. G. Townsend, *J. Chem. Soc.*, 269 (1959).

(25) C. Lifshitz and G. Stein, *ibid.*, 3706 (1962), and references therein.

(26) J. H. Baxendale and G. Hughes, *Z. Phys. Chem.* (Frankfurt am Main), **14**, 306 (1958).

(27) J. W. Benson, *J. Chem. Educ.*, **42**, 502 (1965). The bond dissociation energies are CH_3O—H, 102 kcal mol^{-1}; $HOCH_2$—H, 93 kcal mol^{-1}.

(28) J. Barrett, A. L. Mansell, and R. J. M. Ratcliffe, *Chem. Commun.*, 48 (1968).

(29) L. Dogliotti and E. Hayon, *J. Phys. Chem.*, **71**, 2511 (1967).

(30) A. A. Frost and R. A. Pearson, "Kinetics and Mechanism," John Wiley & Sons, Inc., New York, N. Y., 1962, p 107.

(31) A. F. Trotman-Dickenson, "Free Radicals," John Wiley & Sons, Inc., New York, N. Y., 1959.

(32) S. Seltzer, private communication.

(33) A. Zavitsas and S. Seltzer, *J. Amer. Chem. Soc.*, **86**, 3836 (1964).

(34) According to Streitwieser's[35] treatment the isotope effect should be raised to the power of the number of deuterium atoms involved.

(35) A. Streitwieser, Jr., R. Jagow, R. Fahey, and S. Suzki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958).

(36) This is not to say that radical coupling is expected to exhibit the same α-isotope effect as radical-forming reactions. Indeed, owing to the exothermicity of the former, k_H/k_D would be expected to be less than 12–15 % per deuterium.

thus consistent with the proposed model. The ratio of the intercept to the slope of Figure 3 gives $k_5/k_2 = 11$.

The inequality $k_5 > k_2$ agrees with our suggested mechanism. Dogliotti[29] found that the reactivity of $SO_4 \cdot^-$ toward alcohols increases in the order methanol, ethanol, 2-propanol—the order of expected stability of the incipient radical. Since the substitution of one OH group increases the stability of the radical produced by α-hydrogen abstraction from methanol over a methane radical, substitution of hydrogen by two hydroxyl groups should further increase the stability of the formaldehyde radical.[38]

Subbaraman[17] reports that the peroxydisulfate oxidation of formaldehyde is only about ten times faster than the water oxidation rate. He proposes a radical chain mechanism involving steps 10 and 11.[40] Thus it appears that although k_5 is greater than k_2, k_6 must be much smaller than k_3; the radical $\cdot CH(OH)_2$ would then be able to reach a relatively high steady-state concentration and decrease the chain length in our case by termination with the radical $\cdot CH_2OH$.[41]

Path A.—We attribute the lower rate of loss of peroxydisulfate in path A to a reaction between the reducing radical $\cdot CH_2OH$ and molecular oxygen. Oxygen inhibition probably occurs by a mechanism similar to that proposed by Ball, *et al.*,[7] and Gallopo[13] for the path A oxidations of 2-propanol and ethanol, respectively. There are, however, subtle differences in the behavior of the three alcohols. These differences are reflected in the effects of additives such as Cu^{2+} and EDTA. The reasons for this are not presently clear.

α-Phenylethanol.—We propose the following chain mechanism, initiated by eq 6 to account for the observed kinetics of oxidation of α-phenylethanol.

$$C_6H_5\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 + SO_4 \cdot^- \xrightarrow{k_8} C_6H_5\underset{\displaystyle OH}{\underset{|}{C}}CH_3 + H^+ + SO_4^{2-} \quad (14)$$

$$C_6H_5\underset{\displaystyle OH}{\underset{|}{C}}CH_3 + S_2O_8^{2-} \xrightarrow{k_9} C_6H_5\overset{\displaystyle O}{\overset{\|}{C}}CH_3 + H^+ + SO_4^{2-} + SO_4 \cdot^- \quad (15)$$

$$C_6H_5\underset{\displaystyle OH}{\underset{|}{C}}CH_3 + SO_4 \cdot^- \xrightarrow{k_{10}} \text{products} \quad (16)$$

For long chains these steps lead to the rate law

$$\frac{d[C_6H_5COCH_3]}{dt} = \left(\frac{k_1 k_8 k_9}{k_{10}}\right)^{1/2} [S_2O_8^{2-}][C_6H_5CHOHCH_3]^{1/2} \quad (17)$$

Equation 17 is of the same form as the rate law found experimentally.

(37) The yield data of Table I and the experiments with formaldehyde show that for the concentrations employed the majority of $S_2O_8^{2-}$ is lost by reaction with methanol.

(38) The dissociation energies are CH_3—H, 101[39] kcal mol^{-1}; $HOCH_2$—H, 93[27] kcal mol^{-1}.

(39) T. L. Cottrel, "The Strengths of Chemical Bonds," Butterworth and Co. Ltd., London, 1958, p 177.

(40) The initiation step proposed by Subbaraman is doubtful since it involves a bimolecular reaction between $CH_2(OH)_2$ and $S_2O_8^{2-}$, see E. J. Behrman and J. E. McIsaac in "Mechanisms of Reactions of Sulfur Compounds," N. Kharasch, Ed., Vol. 2, 1968, for a more complete discussion.

(41) Assuming similar preexponential Arrhenius factors for steps 10 and 7, the ratio k_5/k_2 corresponds to an apparent difference of 1.6 kcal mol^{-1} in E_a. The nonlinear rate plots obtained at 60° (*vide ante*) can be rationalized; at the lowest temperature $CH_2(OH)_2$ would be expected to react with $SO_4 \cdot^-$ more rapidly, relative to CH_3OH, than it does at 70°. This argument is supported by the general decrease in the yields of formaldehyde with decreasing temperature; see Table I.

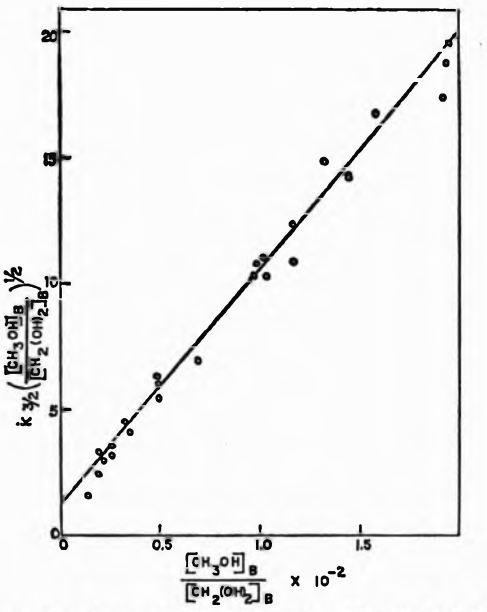

Figure 4.—Fit of experimental data to eq 13: $[S_2O_8^{2-}] \cong 8 \times 10^{-3}$ *M*, $T = 70°$; $[CH_2(OH)_2]_B$ = added $CH_2(OH)_2$ plus $[CH_2(OH)_2]$ theoretically formed during path A.[37]

General Conclusions.—From our work and from the reported rate laws and proposed oxidation mechanisms of alcohols by peroxydisulfate[4-7,13] a general pattern has emerged. Primary and secondary alcohols are, in the absence of oxygen, oxidized by similar mechanisms. The only difference between the two classes of alcohol is that the rate laws for primary alcohols require a chain termination between two organic radicals whereas secondary alcohols must chain terminate by reaction of an organic radical and the sulfate radical ion if the proposed mechanisms are to yield rate laws conforming to experimental results.[42] It has been found that radicals which can exhibit opposite polar effects in chain propagation steps usually favor cross-termination.[43] In radical termination steps the activation energy barrier may be reduced by polar contributions from a donor and an acceptor radical,[43] even though the activation barrier for all such reactions is expected to be small.[30] Gallopo[13] reports a 150-fold rate reduction in going from ethanol to 2,2,2-trifluoroethanol; this is good evidence that electronic effects are indeed important in peroxydisulfate–alcohol reactions.[44] The radicals originating from secondary alcohols would be expected to have electron donor qualities relative to the sulfate radical ion; such qualities should favor cross-termination. Primary alcohol radicals, according to this argument, would then be predicted to self-terminate.[45]

Registry No.—Methanol, 67-56-1; α-phenylethanol, 98-85-1; peroxydisulfate ion, 15092-81-6.

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(42) The only exception is cyclohexanol[8] for which participation by the hydroxyl radical must be invoked.[40]

(43) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 146.

(44) D. D. Tanner and S. A. A. Osman, *J. Amer. Chem. Soc.*, **90**, 6572 (1968).

(45) There is no evidence in the literature, with the exception of that cited,[42] for these reactions requiring other possible termination steps, *e.g.*, those between two $SO_4 \cdot^-$ radicals or others involving $HO \cdot$ radicals.

A Nuclear Magnetic Resonance Study of Intermolecular Hydrogen Bonding in Nitromethane–Methanol Solutions

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Nitromethane (and other nitroalkanes) added to methanol with or without CCl_4 dilution suppresses exchange of the OH proton owing to the formation of strong intermolecular NO_2–HO hydrogen bonds. This prolonged residence time for exchange of the OH proton is sufficient to allow the detection of spin–spin coupling (J_{HCOH}) for the alcohol protons. The observed variability in the displacement of the OH resonance effected by CH_3NO_2 was interpreted in terms of complex formation. Extensive dilution studies (CCl_4) of CH_3NO_2–CH_3OH mixtures provided evidence for the formation of several discrete complexes of this donor–acceptor pair.

The nmr technique of using strongly hydrogen bonding solvents, *e.g.*, acetone, DMSO, or pyridine, for suppressing proton exchange in alcohols to allow the determination of J_{HCOH} has become a well-established procedure.[1] Although this phenomenon appears to be general for strong hydrogen bonding interactions between the OH and CO, SO, or trivalent N functions,[1] no prior reports of spin–spin coupling in alcohols induced by the NO_2 group, the observation of which prompted the present study, have appeared. Furthermore, the few reported studies of intermolecular NO_2–HO interactions,[2] which have been based primarily on the correlation of infrared OH frequency shifts ($\Delta\nu_{OH}$), indicate that hydrogen bonding interactions between nitro groups and the OH function of primary alcohols should be weak. This latter conclusion appears to be inconsistent with the strong intermolecular NO_2–HO interaction indicated by the present study.

Experimental Section

Instrumentation.—Nmr spectra were obtained at 27 ± 1° using a Varian A-60 spectrometer equipped with a variable-temperature probe. Chemical shifts were measured on the basis of separate determinations using the methyl resonance of methanol and 1–5% tetramethylsilane (TMS) as internal references; side-band techniques were used as a check. Calibration of the instrument was accomplished with an audio signal generator (Hewlett–Packard 205AG) monitored by a frequency counter (Hewlett–Packard 5244L) operated in the period mode. After warm-up, the drift and instability of the instrument were better than one part in 10^5. Spectrometer drift during 1 hr approached ±0.2 cps.

Sample Preparation.—High purity nitromethane was generously supplied by Commercial Solvents Corp. Methanol (Fisher Reagent Grade) was purified by distillation from magnesium methoxide, and stored over fresh $CaSO_4$ under nitrogen. Spectral Grade CCl_4 (Fisher) was stored over fresh $CaSO_4$ prior to use. No detectable impurities were apparent in the high gain nmr spectra of the materials used. Samples were prepared using standard volumetric techniques, as applicable. The volume or weight of the solvents was measured directly. Volumetric accuracies were ±1%; gravimetric accuracies were limited by evaporation of volatile solvent but approached ±0.3%. Temperatures were measured using a sealed sample of purified methanol.

Results and Discussion

Nitromethane added to methanol for the range of concentrations indicated in Figure 1 produced a 170.5-Hz extrapolated (143.2 Hz measured) upfield displacement, $\Delta\nu^{\infty}(CH_3OH\text{–}CH_3NO_2)$,[3] of the resonance position of the hydroxylic proton.[4] This marked displacement of the hydroxyl peak did not approach in magnitude the OH shift, $\Delta\nu^{\infty}(CH_3OH\text{–}CCl_4) = 292.8$ Hz,[3] reported for methanol diluted with CCl_4,[5] but greatly exceeded changes in the resonance position for the OH proton induced by acetone (91.5 Hz) or DMSO (48.0 Hz).[6] Variations in the hydroxyl proton shift of alcohols caused by the addition of strong hydrogen bonding acceptor species (acetone, DMSO) have been attributed to depolymerization of hydrogen bonded alcohol telomers and polymers and the inception of a hydrogen bonding association to the acceptor molecule.[1,5] The latter provides only a partial explanation for the results reported below.

The postulation of a strong intermolecular NO_2–HO interaction between nitromethane and methanol was supported by specific spectral changes noted on addition of the nitroalkane (Figure 2). Methanol containing low concentrations of nitromethane showed three broadened singlets (Figure 2a) in the nmr spectrum at τ 5.28, 5.65, and 6.64 ppm; the low- and high-field peaks showed relative intensities of 1:3, assignable to the hydroxyl and methyl resonances. At $[CH_3NO_2]/[CH_3NO_2] + [CH_3OH] = 0.4$ (approximately) spin–spin interaction ($J_{HCOH} = 5.2$ Hz)[7] was observed (Figures 2b and d) and was apparent in the methanol spectrum of all solutions containing higher nitromethane concentrations, *i.e.*, except at $[CH_3NO_2]/[CH_3NO_2] + [CH_3OH] = 0.75$ (approximately). Here, the alcohol resonances coalesced to a singlet. Thus, consistent with the changing $J/\Delta\nu$ ratio, as the OH peak moved upfield[7], the CH_3OH spectrum showed an AX_3 pattern, changed to A_3B and A_4 patterns, and finally reverted to an A_3X pattern as the OH proton resonance appeared at *ca.* 57 Hz (limiting observed shift) upfield of the methyl resonance. The cited spectral changes are consistent

(1) Recently reviewed by P. Laszlo in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. III, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, London, 1967.

(2) (a) W. F. Baitinger, P. von R. Schleyer, T. S. S. R. Murty, and L. Robinson, *Tetrahedron*, **20**, 1635 (1964); (b) Y. S. Su and H. K. Hong, *Spectrochim. Acta*, **24**, 1461 (1968); (c) H. E. Ungrade, E. M. Roberts, and L. W. Kissinger, *J. Chem. Phys.*, **68**, 3225 (1964).

(3) Throughout this communication, $\Delta\nu^{\infty}(CH_3OH\text{–}CH_3NO_2)$ and $\Delta\nu_{\infty}(CH_3OH\text{–}CCl_4)$ signify the extrapolated or infinite dilution shifts (hertz at 60 MHz) for the OH proton of methanol in the indicated solvent. $\Delta\nu(CH_3OH\text{–}CH_3NO_2)$ and $\Delta\nu(CH_3OH\text{–}CCl_4)$ refer to observed shifts.

(4) The initial addition of CH_3NO_2 produced a 1.8-Hz downfield shift of the $-CH_3$ peak of methanol; thereafter, the methyl resonances were essentially invariant in position.

(5) (a) M. Saunders and J. B. Hyne, *J. Chem. Phys.*, **29**, 1319 (1958); (b) A. D. Cohen and C. Reid, *J. Chem. Phys.*, **25**, 790 (1956).

(6) W. Drinkard and D. Kivelson, *J. Phys. Chem.*, **62**, 1494 (1958). The values cited are corrected to 60 MHz.

(7) D. Kivelson and M. G. Kivelson [*J. Mol. Spectrosc.*, **2**, 518 (1958)] also reported $J_{HCOH} = 5.2$ Hz and a complete interpretation of the spectral changes encountered in the acetone–methanol system; W. B. Moniz, C. F. Poranski, Jr., and T. N. Hall [*J. Amer. Chem. Soc.*, **88**, 190 (1966)] have reported the solvent dependency of this parameter for various alcohols.

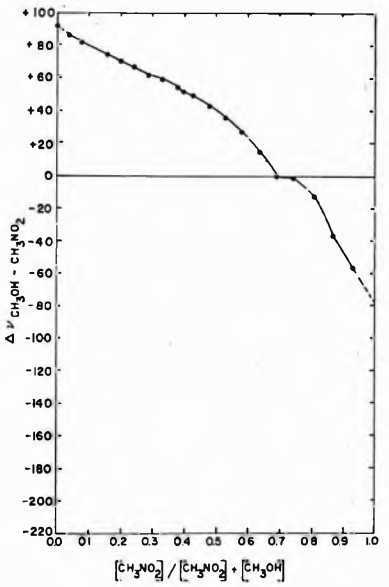


Figure 1.—Effect of CH_3NO_2 on $\Delta\nu$ (CH_3OH). Negative values correspond to shifts of the OH proton upfield of the CH_3 resonance of methanol.

with reported studies of methanol and other alcohols for interactions with strong hydrogen bond acceptors (acetone, DMSO).[5-8] Clearly, the NO_2–HO bond formed between nitromethane and methanol is of sufficient stability to meet at least this nmr criterion for a strong hydrogen bonding acceptor, *i.e.*, the enhancement of the residence time for exchange of the hydroxyl proton.[1] The described phenomenon proved to be general for all nitro compounds tested, including nitroethane, 1- and 2-nitropropane, chloromtromethane, and nitrobenzene, which were studied only over limited concentration ranges in methanol. For each nitroalkane, coalescence of the methanol resonances was observed at nitroalkane concentrations approaching a molar excess. In comparison, the maximum possible shift induced by acetone (10 molar excess) was found to be 91.5 Hz (coalescence) in agreement with a prior study of this system.[6] Furthermore, the NO_2–HO bond formed is apparently highly stable to dilution since the addition of CCl_4 to solutions exhibiting splitting of the alcohol resonances shifted the OH resonance, but did not obliterate the patterns due to spin–spin interaction. This ability of the nitro group to retard exchange of the OH proton in dilute solutions has been rigorously tested in only one case, *i.e.*, nitromethane and methanol. Solutions of this donor–acceptor pair in CCl_4 at a total methanol concentration of less than 0.07 M[9] still showed splitting of the methanol resonances.[10] For nitromethane to induce this effect even in highly dilute solutions is clearly inconsistent with the weak hydrogen acceptor properties for this molecule previously reported.[2] Such weak intermolecular interactions are for the most part easily disrupted under these circumstances.

Previously, Krakower and Reeves[11] reported the observation of fine structure in the ambient temperature spectrum of a specially purified neat sample of methanol. The lack of observable splitting for the present methanol samples at low acceptor concentration might be attributed to acidic impurities or water; checks with carefully purified and degassed samples showed the probable cause to be low concentrations of adsorbed water.[12] Furthermore, an explanation for the observed splitting of the alcohol resonances based on scavenging of traces of acids or water would still require the assignment of strong hydrogen acceptor properties to the nitro group, in contrast to the weakly basic characteristics reported.[13]

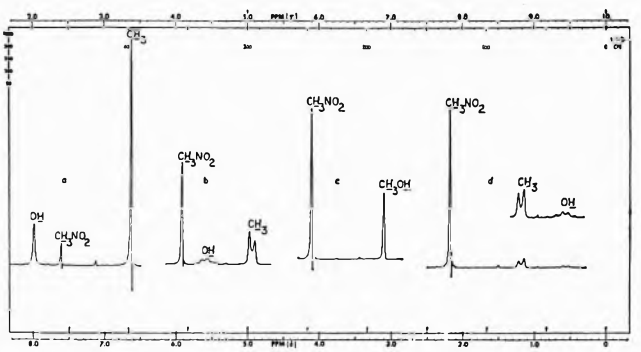


Figure 2.—Nmr spectra of CH_3OH–CH_3NO_2 mixtures at $[CH_3NO_2]/[CH_3OH] + [CH_3NO_2]$ equal to (a) 0.08, (b) 0.48, (c) 0.75, and (d) 0.87.

An intriguing feature of the dilution curve (Figure 1) is the variability of the hydroxyl proton shift over the total range of nitromethane concentrations studied. Maxima in dilution curves, *e.g.*, Figure 1, centering at $[CH_3NO_2]/[CH_3NO_2] + [CH_3OH] = 0.50$ and 0.75 (approximately), have previously been cited as nmr evidence for complex formation between alcohols and strong hydrogen bonding acceptor species, *e.g.*, acetone;[6,14] only weak intermolecular complexes have been reported for nitroalkanes and alcohols on the basis of infrared studies.[2,15] However, since the formation of hydrogen bonded complexes between nitroalkanes and methanol might provide a consistent explanation for the present results, a more detailed nmr study of nitromethane induced shifts in the OH resonance was undertaken.

Contributions to $\Delta\nu$ (CH_3OH–CH_3NO_2)[3] resulting from the autoassociation of either the proton donor or acceptor species were minimized by subjecting the CH_3NO_2–CH_3OH mixtures indicated in Figure 1 to a dilution series. For each CH_3NO_2–CH_3OH mixture (Table I) corresponding to the points indicated in Figure 1, dilutions were carried out using CCl_4 as the noninteracting solvent;[16] the displacement of the hydroxylic proton resonance, plotted *vs.* the volume increment of added inert solvent, gave the extrapolated or

(8) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

(9) At methanol concentrations less than 0.07 M, the OH quartet was barely visible above the background noise of our present instrument.

(10) The purified methanol used throughout this study did not exhibit spin–spin interaction in the nmr spectrum on dilution with CCl_4 to *ca.* 0.05 M; sufficient water was present to maintain rapid OH proton exchange in the absence of the nitroparaffin.

(11) E. Krakower and L. W. Reeves, *Trans. Faraday Soc.*, **59**, 2528 (1963).

(12) Rapid exchange of the OH proton was observed in the nmr spectra of nitromethane–methanol mixtures (undiluted or diluted with CCl_4) if the samples were not protected from atmospheric moisture.

(13) Reviewed by E. M. Arnett in "Progress in Physical Organic Chemistry," Vol. I, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience Publishers, New York, N. Y., 1963.

(14) P. L. Corio, R. L. Rutledge, and J. R. Zimmerman, *J. Mol. Spectrosc.*, **3**, 592 (1959).

(15) M. S. Smith, Jr., and P. A. D. de Maine [*J. Miss. Acad. Sci.*, **12**, 97 and 109 (1966)] used a refined treatment of infrared data to obtain evidence for complexation between nitromethane and methanol.

(16) The major limitations to the use of carbon tetrachloride as an inert diluent have been thoroughly discussed by Laszlo.[1]

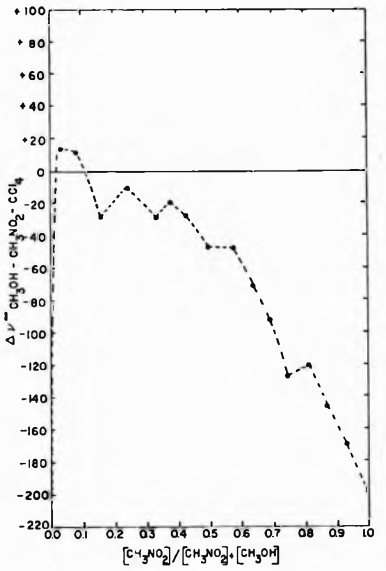


Figure 3.—The relationship between $\Delta\nu^{\infty}$ (CH_3OH–CH_3NO_2–CCl_4) and the nitromethane concentration. The CCl_4 concentration was assumed to be constant; only the concentrations of active species were considered in plotting the abscissa.

infinite dilution shifts of the OH proton, $\Delta\nu^{\infty}$(CH_3OH–CH_3NO_2–CCl_4), for each mixture (Table I). The extrapolated shifts are plotted in Figure 3 to show the relationship to the relative concentrations of active species. Figure 3 is extrapolated at both ends to the corresponding infinite dilution shift, $\Delta\nu^{\infty}$(CH_3OH–CCl_4) for the hydroxyl proton resonance of methanol in CCl_4, *i.e.*, 200 Hz upfield of the CH_3 resonance of methanol. This appeared to be a reasonable value for $\Delta\nu^{\infty}$(CH_3OH–CCl_4) in view of studies carried out in our laboratories[17] and elsewhere.[5,18]

TABLE I

OBSERVED AND EXTRAPOLATED SHIFTS (HERTZ)[a] OF THE OH RESONANCE FOR CH_3NO_2–CH_3OH MIXTURES

	$[CH_3NO_2]/[CH_3NO_2]+[CH_3OH]$	$\Delta\nu$ (CH_3OH–CH_3NO_2)	$\Delta\nu^{\infty}$ (CH_3OH–CH_3NO_2–CCl_4)[b,c]
1	0.038	+87.0	+12.0
2	0.075	+87.0	+15.0
3	0.158	+79.0	−31.0
4	0.245	+68.5	−10.0
5	0.332	+61.0	−31.0
6	0.381	+59.5	−20.0
7	0.429	+50.0	−30.0
8	0.520	+42.0	−48.0
9	0.582	+30.5	−49.0
10	0.663	+29.3	−72.0
11	0.668	+9.5	−96.0
12	0.749	−0.5	−126.0
13	0.810	−21.0	−120.0
14	0.870	−26.0	−146.0
15	0.937	−66.5	−170.0

[a] Internal shift of the OH resonance relative to the methyl resonance of methanol. [b] Extrapolation values were obtained from a series of five dilutions in CCl_4 for each CH_3NO_2–CH_3OH mixture indicated. The total variation in the CCl_4 concentration was from 0 to *ca.* 90 mol %. [c] It should be noted that this abbreviation does not signify a constant, but depends upon the relative concentrations of active species.

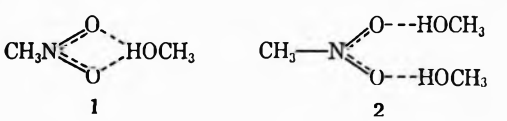
(17) A determination of the association shift for the methanol hydroxyl proton in our laboratories gave an extrapolated value of 293 Hz, in agreement with the Saunder's and Hyne value.[5]

(18) Whether the "high nitromethane" end of the curve for Figure 3 should be extrapolated to $\Delta\nu^{\infty}$(CH_3OH–CCl_4) could not be unequivocally established in view of the present sensitivity limits of our nmr instrument, but this extrapolation is reasonable in view of other treatments of this data carried out in our laboratories. Total shifts due to the nonideality of CCl_4 as an inert solvent should be small, but in the same direction as the observed hydrogen bond shift.[5]

A comparison of $\Delta\nu^{\infty}$ (CH_3OH–CH_3NO_2–CCl_4) and $\Delta\nu^{\infty}$ (CH_3OH–CCl_4) leads to some interesting and important conclusions regarding the CH_3NO_2–CH_3OH interaction. The over-all high-field displacement of the OH resonance which occurred on diluting CH_3NO_2–CH_3OH mixtures with CCl_4 (compared Figures 1 and 3) can be attributed primarily to disruption of the OH–O bonded structure of methanol;[1,5] the infinite dilution curve (Figure 3) should consequently trace the interaction of nitromethane and methanol monomers.[5] In the absence of any NO_2–OH interaction only dilution effects should be noted and $\Delta\nu^{\infty}$ (CH_3OH–CH_3NO_2–CCl_4) for each CH_3NO_2–CH_3OH mixture studied (Table I and Figure 3) should approach $\Delta\nu^{\infty}$(CH_3OH–CCl_4) as a limiting value; *i.e.*, Figure 3 would correspond to a straight line at *ca.* −200 Hz. This is clearly not the case and, excluding any marked effect of CCl_4,[18] the only reasonable explanation for the general downfield displacement of this curve [Figure 3 relative to $\Delta\nu^{\infty}$(CH_3OH–CCl_4)] is the formation of strong NO_2–HO bonds, in support with the above conclusion based on the magnitude of $\Delta\nu^{\infty}$ (CH_3OH–CH_3NO_2) and the splitting of the alcohol resonances induced by nitromethane and other nitroalkanes.

Finally, the marked variability in the dependence of $\Delta\nu^{\infty}$ (CH_3OH–CH_3NO_2–CCl_4) on the relative nitromethane concentration, resulting in a series of maxima in Figure 3 at $[CH_3NO_2]/[CH_3NO_2] + [CH_3OH]$ = 0.05, 0.25, 0.33, 0.55, and 0.75 (approximately), can be qualitatively, but reasonably, explained on the basis of two competing effects: (a) deshielding of the OH proton owing to the formation of NO_2–HO bonds between nitromethane and one or more methanol monomers, and (b) increase in shielding of the OH proton as the average number of methanol monomer units associated with nitromethane decreases.[19] Relative to $\Delta\nu^{\infty}$ (CH_3OH–CCl_4), the maximum displacement of the OH proton (*ca.* 210 Hz) occurring in Figure 3 at low nitromethane concentration ($[CH_3NO_2]/[CH_3NO_2] + [CH_3OH]$ = *ca.* 0.05) is already indicative of the formation of a strong NO_2–HO bond between these species. This conclusion is consistent with the sharply inclined initial slope of this curve[20] and the splitting of the methanol CH_3 resonance observed on diluting even these CH_3NO_2–CH_3OH mixtures with CCl_4.[21] Past this initial maximum, the "average" slope of the curve is relatively shallow and can be accounted for by the balanced

(19) The present data provide no clear indication of the nature of complex formation (see text); however, by invoking the formation of "bridged" and "open" hydrogen bonded complexes, *e.g.*, structures **1** and **2**, one might



1 **2**

anticipate increased shielding for the –OH proton in the bridged structure (**1**) relative to **2**.

(20) The slope of this curve at low CH_3NO_2 concentrations exceeds that for the –OH···O– interaction of methanol in CCl_4, *i.e.*, indicative of the formation of a stronger hydrogen bond in the CH_3OH–CH_3NO_2 system.

(21) On diluting this CH_3NO_2–CH_3OH mixture with CCl_4, the CH_3– and –OH resonances for methanol were, respectively, a broad doublet and a very broad "lump," showing the presence of both bonded and exchanging alcohol species. It would appear that traces of nitromethane can retard –OH exchange for a relatively large number of methanol monomers.

but opposed shielding effects of hydrogen bonding and complex formation. Minima in Figure 3[19] corresponding to approximately 4:1, 2:1, and 1:1 complexes ($OH–NO_2$) appear indicative of some enhanced stability for aggregates having these stoichiometries. Above $[CH_3NO_2]/[CH_3NO_2] + [CH_3OH] = 0.5$, the definite increase in the slope of this curve would seem to corroborate the argument based on an increase in shielding for the OH proton in a 1:1 complex;[19] *i.e.*, if the increased slope of this curve at higher nitromethane concentrations were due simply to a dissociation of the $NO_2–HO$ bonds, the disappearance of splitting patterns in the alcohol should also have been observed.[10]

To conclude these arguments supporting a strong $NO_2–HO$ interaction, it is not difficult to explain the curvature deviations (Figure 3) in terms of discrete $CH_3NO_2–CH_3OH$ complexes involving the nonbonding orbitals in the nitro group with one or more hydroxylic protons. However, the apparent minimum in this curve corresponding approximately to a 3:1 complex ($NO_2–OH$) is not readily explained in the absence of definitive evidence for $NO_2–HC$ interactions.[22] Any participation of the CH protons of methanol in hydrogen bonding with a nitro group might be expected to result in some variation of the chemical shift for this peak. As noted above, neither of the CH_3 resonances in the spectrum exhibited a meaningful change in chemical shift (*i.e.*, >2.0 Hz)[4] relative to internal TMS over the entire range of concentrations studied. Thus, the observations reported here are consistent with a highly localized interaction between nitromethane and methanol. The nature of complex formation in this and other nitroalkane–alcohol systems is presently under study in our laboratories.

Attempts to compare the present results with nmr data available for other systems, *e.g.*, acetone or DMSO with methanol, have been inconclusive. It was possible to evaluate independently autoassociation effects for nitromethane and methanol, and apply empirical corrections to Figure 1;[23] the hypothetical curve obtained for the interaction of the monomeric species bore little resemblance to Figure 3 and the method was discarded. The present data are, in part, amenable to treatment using the Lussan method[24] for which the hydrogen bond shift (δ_B), crudely approximated by the difference $\Delta\nu^\infty$ (ROH–CCl_4) minus $\Delta\nu^\infty$ (ROH–CH_3NO_2), can be used to compare relative hydrogen bond strengths. δ_B shifts calculated for the $CH_3OH–CH_3NO_2$ and *t*-butyl alcohol–CH_3NO_2 systems are, respectively, 2.03[25] and 1.08 ppm,[24] in line with the increased steric effect expected with the latter alcohol. However, any firm comparisons regarding the nature of complexation and relative strengths of hydrogen bond formation in nitroalkane–alcohol systems will be reserved until the studies in progress are concluded.

There remains the apparent discrepancy which exists between infrared and nmr data with regard to the strength of the $NO_2–HO$ interaction. On the basis of our studies in progress, it would appear that these differences arise in part from the practice of maintaining a relatively high excess of the nitro compound during the recording of infrared data. If, as the present nmr data indicate, the complexation of the nitroalkane and an aliphatic alcohol is a highly favored process, the small infrared OH frequency shifts noted for the interaction of these species may not be a reliable indication of this interaction.

Registry No.—Nitromethane, 75-52-5; methanol, 67-56-1.

Acknowledgments.—We are grateful to Commercial Solvents Corp. for a generous gift of high purity nitromethane and to the administrators of the Petroleum Research Fund, American Chemical Society (PRF No. 1037-G1), for partial support of this research. We also wish to thank the Materials Branch of NASA for supplying funds to purchase a Varian A-60 nmr spectrometer.

(22) A. Allerhand and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 1715 (1963).

(23) B. B. Howard, C. F. Jumper, and M. T. Emerson, *J. Mol. Spectrosc.*, **10**, 117 (1963).

(24) C. Lussan [*J. Chim. Phys.*, **60**, 1100 (1963)] has calculated hydrogen bond shifts (δ_B) and equilibrium constants for complex formation in systems dealing mainly with 1:1 complexes.

(25) This study.

Nuclear Magnetic Resonance Spectra of *cis*-5,6-Disubstituted Norbornenes. Correlation of Proton Chemical Shifts with the Taft Inductive Substituent Constant

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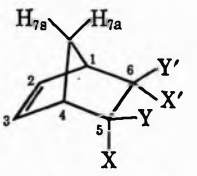
The ^1H nmr spectra of *exo,cis*- and *endo,cis*-5,6-dihydroxynorbornene and *exo,cis*- and *endo, cis*- 5,6-diacetoxynorbornene have been analyzed. The chemical shifts of H_{7a} and H_{7s} obtained from these analyses, together with the corresponding chemical shifts of several other *cis*-5,6-disubstituted norbornenes whose spectra have been analyzed and reported in the literature, have been found to be linear functions of the value of the Taft inductive substituent constant for the substituents at C_5 and C_6. These relations show that the nature of the substituents determines whether H_{7a} or H_{7s} is more shielded in *exo,cis*-5,6-disubstituted norbornenes.

Recent reports of work on norbornene[1-3] (**1**) and substituted norbornenes[4] have served to clear up much of the previous confusion regarding the nmr spectra of these compounds. The synthesis of two additional sets of *exo,cis*- and *endo,cis*-5,6-disubstituted norbornenes and the analysis of their nmr spectra have provided additional insight into the nature of these compounds, and have allowed us to obtain a quantitative measure of the effect of *cis*-5,6-disubstitution on the chemical shifts of norbornene protons. We have found that the chemical shifts of H_{7a} and H_{7s} are linearly related to Taft's[5] σ_I value for the substituents. These correlations are discussed below.



1, X = X′ = Y = Y′ = H
2, X = X′ = H; Y = Y′ = OH
3, X = X′ = OH; Y = Y′ = H
4, X = X′ = H; Y = Y′ = OAc
5, X = X′ = OAc; Y = Y′ = H

Experimental Section

Compounds synthesized and used in this study were *exo,cis*-5,6-dihydroxy-2-norbornene (**2**), *endo,cis*-5,6-dihydroxy-2-norbornene (**3**), *exo,cis*-5,6-diacetoxy-2-norbornene (**4**), and *endo, cis*-5,6-diacetoxy-2-norbornene (**5**).[6,7]

The nmr spectra of the four compounds were obtained with a Varian A-60A spectrometer equipped with a Varian V-6058A spin decoupler on solutions in chloroform-*d* ($CDCl_3$). Additional spectra of **2** and **3** were obtained on solutions in dimethylsulfoxide-d_6 (DMSO-d_6). In both solvents, tetramethylsilane (TMS) was used as the internal reference. Chemical shifts for **2** and **3** were determined in both solvents. Coupling constants for these compounds were calculated from the spectra of the DMSO-d_6 solutions; resolution was better than in $CDCl_3$, the chemical shifts of H_{7s} and H_{7a} were more favorable, and coupling with the -OH protons was easily eliminated by exchange with deuterium oxide. Chemical shifts are accurate to within ±0.02 ppm; coupling constants are accurate to within ±0.2 Hz.

Results and Discussion

Assignments of the nmr spectra were made on the basis of spin-decoupling experiments. H_{7a} and H_{7s} were identified by means of the well-established stereospecific long-range couplings[8] between H_{7a} and H_2 (H_3), and between H_{7s} and the *endo* protons at C_5 and C_6. Our assignments are in agreement also with the observation[8] that, for the same substituents, H_5 and H_6 are more shielded in *exo,cis*-5,6-disubstituted norbornenes than in the corresponding *endo*-derivatives.

Analysis of the H_{7s},H_{7a} portion of each spectrum was accomplished by treating it as an AB spectrum on which were superimposed first-order couplings with H_1, H_2, H_3, H_4 (and, in the case of the *exo* derivatives, H_5 and H_6). The H_2,H_3 multiplet was assumed to be one-half of an AA′XX′ spectrum[3] (H_2 and H_3 coupling with both H_1 and H_4) on which was superimposed a first-order coupling with H_{7a}. In the case of compounds **2** and **3**, calculations were made to determine the magnitudes of $J_{1,2}$, $J_{1,3}$, $J_{1,4}$, and $J_{2,3}$ from the H_2,H_3 multiplet. The chemical shift of H_1 (H_4) was taken to be the center of the H_1,H_4 multiplet.

As reported by Subramanian, Emerson, and LeBel[4] for dihalonorbornenes, the multiplet due to H_5 and H_6 in compounds **3** and **5** is more complex than might be expected. We found, however, that for **5**, and for **3** in DMSO-d_6, the pattern is that expected for an AA′XX′ spectrum. (The weak outer peaks can be observed at increased gain.) This pattern was not easily recognized in the spectrum of the $CDCl_3$ solution of **3**, but was readily apparent in the spectrum of the DMSO-d_6 solution. From our observations, and from the description of the spectra of *endo,cis*-5,6-dihalonorbornenes by Subramanian, it appears that for *exo*-5,6 protons in the *endo, cis*-5,6-disubstituted norbornenes there is a small but finite coupling between H_1 and H_5, and between H_4 and H_6, which renders H_5 and H_6 magnetically nonequivalent although they are chemical-shift equivalent.

We accordingly treated the H_5,H_6 multiplet as one-half of an AA′XX′ spectrum (H_5 and H_6 coupling with both H_1 and H_4). $J_{5,6}$ and $J_{1,6}$ ($J_{4,5}$) so determined do

(1) B. Franzus, W. C. Baird, Jr., N. F. Chamberlain, T. Hines, and E. I. Snyder, *J. Amer. Chem. Soc.*, **90**, 3721 (1968).

(2) A. P. Marchand and J. E. Rose, *ibid.*, **90**, 3724 (1968).

(3) E. W. Garbisch, Jr., *Chem. Commun.*, 332 (1968).

(4) P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965).

(5) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963). In the case of compounds **9** and **10**, in which the substituents at C_5 and C_6 were not the same, the arithmetic mean of the σ_I values for the two substituents was used.

(6) Y. F. Shealy and J. D. Clayton, *J. Amer. Chem. Soc.*, **88**, 3885 (1966). Complete details of the preparation of these compounds are being published separately: Y. F. Shealy and J. D. Clayton, *ibid.*, in press.

(7) The nomenclature and numbering system used here conform to those used in recent descriptions of nmr studies on related compounds.[1,2,4] According to *Chemical Abstracts* practice, the preferred names are *exo,cis*-5-norbornene-2,3-diol (**2**), *endo,cis*-5-norbornene-2,3-diol (**3**), *exo,cis*-5-norbornene-2,3-diol diacetate (**4**), and *endo,cis*-5-norbornene-2,3-diol diacetate (**5**).

(8) Reference 2, and references cited therein.

not differ significantly from values reported by Subramanian, and $J_{1,5}$ ($J_{4,6}$) is shown to be very small. Nevertheless, treatment as half of an AA'XX' spectrum appears to afford a straightforward explanation of the H_5,H_6 multiplet, does not require a difference in chemical shift for H_5 and H_6 as proposed by Subramanian, and produces a value of $J_{5,6}$ in good agreement with comparable values determined by other workers.[4,9,10] By this analysis, $J_{1,4}$ is shown to be nonzero. Additional support for this treatment of the H_5,H_6 multiplet is given by the agreement of the two values obtained for $J_{1,4}$ from the spectrum of **3**, 1.1 and 1.2 Hz. One value is obtained from the analysis of the H_2,H_3 multiplet (when decoupled from H_{7a}) as half of an AA'XX' spectrum, and the other value from the analysis of the H_5,H_6 multiplet as half of an AA'XX' spectrum.

Previously, $J_{1,4}$ has generally been reported to be zero,[2,9,10] although Subramanian[4] estimated it to be approximately 1 Hz for 5,6-dihalonorbornenes. Recently, analysis by Garbisch[3] has shown $J_{1,4}$ to be nonzero in norbornene. Our findings with regard to $J_{1,4}$ for *cis*-5,6-disubstituted norbornenes with hydroxyl and acetoxy substituents are in agreement with those of Garbisch[3] and Subramanian,[4] but appear to be in conflict with those of Davis and Van Auken,[9] Marchand and Rose,[2] and Laszlo and Schleyer.[10] It now appears likely that, in general, $J_{1,4}$ is not zero. Thus, it is difficult to understand the failure of Davis and Van Auken[9] to observe coupling between H_1 and H_4 in the 5-monosubstituted norbornenes, where H_1 and H_4 have different chemical shifts, unless $J_{1,4}$ is much smaller in those compounds than it is in norbornene and in *cis*-5,6-disubstituted norbornenes.

Chemical shifts from our analyses of compounds **2**, **3**, **4**, and **5** are shown in Table I; coupling constants are listed in Table II.

In seeking a quantitative measure of substituent effects on the chemical shifts of H_{7s} and H_{7a}, chemical shift data from our analyses of the spectra of **2**, **3**, **4**, and **5** in $CDCl_3$ were used, together with data on additional compounds from the literature. The additional compounds are shown in Table III.

Although the chemical shift of H_{7s} was reported by Subramanian[4] to be nearly constant for 5,6-dihalonorbornenes, we find that this is not true for all substituents. The chemical shifts of both H_{7s} and H_{7a} are dependent on the nature of substituents at C_5 and C_6. The chemical shift of H_{7a} is highly dependent on the orientation of such substituents, whereas the chemical shift of H_{7a} has little or no dependence on orientation. As pointed out by Wells,[5] Taft based his list of inductive σ-values on data from 4-substituted bicyclo[2.2.2]octane-1-derivatives. The saturated portion of the norbornenes considered in our investigation is sufficiently similar structurally to such bicyclooctanes that it appeared reasonable to test whether the chemical shifts of H_{7s} and H_{7a} might be represented as functions of the σ_I values of substituents at C_5 and C_6. Linear regression analysis confirms that this is indeed the case, and that the chemical shift of either H_{7s} or H_{7a} may be expressed as a function of the value of the Taft[5] σ_I for the 5,6 substituents. These Taft constants are regarded as measures of the electron-withdrawing power of substituents in compounds where resonance effects are not expected to be important, as in these norbornene derivatives. In fact, Swain and Lupton[11] have recently shown that the effect measured by σ_I is >96% "field effect." Their term "field effect" lumps together both inductive effects through σ bonds and effects through space. The former should be of negligible importance through two or more intervening carbons.[12]

For the *exo,cis*-5,6-disubstituted norbornenes (**1**, **2**, **4**, **8**, and **10**), the equations of the correlations, the standard deviations in δ_H (s), and the correlation coefficients (r), are $\delta_{H_{7a}} = 1.04 + 2.68\,\sigma_I$, $s = 0.04$, $r = 0.997$, and $\delta_{H_{7s}} = 1.31 + 1.08\,\sigma_I$, $s = 0.02$, $r = 0.995$, where $\delta_{H_{7a}}$ and $\delta_{H_{7s}}$ are the chemical shifts of H_{7a} and H_{7s} in ppm downfield from TMS.

These correlations are illustrated in Figure 1. It is especially interesting that the lines representing the equations for the chemical shifts of H_{7a} and H_{7s} intersect. These correlations thus predict the "crossover" of the chemical shifts of H_{7s} and H_{7a} in *exo,cis*-5,6-disubstituted norbornenes observed by Marchand[2] on more

TABLE I

CHEMICAL SHIFTS (PARTS PER MILLION DOWNFIELD FROM TMS)

Compound	Solvent	H_1,H_4	H_2,H_3	H_5,H_6	H_{7a}	H_{7s}
2	$CDCl_3$	2.69	6.03	3.69	1.88	1.62
2	DMSO-d_6	~2.5[a]	5.99	3.46	1.79	1.41
3	$CDCl_3$	2.99	6.23	4.14	1.20	1.49
3	DMSO-d_6	2.81	6.06	~4.0[b]	1.11	1.24
4	$CDCl_3$	2.82	6.16	4.73	2.03	1.72
5	$CDCl_3$	3.12	6.20	5.22	1.36	1.58

[a] Multiplet superimposed on solvent peak. [b] H_5, H_6 and $(OH)_5$, $(OH)_6$ were superimposed. Analysis of H_5, H_6 multiplet performed on spectrum obtained after exchanging OH by addition of D_2O.

TABLE II

COUPLING CONSTANTS (HERTZ)

	Compound 2	3	4	5
$\lvert J_{7a,7s}\rvert$	8.8	9.4	9.2	9.9
$\lvert J_{7s,6}\rvert = \lvert J_{7s,5}\rvert$	1.7	0.0	1.8	0.0
$\lvert J_{7s,1}\rvert = \lvert J_{7s,4}\rvert$	1.7	2.0	1.5	2.1
$\lvert J_{7a,1}\rvert = \lvert J_{7a,4}\rvert$	1.5	1.5	1.6	1.5
$\lvert J_{7a,2}\rvert = \lvert J_{7a,3}\rvert$	~0.5	~0.5	~0.6	~0.5
$\lvert J_{1,4}\rvert$	1.6[a]	1.1, 1.2[c,d]	...[f]	1.4
$\lvert J_{2,3}\rvert$	6.0[a]	6.0	...[f]	...[f]
$\lvert J_{1,2}\rvert = \lvert J_{3,4}\rvert$	2.6[b]	2.5[b]		
$\lvert J_{2,4}\rvert = \lvert J_{1,3}\rvert$	1.1[b]	1.4[b]		
$\lvert J_{5,6}\rvert$	...[f]	7.6[d]	...[f]	7.4
$\lvert J_{4,5}\rvert = \lvert J_{1,6}\rvert$	0.0	3.7[e]	0.0	4.0[g]
$\lvert J_{1,5}\rvert = \lvert J_{4,6}\rvert$	0.0	0.1–0.2[e]	0.0	0.2[g]
$\lvert J_{1,2} + J_{1,3}\rvert$			3.4	3.8

[a] $J_{1,4}$ and $J_{2,3}$ have the same sign. It was assumed that $|J_{2,3}| > |J_{1,4}|$. [b] $J_{1,2}$ and $J_{2,4}$ have the same sign. It was assumed that $|J_{1,2}| > |J_{2,4}|$. [c] Values from calculations of two separate AA'XX' subspectra. [d] $J_{5,6}$ and $J_{1,4}$ are of the same sign. It was assumed that $|J_{5,6}| > |J_{1,4}|$. [e] $J_{1,5}$ and $J_{4,5}$ appear to have the same sign. It was assumed that $|J_{4,5}| > |J_{1,5}|$. [f] Not determined. [g] $J_{1,5}$ and $J_{4,5}$ appear to be of different sign. It was assumed that $|J_{4,5} > |J_{1,5}|$.

(9) J. C. Davis, Jr., and T. V. Van Auken, *J. Amer. Chem. Soc.*, **87**, 3900 (1965).

(10) P. Laszlo and P. von R. Schleyer, *ibid.*, **86**, 1166 (1964).

(11) C. G. Swain and E. C. Lupton, Jr., *ibid.*, **90**, 4328 (1968).

(12) K. B. Wiberg, "Physical Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1964, Part II, Chapter 8.

TABLE III

CHEMICAL SHIFTS OF ADDITIONAL COMPOUNDS, TAKEN FROM THE LITERATURE
(PARTS PER MILLION DOWNFIELD FROM TMS)

Compound	Substituents	Chemical shift			Solvent
		H_{7a}	H_{7s}	H_1 (H_4)	
1	X = X′ = H, Y = Y′ = H	1.03	1.32	2.80	CCl_4[a]
6	X = X′ = Br, Y = Y′ = H	1.50	1.80	3.28	$CDCl_3$[b]
7	X = X′ = Cl, Y = Y′ = H	1.42	1.77	3.22	CCl_4[b]
8	X = X′ = H, Y = Y′ = Br	2.28	1.83	3.17	CCl_4[b]
9	X = Cl, X′ = Br, Y = Y′ = H	1.45	1.73	3.28	$CDCl_3$[b]
10	X = X′ = H, Y = Cl, Y′ = Br	2.25	1.80	2.98	CCl_4[b]

[a] Ref 1. [b] Ref 4.

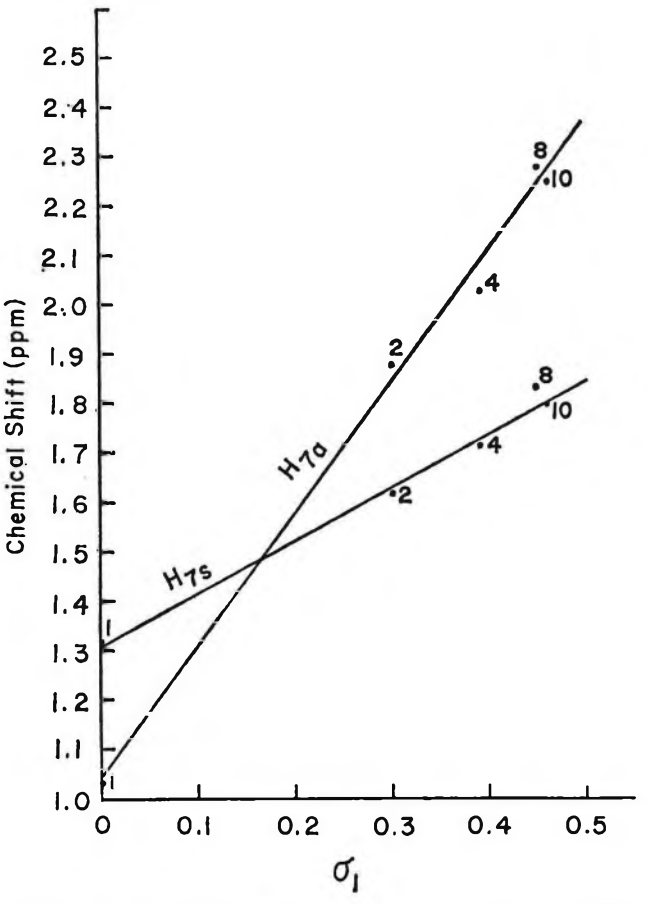


Figure 1.—Chemical shifts of H_{7a} and H_{7s} as functions of the value of σ_I for the substituents in *exo*-5,6-disubstituted norbornenes.

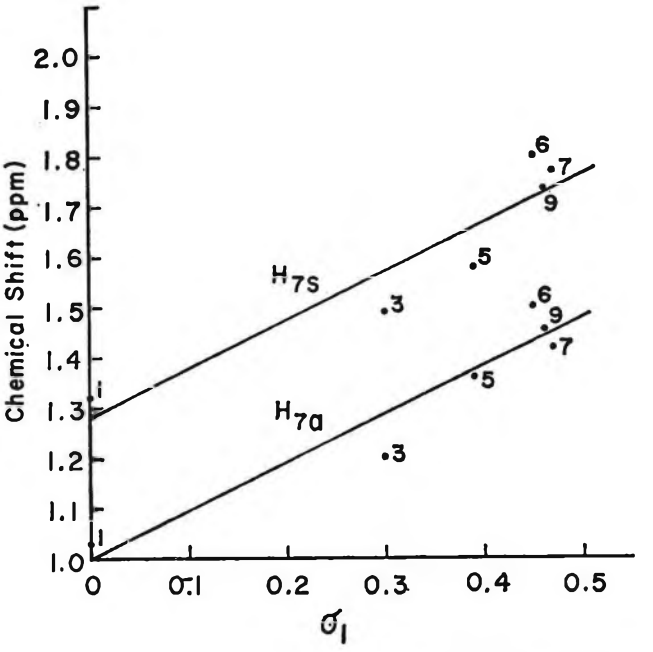


Figure 2.—Chemical shifts of H_{7a} and H_{7s} as functions of the value of σ_I for the substituents in *endo*-5,6-disubstituted norbornenes.

complex compounds, and observed by us in the present series. These correlations thus obviate the need for explanations of the reversal of relative chemical shifts of H_{7a} and H_{7s} based on geometrical considerations other than those implicit in the different slopes of the lines for $\delta_{H_{7a}}$ and $\delta_{H_{7s}}$.

Regression analyses were also performed for the chemical shifts of H_{7a} and H_{7s} in the *endo*-5,6-disubstituted norbornenes (**1**, **3**, **5**, **6**, **7**, and **9**) as functions of the value of σ_I for the substituents.

Equations relating $\delta_{H_{7a}}$ and $\delta_{H_{7s}}$ to the σ_I value of the substituent are $\delta_{H_{7a}} = 1.00 + 0.96\ \sigma_I$, $s = 0.06$, $r = 0.952$, and $\delta_{H_{7s}} = 1.28 + 0.98\ \sigma_I$, $s = 0.08$, $r = 0.934$. These equations are illustrated in Figure 2.

The lines representing $\delta_{H_{7a}}$ and $\delta_{H_{7s}}$ for *endo,cis*-5,6-disubstituted norbornenes and the line representing $\delta_{H_{7s}}$ for *exo,cis*-5,6-disubstituted norbornenes have approximately equal slopes. This indicates that a change in the σ_I value for the substituents at C_5 and C_6 results in nearly equal chemical shift changes for the three cases. The line representing $\delta_{H_{7a}}$ for *exo,cis*-5,6-disubstituted norbornenes has a greater slope, indicative of the larger substituent effect which is observed when the substituents and the affected proton are in spatial proximity. This enhanced effect with decreased distance is to be expected, and supports the view, discussed above, that σ_I is a good measure of the through-space effect.

The chemical shift of H_1 (H_4) also appears to increase as the value of σ_I for substituents at C_5 and C_6 increases. The relation does not appear linear, however, if the chemical shift of H_1 (H_4) of norbornene itself is included. Similarly, the chemical shifts of H_5 and H_6 do not appear to correlate in a simple fashion with the nature of the substituents at C_5 and C_6. It is possible that a correlation between δ_{H_5} and δ_{H_6} and the value of σ_I for substituents at C_5 and C_6 may hold if the halogen substituents are omitted from consideration. It has been pointed out by Subramanian[4] that the effects of halogen substitution are complicated at best. Without the halogen-substituted derivatives, however, the available data are too few for more than speculation. As additional compounds are synthesized, doubtless a clearer picture will emerge.

For these *cis*-5,6-disubstituted norbornenes, the

chemical shifts of H_{7a} and H_{7s} may also be expressed as linear functions of the group electronegativities of the substituents, calculated by the method of Wilmshurst.[13] Correlations with group electronegativity appear equally as good as those with σ_I, except that in neither case does the equation fit the chemical shift of the appropriate proton of norbornene itself. Therefore, it appears that σ_I is a better measure of the effect of substituents at C_5 and C_6 than is group electronegativity.

Although the same trends are observed if the chemical shifts of H_{7a} and H_{7s} are treated as functions of $\mathcal{F}$, the field substituent constant of Swain and Lupton,[11] the correlations are not so good as those with σ_I.

(13) J. K. Wilmshurst, *J. Chem. Phys.*, **27**, 1129 (1957).

Registry No.—**2**, 20224-38-8; **3**, 20224-39-9; **4**, 20224-40-2; **5**, 20224-41-3.

Acknowledgment.—Spectral data used in this study were acquired as part of an investigation supported by the C. F. Kettering Foundation and by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract PH-43-64-51. Discussions with Dr. Y. F. Shealy were of great help in the completion of this work.

1,3-Diaza-2,4-diborolidines. Isocyanide–Borane Adducts. III[1]

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Evidence is presented supporting a 1,3-diaza-2,4-diborolidine structure for the thermodynamically most stable member of a series of isomers obtained from the reaction of isocyanides with organoboranes. Several compounds possessing that ring system have been prepared, and factors which influence the formation of these compounds are discussed.

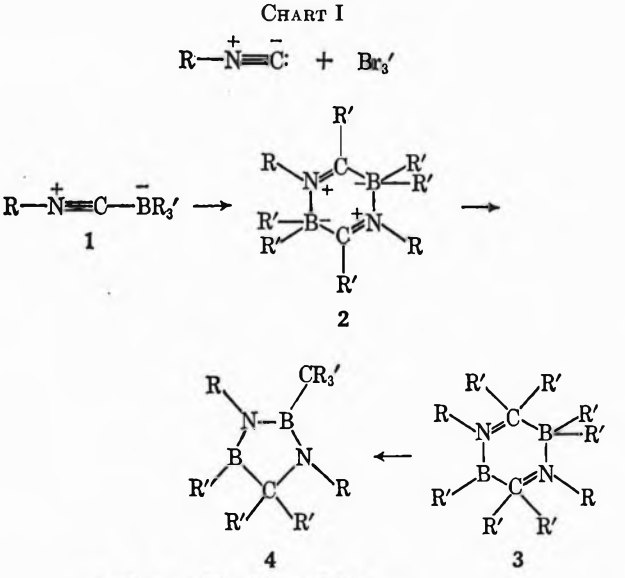
Interest in the chemistry of compounds which contain the >B—N< bond is reflected in the appearance of recent reviews[2] and reference books.[3] Substituted 2,5-dibora-3,6-dihydropyrazines represent an interesting case of this type. From them, 1,3-diaza-2,4-diborolidines may be prepared. The unusual stability of the latter compounds and factors which influence their preparation are the subjects of this paper.

Results and Discussion

The reaction between isonitriles and organoboranes to form 1:1 adducts had been reported.[4,5] Compounds of the general structure **1** (Chart I) are thermodynamically unstable with respect to the dimer **2**, first observed by Hesse and Witte.[6] Other examples of **2** have been reported by the same[7a] and other[7b-d] workers. Upon being heated, compounds of structure **2** rearrange to isomer **3**.

When certain compounds of structure **3** are heated briefly at 300–310°, ring contraction occurs to produce compounds which display the 1,3-diaza-2,4-diborolidine ring system **4**. Synthesis of this ring system from a compound of structure **3** using aluminum chloride has been reported previously for one case.[7e] An earlier report from this laboratory[1] suggested, incorrectly, the 1,3-diaza-2,4-diboretidine structure for compounds of

CHART I



a, R = C_6H_5; R′ = C_2H_5
b, R = *p*-ClC_6H_4; R′ = C_2H_5
c, R = *p*-$O_2NC_6H_4$; R′ = C_2H_5
d, R = *p*-$H_2NC_6H_4$; R′ = C_2H_5
e, R = C_6H_5; R′ = CH_3
f, R = C_6H_5; R′ = *n*-C_4H_9
g, R = *p*-$CH_3CONHC_6H_5$; R′ = C_2H_5
h, R = *p*-$Cl^-H_3N^+C_6H_4$; R′ = C_2H_5
i, R = *c*-C_6H_{11}; R′ = *n*-C_4H_9

structure **4**. Conclusive differentiation has now become possible through 32.1-Mc ^{11}B nmr and X-ray crystallographic analysis.[8] Efforts to carry out ring contraction to the 1,3-diaza-2,4-diboretidine nucleus have thus far been without success.

Preparation and Reactions of 4a.—Compound **4a** can be obtained in nearly quantitative yield upon heating **3a** at 305°. A summary of the reactions of **4a** is shown in Chart II. The chemical and thermal stability of **4a** is unusual. The failure of **4a** to react with hydroxide is distinctly apart from observations for

(1) Paper II: J. Casanova, Jr., H. R. Kiefer, D. Kuwada, and A. H. Boulton, *Tetrahedron Lett.*, 703 (1965).

(2) K. Niedenzu, *Angew. Chem. Intern. Ed. Engl.*, **3**, 86 (1964).

(3) (a) Advances in Chemistry Series, No. 42, K. Niedenzu, Ed., American Chemical Society, Washington, D. C., 1964; (b) K. Niedenzu and J. W. Dawson, "Boron–Nitrogen Compounds," Springer Verlag, New York, N. Y., 1965; (c) M. F. Lappert, *Chem. Rev.*, **56**, 959 (1956); (d) K. Ziegler, *Advan. Organometal. Chem.*, **6**, 1 (1968); (e) D. Seyferth, "Survey of Organometallic Chem," Vol. 3, Elsevier Publishing Co., New York, N. Y., 1967.

(4) J. Casanova, Jr., and R. E. Schuster, *Tetrahedron Lett.*, 405 (1964).

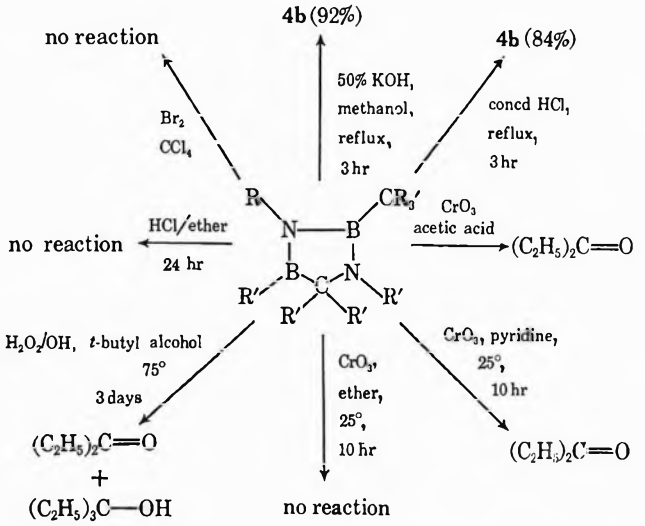
(5) G. Hesse, H. Witte, and G. Bittner, *Ann.*, **687**, 9 (1963).

(6) G. Hesse and H. Witte, *Angew. Chem.*, **75**, 791 (1963).

(7) (a) G. Hesse and H. Witte, *Ann.*, **687**, 1 (1965); (b) S. Bresadola, G. Carraro, C. Pecile, and A. Turro, *Tetrahedron Lett.*, 3185 (1964); (c) J. Tanaka and J. C. Carter, *ibid.*, 329 (1965); (d) S. Bresadola, F. Rosetto, and G. Puosi, *ibid.*, 4775 (1965); (e) H. Witte, *ibid.*, 1127 (1965).

(8) C. Tsai and W. E. Streib, *Tetrahedron Lett.*, 669 (1968).

CHART II



borazenes and aminoboranes.[9] Compound **4a** was unreactive toward potassium metal in tetrahydrofuran at room temperature, and did not produce an electron spin resonance spectrum either in the presence or absence of potassium. Although irradiation of **2a** in pentane produced a 75% yield of **3a**, no **4a** was formed upon irradiation of **3a**.

Because of variability in the success of converting compounds of structure **3** into the corresponding compound **4**, a number of N-aryl derivatives were prepared to study the effect of variation in *p*-aryl substituents. The nitrogen substituent, R, was held constant (R = C_2H_5). As with the N-phenyl series (**a**), the N-*p*-chlorophenyl series (b) could be prepared in very high yields throughout, starting with *p*-chlorophenylisonitrile. The *p*-nitrophenyl series (**c**) was very different in behavior. Even the mildest conditions for reaction sufficed to carry the reaction to compound **3c**. Although material which corresponded to the properties anticipated for **2c** could be isolated from the mother liquors of this reaction, **2c** could not be isolated in a pure state. Compound **3c** could not be converted into **4c**, but decomposed at 330°. However, **4c** could be prepared directly by nitration of **4a**, using fuming red nitric acid in trifluoroacetic acid at −5°. This latter reaction illustrates the great resistance of the 1,3-diaza-2,4-diborolidine ring in these compounds to chemical degradation, and the orientation effect of the −N(B)B and −N(B)B groupings in aromatic electrophilic substitution. Compound **3c** could be prepared in good yield by direct nitration of **3a**. The nitro groups of **3c** were smoothly reduced by hydrogen over platinum oxide to give the *p*-aminophenyl derivative, **3d**. Compound **3d** could be converted into **4d**, which could be converted into **4b** by a Sandmeyer reaction. Since compounds in series **a**, **b**, and **c** have been prepared separately from the corresponding *para*-substituted isonitriles, and are related to each other by interconversion, the aromatic ring substitution patterns are established.

Because of the lack of chemical reactivity of **4a**, most of the evidence which bears on its structure is physical rather than chemical in nature. The structure assigned is supported by elemental analysis, molecular weight determinations, infrared, ^1H and ^{11}B resonance spectra, mass spectra and X-ray crystallographic analysis. The ^1H and ^{11}B data are summarized in Table I.

TABLE I

^{11}B AND ^1H NMR SPECTRA OF SOME COMPOUNDS OF STRUCTURES **3** AND **4**

Compd	^{11}B δ[a]	^1H δ,[b] ppm (relative no. of H) $H_{aromatic}$	$H_{C\text{-}alkyl}$	$H_{B\text{-}alkyl}$
3e		7.23 (5)	1.14 (6)[c]	0.10 (3)[c]
3a	−48.6	7.18 (5)	1.1 (10)[d]	0.53 (5)[c]
3b	−42.0	7.1 (4)[d]	1.1 (10)[d]	0.55 (5)[c]
3c		7.75 (4)[c]	1.0 (10)[d]	0.59 (5)[c]
3d		6.75 (4)[d]	1.2 (10)[d]	0.60 (5)[c]
4a	−43.2[e]	7.2 (5)[d]	1.3–0.8 (15)[d]	
4b	−45.0	7.1 (4)[f]	0.75 (15)[d]	
4c		7.65 (4)[f]	0.73 (15)[d]	
4d		6.6 (4)[d]	0.85 (15)[d]	
4f[g]	−45.0	6.9 (5)[d]	0.9 (~27)[d]	

[a] Relative to external boron trifluoride etherate. [b] Positive value is downfield from tetramethylsilane. [c] Sharp singlet. [d] Complex multiplet centered at the value shown. [e] The ^{11}B chemical shift of this compound was previously reported as −36 ± 5 ppm (ref 1, this paper) and has been refined. [f] A_2B_2 spectrum. [g] We are grateful to Professor G. Hesse for this sample.

Possible Sources of Stability of 4a.—The chemical stability of the 1,3-diaza-2,4-diborolidine ring probably arises from steric shielding of the heteroring atoms, blocking the approach of polar reagent along an axis perpendicular to the ring plane. A dramatic decrease in reactivity toward polar reagents due to steric effects is not without precedent in BN ring compounds. Nagasawa[10] has recently shown B-trixylyl- and B-trimesityl-N-trimethylborazines are recovered quantitatively after standing for 150 hr at room temperature in either dilute sodium hydroxide or dilute hydrochloric acid in aqueous dioxane.

Anomalies in the Pattern of Conversion of 3 into 4.—Table II shows the result of heating compounds of structure **3** at 300–310° in a sealed tube for 5–10 min.

TABLE II

BEHAVIOR OF **3** AT 300–310°.

Compd	σ_I[a]	Mp of 3,[b] °C	Observation[c]
3a	0.00	203–205	**4a** (96%)
3d	+0.13	226–228	**4d** (75%)
3g	+0.27	350	Dec <350°
3b	+0.47	201–202	**4b** (84%)
3c	+0.63	256–260 dec	Dec <330°
3h	+0.90	350	Dec <330°
3e	0.00	170.5–171	Dec <330°
3f[d]	0.00	168–169	**4f** (92%)
3i		142–144	Dec <300°

[a] P. R. Wells, *Chem. Rev.*, **63**, 171 (1963). [b] Corrected. [c] Compound identification (yield, per cent recrystallized). [d] We are grateful to Professor G. Hesse for this sample.

The results were strikingly different. Four compounds of structure **3** (**a**, **b**, **d**, **f**) gave compound **4** in high yield. The remaining five studied (**c**, **e**, **g**, **h**, **i**) gave a complex decomposition, yielding 5 to 15 spots on thin layer chromatography. No single product appeared to predominate, and no crystalline product could be isolated in these cases, in spite of the fact that com-

(9) *Cf.* ref 3b, pp 131–138.

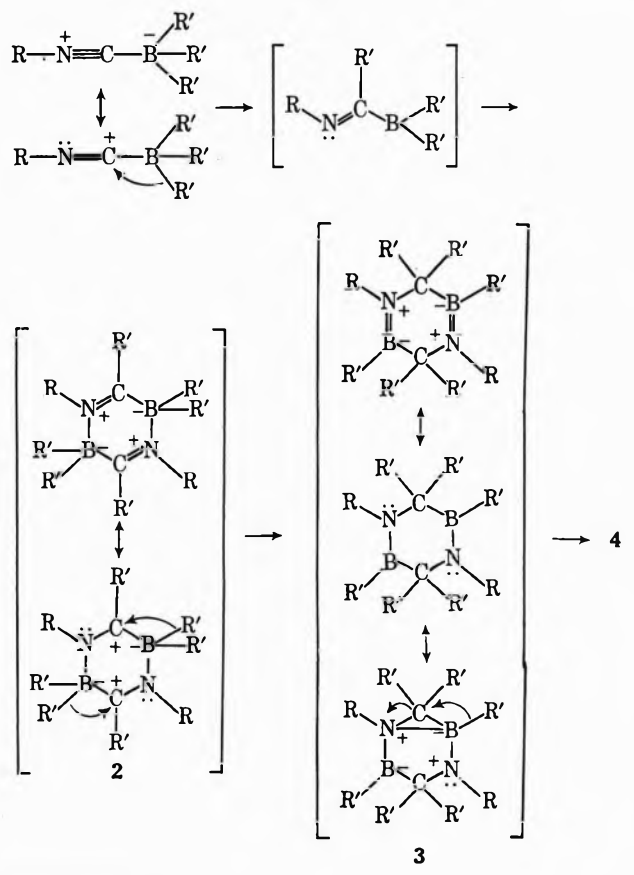
(10) K. Nagasawa, *Inorg. Chem.*, **5**, 442 (1966).

pounds of structure **4**, when they were present, could be isolated from the reaction mixture with no particular difficulty. The abrupt change in behavior which accompanies the change of ethyl to methyl as the boron substituents (**4a**–**4e**) is noteworthy.

Several common structural features which are present in those compounds of structure **3**, which can be isomerized to **4**. Those which do undergo rearrangement bear an aromatic substituent at the nitrogen atom. Of the B-ethyl, N-aryl compounds of structure **3** which fail to rearrange, all are crystalline solids at 300°. Those which do undergo rearrangement are molten at that temperature. It is possible that the reaction **3** → **4** may depend on the physical state of **3**. Still the behavior of **3e** (B-methyl) remains an anomaly.

Possible Mechanisms for the Conversion of 3 into 4.—In each step in the interconversion of isomers in this series one or two boron-to-carbon alkyl group migrations occur, leading to products which are thermodynamically more stable than the starting materials. Each rearrangement may be viewed as the migration of an alkyl group from B^- to C^+, thus classifying these reactions as electron-deficient rearrangements of the Wagner–Meerwein type. For each compound which undergoes rearrangement it is possible to write a resonance structure in which an electron-deficient carbon atoms is located adjacent to (or transannular to) a tetracoordinated boron atom. This is shown in Chart III. Such a rearrangement is not unlike the Baeyer–Villager oxidation or the Kuivila mechanism for the oxidation of organoboranes by alkaline hydrogen peroxide.[11]

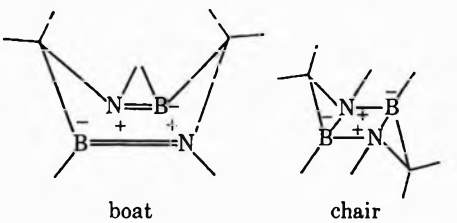
CHART III



(11) H. G. Kuivila, *J. Amer. Chem. Soc.*, **76**, 870 (1954).

The factors which determine whether or not conversion of **3** → **4** will occur are yet unknown. Although N-aryl substitution is necessary for the conversion of **3** to **4**, an additional requirement is that the alkyl group be larger than methyl. This invites speculation that diaxial nonbonded interaction between large alkyl groups in the normally more stable "boat" conformer is sufficiently large to overcome electronic favorability of the "boat" and force the ring into the "chair" conformer. Thus denied electron delocalization to an adjacent boron atom, because of unfavorable p-orbital overlap, the nitrogen atom is electronically better disposed to participate in transannular attack on a boron atom (see Chart IV). However the B—N stretching

CHART IV



4

frequency provides a reliable measure of bond order in the B—N bond, lower frequency reflecting a lower bond order.[12] Table III shows the B—N infrared frequencies of compounds of structures **3** and **4**. These frequencies are remarkably constant from one compound to another, and provide no support for the "boat–chair" argument.

TABLE III

INFRARED B—N STRETCHING FREQUENCIES OF SOME COMPOUNDS OF STRUCTURES **3** AND **4**

	Infrared maxima, ν (cm^{-1})			
Designation			B—N[a]	NO_2
3a		1453	1397	
3b		1453	1397	
3c	1504	1453	1397[b]	1333[a]
3d	1504	1453	1397	
3g	1504		1397	
3e			1399	
3i			1471[c]	
4a	1481	1449	1385	
4b	1481	1449	1387	
4c	1490	1449	1389[b]	1337[a]
4f	1481	1449	1387	

[a] Most intense band in the spectrum. [b] Second most intense band in the spectrum. [c] *Cf.* ref 7a.

Experimental Section

Starting Materials.—Cyclohexylisonitrile (Aldrich Chemical Co.) was distilled before use. Phenyl-, *p*-chlorophenyl-, and *p*-nitrophenylisonitrile were prepared according to the method of Ugi.[13] Trimethylborane and triethylborane were prepared by a modification[14a] of the the method of Koster:[14b] bp −78° (25 mm) and −20° (755 mm)[14c] and bp 93–94° (755 mm),[14c] respectively.

(12) (a) H. J. Becher, *Spectrochim. Acta*, **19**, 575 (1965); (b) *cf.* ref 3b, p 50.

(13) I. Ugi, U. Fetzer, H. Knupfer, and K. Offermann, *Angew. Chem. Intern. Ed. Engl.*, **4**, 472 (1965).

(14) (a) J. Casanova, Jr., H. R. Kiefer, and R. E. Williams, *Org. Prep. Proc.*, **1**, 57 (1969); (b) R. Koster, *Ann.*, **618**, 31 (1958); (c) G. E. Coates, "Organometallic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1960, p 94.

Compound 4a.—A 1.50-g sample of **3a**,[7a,e] mp 204°, was heated in an evacuated sealed tube at 300–305° for 5–6 min, 1.15 g, mp 138–140° (methanol). Recrystallization gave 1.02 g of white solid, mp 140–141°. Mother liquors gave 0.46 g, mp 138–140°, combined yield 1.46 g (97%).

Anal. Calcd for $C_{25}H_{40}B_2N_2$: C, 77.63; H, 10.02; N, 6.96. Found: C, 77.48; H, 10.04; N, 6.82.

The molecular weight, osmometric in benzene, was 390 ± 8; isopiestic in benzene,[15] 395 (required for $C_{26}H_{40}B_2N_2$, 402.24). Spectral data for compound **4a** are found in Tables I, III, and IV.

TABLE IV

ULTRAVIOLET SPECTRA OF SOME COMPOUNDS OF STRUCTURE 4

Designation	Absorption maxima, λ, mμ (log ε)[a]			
a	272 (2.72)	265 (2.92)	233 (3.7)	216 (4.2)
b	280 (2.87)	272 (3.04)	266 (4.7)	
c	283 (4.34)			216 (4.2)

[a] All values reported are for solutions in 95% ethanol.

Attempted Saponification of 4a.—**4a** (50 mg) in 20 ml of 50% aqueous potassium hydroxide and 5 ml of methanol was refluxed for 3 hr. Water (10 ml) was added. Ether extraction gave **4a** (92%), identified by tlc, melting point, and ir.

Attempted Acid Hydrolysis of 4a.—**4a** (50 mg) was refluxed in 30 ml of concentrated hydrochloric acid for 3 hr. Ether extraction gave **4a** (42 mg, 84%) identified by tlc, melting point, and ir.

Chromic Anhydride Oxidation of 4a in Acetic Acid.—Chromic anhydride (95 mg, 0.82 mmol) in glacial acetic acid (7 ml) at 90° was treated with 216 mg (0.54 mmol) of **4a**. The cooled, diluted reaction mixture was extracted with ether. The ether was washed with aqueous sodium bicarbonate. The dried extract was concentrated to *ca.* 1 ml using a 4-ft Vigreaux column. The volatile portion of this residue was separated by a high vacuum transfer and analyzed by glpc, which showed 15% 3-pentanone. No 3-ethyl-3-pentanol was present. In a control experiment, 3-ethyl-3-pentanol was found to react with chromic anhydride in acetic acid at 90° to give 3-pentanone in low yield.

Chromic Anhydride Oxidation of 4a in Pyridine.—**4a** (40 mg) was dissolved in 2 ml of pyridine and 200 mg of chromic anhydride in 2 ml of pyridine was added and the solution was stirred at room temperature overnight. The cooled solution was acidified to Congo red with hydrochloric acid and extracted with ether. The dried ether extract afforded 12 mg of an oil. 2,4-Dinitrophenylhydrazine reagent[16a] gave red crystals (18 mg), mp 144–148°. Recrystallization from (ethanol–ethyl acetate) raised this to 157–159°. This material was identical (melting point and tlc) with authentic 3-pentanone 2,4-dinitrophenylhydrazone, mp 157–159° (lit.[16b] mp 156°).

Attempted Oxidation of 4a with Chromic Acid in Ether.[17]—To 40 mg of **4a** in 15 ml of ether, 0.5 ml of chromic acid (prepared from 5.5 g of sodium dichromate, 4.1 ml of 96% sulfuric acid and diluted to 22.5 ml with water) was added dropwise. The mixture was stirred overnight at room temperature. The ether was separated, washed with saturated salt water, and dried to give **4a** (32 mg, 80%), identified by tlc, melting point, and ir.

Oxidation of 4a with Alkaline Hydrogen Peroxide.—A 400-mg sample of **4a** in 15 ml of *t*-butyl alcohol was heated to 70°. To this solution was added 150 mg of sodium hydroxide in 0.5 ml of water, followed by 0.3 ml of 33% hydrogen peroxide. The mixture was stirred overnight. The *t*-butyl alcohol was removed by slow concentration through a spinning-band column up to 85°. The distilled *t*-butyl alcohol was 99.4% pure by glpc. The residue from the distillation was made strongly alkaline with 2 *N* sodium hydroxide and extracted with several small portions of ether. The extract was washed with dilute hydrochloric acid, then water, and dried. The residual oily solid was distilled at 50° (0.1 mm). The residue 210 mg (52%, methanol) was **4a**, identified by melting point and ir. The distillate (30 mg) gave three peaks on glpc, identified as *t*-butyl alcohol (10%), 3-pentanone (30%), and 3-ethyl-3-pentanol (60%). A 500-mg sample of authentic pure 3-ethyl-3-pentanol, when treated in the same way, gave 322 mg after distillation (25% 3-pentanone and 75% 3-ethyl-3-pentanol).

(15) D. A. Sinclair, *J. Phys. Chem.*, **37**, 495 (1933); R. A. Robinson and D. A. Sinclair, *J. Amer. Chem. Soc.*, **56**, 1830 (1934).

(16) (a) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y., 1964, p 253; (b) p 362.

(17) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).

Tests of Basicity and Saturation of 4a.—Compound **4a** in ether saturated with dry hydrogen chloride gave no solid even on standing overnight. Compound **4a** was recovered unchanged by evaporation of the solvent. Compound **4a** failed to decolorize a solution of bromine in carbon tetrachloride.

Preparation of 2b.—*p*-Chlorophenylisonitrile[13] (12 g, 0.087 mol) in 50 ml of anhydrous ether was cooled and treated with 9 g (0.092 mol) of triethylborane in 80 ml of ether in an inert atmosphere. The isonitrile was added over 30 min. The mixture was stirred at room temperature for 2 hr. The white precipitate was washed with pentane. The filtrate was evaporated to 30 ml and cooled to give a second crop of solid. The combined solids were recrystallized to give 15 g (75%, acetone): mp 171–172°; ir (CCl_4) 1548 cm^{-1} (>C=N⁺<); ^1H nmr 7.08 ppm (4 H), a quartet (J = 5.6 Hz) at 2.22 ppm (2 H), a complex region at 0.79 ppm (10 H), and a triplet (J = 5.6 Hz) at 0.35 ppm (3 H). The ^{11}B nmr of this compound was a very broad single line at +2.4 ppm [relative to $(C_2H_5)_2O \cdot BF_3$].

Anal. Calcd for $C_{26}H_{38}B_2Cl_2N_2$: C, 66.28; H, 8.14; N, 5.94. Found: C, 66.30; H, 8.12; N, 5.88.

Preparation of 3b.—Compound **2b** (3.80 g) was heated in a sealed tube at 185° (10 min). The product gave 3.51 g (92%, benzene–methanol) of **3b**: mp 201–202°; ir (CCl_4) 1389 cm^{-1} (>B—N<). The ^{11}B and ^1H resonance spectra are shown in Table I.

Anal. Calcd for $C_{26}H_{38}B_2Cl_2N_2$: C, 66.28; H, 8.14; N, 5.94. Found: C, 66.11; H, 8.03; N, 5.90.

Preparation of 4b.—Compound **3b** (3.00 g), heated in a sealed tube at 305° (12 min), gave (2.50 g, 84%, acetone), mp 158–160°.

Anal. Calcd for $C_{26}H_{38}B_2Cl_2N_2$: C, 66.28; H, 8.14; N, 5.94; Cl, 15.05. Found: C, 66.08; H, 7.97; N, 6.02; Cl, 15.15.

Spectral data for **4b** are found in Tables I, III, and IV.

Preparation of 4f.—A 300-mg sample of **3f**[18] was heated at 305° (10 min) in a sealed tube and gave 275 mg (91%, acetone), mp 131°.

Anal. Calcd for $C_{38}H_{64}B_2N_2$: C, 79.99; H, 11.31; N, 4.91. Found: C, 79.58; H, 11.16; N, 5.04.

Spectral data for compound **4f** are found in Tables I and III.

Preparation of 3c from *p*-Nitrophenylisonitrile.—*p*-Nitrophenylisonitrile[13] (1.3 g) in 10 ml of tetrahydrofuran was added dropwise to a stirred solution of 900 mg of triethylborane in 20 ml of tetrahydrofuran at 0°. A dense precipitate was formed after 10 min. The reaction mixture was stirred at 50° for 1 hr, cooled in ice, and 1 ml of methanol was added. The solvent was evaporated under reduced pressure at 20°, and the residue was recrystallized to give 200 mg (10%, chloroform), mp 256° dec.

Anal. Calcd for $C_{26}H_{38}B_2N_4O_4$: C, 63.44; H, 7.78; N, 11.38. Found: C, 63.09; H, 7.67; N, 11.47.

Spectral data relevant to compound **3c** are found in Tables I, III, and IV.

Preparation of 3c by Nitration of 3a.—A finely powdered sample of **3a** (2.5 g) suspended in 100 ml of trifluoroacetic anhydride at −5° was stirred, treated with 10 ml of red fuming nitric acid (dropwise over a period of 15 min), and stirred at this temperature for 45 min. The reaction mixture was poured cautiously onto *ca.* 500 g of crushed ice, and the solid which separated was removed by filtration and washed with cold acetone. Recrystallization afforded 1.5 g (48%, chloroform), mp 256° dec. The ir of this material was identical with that of a sample prepared from *p*-nitrophenylisonitrile and triethylborane.

Reduction of 3c to 3d.—A solution of 2.0 g of **3c** in 150 ml of acetic acid was shaken in an atmosphere of hydrogen at 29 psi in a Parr apparatus for 14 hr, using 150 mg of platinum oxide as a catalyst. A tan solid which rapidly darkened in air was obtained. A sample was prepared for analysis by chromatography on alumina followed by rapid recrystallization, mp 226–228° (methanol). The analysis was unsatisfactory, owing to the instability of **3d**.

Anal. Calcd for $C_{26}H_{42}B_2N_4$: C, 72.23; H, 9.79; N, 12.96. Found: C, 71.20; H, 9.68; N, 14.16.

Spectral data for compound **3d** are found in Tables I, II, and III.

Compound **3d** was usually converted quickly into the acetamide or hydrochloride. The acetamido derivative (**3g**) was prepared by dissolving 300 mg of **3d** in 5 ml of anhydrous pyridine and adding 0.5 ml of acetyl chloride to the cooled solution. The mixture was poured into ice water, filtered, and the solid residue

(18) The authors are indebted to Professor G. Hesse for a generous supply of this compound.

(350 mg) recrystallized from 95% ethanol (mp >350°): ir (KBr) 3247 (NH), 1665 (amide I), and 1600 cm^{-1} (amide II).

The hydrochloride (**3h**) was prepared by treating a solution of 100 mg of **3d** dissolved in 5 ml of anhydrous ether with dry hydrogen chloride gas. Recrystallized of the residue from evaporation gave 80 mg, mp 336–340° dec (methanol–ethanol).

Preparation of 4c by Nitration of 4a.—A finely powdered sample of **4a** (500 mg) in 50 ml of acetic anhydride at −5° was treated with 6 ml of fuming red nitric acid by dropwise addition. The mixture was stirred for 1 hr, then poured into ice water. The product was 240 mg (33%, ethanol), mp 225–228°. Two further recrystallizations raised the melting point to 230°.

Anal. Calcd for $C_{26}H_{38}B_2N_2O_4$: C, 63.44; H, 7.78; N, 11.38. Found: C, 63.16; H, 7.78; N, 11.49.

Spectral data for compound **4c** are found in Tables I, III, and IV.

Conversion of 4h to 4b.—**4h** (100 mg) in 4.5 ml of concentrated hydrochloric acid in an ice bath was treated with sodium nitrite (1.4 g) in small portions. A cold solution of 3 g of freshly prepared cuprous chloride[19] in 10 ml of 8 *N* hydrochloric acid was added and the mixture allowed to warm to room temperature. It was heated for 30 min on a steam bath, then diluted with cold water. The brown residue which remained was chromatographed on Florisil using ether to give 20 mg of a pale yellow semisolid which was identical with authentic **4b** (ir).

(19) H. Zollinger, "Azo and Diazo Compounds," Interscience Publishers, New York, N. Y., 1961, Chapter 7.

Registry No.—**2b**, 20116-72-7; **3a**, 1756-53-2; **3b**, 20122-54-7; **3c**, 20122-55-8; **3d**, 20122-56-9; **3e**, 3657-04-3; **3f**, 4040-72-6; **3g**, 20122-59-2; **3h**, 20122-60-5; **3i**, 3657-05-4; **4a**, 20122-62-7; **4b**, 20122-63-8; **4c**, 20122-64-9; **4d**, 20122-65-0; **4f**, 2179-88-6.

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Heteronuclear Stabilized Carbonium Ions. I. Nuclear Magnetic Resonance Examination of Aryl Oxocarbonium Ions

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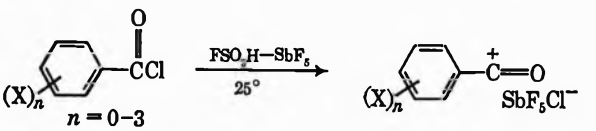
Aryl oxocarbonium ions were generated by the addition of benzoyl chlorides to FSO_3H–SbF_5 and were characterized by nmr spectroscopy at room temperature. In some instances ionizations were observed in neat FSO_3H. Chemical shift assignments were deduced from model compounds. For 28 cations the ranges of deshielding from the covalent precursors were as follows: $\Delta\delta_o$ 0.44–0.62 ppm, $\Delta\delta_m$ 0.44–0.57 ppm, and $\Delta\delta_p$ 0.93–1.09 ppm. Evidence is presented for alternating charge delocalization in the aromatic nucleus. Sulfonation products were observed when the cations possessed suitable electron-donating groups.

Oxocarbonium ions have been generated from acyl fluorides and SbF_5,[1-4] acyl chlorides and silver hexafluoroantimonate[1,2] or in some cases $SbCl_5$,[2,5] acyl sulfinylamines, or isocyanates and nitrosonium salts[6] as well as from the cleavage of esters[7] or carboxylic acids[8] in strong acid media. To date alkenyl,[8] alkylene,[9] cycloalkyl,[10] and alkyl[1-4] oxocarbonium ions have been directly observed and systematicly examined by nmr spectroscopy; however, such an examination of aryl oxocarbonium ions has not yet been reported.[11] As part of a related study of the behavior of methyl benzoates in strong acid media[12] it was necessary to characterize spectroscopically a number of aryl oxocarbonium ions. Characterization of these carbonium ions is reported herein.

(1) G. A. Olah, *Rev. Chim. Acad. Rep. Populaire Roumaine* (1962).
(2) G. A. Olah, S. J. Kuhn, W. S. Tolgyesi, and E. B. Baker, *J. Amer. Chem. Soc.*, **84**, 2733 (1962).
(3) G. A. Olah, *Rev. Chim. Acad. Rep. Populaire Roumaine*, **7**, 1139 (1962).
(4) G. A. Olah, W. S. Tolgyesi, S. J. Kuhn, M. E. Moffatt, I. J. Bastien, and E. B. Baker, *J. Amer. Chem. Soc.*, **85**, 1328 (1963).
(5) H. Volz and J. J. Volz de Leca, *Tetrahedron Lett.*, **38**, 3413 (1965).
(6) G. A. Olah, N. Friedman, J. M. Bollinger, and J. Lukas, *J. Amer. Chem. Soc.*, **88**, 5328 (1966).
(7) G. A. Olah, D. H. O'Brien, and A. M. White, *ibid.*, **89**, 5694 (1967).
(8) G. A. Olah and A. M. White, *ibid.*, **89**, 405, 3591, 4752 (1967).
(9) G. A. Olah and M. B. Comisarrow, *ibid.*, **88**, 3313 (1966).
(10) G. A. Olah and M. B. Comisarrow, *ibid.*, **88**, 442 (1966).
(11) Cryoscopic measurements of a number of aryl oxocarbonium have been reported and are reviewed in "Carbonium Ions," D. Bethell and V. Gold, Ed., Academic Press, New York, N. Y., 1967, p 284.
(12) D. A. Tomalia, to be published.

Results and Discussion

Using a modified version of the procedures employed by Volz[5] and Olah[1-4] a number of *ortho*-, *meta*-, and *para*-substituted aryl oxocarbonium ions were prepared, by merely adding appropriate benzoyl chlorides to an excess of 1:1 *M* FSO_3H–SbF_5 solutions. The resulting



homogeneous, although sometimes colored, solutions were for the most part stable enough to be examined by nmr spectroscopy at room temperature. Well-resolved spectra were generally obtained. In some cases, when steric and electronic effects were appropriate, the benzoyl chlorides could be ionized to their respective oxocarbonium ions in neat FSO_3H at room temperature.

The adequacy of the FSO_3H–SbF_5 method was demonstrated by converting acetyl chloride into its previously reported oxocarbonium. By this method a singlet was observed for this cation at −3.91 ppm and compares with a value of −3.93 ppm (20% oleum) reported by Deno and coworkers.[13] Additional efficacy was provided by observing chemical shift changes that occurred upon dissolving the benzoyl chlorides in neat

(13) N. C. Deno, C. U. Pittman, Jr., and M. J. Wisotsky, *J. Amer. Chem. Soc.*, **86**, 4370 (1964).

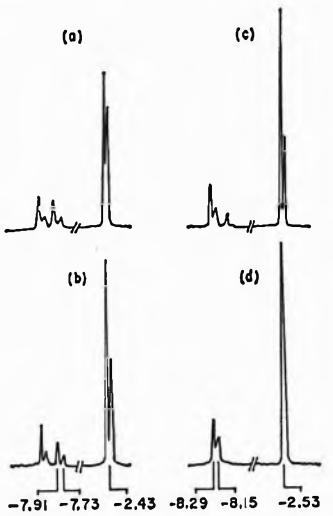
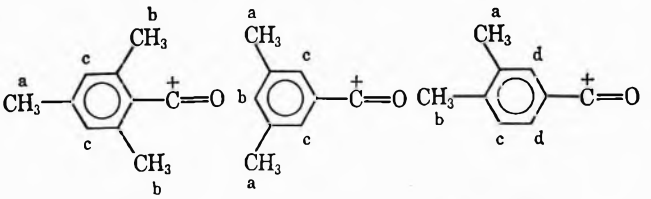


Figure 1.—Nmr spectra (δ) of 3,5-dimethylbenzoyl chloride: (a) in neat FSO_3H; (b, c) addition of less than a stoichiometric amount of SbF_5; (d) addition of a stoichiometric excess of SbF_5.

FSO_3H and then subsequently adding SbF_5. 2,4,6-Trimethyl and 2,6-dimethyl benzoyl chloride were completely ionized to their respective oxocarbonium ions in neat FSO_3H giving the chemical shift parameters for cations **1** and **4** shown in Table I. The addition of even a molar excess of SbF_5 did not cause any further deshielding. Furthermore the chemical shifts observed for cation **1** were essentially identical with those previously reported by Deno[13] and Volz.[5] When benzoyl chloride precursors to cations **2**, **3**, **5**, **6**, and **7** were added to neat FSO_3H, various degrees of ionization to the respective oxocarbonium ions were observed. Two discernible species could be observed by nmr in each of these cases. Figure 1 illustrates the spectrum (a) that was obtained for 3,5-dimethylbenzoyl chloride in neat FSO_3H, and those spectra (b and c) which were recorded for successive additions of SbF_5. Spectrum d shows the oxocarbonium ion, **2**, which was obtained by adding an excess (molar) of SbF_5. The downfield signals at −8.29, −8.15, and −2.53 ppm were assigned to the oxocarbonium ion and the upfield signals at −7.91, −7.73, and −2.43 ppm were assigned to protonated benzoyl chloride which is presumably undergoing proton exchange with the benzoyl chloride. This is supported by the fact that no highly deshielded $-C{=}O^+H$ signals were observed downfield except those for FSO_3H. Second, successive additions of an external chloride ion source (*e.g.*, LiCl) caused progressive upfield shifts in both the oxocarbonium ion and protonated acid chloride resonances accompanied by considerable signal broadening. As LiCl was added, the protonated acid chloride peaks increased commensurate amounts whereas the oxocarbonium ion signals decreased. By integrating either the aromatic or methyl protons of samples, which had been allowed to equilibrate for 1 hr, the per cent of ionization was determined for all of the cations listed in Table I. In the order listed (*i.e.*, cations **1**–**9**), the per cent of ionization was found to be as follows: 100, 48, 48, 100, 66, 64, 67, 0, and 0. Qualitatively the degree of ionization in this series appears to be more profoundly influenced by the amount of substitution in the *ortho* position rather than by favorable electronic effects that might arise from methyl substituents in the other

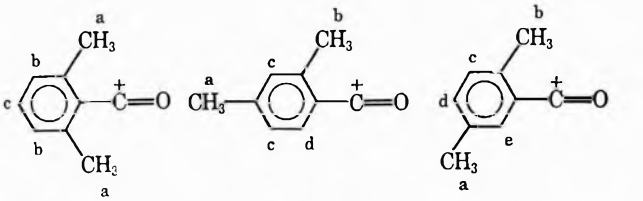
TABLE I



1
a 2.62 (s)
b 2.75 (s)
c 7.46 (s)
a:c:b 3:6:2

2
a 2.53 (s)
b 8.22 (s)
c 8.29 (s)
a:(b + c) 2:1

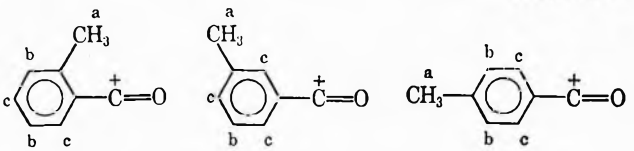
3
a 2.48 (s)
b 2.65 (s)
c 7.77 (d)
d 8.42 (d)
a:b:c:d 3:3:1:2



4
a 2.83 (s)
b 7.66 (d)
c 8.24 (t)
a:b:c 6:2:1

5
a 2.69 (s)
b 2.89 (s)
c 7.66 (d)
d 8.39 (d)
a:b:c:d 3:3:2:1

6
a 2.51 (s)
b 2.83 (s)
c 7.66 (d)
d ~8.21 (m)
e ~8.31 (s)
a:b:c (d + e) 3:3:1:2

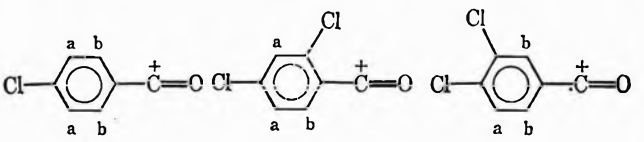


7
a 2.88 (s)
b 7.83 (m)
c 8.46 (m)
a:b:c 3:2:2

8
a 2.59 (s)
b 7.90 (t)
c 8.47 (t)
a:b:c 3:1:3

9
a 2.75 (s)
b 7.87 (d)
c 8.54 (d)
a:b:c 3:2:2

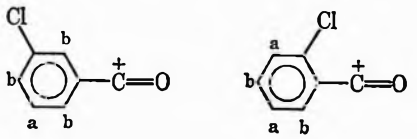
TABLE II



10
a 8.01 (d)
b 8.61 (d)
a:b 1:1

11
a 7.96 (m)
b 8.53 (d)
a:b 2:1

12
a 8.14 (d)
b 8.60 (m)
a:b 1:2



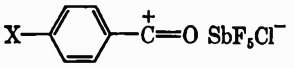
13
a 7.98 (t)
b 8.56 (m)
a:b 1:3

14
a 7.97 (t)
b 8.55 (m)
a:b 1:1

positions. This is particularly apparent if one examines cations **7**, **8**, and **9**. It should be noted, however, that two methyl groups in either the *meta* or *meta* and *para*

TABLE III

NMR CHEMICAL SHIFTS OF *para*-SUBSTITUTED ACYLIUM IONS AT 25° IN FSO_3H–SbF_5 (1:1 MOLAR)

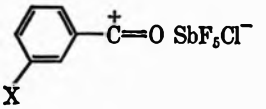


X	Registry no.	*ortho* protons	*meta* protons	X protons	$\Delta\delta_o$ [a]	$\Delta\delta_m$ [b]	$\Delta\delta_s$
$(CH_3)_3C$	20116-73-8	8.61 (d)	8.13 (d)	1.43 (s)	0.61	0.64	0.07
CH_3	20116-80-7	8.54 (d)	7.87 (d)	2.75 (s)	0.64	0.65	0.34
H	20116-74-9	~8.71 (m)	8.03 (t)		0.65	0.57	
F	20116-75-0	8.79 (m)	7.72 (t)		0.65	0.55	
Cl	20116-76-1	8.61 (d)	8.01 (d)		0.60	0.57	
Br	20116-77-2	8.49 (d)	8.21 (d)		0.52	0.58	
F_3C	20116-78-3	8.90 (d)	8.30 (d)		0.64	0.50	
NO_2	20116-79-4	9.06 (s)	9.06 (s)		0.67	0.67	

[a] $\Delta\delta_{c(av)}$ 0.62 ppm. [b] $\Delta\delta_{m(av)}$ 0.59 ppm.

TABLE IV

NMR CHEMICAL SHIFTS OF *meta*-SUBSTITUTED ACYLIUM IONS AT 25° IN FSO_3H–SbF_5 (1:1 MOLAR)

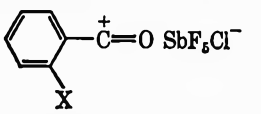


X	Registry no.	*ortho* protons	*meta* protons	*para* protons	X protons	$\Delta\delta_o$ [a]	$\Delta\delta_m$ [b]	$\Delta\delta_p$ [c]	$\Delta\delta_s$
CH_3	20147-91-5	8.47 (t)	7.80 (t)	8.47 (t)	2.59 (s)	0.63	0.54	1.11	0.16
H		~8.71 (m)	8.03 (t)	~8.50 (m)		~0.65	0.57	~0.88	
F	20116-81-8	8.29 (m)	8.29 (m)	8.29 (m)		~0.70	~0.70	~0.70	
Cl	20116-82-9	8.56 (m)	7.98 (t)	8.56 (m)		0.56	0.45	1.03	
Br	20116-83-0	8.68 (m)	7.91 (t)	8.68 (m)		0.72	0.51	0.72	
F_3C	20116-84-1	8.86 (t)	8.26 (t)	8.86 (t)		0.66	0.46	1.06	
NO_2	20116-85-2	2 H 9.57 (m)	8.33	9.15 (m)		2 H 0.60	0.50	0.61	
		6 H 9.15 (m)				6 H 0.61			

[a] $\Delta\delta_{o(av)}$ 0.62 ppm. [b] $\Delta\delta_{m(av)}$ 0.49 ppm. [c] $\Delta\delta_{p(av)}$ 0.93 ppm.

TABLE V

NMR CHEMICAL SHIFTS OF *ortho*-SUBSTITUTED ACYLIUM IONS AT 25° IN FSO_3H–SbF_5 (1:1 MOLAR)



X	Registry no.	protons	*ortho* protons	*meta* protons	*para* X protons	$\Delta\delta_o$ [a]	$\Delta\delta_m$ [b]	$\Delta\delta_p$ [c]	$\Delta\delta_s$
CH_3	20116-86-3	~8.56 (m)	7.83 (m)	~8.43 (m)	2.88 (s)	0.38	0.45	0.94	0.34
H		~8.71 (m)	8.03 (t)	~8.50 (m)		0.65	0.57	0.88	
F	20116-87-4	~8.70 (m)	7.79 (q)	~8.56 (m)		0.63	0.59	0.90	
Cl	20116-88-5	~8.55 (m)	7.97 (t)	~8.55 (m)		0.49	0.47	1.15	
Br	20116-89-6	~8.51 (m)	8.04 (m)	~8.51 (m)		0.47	0.48	0.95	

[a] $\Delta\delta_{o(av)}$ 0.44 ppm. [b] $\Delta\delta_{m(av)}$ 0.44 ppm. [c] $\Delta\delta_{p(av)}$ 1.02 ppm.

positions (*e.g.*, cations **2** or **3**) provide a sufficient driving force to produce ionization to the extent of 47–48%. Spontaneous ionization was not detected in neat FSO_3H for any of the more electron-deficient benzoyl chlorides including monosubstituted *o*-bromo-or *o*-chlorobenzoyl chloride. By adding less than stoichiometric amounts of SbF_5 to these more electron-deficient benzoyl chlorides one could observe mixtures of the oxocarbonium ions and protonated acid chlorides. For example, 4-trifluoromethylbenzoyl chloride exhibited two doublets centered at −8.46 and −8.00 ppm in neat FSO_3H. By adding less than a stoichiometric amount of SbF_5 one could generate the oxocarbonium ion as two downfield doublets centered at −8.93 and −8.36 ppm in addition to and at the expense of the upfield signals. Complete conversion to the carbonium ion was observed when an excess of SbF_5 was added.

In several instances the FSO_3H–SbF_5 solutions of the acid chlorides were examined by infrared spectroscopy and were found to contain characteristic oxocarbonium ion absorptions in the 2200–2300-cm^{-1} region.[4] Extensive etching of the cells (AgCl) precluded extensive characterization by this means.

Anomalous behavior was noted in the FSO_3H–SbF_5 medium for those acid chlorides containing substituents at each extreme of the Hammett σ range. These features will be commented on later.

Proton chemical shift assignments for the methyl- and chloro-substituted aryl oxocarbonium ions are summarized in Tables I and II. Assignments for mono-*para*-, *meta*-, and *ortho*-substituted cations are listed in Tables III, IV, and V, respectively.

These assignments were based on consideration of both the respective proton integrations as well as on the relative proton deshielding that was observed in suitably substituted model compounds. For example, 4-methylphenyl oxocarbonium ion, **9**, exhibited two symmetrical doublets in a ratio of 1:1 at −8.54 and

−7.87 ppm. The downfield signal was tentatively assigned to the *ortho* protons.[14] This assignment was corroborated by examination of those cations in Table I possessing *ortho* protons which could be unequivocally identified and distinguished from *meta* protons by integration. 3,4-Dimethylphenyl oxocarbonium ion, **3**, contains two *ortho* protons and one *meta* proton. This cation exhibited two unsymmetrical doublets at −8.42 and −7.77 ppm in a ratio of 2:1, respectively. Cation **2** which possesses only *ortho* and *para* protons exhibits singlets at −8.29 and −8.22 ppm in a ratio of 2:1 and were identified as *ortho* and *para* protons, respectively. From a series of these comparisons it becomes apparent that the chemical shift ranges for this group of cations are as follows: *meta*, −7.46 to −7.87; *para*, −8.22 to −8.47 and *ortho*, −8.29 to −8.54.

A series of chlorophenyl oxocarbonium ions (cations **10–14**) was examined in the same manner. As shown in Table II, chemical shift assignments could be made unambiguously by referring to the respective proton integrations.

Similar analyses of the other members of this carbonium ion system revealed the same general trend wherein the *ortho* protons are most deshielded followed by the *para* and then the *meta* hydrogens. The general range of chemical shifts for the respective protons in the 28 carbonium ions which were examined is as follows: *ortho* (−9.15 to −8.29 ppm, average −8.57 ppm); *para* (−8.86 to −9.22 ppm, average −8.53 ppm); *meta* (−8.26 to −7.46 ppm, average −7.92 ppm). These assignments paralleled those which were made in the cumyl cation[15] and 2-aryl-1,3-dioxolenium cation (cyclic dialkoxycarbonium ion)[16] systems.

In an effort to gain some insight as to the extent of charge delocalization to the various positions in the aromatic ring it was of interest to compare the chemical shift values of the carbonium ions with their respective benzoyl chloride precursors. The deshielding experienced in going from the covalent to the ionic species is indicated in Tables I–VII by $\Delta\delta_o$, $\Delta\delta_m$, $\Delta\delta_p$, and $\Delta\delta_s$ for the respective positions and substituents. One must exercise due caution in rationalizing relative deshielding entirely as a function of charge delocalization since other effects may contribute to the observed shielding. Many of these pitfalls are described by Fraenkel and Farnum,[16] particularly in the case of the triphenylcarbonium ion system. As cited by Farnum,[17] shielding due to the ring current effects of adjacent phenyl groups in these cations can profoundly affect relative deshielding of the respective aromatic positions. This is most pronounced for the *ortho* position. Upon appropriate treatment of the spectral data for these effects, Farnum did conclude that there is definitely charge alternation in these cations with the greatest amount of charge being delocalized to the *ortho* and *para* positions.

In an attempt to detect such a parallelism in the aryl oxocarbonium ion series, the monosubstituted cations

(14) Olah has reported that the *ortho* protons in phenyl oxocarbonium hexafluoroantimonate are the most deshielded ring hydrogens in that cation. (See ref 1.)

(15) G. Fraenkel and D. G. Farnum in "Carbonium Ions," Vol. I, G. A. Olah and P. V. R. Schleyer, Ed., Interscience Publishers, New York, N. Y., 1968, p 251.

(16) D. A. Tomalia, unpublished results.

(17) D. G. Farnum, *J. Amer. Chem. Soc.*, **89**, 2970 (1967).

TABLE VI

DESHIELDING OF METHYL-SUBSTITUTED ACYLIUM IONS COMPARED WITH BENZOYL CHLORIDE PRECURSORS (CCl_4)

Cation	$\Delta\delta_o$ [a]	$\Delta\delta_m$ [b]	$\Delta\delta_p$ [c]	$\Delta\delta_{o\text{-}CH_3}$ [d]	$\Delta\delta_{m\text{-}CH_3}$ [e]	$\Delta\delta_{p\text{-}CH_3}$ [f]
1		0.64		0.40		0.34
2	0.65		0.97		0.16	
3	0.70	0.60			0.19	0.36
4		0.53	1.11	0.43		
5	0.32	0.57		0.38		0.30
6	0.36	0.64	0.95	0.34	0.11	
7	0.28	0.45	1.08	0.34		
8	0.63	0.54	1.11		0.16	
9	0.64	0.65				0.34

[a] $\Delta\delta_{o(av)}$ 0.58 ppm. [b] $\Delta\delta_{m(av)}$ 0.57 ppm. [c] $\Delta_{p(av)}$ 1.07 ppm. [d] $\Delta\delta_{o\text{-}CH_3(av)}$ 0.39 ppm. [e] $\Delta\delta_{m\text{-}CH_3(av)}$ 0.17 ppm. [f] $\Delta\delta_{p\text{-}CH_3(av)}$ 0.35 ppm.

TABLE VII

DESHIELDING OF CHLORO-SUBSTITUTED ACYLIUM IONS COMPARED WITH BENZOYL CHLORIDE PRECURSORS (CCl_4)

Cation	$\Delta\delta_o$ [a]	$\Delta\delta_m$ [b]	$\Delta\delta_p$ [c]
1	0.60	0.57	
2	0.47	0.54	
3	0.59	0.55	
4	0.56	0.45	1.03
5	0.49	0.47	1.15

[a] $\Delta\delta_{o(av)}$ 0.54 ppm. [b] $\Delta\delta_{m(av)}$ 0.52 ppm. [c] $\Delta\delta_{p(av)}$ 1.09 ppm.

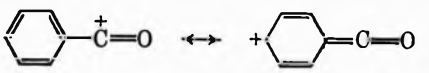
were examined both as a function of their substituent position and as a function of the Hammett σ values of the substituent. By comparing the individual $\Delta\delta_o$, $\Delta\delta_m$, and $\Delta\delta_p$ values for 22 mono-*ortho*-, *meta*-, and *para*-substituted oxocarbonium ions (Tables III–V) one finds that, with but few exceptions, the deshielding values ($\Delta\delta$) decrease in the following order: $\Delta\delta_p > \Delta\delta_o > \Delta\delta_m$. This is most apparent by comparing average values which were determined for the respective positions as shown in Tables III and IV. The average $\Delta\delta$ values shown in Table V do not make this distinction between the *ortho* and *meta* positions as obvious. This may be due to the fact that resonance signals for the *ortho* and *para* protons were usually badly overlapped. This undoubtedly introduces some error in determining exact chemical shift values for these positions. However, large differences in the $\Delta\delta$ values for the *meta* and *para* positions are quite evident. These tables list the substituents in each case in order of their Hammett σ values (*i.e.*, from σ −0.27 to σ +0.78). Any deshielding effects as a function of the the substituents ability to accommodate charge (*i.e.*, as a function of the substituents Hammett σ value) should become apparent by vertically examining the δ and $\Delta\delta$ values in Tables III–V. Although the chemical shift values tend to move downfield as the σ value becomes more positive, no regular or quantitative trend is evident. Such a trend for the $\Delta\delta$ values is even less obvious.

As suggested by Fraenkel and coworkers,[18] π-electron densities in aromatic systems might be estimated from nmr data if other contributions to the chemical shifts such as special solvent effects, paramagnetic shifts, and substituent anisotropies were absent or could be determined independently. In an attempt to assess charge delocalization in a system where varying substituent an-

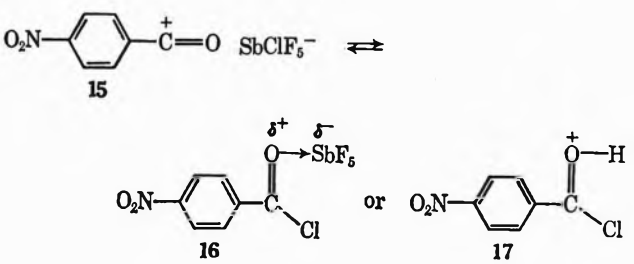
(18) G. Fraenkel, R. E. Carter, A. McLachlan, and J. H. Richards, *ibid.*, **82**, 5846 (1960).

sotropy effects were minimized or at least constant we next compared deshielding values ($\Delta\delta$) for the methyl- and chloro-substituted aryl oxocarbonium ions described in Tables I and II. These data are presented in Tables VI and VII. In each system charge alternation is suggested as reflected by the relative $\Delta\delta$ values; however, dramatic differences between $\Delta\delta_o$ and $\Delta\delta_m$ are not apparent. This alternation effect is dramatically illustrated, however, by the $\Delta\delta$ values for the methyl substituents.

It should be noted that in all cases examined the *para* aromatic protons are consistently deshielded approximately twice as much as the *ortho* or *meta* protons [*i.e.*, $\Delta\delta_p \cong (2)(\Delta\delta_o)$ or $(2)(\Delta\delta_m)$]. This suggests that there may be considerable charge delocalization to the *para* position and reflects on the importance of the following resonance contribution.



As stated earlier, unusual behavior was noted for those acid chlorides which contained either strong electron-withdrawing substituents or strong electron-donating moieties. For example, 4-nitrobenzoyl chloride (σ +0.78) did not appear to be completely converted into its acylium ion at room temperature. An nmr spectrum of this reaction mixture consisted of a broad singlet at −9.06 ppm which partially overlaps with what appears to be a quartet centered at −8.84 ppm. The downfield signal was assigned to the carbonium ion, **15**. This assignment was based on the fact that this signal is 0.67 ppm downfield from 4-nitrobenzoyl chloride (CCl_4). This is consistent with the $\Delta\delta$ values of 0.64 and 0.50 ppm for the *ortho* and *meta* positions in the closely related 4-trifluoromethyl phenyl oxocarbonium ion (σ +0.55). The upfield signal was assigned to a donor-type complex, **16**, or perhaps the protonated acid chloride, **17**. Birchall and Gillespie have observed the closely related protonated 4-nitroacetophenone as a quartet centered at −8.87 ppm.[19] Judging from the broadness of the resonances a slow equilibrium may exist such as



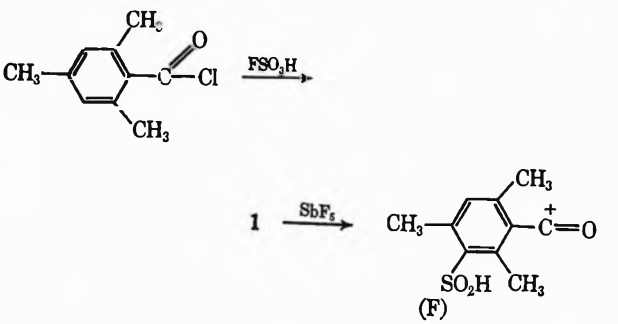
Broadness of the nmr resonance signals for 3-nitrobenzoyl chloride (σ +0.71) in FSO_3H–SbF_5 was also observed at room temperature. Although two discernible species could not be detected, an equilibrium as shown above may account for the poorer resolution.

In some instances observation of oxocarbonium ions was troubled by secondary reactions. This was particularly true of electron rich benzoyl chlorides which contained methoxy, cyclopropyl, or polymethyl groups.

(19) T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **43**, 1045 (1965).

Most notable was the complete decomposition of 4-cyclopropylbenzoyl chloride in FSO_3H–SbF_5 even at temperatures as low as −50°. Samples were prepared by dropping the acid chloride into a mixture consisting of equal volumes of FSO_3H–SbF_5 (1:1 *M*) and sulfur dioxide at ∼−80°. Brilliant orange-red solutions were obtained which quickly degenerated into dark resinous syrups upon attempting to record spectra at −50°. Although this aspect was not investigated in detail, protonation of the cyclopropane ring is suspected as the source of this disturbance.[20-22]

In order to obtain a spectrum of the 2,4,6-trimethylphenyl oxocarbonium ion, **1** in FSO_3H–SbF_5 (1:1 *M*, 25°), it was necessary to scan immediately after sample preparation. In this manner one could obtain chemical shift parameters which were in agreement with previously reported values.[5,13] Within minutes, however, four new singlets began to appear downfield at −7.51, −2.82, −2.76, and −2.70 ppm. With time these peaks were enhanced at the expense of the upfield signals for the oxocarbonium ion **1** (*i.e.*, at −7.46, −2.75, and −2.62 ppm). Rapid integration of the aromatic and aliphatic protons during this time revealed that considerable loss of aromatic protons occurred (∼50% of theory) based on that expected for cation **1**. Within 15 min the homogeneous liquid sample solidified to a tan crystalline mass. These data suggest that rapid sulfonation is occurring. By analogy to the known sulfonation of anisole in $ClSO_3H$, this sulfonation product may be a sulfonyl fluoride.[23] It should be mentioned that the ionization of 2,4,6-trimethylbenzoyl chloride to cation **1** in neat FSO_3H is not troubled by these secondary reactions. No changes in the spectrum of cation **1**, prepared in this manner, were noted even after 16 hr at room temperature. Upon adding an excess of SbF_5 to this sample, however, a sulfonation product developed to the extent of ∼43% over a period of 12 hr. At this time

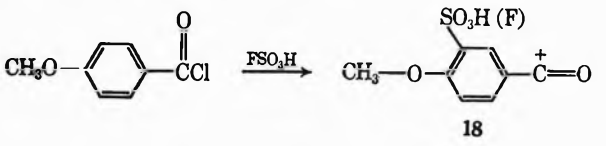


it is not known whether sulfonation is occurring on the oxocarbonium ion **1** or whether equilibrium concentrations of the acid chloride are involved in this transformation. The former is certainly possible in view of the evidence reported by Hart[24] for the sulfonation of triarylcarbonium ions in concentrated sulfuric acid. This appears to be the second reported observation of sulfonation products resulting from attempts to generate cations in a FSO_3H medium.[23]

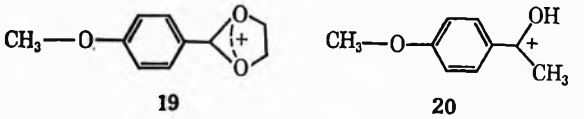
The behavior of 2-, 3-, and 4-methoxybenzoyl chlorides in neat FSO_3H was somewhat complicated.

(20) R. L. Baird and A. A. Aboderin, *J. Amer. Chem. Soc.*, **86**, 252 (1964).
(21) H. Hart and R. H. Schlosberg, *ibid.*, **88**, 5030 (1966).
(22) N. C. Deno and D. N. Lincoln, *ibid.*, **88**, 5357 (1966).
(23) B. G. Ramsey, *ibid.*, **88**, 5358 (1966).
(24) H. Hart and T. Sulzberg, *J. Org. Chem.*, **28**, 1159 (1963).

All three of the methoxy-substituted benzoyl chlorides appear to undergo complete monosulfonation over a period of 16 hr. When 4-methoxybenzoyl chloride is added to neat FSO_3H, a spectrum scanned within 5–7 min consists of multiplets at −8.90 to −8.12 ppm and −7.64 to −7.14 ppm accompanied by three upfield singlets at −4.24, −4.16, and −4.06 ppm. These singlets are designated A, B, and C in the order given above and are present in approximately the following relative amounts: B ≫ C > A. After approximately 20 min the relative amounts become B ≫ A > C and after 3 hr the ratio is A ≫ B ≅ C. A considerably more simplified spectrum is obtained by storing the sample for 16 hr at room temperature. After this time the spectrum consists of a multiplet centered at −8.76, a doublet at −7.54, and a singlet at −4.26 ppm. These resonance signals are present in a ratio of 2:1:3. Based on previous aromatic proton assignments it appears as though monosulfonation at the *meta* position has occurred. According to the data available at this time, the sulfonated product is believed to be in the oxocarbonium ion form, **18**. This is based on the fact that by adding a stoichiometric excess of SbF_5 and allowing to equilibrate for 12 hr one observes a downfield shift of only 0.08 ppm for the methoxy group. This is in accord with a solvent shift rather than an ionization. Ultraviolet spectral data also corroborates this speculation. Fresh samples of 4-methoxybenzoyl chloride in FSO_3H gave λ_{max} at 232.6 and 302.5 mμ. The spectrum was unchanged after 12 hr at 25°. These data agree well with values obtained by Olah and coworkers[25] for 4-methoxyphenyl oxocarbonium in 33% oleum. Furthermore the related cations **19**[26] and **20**[19] exhibit methoxy resonance signals in approximately the same region at −4.08 and −4.38 ppm, respectively, in neat FSO_3H.



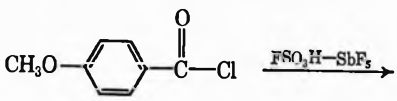
18

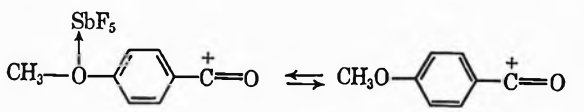


19 20

Analogous observations were made for 2- and 3-methoxybenzoyl chlorides. After 16 hr in neat FSO_3H, 2-methoxybenzoyl chloride gave an nmr spectrum consisting of a complex multiplet at −9.07 to −7.29 ppm, a major singlet at −4.44 ppm, and two minor singlets at −4.47 and −4.29 ppm. The aromatic to aliphatic proton ratio at this time was 3:3.27, indicating essentially complete monosulfonation. By adding a stoichiometric excess of SbF_5 the spectrum simplified to four doublets in the aromatic region at −8.95, −8.71, −8.55, and −7.82 ppm and a singlet in the aliphatic region at −4.47 ppm. The aromatic to aliphatic proton ratio remained the same. In the aromatic region the ratio of the most deshielded doublet (−8.95 ppm), the two intermediate doublets (−8.71, −8.55 ppm), and the upfield doublet was 1:1:1. Of the four possible monosulfonation products and based on previous aromatic proton assignments, these data are most consistent with sulfonation at positions either *ortho* or *para* to the methoxy groups.

3-Methoxybenzoyl chloride gave a spectrum consisting of a complex multiplet at −8.45 to −7.80 ppm accompanied by two minor singlets (−4.64 and −4.13 ppm) and two major singlets (−4.25 and −4.03 ppm). The ratio of aromatic to aliphatic protons was 3.12:3.00. Upon adding a stoichiometric excess of SbF_5 and scanning the spectrum reduced to a complex multiplet at −8.96 to −7.80 ppm and a singlet at −4.37 ppm. Although adding 4-methoxybenzoyl chloride to a 1:1 *M* mixture of FSO_3H–SbF_5 (25°) gave only a small amount of sulfonation even after 12 hr, ionization in this medium did not give a simple spectrum. Upon addition of acid chloride to the FSO_3H–SbF_5 medium and scanning within 15 min a spectrum was obtained which consisted of two doublets centered at −8.60 and −7.46 ppm accompanied by two singlets at −4.48 and −4.33 ppm. The aromatic to aliphatic proton ratio was 3.96:3.00 whereas the downfield to upfield singlet ratio was 1.00:0.85. Over a period of 12 hr the upfield singlet increased at the expense of the downfield singlet. The ratio of downfield to upfield singlet after 12 hr was 1.00:1.60. At this point the aromatic signals had not changed significantly from the original 15-min scan aromatic to aliphatic proton ratio was 3.81:3.00 thus indicating negligible sulfonation. The changes that occurred in the methoxy region are believed to be due to complexing of the methoxy group by SbF_5 thus yielding kinetically controlled mixtures of methoxy complexed oxocarbonium ion **21** and uncomplexed oxocarbonium as shown below. With time the complexed oxocarbonium presumably dissociates until a thermodynamically controlled equilibrium mixture is reached.





21

Similar observations were made for 3-methoxybenzoyl chloride. After allowing to equilibrate for 62 hr, 3-methoxybenzoyl chloride in FSO_3H–SbF_5 was observed as a multiplet at −9.01 to −7.98 ppm and a singlet at −4.35 ppm. The aromatic to aliphatic proton ratio was 3.25:3.00, indicating substantial monosulfonation.

The behavior of 2-methoxybenzoyl chloride in FSO_3H–SbF_5 was very complex. A spectrum scanned 20 min after sample preparation consisted of a multiplet at −9.20 to −7.27 ppm and −4.76 to −4.24 ppm. During a period of 62 hr the sample solidified to a black resinous product which was not further characterized.

Experimental Section

Materials.—All of the acid chlorides or carboxylic and precursors were obtained from commercial sources (Eastman, Ald-

(25) G. A. Olah, C. U. Pittman Jr., R. Waack, and M. Doran, *J. Amer. Chem. Soc.*, **88**, 1488 (1966).

(26) D. A. Tomalia and H. Hart, *Tetrahedron Lett.*, **29**, 3389 (1966).

rich or Frinton Laboratories) except for 4-cyclopropylbenzoyl chloride. The preparation of which is described below. The acid chlorides were prepared in the usual manner from the respective carboxylic acids and thionyl chloride. Fluorosulfonic acid was obtained from Allied Chemical Co. and antimony pentafluoride was procured from Alfa Inorganic.

Nmr Spectra.—All spectra were recorded on a Varian A-60 nmr spectrometer equipped with a variable-temperature probe. Spectra were scanned within 15 min after sample preparation. The chemical shifts (δ) are reported in parts per million downfield from TMS using tetramethylammonium tetrafluoroborate (δ 3.10) as the secondary standard.

Infrared Spectra.—Spectra were recorded on a Perkin-Elmer Infracord Model 137-G using a AgCl cell. The cation samples in FSO_3H–SbF_5 caused substantial etching of the cell.

Ultraviolet Spectra.—Spectra were recorded on a Model 202 Perkin-Elmer recording spectrometer using 0.2-cm quartz absorption cells. Sample concentration were 10^{-2} to 10^{-3} M.

Sample Preparation.—Samples were prepared by adding ~0.1 g of the acid chloride in a dropwise manner to ~1.0 ml of FSO_3H–SbF_5 (1:1 M) at room temperature. A ratio of 1:1 by volume of sulfur dioxide was used for the low-temperature samples. The usual intense peak at −10.9 ppm and that of $H_3{}^+O$ at −10.5 ppm were observed in all cases.

4-Cyclopropylbenzoyl Chloride.—Cyclopropylbenzene[27] was brominated according to the method of Levina and coworkers.[28] 4-Bromocyclopropylbenzene was obtained as a colorless liquid boiling at 97–98° (10 mm) (63%).

4-Cyclopropylbenzoic acid was prepared *via* the Grignard reagent and was obtained as a white crystalline solid melting at 156–157° (45%). Hart and Levitt[29] report a melting point of 157–158°. 4-Cyclopropylbenzoyl chloride was prepared by refluxing the carboxylic acid with 1 M excess of thionyl chloride for 2 hr. The acid chloride distilled as a colorless liquid, bp 89–90° (0.5 mm). The product gave an nmr spectrum consisting of two doublets centered at −7.93 and −7.09 ppm and two complex multiplets centered at −1.96 and −0.95 ppm in a proton ratio of 2:2:1:4, respectively.

Registry No.—**1**, 1571-83-1; **2**, 20122-33-2; **3**, 20122-34-3; **4**, 20122-35-4; **5**, 20122-36-5; **6**, 20122-37-6; **7**, 20122-38-7; **8**, 20122-39-8; **9**, 20122-40-1; **10**, 20122-41-2; **11**, 20122-42-3; **12**, 20122-43-4; **13**, 20122-44-5; **14**, 20122-45-6.

Acknowledgment.—The author would like to acknowledge the assistance of Mr. J. W. Lalk for the preparation of some of the acid chlorides.

(27) T. F. Corbin, R. C. Hahn, and H. Schechter, *Org. Syn.*, **44**, 30 (1964).

(28) R. Y. Levina, P. A. Gembitskii, and E. G. Treshchova, *Zh. Obshch. Khim.*, **33**, 371 (1963); *J. Gen. Chem.*, **33**, 364 (1963).

(29) H. Hart and G. Levitt, *J. Org. Chem.*, **24**, 1261 (1959).

The Alkylation of Difluoramine with Carbonium Ions[1]

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The acid-catalyzed reactions of difluoramine with olefins, alcohols, alkyl halides, ketones, and acetals yield organic difluoramino derivatives. These reactions appear to take place by reaction of a carbonium ion with difluoramine. Interpretation of the results is discussed in terms of carbonium ion stability and reactivity.

Previous reports of the chemistry of difluoramine from these laboratories have focused on its reactions with basic reagents, such as amines[2,3] and imines,[4] in which the fluorine–nitrogen bonds were broken. Recently, the addition of difluoramine to aldehydes and ketones was reported.[5] This reaction may be viewed as a special example of an alkylation reaction whereby a difluoramino group is attached to carbon. A preliminary report of other alkylations has also appeared.[6]

Results

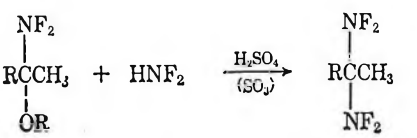
It has been found that a variety of compounds which react with acids to produce carbonium ions will alkylate difluoramine to produce new organic difluoramino compounds. The conditions required for alkylation depend on the ease of carbonium ion formation and the reactivity of the carbonium ion. Some comment will be made on the various factors involved during the discussion of these reactions. Some difluoramines prepared in this way are listed in Table I.

Olefins.—1,1-Dialkylethylenes, enol ethers and esters, and ketene acetals react with difluoramine in the presence of acid catalysts to produce the corresponding alkyl difluoramine. α,β-Unsaturated carbonyl compounds also add difluoramine readily.

The conditions of this addition reaction appeared to depend upon the nucleophilic character of the olefin. For example, ketene acetals and enol ethers reacted directly with difluoramine without added acid, enol esters required an added acid catalyst (a sulfonic acid ion-exchange resin, Amberlyst 15,[7] proved useful), and hydrocarbon olefins required concentrated sulfuric acid as catalyst.

Acrolein and methyl vinyl ketone reacted with difluoramine without catalyst to yield the conjugate addition products. Acrolein reacted further by addition to the carbonyl group. Acrolein diethyl acetal, on the other hand, reacted initially at the α-ether carbon atom, but with acid catalysis the bis product resulting from reaction at both carbonium ion centers was produced.

When the HNF_2–enol ether or enol ester products were treated with more difluoramine in the presence of 100% sulfuric acid or fuming sulfuric acid, the ether or ester function was replaced by a difluoramino group.



(1) This work was carried out under Army Ordnance Contract No. DA-01-021 ORD-5135.

(2) C. L. Bumgardner, K. J. Martin, and J. P. Freeman, *J. Amer. Chem. Soc.*, **85**, 97 (1963).

(3) C. L. Bumgardner and J. P. Freeman, *ibid.*, **86**, 2233 (1964).

(4) W. H. Graham, *ibid.*, **88**, 4677 (1966).

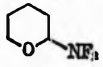
(5) J. P. Freeman, W. H. Graham, and C. O. Parker, *ibid.*, **90**, 120 (1968).

(6) W. H. Graham and J. P. Freeman, *ibid.*, **89**, 716 (1967).

(7) Trademark of Rohm and Haas Co., Philadelphia, Pa.

TABLE I

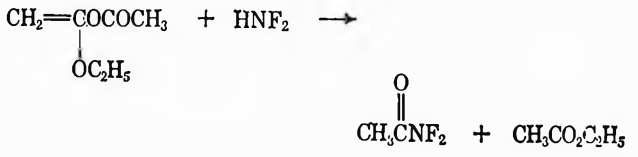
ALKYLATIONS OF DIFLUORAMINE

Alkylating agent	Catalyst	Product	Registry no.	Analysis: Calcd, % C	H	N	F	Found, % C	H	N	F	^{19}F nmr shift), ϕ
$(C_6H_5)_3CBr$	Liquid SO_2	$(C_6H_5)_3CNF_2$[a]										−32.4
$(C_6H_5)_2CHOH$	SO_2, Amberlyst 15	$(C_6H_5)_2CHNF_2$	14092-52-5	71.22	5.06	6.39	17.33	71.18	5.17	6.55	17.4	−48.6
$C_6H_5CCl_3$[c]	CF_3CO_2H	$(C_6H_5)CCl_2NF_2$	14092-53-6	39.65	2.38	6.61	17.92	39.51	2.84	6.78	18.7	−43.5
$(C_6H_5)_2C(Cl)_2$	Neat	$(C_6H_5)_2C(Cl)NF_2$	20122-15-0	61.5	3.95	5.52	15.0	61.57	4.02	5.41	16.38	−27.1
$(CH_3)_2C{=}CH_2$	H_2SO_4	$(CH_3)_2CNF_2$[a]	646-55-9									
$(CH_3)_2C{=}CHCH_3$	H_2SO_4	$(CH_3)_2C(C_2H_5)NF_2$	14092-55-8	48.76	9.00	11.38		48.96	9.01	11.54		−25.1
$CH_2{=}C(Cl)CH_3$	Amberlyst 15	$(CH_3)_2C(Cl)NF_2$	20122-18-3	28.8	4.5	10.9	29.3	28.9	5.1	11.2	27.7	−34.3
	Neat		14092-58-1	43.8	6.57	10.21	27.7	43.89	6.56	10.42	27.2	−28.1[b]
$CH_2{=}CHOCH_2CH(CH_3)_2$	Amberlyst 15	$CH_3CH(NF_2)OCH_2CH(CH_3)_2$	20122-20-7	47.06	8.50	9.15	24.84	49.95	8.91	9.80	21.04	−39.5[b]
$CH_2{=}CHCH(OC_2H_5)_2$	Neat	$CH_2{=}CH{-}CH(NF_2)OC_2H_5$	16452-22-5	43.79	6.62	10.22	27.72	43.86	6.79	10.32	27.1	−26.1[b]
$CH_2{=}CHCH(OC_2H_5)_2$	Amberlyst 15	$NF_2CH_2CH_2CH(NF_2)OC_2H_5$	20122-22-9	31.58	5.80	14.74	39.93	32.00	5.74	14.73	39.2	−53.6; −25.5[b]
$CH_2{=}CCH_3$ $\quad\quad\vert$ $\quad OCOCH_3$	Amberlyst 15	$(CH_3)_2C(NF_2)OCOCH_3$	20122-23-0	39.22	5.90	9.15	24.84	39.16	6.11	8.94	24.20	−20.6
$CH_2{=}CHOCOCH_3$	Amberlyst 15	$CH_3CH(NF_2)OCOCH_3$	20122-24-1	34.54	5.07	10.07	27.32	34.74	5.27	10.48	26.41	−26.6[b]
$CH_2{=}C(OC_2H_5)_2$	Neat	$CH_3C(NF_2)(OC_2H_5)_2$	20122-25-2									−18.7
$CH_3C(OCH_3)_3$	Neat	$CH_3C(NF_2)(OCH_3)_2$[d]	14092-57-0									−18.7
$CH_2{=}CHCOCH_3$	Neat	$NF_2CH_2CH_2COCH_3$	20122-27-4	39.02	5.73	11.38	30.87	39.33	6.13	11.28	29.3	−54.1
$CH_2{=}CHCHO$	Neat	$NF_2CH_2CH_2CH(OH)NF_2$	20122-28-5	22.37	3.13	17.38	47.18	23.06	4.35	17.33	47.04	c

[a] An example of the reverse of this reaction has been reported. Dissolution of triphenylmethyl difluoramine in sulfuric acid produces difluoramine. W. H. Graham and C. O. Parker, *J. Org. Chem.*, **28**, 850 (1963). [b] The ^{19}F nmr spectrum was interpreted as the AB portion of an ABX pattern. Typically J_{AB} = 590–600 cps. Details of such spectra will be reported in a separate publication. The values reported here represent the center of the overlapped center lines of the AB quartets. In some cases the outer lines were detectable, at other times not. [c] See Experimental Section. [d] These products were not easily purified for analysis. [e] Cl 32.6% (Calcd 33.44%).

This reaction is analogous to the recently reported conversion of ketones to *gem*-difluoramines[8] by difluoramine and sulfuric acid which probably proceeds through the ketone–HNF_2 adduct.[5]

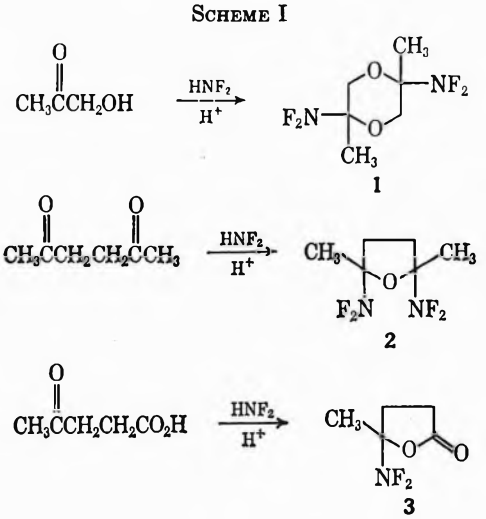
In a unique case the difluoramine adduct of a vinyl ester decomposed spontaneously. Addition of difluoramine to α-ethoxyvinyl acetate[9] produced a mixture of ethyl acetate and N,N-difluoracetamide.[10] This reaction is similar to that of hydrogen chloride and this ester which yields acetyl chloride.[9] Anhydrides react with difluoramine in the presence of Amberlyst 15 to produce difluoramides also.



Alcohols and Alkyl Halides.—Certain alcohols such as triphenylcarbinol, *t*-butyl alcohol, and benzhydrol react with difluoramine in the presence of acids to yield the corresponding difluoramines.[11] Similarly, certain halides such as triphenylmethyl bromide and benzotrichloride alkylate difluoramine. In concentrated sulfuric acid in the presence of difluoramine 2-chloro-2-difluoraminopropane is converted in low yields into 2,2,-bis(difluoramino)propane. In general, vinyl halides did not prove to be a useful source of *gem*-difluoramines.

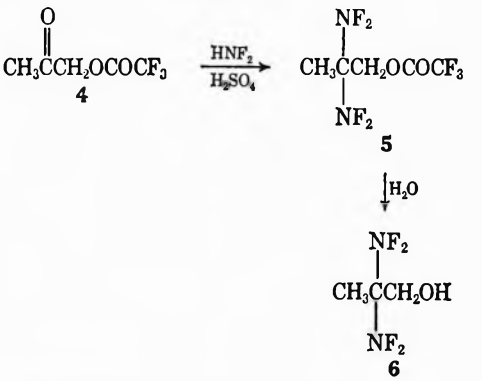
Aldehydes, Ketones, and Their Derivatives.—It has been reported that simple ketones are converted into *gem*-difluoramines by reaction with difluoramine in sulfuric acid.[8] During that study it was noted that certain nucleophilic functional groups interfere with the reaction. For example, hydroxyacetone is converted into 2,5-bis(difluoramino)-2,5-dimethyl-1,5-dioxane (**1**), acetonylacetone into 2,5-bis(difluoramino)-2,5-dimethylfuran (**2**), and levulinic acid into γ-difluoramino-γ-valerolactone (**3**) (Scheme I). Use of stronger acids effects cleavage of ether **2** to the tetrakis(difluoramine).[8]

Scheme I

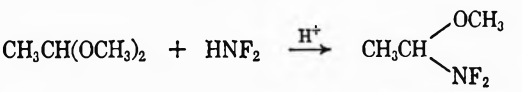


It has now been found that the carbonyl group of trifluoroacetoxyacetone (**4**) but not of acetoxyacetone is readily converted into a *gem*-difluoramino group (**5**) by HNF_2–H_2SO_4. The trifluoroacetate (**5**) may in turn be hydrolyzed to the alcohol **6** which could not be prepared directly from hydroxyacetone (Scheme II).

Scheme II



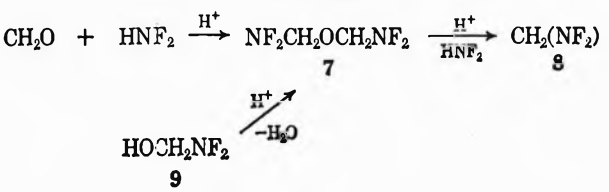
Acetals react smoothly with difluoramine in the presence of Amberlyst 15 to yield α-difluoramino ethers. These compounds, in turn, react as outlined above with difluoramine in the presence of sulfuric acid to yield the bis(difluoramine). *ortho* esters react with difluoramine itself to yield α-difluoramino ketals. However, efforts



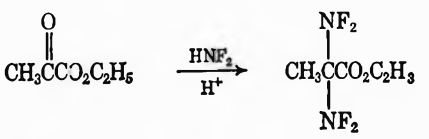
to replace the other alkoxy groups with difluoramine failed.

Formaldehyde reacts with difluoramine in concentrated sulfuric acid to yield α,α'-bis(difluoramino)-methyl ether (**7**),[12] but in 100% sulfuric acid it is converted into bis(difluoramino)methane (**8**). Treatment of difluoraminomethanol (**9**)[6] with difluoramine in concentrated sulfuric acid also produced the ether **7** (Scheme III).

Scheme III



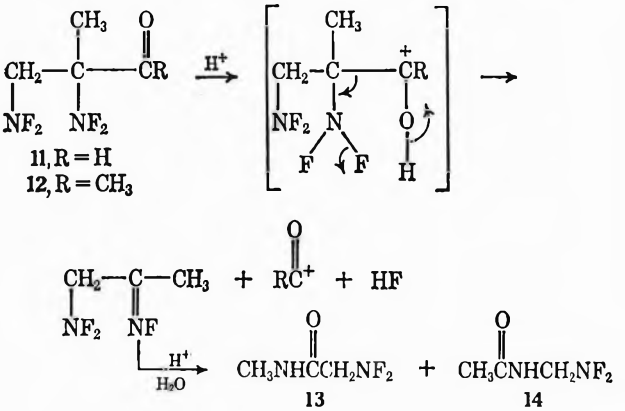
In general, negatively substituted carbonyl compounds were more resistant into conversion into the *gem*-difluoramine. Efforts to convert biacetyl or glyoxal into tetrakis(difluoramines) were completely unsuccessful. However, it was possible to convert ethyl pyruvate into ethyl α,α-bis(difluoramino)propionate (**10**).



(8) K. Baum, *J. Amer. Chem. Soc.*, **90**, 7083 (1968).
(9) H. H. Wasserman and P. S. Wharton, *ibid.*, **82**, 661 (1960).
(10) R. C. Petry and J. P. Freeman, *ibid.*, **83**, 3912 (1961).
(11) See Table I, footnote *a*.
(12) S. F. Reed, Jr., and R. C. Petry, *Tetrahedron*, **24**, 5089 (1968).

Part of the problem with α-dicarbonyl compounds appears to be related to the instability of α-difluoramino carbonyl compounds in acid. Thus, 2,3-bis-(difluoramino)-2-methylpropionaldehyde (**11**) and 1,2-bis(difluoramino)-2-methyl-3-butanone (**12**) decomposed in a mixture of difluoramine and sulfuric acid to a mixture of amides **13** and **14**. Carbon monoxide was identified as another decomposition product of aldehyde **11**. It is believed that their products arise according to Scheme IV. Beckmann rearrangements

SCHEME IV

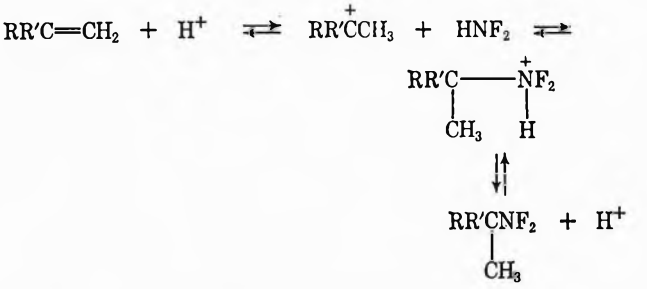


of fluorimines have been observed frequently in sulfuric acid.[13] This fragmentation appears to be chemically related to the instability of vinyl difluoramines[14,15] and of α-difluoraminosilanes.[16] In all these cases a difluoramino group is attached to a carbon atom adjacent to an atom with an available bonding orbital (sp^2 carbon and sp^3d^0 silicon).

Discussion

All of these alkylation reactions can be explained in terms of carbonium ion theory. The type of acid catalyst required directly reflected the stability of the carbonium ion intermediate. For example, among the olefins examined the order of reactivity found was vinyl ethers > vinyl esters > 1,1-dialkylethylenes. No added acid was necessary with the vinyl ethers, a sulfonic acid ion-exchange resin functioned for the esters, and concentrated sulfuric acid was required for the ethylenes. It appeared that some olefins yielded too stable carbonium ions while others were not stable enough. Thus, no difluoramines were obtained in this study from styrenes of *sym*-dialkylethylenes nor from simple olefins like propylene and cyclohexene under the same conditions that isobutylene reacted rapidly.

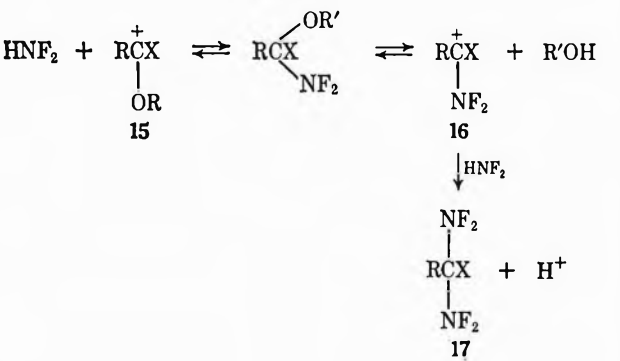
These reactions can be understood in terms of the equilibria involved. At high acid concentrations there will be a high concentration of carbonium ion. Since difluoramine must be a very weak nucleophile, the carbonium ion must be electrophilic enough to drive the reaction to product. If the ion is a stable one [*e.g.*, $(RO)_2CH^+$, $(C_6H_5)_2C^+CH_3$], very little difluoramino compound is produced, because in strong acid the reverse



reaction is favored; upon dilution of the reaction mixture with water difluoramine is recovered. If the carbonium ion is too reactive [*e.g.*, $(CH_3)_2CH^+$, $CH_3CH_2^+$], it will react with olefin or solvent and little if any difluoramino compound is found.

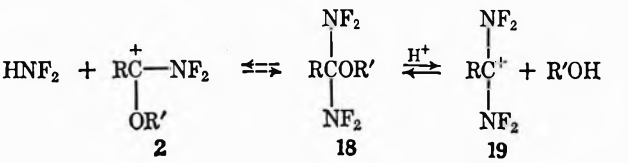
The behavior of α-alkoxydifluoramines is of particular interest. The monoalkoxy compounds react to produce *gem*-difluoramines, but dialkoxy derivatives liberate difluoramine in strong acid. These results may be understood as shown in Scheme V. Undoubtedly, when

SCHEME V



X = H or alkyl, ion **15** is more stable than ion **16** but no reaction occurs that removes ion **15** from the reaction scene. On the other hand, ion **16** is siphoned off to the *gem*-difluoramine by reaction with HNF_2. The *gem*-difluoramines are generally insoluble in sulfuric acid and separate as an insoluble layer which displaces the equilibrium. The position of equilibrium is also affected by the relatively greater basicity of the alcohol than of difluoramine. When the alcohol is tied up as an oxonium salt, reversal of the ionization of the α-alkoxydifluoramine is prevented.

However, when X = OR′, the chemistry of the whole system changes. The stability of ion **15** becomes extremely high and the equilibrium is displaced far to the left. In addition, the *gem*-difluoramine **17** is no longer acid insoluble because of the presence of the ether function and it is no longer removed from the reaction zone.[17,18] While, in principle, ionization of a compound such as **18** to ion **19** is possible, in fact, no



(13) T. E. Stevens, *Tetrahedron Lett.*, 3017 (1967).

(14) R. C. Petry, C. O. Parker, F. A. Johnson, T. E. Stevens, and J. P. Freeman, *J. Org. Chem.*, **32**, 1534 (1967).

(15) W. H. Graham, Abstracts of Papers, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(16) R. C. Petry and J. P. Freeman, *J. Org. Chem.*, **32**, 4026 (1967).

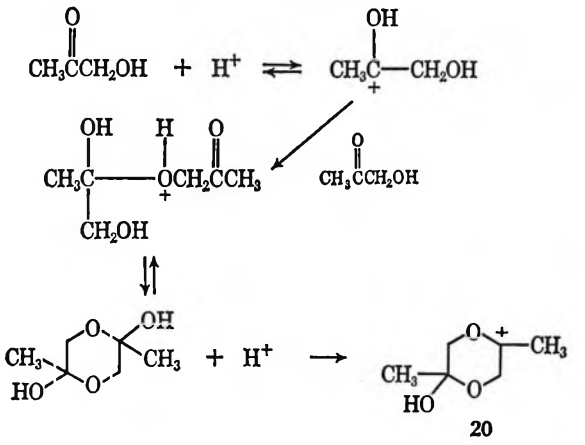
(17) Removal of the difluoramino product from the acid solution has important practical implications also since organic difluoramines are decomposed through nitrogen–fluorine bond cleavage in strong acids.

(18) K. Baum and H. M. Nelson, *J. Amer. Chem. Soc.*, **88**, 4459 (1966).

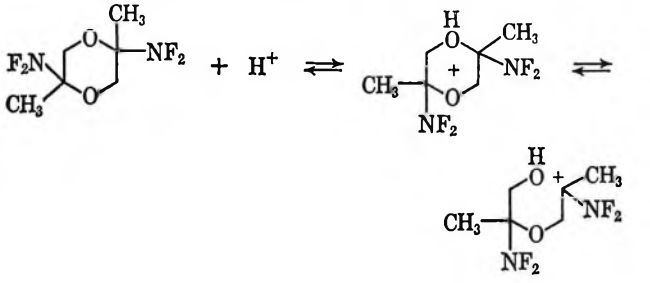
products derived from such an ion have ever been obtained, regardless of the acid strength or difluoramine concentration. The relatively greater stability of ion **2** over ion **19** favors the reverse reaction.

The other observations on reactivity appear to be consistent with these generalizations. The cyclizations of hydroxyacetone, acetonylacetone, and levulinic acid are due to the fact that groups like hydroxyl and carbonyl are more nucleophilic than difluoramine and react more rapidly with the carbonium ion. Probably more important is the fact that these cyclization reactions yield more stable carbonium ions. For example, the reaction of hydroxyacetone in acid may be viewed according to Scheme VI. Carbonium ion **20** is appar-

SCHEME VI



ently a more stable ion than the simple protonated carbonyl compound. It may in turn now react with difluoramine to give the final product **1**.[19] Probably



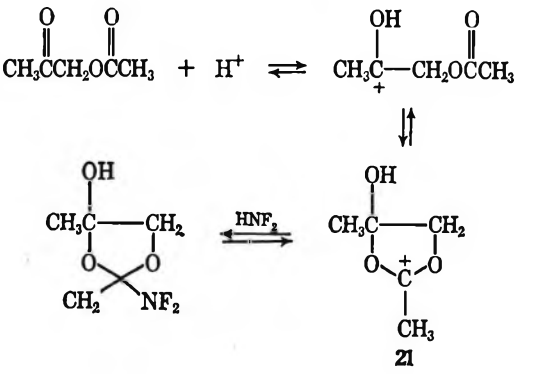
the reason that acetoxyacetone yields no product is due to the great stability of the cyclized carbonium ion, **21** (Scheme VII). There is little driving force for reaction of this ion with difluoramine. Again, the difluoramino product, being still highly oxygenated, cannot separate from the acid as an insoluble layer.

Consistent with this hypothesis is the fact that α-trifluoroacetoxyacetone can be converted into 2,2-bis-(difluoramino)propyl trifluoroacetate (**22**) by HNF_2–H_2SO_4. In this case the cyclized carbonium ion is destabilized by the trifluoromethyl group and the unfavorable equilibrium present in the acetate is displaced (Scheme VIII).

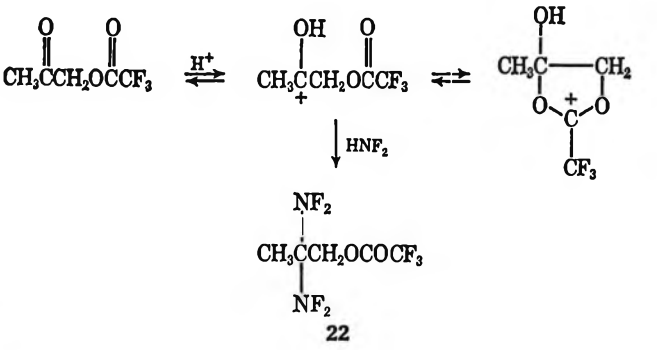
These reactions are very sensitive to acid strength. Many reactions that could not be accomplished in concentrated sulfuric acid proceed quite smoothly in

(19) Since α-difluoramino ethers can be cleaved by HNF_2–H_2SO_4, it might at first be surprising that further reaction does not occur with ether **1**. Apparently, the equilibrium is very unfavorable in this case because of ease of cyclization.

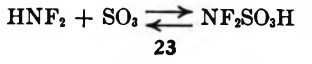
SCHEME VII



SCHEME VIII



15% fuming sulfuric acid or with sulfur trioxide itself. Fluorosulfonic acid also proved to be a very useful catalyst. The effectiveness of sulfur trioxide (Sulfan B) is in part due to its reaction with difluoramine to produce difluoraminosulfonic acid (**23**).[20] While this



compound is not very stable, it serves as a very powerful acid catalyst in its own right and as a source of solubilized difluoramine.[21] The stronger acids also serve, of course, to produce carbonium ions from more highly electronegatively substituted substrates.

A typical example of the effect of acid strength may be seen in the formaldehyde–HNF_2 reaction. In concentrated sulfuric acid the ion $NF_2CH_2^+$ is probably not produced in any reasonable concentration or is immediately trapped by water or formaldehyde which are better nucleophiles than difluoramine. In stronger acid where the better nucleophiles are probable completely protonated this ion is produced and finds only difluoramine to react with.

Experimental Section

Safety Precautions.—It should be recalled that difluoramine is highly explosive in the condensed state and particularly during melting.[22] While a −130° bath (methylcyclohexane) has been used successfully as indicated in the experiments described, a −117° bath (80% Freon 11–20% CCl_2=CHCl) proved to be more reliable and is recommended.

(20) W. H. Graham, unpublished results.

(21) Difluoramine is not particularly soluble in concentrated sulfuric acid and there was no evidence for its extensive protonation in this solvent. Little remains in solution unless an atmosphere of difluoramine is maintained above the solvent.

(22) J. P. Freeman, A. Kennedy, and C. B. Colburn, *J. Amer. Chem. Soc.*, **82**, 5304 (1960).

Olefin Addition Reactions.—Three techniques were used: (1) a mixture of the olefin and difluoramine alone; (2) a mixture of difluoramine and olefin with a small amount of Amberlyst 15 resin added; and (3) a mixture of difluoramine and olefin in sulfuric acid as solvent. In some early experiments these reactions were carried out at subatmospheric pressures in U tubes on a vacuum line. Later it was found convenient to use pressure reactors equipped with a magnetic stirring bar and a Fischer–Porter Teflon pressure valve. These reactors have been described.[23] Typical examples of these techniques will be given.

Addition of Difluoramine to Dihydropyran.—Into a U tube containing a magnetic stirring bar and manometer (total volume 260 ml) attached to a vacuum line was placed 0.42 g (0.005 mol) of dihydropyran. The sample was degassed by alternate freeze–thaw cycles; 224 cc (STP) (0.010 mol) of difluoramine was condensed into the tube by means of a −130° slush bath. The mixture was warmed to ambient temperature and stirred overnight. The pressure had dropped from a maximum of 430 mm to 120 mm during this time. Fractionation of the mixture through traps at −80 and −130° gave 40 cc (STP) of recovered HNF_2 in the −130° trap. The −80° trap contained the liquid product. Vpc analysis showed essentially no starting material and only one major product peak. (See Table I for characterization.)

Addition of Difluoramine to Isopropenyl Acetate.—A heavy-walled 10-ml Pyrex tube[22] fitted with a Fischer–Porter Teflon needle valve, a ball joint for attachment to the vacuum line, and a magnetic stirring bar was charged with 0.40 g (0.004 mol) of isopropenyl acetate and approximately 0.05 g of Amberlyst 15 catalyst. The tube was degassed in the vacuum line by alternate freeze–thaw cycles and 132 cc (0.004 mol) of HNF_2 was condensed into the tube at −130°. The valve was closed and the contents were warmed to ambient temperature and stirred for 1 hr. The reaction mixture was fractionated through traps at −80 and −130°. Essentially no difluoramine was recovered in the −130° trap. The product, 2-difluoramino-2-propyl acetate, was obtained in quantitative yield in the −80° trap as a water-white liquid. (See Table I.)

Addition of Difluoramine to Isobutylene.—A 100-ml U tube containing 10 ml of concentrated sulfuric acid was degassed and 67 cc (0.003 mol) of difluoramine was condensed in at −130°. The mixture was allowed to warm to room temperature and stirred for 15 min. The contents of the U tube were distilled through traps at −80, −130, and −196°. The liquid in the −80° trap was identified as *t*-butyldifluoramine by its mass spectrum and by comparison of its infrared spectrum with that of an authentic sample.[11]

Acrolein and HNF_2.—A heavy-walled Pyrex tube equipped with a Teflon needle valve and a magnetic stirrer was loaded with 0.26 g (0.004 mol) of degassed acrolein and 264 cc (0.0118 mol) of difluoramine at −130°. The mixture was allowed to warm to room temperature and was stirred for 2.5 hr. The contents were then distilled on a vacuum line through traps at −24, −80, and −130°.

1,3-Bis(difluoramino)propanol had a vapor pressure of 10 mm at −24°.

Anal. Calcd for $C_3H_6F_4N_2O$: C, 22.37; H, 3.13; N, 17.38; F, 47.18. Found: C, 23.06; H, 4.35; N, 17.33; F, 47.04.

Its infrared spectrum showed a strong band in the OH region and no band attributable to a carbonyl group. Its ^{19}F nmr spectrum consisted of a triplet at ϕ −52.8, J_{HF} = 27 cps (CH_2NF_2); the secondary NF_2 group is the AB portion of an ABX pattern, F_A at ϕ −25.6, F_B at ϕ −21.2, J_{AB} = 602 cps, J_{AX} = 10 cps, J_{BX} = 30 cps [$CH(NF_2)OH$].

Preparation of 2,2-Bis(difluoramino)propane.—The procedure used for the isobutylene–HNF_2 reaction was followed using 1.0 ml of 100% sulfuric acid, 0.3 g (0.002 mol) of 2-difluoramino-2-propyl acetate (Table I), and 124 cc (0.0055 mol) of difluoramine. The mixture was stirred for 1.5 hr and then distilled on a vacuum line. The recovered difluoramine amounted to 0.0039 mol. The product, 2,2-bis(difluoramino)propane, was retained in a −80° bath and was identified by comparison of its infrared and nmr spectra with those of an authentic sample,[8] yield 0.001 mol (50%).

Preparation of 2,2-Bis(difluoramino)propanol.—Acetonyl trifluoroacetate was prepared by adding 37 g (0.5 mol) of hydroacetone to 125 g (0.6 mol) of trifluoroacetic anhydride at 10°. The mixture was stirred at room temperature for 30 min and then refluxed for 30 min. The excess trifluoroacetic anhydride was removed by distillation and the ester, bp 45° (170 mm), was obtained in 72% yield.

A mixture of 5 ml of concentrated sulfuric acid and 5 ml of 30% fuming sulfuric acid was placed on a 1-l. round-bottomed flask containing a magnetic stirrer and cooled to −80°. Acetonyl trifluoroacetate, 2.0 g (0.012 mol), was added and the resulting solution was degassed thoroughly. Difluoramine (500 cc) was condensed in at −80° and the mixture was stirred at room temperature for 3.5 hr. It was then distilled through a trap at −63° which retained the 2,2-tris(difluoramino)propyl trifluoroacetate, which was further purified by distillation, bp 52° (30 mm), yield 1.1 g (40%).

The trifluoroacetate was added to 3 ml of methanol and heated until all the methyl trifluoroacetate had distilled. The residue was distilled through traps at −25 and −80°. Several distillations of this type freed the product of methanol at which time it crystallized in the −25° trap. 2,2-Bis(difluoramino)propanol was obtained as a water-white liquid.

Anal. Calcd for $C_3H_6F_4N_2O$: C, 22.22; H, 2.73; N, 17.28; F, 46.89. Found: C, 22.61; H, 4.22; N, 16.60; F, 45.1.

Its ^{19}F nmr spectrum showed a singlet at ϕ −26.8. Its ^1H spectrum consisted of a pentuplet at τ 8.33 [$CH_3C(NF_2)_2$], a sharp singlet at τ 6.56 (OH), and a pentuplet at τ 5.9 [$(NF_2)_2$-CCH_2–].

Paraformaldehyde and Difluoramine. A. Sulfuric Acid Catalyst.—A solution of 0.12 g (0.004 mol) of concentrated sulfuric acid in a 100-ml U tube on a vacuum line was degassed and 224 cc (0.01 mol) of difluoramine was condensed in at −130°. The mixture was warmed to room temperature and stirred there overnight. The mixture was then distilled through traps at −80, −130, and −196°. The product in the −80° trap was identified as α,α'-bis(difluoraminomethyl) ether by comparison of its infrared spectrum with that of an authentic sample.[18,24]

B. 100% Sulfuric Acid Catalyst.—Into an evacuated U tube equipped with magnetic stirring bar and manometer (total volume of 250 ml) and containing 10 ml of 100% sulfuric acid and 0.3 g (0.01 mol) of paraformaldehyde was condensed 448 cc (0.02 mol) of HNF_2 by means of a −130° methylcyclohexane slush bath. The mixture was stirred for 3 hr at room temperature at which time the pressure was steady at 455 mm. A mass spectrum at this point indicated that about 90% of the vapor phase was bis(difluoramino)methane. This would indicate a yield of at least 60%. When the product was fractionated through −80, −130, and −196° traps, the bulk of the product was held up in the −80° trap but some reached the −130° methyl cyclohexane slush trap. A small amount of bis(difluoraminomethyl) ether was also retained in the −80° trap. The complete separation of bis(difluoramino)methane from the ether and difluoramine was accomplished by stirring the mixture over fuming sulfuric acid (to remove HNF_2), removing the volatile contents, and stirring them over water (to remove SO_3), and removing the water over concentrated sulfuric acid.

Bis(difluoramino)methane is a colorless liquid with a vapor pressure of 690 mm at 28°. Its ^{19}F nmr spectrum showed a broad singlet at ϕ −43.4; its proton spectrum consisted of a pentuplet centered at τ 4.7 (J = 22 cps). Its mass spectrum showed no parent molecular ion but major peaks at m/e of 66 ($CH_2NF_2^+$), 47 (CH_2NF^+), 47 ($CHNF^+$), 28 (CH_2N^+), and 27 (CHN^+). Because of its highly explosive and volatile nature no attempt to obtain an elemental analysis was made.

Preparation of Ethyl α,α-Bis(difluoramino)propionate.—Ethyl α-difluoramino-α-hydroxypropionate[5] (2.15 g, 12.7 mol) was placed in a 25-ml pressure bulb equipped with a magnetic stirring rod and a Fischer–Porter needle valve.[22] The bulb was cooled to −80° and 4.5 g of 27% fuming sulfuric acid (which contained 15.2 mmol of free SO_3) was pipetted through the valve opening. The bulb was attached to vacuum line and evacuated, and 20 mmol of HNF_2 condensed into it at −130°. The bulb was then allowed to warm to room temperature and the contents were stirred overnight. The bulb was cooled again to −80° and excess HNF_2 (90 cc, STP) was removed by distillation. The pressure bulb was opened and the residual liquid transferred to a round-bottomed flask and distilled through a −80° trap. The contents of this trap were distilled again under vacuum at room temperature giving ethyl α,α-bis(difluoramino)propionate retained at −40° with vapor pressure of 4.0 mm at 0°: yield 1.60 g (61.7%). The product was dissolved in Freon 11, extracted

(23) R. P. Rhodes, *J. Chem. Educ.*, **40**, 423 (1963).

(24) M. J. Cziesla, K. F. Mueller, and O. Jones, *Tetrahedron Lett.*, 3683 (1964).

with ice water until the washes were neutral, dried, and reisolated by retention at −40° during vacuum transfer, thereby removing acidic impurities.

Anal. Calcd for $C_5H_3F_4N_2O_2$: C, 29.41; H, 3.92; N, 13.73; F, 37.25. Found: C, 29.51; H, 4.75; N, 14.04; F. 36.92.

The ^{19}F nmr spectrum consisted of a very strong line at ϕ −13 flanked at ±630 cps by two weak lines. The spectrum was interpreted as an AA′BB′X$_3$ type with $J_{AB} = J_{A'B'} = 630$ cps. Coupling of all fluorine with the methyl group is visible in the proton spectrum with $J_{AX} \sim 2.5$ cps.

Registry No.—Difluoramine, 10405-27-3; 2,2-bis(difluoramino)propanol, 20122-29-6; bis(difluoramino)methane, 18338-50-6; ethyl α,α-bis(difluoroamino)propionate, 20122-31-0.

General Base Catalyzed Hydrolysis of N,N′-Dimethyl-N,N′-diphenylamidinium Salts

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The hydrolyses of N,N′-dimethyl-N,N′-diphenylformamidinium, -acetamidinium, and -benzamidinium salts in aqueous solutions are general base catalyzed, with Brønsted catalysis law β values near 0.4. Hydroxide ion catalyzed hydrolysis of tetrasubstituted amidinium salts is characterized by large negative entropies of activation and by kinetic solvent isotope effects, k_{H_2O}/k_{D_2O}, less than unity. Base-catalyzed hydrolysis of amidinium cations is slowed by bulky acyl substituents, and hydrolysis of substituted benzamidinium cations is accelerated by electron-attracting aryl substituents ($\rho = 1.6$). Hydroxide ion catalyzed hydrolysis of the formamidinium and benzamidinium salts is approximately first order in hydroxide ion concentration. The rate of hydrolysis of the acetamidinium salt tends to become independent of hydroxide ion concentration at high hydroxide ion concentrations, possibly due to reversible formation of a ketene aminal. All of these observations are satisfactorily accounted for by a mechanism involving rate-limiting general base catalyzed conversion of a tetrahedral hydrate of the amidinium cation into N-methylaniline and an N-methylanilide.

Hydrolysis reactions of N,N′-diarylformamidines and N,N′-diarylacetamidines in acidic solutions are characterized by large positive Hammett ρ values, large negative entropies of activation, and rates which are directly proportional to the hydrogen ion concentration and water activity, and inversely proportional to the acidity (h_0) of the reaction solutions. The diarylformamidines are about a thousand times more reactive than the diarylacetamidines in aqueous 20% dioxane hydrochloric acid solutions.[2-4] Hydrolysis of N,N′-diarylformamidinium ions is general base catalyzed, with a Brønsted catalysis law β value of 0.3.[2,3] These observations are consistent with a mechanism involving rate-limiting general base catalyzed conversion of a protonated tetrahedral intermediate into products (eq 1).[3,5]

$$\mathrm{ArN{=}CR{-}NHAr + H_3O^+ \rightleftharpoons ArN\overset{+}{H}_2{-}\underset{\displaystyle R}{\overset{\displaystyle OH}{\overset{|}{C}}}{-}NHAr \xrightarrow{B:}}$$
$$\mathrm{ArNH_2 + RCONHAr + BH^+} \quad (1)$$

The kinetics of hydrolysis of N,N′-diarylformamidines under alkaline conditions is complex.[6] The rate of hydrolysis of formamidines having electron-releasing N-aryl substituents is nearly independent of hydroxide ion concentration and the structure of the aryl groups. Amidines having electron-withdrawing aryl substituents undergo hydrolysis by two processes, one which is independent of hydroxide ion concentration, and another whose rate is a nonlinear function of hydroxide ion concentration. Hydroxide ion catalyzed hydrolysis of N,N′-diarylformamidines probably involves rate-limiting reaction of a tetrahedral hydrate of the amidine with hydroxide ion, complicated by a side equilibrium between the amidine and an unreactive conjugate base (eq 2).

$$\mathrm{ArN{=}CH{-}NHAr + OH^- \rightleftharpoons ArN{\cdots}\bar{C}H{\cdots}NAr + H_2O}$$
$$\mathrm{ArN{=}CH{-}NHAr + H_2O \rightleftharpoons ArNH{-}CH(OH){-}NHAr \xrightarrow{OH^-}}$$
$$\mathrm{ArNHCHO + ArNH^- + H_2O} \quad (2)$$
$$\mathrm{ArNH^- + H_2O \rightleftharpoons ArNH_2 + OH^-}$$

The hydroxide-independent reaction is best rationalized in terms of rate-limiting reaction of the hydrated conjugate acid of the amidine with hydroxide ion (eq 1).

Alkaline hydrolysis of N,N′-disubstituted amidines is complicated by the existence of pH-dependent equilibria between the free amidines, their conjugate acids, and their conjugate bases. The amidinium ions are the more interesting of these three species, since they are implicated as intermediates under both acid and alkaline conditions.

Accordingly, we selected a series of N,N′-dimethyl-N,N′-diphenylamidinium cations, $C_6H_5N(CH_3){\cdots}\overset{+}{C}R{\cdots}N(CH_3)C_6H_5$, as substrates for a study of solvent, salt, and substituent effects on amidinium ion hydrolysis. These tetrasubstituted amidinium ions are isoelectronic with the conjugate acids of N,N′-disubstituted amidines, but possess no acidic proton.

Experimental Section

Preparation of Amidinium Salts.—N,N′-Dimethyl-N,N′-diphenylformamidinium tetrafluoroborate was prepared by adding 10 g of N,N′,N″-trimethyl-N,N′,N″-triphenyl orthoformamide[7] to 90 ml of 12% fluoroboric acid, heating the mixture on a steam bath until the orthoamide dissolved, adding 200 ml of water, and

(1) Taken from the M.A. Thesis of M. W. C.

(2) R. H. DeWolfe and R. M. Roberts, *J. Amer. Chem. Soc.*, **75**, 2942 (1953).

(3) R. H. DeWolfe, *ibid.*, **82**, 1581 (1960).

(4) R. H. DeWolfe and J. R. Keefe, *J. Org. Chem.*, **27**, 493 (1962).

(5) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4971 (1961).

(6) R. H. DeWolfe, *ibid.*, **86**, 864 (1964).

(7) D. H. Clemens, E. Y. Shropshire, and W. D. Emmons, *J. Org. Chem.*, **28**, 1108 (1963).

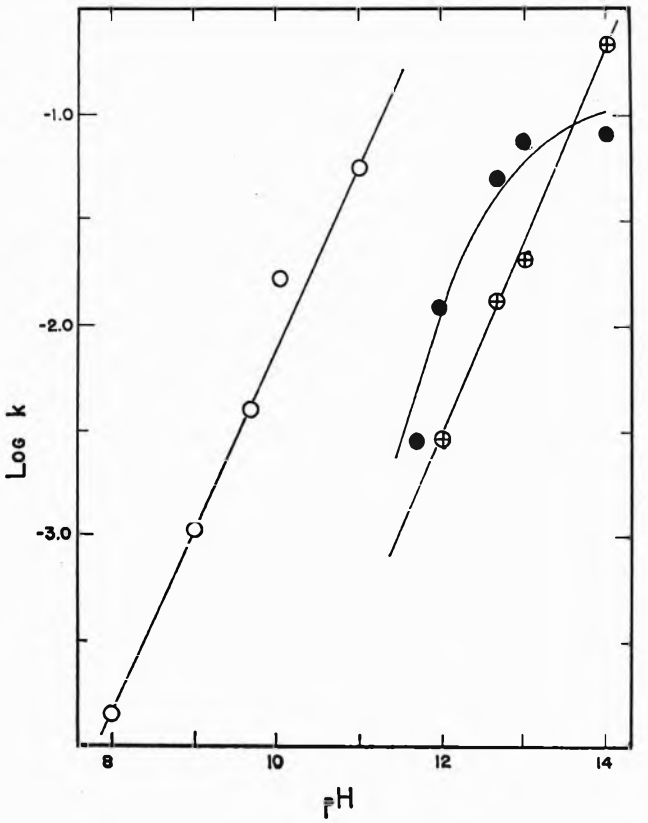

Figure 1.—Log k *vs.* pH for hydrolysis of tetrasubstituted amidinium salts in aqueous solutions at 30°: open circles, N,N′-dimethyl-N,N′-diphenylformamidinium fluoborate; filled circles, N,N′-dimethyl-N,N′-diphenylacetamidiniumperchlorate; crossed circles, N,N′-dimethyl-N,N′-diphenylbenzamidinium perchlorate.

cooling the resulting solution in an ice bath. The crude product (10.2 g), collected by suction filtration, was recrystallized from dichloromethane–carbon tetrachloride: mp 110–113° (lit.[7] mp 115–117°).

N,N′-Dimethyl-N,N′-diphenylacetamidinium perchlorate was prepared by the procedure of Jutz and Amschler.[8] A similar procedure was used for the preparation of a series of N,N′-dimethyl-N,N′-diphenylbenzamidinium perchlorates. The appropriate benzoic acid (0.075 mol) and 32.1 g (0.3 mol) of N-methylaniline were added slowly at 0° to 30.6 g (0.2 mol) of phosphorus oxychloride. The reaction mixture was heated at a temperature between 130 and 160° for 2 hr, and 200 ml of ice-cold 17% sodium perchlorate solution was added to the cooled, syrupy mixture. The solid N,N′-dimethyl-N,N′-diphenylbenzamidinium perchlorates were recrystallized from 95% ethanol. Yields ranged from 70 to 90%. Meltingpoints and ultraviolet absorption maxima and minima of aqueous solutions of the amidinium perchlorates are summarized in Table I.

Table I

N,N′-Dimethyl-N,N′-Diphenylamidinium Perchlorates, $R-\overset{+}{C}[N(CH_3)C_6H_5]_2ClO_4^-$

R	Registry No.	λ_{max}, mμ	λ_{min}, mμ	Mp, °C Obsd	Mp, °C Lit.[8]
CH_3	20449-29-0	255	230	155–158	167–168
C_6H_5	20449-30-3	280	255	208–212	216–217
p-$CH_3C_6H_4$	20449-31-4	285	247	218–223	225–226
m-$CH_3C_6H_4$	20449-32-5	282	245	110–116	...
p-ClC_6H_4	20449-33-6	287	245	160–163	165–166
m-ClC_6H_4	20449-26-7	285	255	120–125	...
p-$NO_2C_6H_4$	20449-27-8	293	250	199–200	199–200
p-$CH_3OC_6H_4$	20449-28-9	325	250	173–174	...

Solutions for Kinetic Runs.—Sodium hydroxide solutions which were 1.0, 0.1, 0.05, 0.01, and 0.005 N in NaOH were prepared by diluting British Drug House Ltd. standardized solutions with boiled distilled water. A series of solutions which were 0.005 N in NaOH and 0.05, 0.025, 0.01, and 0.005 N in NaCl were prepared similarly from standardized NaOH solutions and reagent grade sodium chloride.

Buffer solutions were prepared by the procedure of Perrin,[9] using n-butylamine [bp 76–78° (760 mm)] from Matheson Coleman and Bell, standardized hydrochloric acid solutions from British Drug House Ltd. reagent grade sodium carbonate monohydrate from Allied Chemical Corp., sodium bicarbonate from Hoyt Brothers, and reagent grade borax and boric acid from Mallinckrodt Chemical Works. n-Butylamine–butylammonium chloride, sodium carbonate–sodium bicarbonate, and borax–boric acid buffers were used for rate determinations at pH 10.85, 10, and 9 respectively. The ionic strength of all of these solutions was adjusted to 0.01 with sodium chloride.

Kinetic Measurements.—Hydrolysis rates were determined spectrophotometrically by measuring the decrease in absorbance as the amidinium salt hydrolyzed. Reactions having first-order rate constants larger than 3×10^{-5} sec^{-1} were followed using a Cary Model 14 spectrophotometer or a Gilford recording spectrophotometer, each of which was equipped with a thermostated cell compartment. Cell temperatures were regulated to within ± 0.05°. Reactions were started by adding stock solutions of the amidinium salts to 3 ml of the thermostated buffer solution by means of a microsyringe. Runs having first-order rate constants smaller than 3×10^{-5} sec^{-1} were carried out by spectrometric analysis of aliquots of reaction solutions which were kept in a thermostated water bath. The wavelength used in following a hydrolysis reaction was chosen so as to give a maximum change in absorbance.

Identification of Hydrolysis Products.—The hydrolysis products of N,N′-dimethyl-N,N′-di-p-nitrophenylformamidinium tetrafluoroborate in neutral solution were reported to be N-methyl-p-nitroaniline and N-methyl-p-nitroformanilide.[7] N-Methylacetanilide, mp 98–100° (lit.[10] mp 101°), was isolated from the products of hydrolysis of N,N′-dimethyl-N,N′-diphenylacetamidinium perchlorate in 4 N NaOH, and N-methyl-p-toluanilide, mp 68–69° (lit.[11] mp 70°), was isolated from the products of alkaline hydrolysis of N,N′-dimethyl-N,N′-diphenyl-p-toluamidinium perchlorate.

Calculations.—The hydrolysis reactions are kinetically first order under the conditions used. First-order rate constants, expressed in reciprocal seconds, were calculated from slopes of log $(A_t - A_\infty)$ *vs.* t plots, or by the Guggenheim method.[12] Arrhenius activation energies were calculated from slopes of log k *vs.* $1/T$ plots, and entropies of activation at 30° were calculated from the relation $\Delta S^{\pm} = 4.576 (\log k - 10.753 - \log T + E_a/4.576)$, where k is the rate constant at temperature T.[13]

Results

Variation of Hydrolysis Rate with Hydroxide Ion Concentration.—N,N′-Dimethyl-N,N′-diphenylformamidinium tetrafluoroborate, N,N′-dimethyl-N,N′-diphenylacetamidinium perchlorate, and N,N′-dimethyl-N,N′-diphenylbenzamidinium perchlorate were hydrolyzed in solutions of different hydroxide ion concentrations at 30°. The kinetic data are summarized in Table II and Figure 1.

The log k_{OH} *vs.* pH plots for hydrolysis of the formamidinium and acetamidinium salts are linear, with slopes of 0.85 and 0.96, respectively. The plot for the acetamidinium salt levels off at high hydroxide ion concentration. A possible explanation for this behavior is discussed below.

Buffer Catalysis.—Hydrolyses of N,N′-dimethyl-N,N′-diphenylformamidinium-, -acetamidinium, and -benzamidinium salts are general base catalyzed in

(8) C. Jutz and H. Amschler, *Chem. Ber.*, **97**, 2100 (1963).

(9) D. D. Perrin, *Australian J. Chem.*, **16**, 572 (1963).

(10) W. Staedel, *Ber.*, **12**, 1947 (1886).

(11) E. Lellmann and R. Just, *ibid.*, **24**, 2114 (1891).

(12) E. A. Guggenheim, *Phil. Mag.*, (7) **2**, 538 (1926).

(13) J. F. Bunnett in "Technique of Organic Chemistry: Investigation of Rates and Mechanisms of Reactions," Vol. III, 2nd ed, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p 601.

Table II

pH Dependence of Hydrolysis of N,N′-Dimethyl-N,N′-diphenylamidinium Salts at 30°

$HC[N(CH_3)C_6H_5]_2^+$

pH	8	9	9.7	10.3	11
$10^4 k$, sec^{-1} [a]	1.55	10.6	39.9	165	548

$CH_3C[N(CH_3)C_6H_5]_2^+$

pH	11.7	12	12.7	13	14
$10^4 k$, sec^{-1} [a]	28.1	123	513	763	796

$C_6H_5C[N(CH_3)C_6H_5]_2^+$

pH		12	12.7	13	14
$10^4 k$, sec^{-1} [a]		28.6	133	204	2140

[a] Hydroxide-catalyzed reaction.

butylamine, carbonate, and borate buffers. The rate equation for these reactions in buffer solutions is $k_{obsd} = k_0 + k_{OH}[OH^-] + \sum_i k_{B_i}[B_i]$. The rate of the spontaneous reaction is negligible in the buffers used in this study. Buffer base catalytic coefficients, k_B, obtained from slopes of plots of k_{obsd} *vs.* [B], are summarized in Table III.

Table III

Buffer Base Catalytic Coefficients for Hydrolysis of $RC[N(CH_3)C_6H_5]_2^+$ in Aqueous Buffers

R	Buffer base	Temp, °C	$10^2 k_B$, l./mol sec
H	$BuNH_2$	30	183
H	CO_3^{2-}	30	127
H	$B(OH)_4^-$	30	1.68
CH_3	$BuNH_2$	30	2.24
CH_3		40	2.79
CH_3		60	8.15
CH_3	CO_3^{2-}	30	1.83
CH_3	$B(OH)_4^-$	30	8.2×10^{-3}
C_6H_5	$BuNH_2$	30	0.783
C_6H_5		40	1.73
C_6H_5		50	2.45
C_6H_5		60	4.33
C_6H_5	CO_3^{2-}	30	0.559
C_6H_5	$B(OH)_4^-$	30	1.2×10^{-2}

Plots of $-pK_B$ *vs.* log k_B for hydroxide ion, butylamine, and carbonate ion catalyzed hydrolyses are linear, with slopes $\beta = 0.4$ for the formamidinium and acetamidinium salts and 0.35 for the benzamidinium salt. These β values are only approximate, owing to the small number of bases used.

Energies and Entropies of Activation.—Arrhenius activation energies and entropies of activation at 30° were calculated for hydroxide ion catalyzed hydrolysis of the formamidinium, acetamidinium, and benzamidinium salts, and for the *n*-butylamine catalyzed hydrolysis of the acetamidinium and benzamidinium salts. The catalytic coefficients, energies of activation, and entropies of activation are given in Table IV.

Substituent Effects.—Whether the catalyst is hydroxide ion, butylamine, or carbonate ion, N,N′-dimethyl-N,N′-diphenylformamidinium ion is much more reactive than N,N′-dimethyl-N,N′-diphenylacetamidinium ion, which is somewhat more reactive than N,N′-dimethyl-N,N′-diphenylbenzamidinium ion (see Table V).

Table VI lists hydrolysis rates of a series of *meta*- and *para*-substituted N,N′-dimethyl-N,N′-diphenylbenzamidinium salts in butylamine buffers ($[BuNH_2] = 0.0153\ M$, $[BuNH_3^+] = 0.0092\ M$) at 30°. The rate constants are composites of hydroxide and butylamine catalyzed terms in which the hydroxide term predominates. They give an excellent Hammett $\rho\sigma$ plot with $\rho = 1.57$ (Figure 2).

Table IV

Activation Parameters for Hydroxide Ion and Butylamine Catalyzed Hydrolysis of $RC[N(CH_3)C_6H_5]_2^+$

R	Temp, °C	k_B, l./mol sec	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu[a]
Hydroxide Ion Catalyzed Hydrolysis				
H	10	11.3		
			13.4	−8
H	30	54.8		
CH_3	30	0.562		
CH_3	40	1.19	11.7	−23
CH_3	50	1.83		
C_6H_5	30	0.122		
C_6H_5	40	0.288	15.8	−13
C_6H_5	50	0.622		
Butylamine Catalyzed Hydrolysis				
CH_3	30	0.0224		
CH_3	40	0.0279	9.0	−38
CH_3	60	0.0815		
C_6H_5	30	0.0078		
C_6H_5	40	0.0173		
C_6H_5	50	0.0245	11.0	−34
C_6H_5	60	0.0533		

[a] Calculated for 30°.

Table V

Relative Reactivities of $RC[N(CH_3)C_6H_5]_2^+$ at 30°

R	k_B	$k_{B(rel)}$
Hydroxide Ion Catalysis		
H	54.8	450
CH_3	0.562	4.60
C_6H_5	0.122	1.00
Butylamine Catalysis		
H	1.83	234
CH_3	2.24×10^{-2}	2.86
C_6H_5	7.83×10^{-3}	1.00
Carbonate Ion Catalysis		
H	1.27	227
CH_3	1.83×10^{-2}	3.27
C_6H_5	5.6×10^{-3}	1.00

Table VI

Rate Constants for Hydrolysis of $Y\text{-}C_6H_5C(NMeC_6H_5)_2^+ClO_4^-$ in $BuNH_3^+$–$BuNH_2$ Buffer Solutions (pH 10.85) at 30°

Y	σ[a]	$k \times 10^4$, sec^{-1}
p-NO_2	0.778	53.5
m-Cl	0.366	10.4
p-Cl	0.227	7.28
p-H	0.000	2.75
p-CH_3	−0.170	1.78
m-CH_3	−0.082	1.55
p-OCH_3	−0.268	1.21

[a] E. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, & Winston, Inc., New York, N. Y., 1959, p 221.

Salt Effects.—N,N′-Dimethyl-N,N′-diphenylacetamidinium perchlorate and N,N′-dimethyl-N,N′-diphenylbenzamidinium perchlorate were hydrolyzed

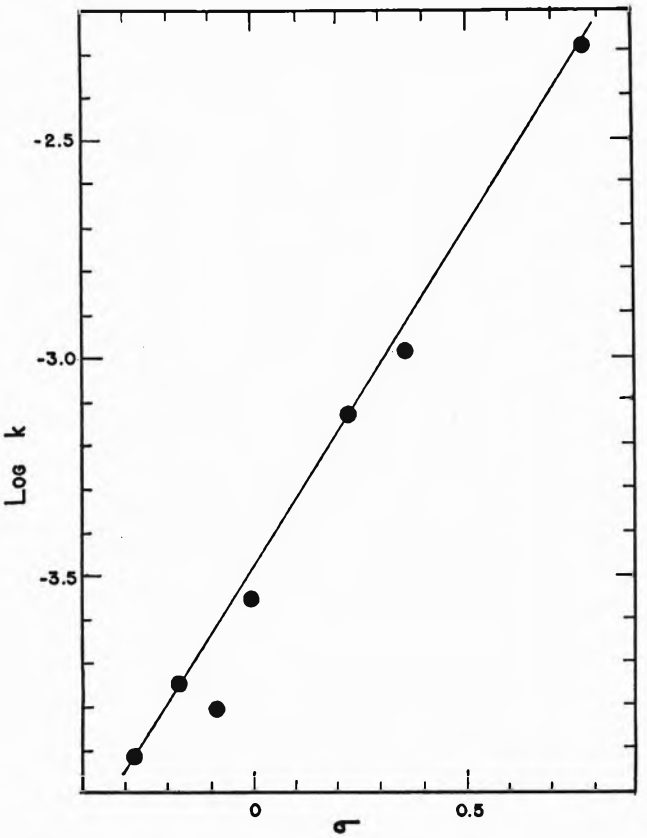

Figure 2.—Hammett $\rho\sigma$ plot for hydrolysis of N,N′-dimethyl-N,N′-diphenylbenzamidinium perchlorates in aqueous butylamine buffers at 30°.

at 30° in 0.005 *N* sodium hydroxide solutions which were 0.0025, 0.005, 0.01, 0.025, and 0.05 *N* in sodium chloride. For each compound the hydrolysis rates were the same within experimental error, and showed no systematic dependence upon ionic strength. These reactions show a negligible salt effect.

Solvent Isotope Effect.—The solvent isotope effect on hydrolysis of N,N′-dimethyl-N,N′-diphenylacetamidinium and -benzamidinium perchlorates is shown in Table VII.

Table VII

Solvent Isotope Effect on Hydrolysis of $RC[N(CH_3)C_6H_5]_2^+$ in Alkaline Solutions at 30°

R	[OH⁻]	$10^3k_{H_2O}$	$10^3k_{D_2O}$	k_{H_2O}/k_{D_2O}
CH_3	0.0152	21.4	26.9	0.79
C_6H_5	0.0115	3.42	6.06	0.56

Discussion

The experimental results described above show that hydrolysis of N,N,N′,N′-tetrasubstituted amidinium cations is general base catalyzed, with Brønsted catalysis law β values near 0.4. The hydrolysis reactions have large negative entropies of activation, are retarded by bulky acyl substituents, and are accelerated by electron-withdrawing groups on the acyl substituent. They exhibit negligible salt effects and are faster in deuterium oxide solutions than in protium oxide solutions.

A mechanism similar to that recently proposed by Jencks and Robinson[14,15] for the general base catalyzed hydrolysis of 1,3-diphenylimidazoliniu m chloride, a heterocyclic formamidinium salt, satisfactorily accounts for these experimental observations. This mechanism is outlined in eq 3.

$$C_6H_5N(CH_3)-\overset{+}{C}R-N(CH_3)C_6H_5 + OH^- \overset{K_1}{\rightleftharpoons} C_6H_5N(CH_3)-CR(OH)-N(CH_3)C_6H_5$$
$$\text{I}$$
$$\text{I} + H_2O \overset{K_2}{\rightleftharpoons} C_6H_5N(CH_3)-CR(OH)-\overset{+}{N}H(CH_3)C_6H_5 + OH^- \quad (3)$$
$$\text{II}$$
$$\text{II} + B: \xrightarrow[\text{slow}]{k_3} \left[C_6H_5N(CH_3)-CR(O)\cdots\overset{\delta+}{N}H(CH_3)C_6H_5 \cdots H\cdots\overset{\delta+}{B}\right] \longrightarrow C_6H_5N(CH_3)CRO + C_6H_5NHCH_3 + BH^+$$

Robinson[15] obtained experimental evidence for the formation of a tetrahedral intermediate analogous to I in the hydroxide ion catalyzed hydrolysis of 1,3-diphenylimidazolinium chloride, and Robinson and Jencks[14] presented convincing arguments that the rate-limiting step of the second-order portion of the reaction involves a general base catalyzed reaction of an intermediate analogous to II. Mechanism 3 requires that the reaction be first order in amidinium salt and catalyzing base, as observed for the formamidinium and benzamidinium salts.

Alkaline hydrolyses of the formamidinium and benzamidinium salts studied in this work differ from hydrolysis of the diphenylimidazolinium salt in one significant respect. Hydrolysis of the acyclic amidinium cations is first order in hydroxide ion up to pH 11 for the formamidinium salt and up to pH 14 for the benzamidinium salt (see Table II and Figure 1), whereas hydrolysis of the imidazolinium salt above pH 10 is largely due to a reaction which is second order in hydroxide ion.[14] This second-order hydroxide dependence was ascribed to a general acid catalyzed reaction of the conjugate base of the tetrahedral intermediate. The absence of terms second order in hydroxide ion for hydrolysis of the acyclic amidinium salts indicates that the tetrahedral intermediates II (R = H, C_6H_5) are substantially less acidic than 2-hydroxy-1,3-diphenylimidazolidine.

As shown in Figure 1, the rate of hydrolysis of N,N′-dimethyl-N,N′-diphenylacetamidinium ion levels off at high pH. This result may be due to reversible reaction of the acetamidinium ion with hydroxide to form a ketene aminal (eq 4). If reaction 4 is a parasitic side

$$CH_3\overset{+}{C}[N(CH_3)C_6H_5]_2 + OH^- \overset{K}{\rightleftharpoons} CH_2{=}C[N(CH_3)C_6H_5]_2 + H_2O \quad (4)$$

equilibrium, the observed rate constant would be $k_{obsd} = k_2[OH^-]/(1 + K[OH^-])$, where k_2 is the rate constant for reaction of the acetamidinium ion with

(14) D. R. Robinson and W. P. Jencks, *J. Amer. Chem. Soc.*, **89**, 7088 (1967).
(15) D. R. Robinson, *Tetrahedron Lett.*, 5007 (1968).

hydroxide ion and K is the equilibrium constant for ketene aminal formation. When $K[OH^-] \gg 1$, the experimental hydrolysis rate is independent of hydroxide ion concentration.

Ketene acetals are known to react rapidly with water under acidic conditions, but more slowly under neutral conditions.[16] It seems likely that ketene aminals may behave similarly. Obvious experimental tests of the validity of this proposal would be to isolate the ketene aminal from a reaction mixture, and to demonstrate that pre-synthesized ketene aminal hydrolyzes at the same rate as the acetamidinium salt.

N,N′-Dimethyl-N,N′-diphenylformamidinium, -acetamidinium and -benzamidinium salt hydrolyses all exhibit buffer catalysis, which we attribute to catalysis by the buffer bases (see Table III). Brønsted catalysis law plots of log K_b *vs.* log k_B for the hydroxide, butylamine, and carbonate ion catalyzed reactions are straight lines of slopes $\beta = 0.4$, 0.4, and 0.35 for hydrolysis of the formamidinium, acetamidinium, and benzamidinium salts, respectively. The points for borate catalysis fall below the lines defined by the other three catalysts. These admittedly imprecise β values are similar to the value of 0.44 observed for general base catalyzed hydrolysis of 1,3-diphenylimidazolinium chloride.[14]

The large negative entropies of activation observed for the hydroxide and butylamine catalyzed hydrolysis of the tetrasubstituted amidinium salts are consistent with the mechanism outlined in eq 3. The transition state for this mechanism is assembled from the amidinium ion, a water molecule, and the basic catalyst. A substantial decrease in entropy should accompany its formation from its components.

Reactions of nucleophiles with substances at the carboxyl level of oxidation are sensitive to both the steric and electronic properties of substituents on the acyl carbon, and amidinium ions are no exception. N,N′-Dimethyl-N,N′-diphenylformamidinium ion hydrolyzes much more rapidly than N,N′-dimethyl-N,N′-diphenylacetamidinium ion, which hydrolyzes somewhat more rapidly than N,N′-dimethyl-N,N′-diphenylbenzamidinium ion, whether the catalyst is hydroxide ion, *n*-butylamine, or carbonate ion (Table V). This reactivity sequence can be accounted for by considering the effects of acyl substituents on the free energy of activation for amidinium ion hydrolysis. The energy of activation is equal to the energy difference between the rate-limiting transition state and the amidinium ion, water molecule, and basic catalyst from which it is assembled (see eq 3). Structural features which stabilize the amidinium ion or destabilize the transition state will increase the free energy of activation; those which stabilize the transition state or destabilize the initial state reduce the energy of activation.

If the free energy of the formamidinium ion is selected as the reference point, replacing the formyl proton by a methyl group might be expected to stabilize the amidinium ion, which is a diaminocarbonium ion. The acyl methyl group will destabilize the nearly tetrahedral transition state by steric interaction with the two methylphenylamino groups, and slightly stabilize it by a charge–dipole interaction with the protonated nitrogen atom. The net result of stabilizing the initial state and destablizing the transition state is to make the acetamidinium ion less reactive than the formamidinium ion. If the acyl phenyl group of the benzamidinium ion can enter into resonance with the bismethylphenylaminocarbonium system, it should be even more effective than a methyl group in stabilizing the amidinium ion. It should destabilize the transition state both by steric interactions with the methylphenylamino groups and by charge–dipole interaction with the protonated nitrogen. All three of these interactions would increase the energy of activation relative to that for hydrolysis of the formamidinium ion. Since carbonium ion stabilization and steric bulk[17] are both predicted to be greater for the acyl phenyl than for the acyl methyl substituent, it is not surprising that the benzamidinium ion is less reactive than the acetamidinium ion. What is surprising is that the reactivity difference is so small. This small reactivity difference, together with the fact that substituents on the acyl phenyl group of substituted benzamidinium ions appear to influence reactivity by an inductive rather than a mesomeric process, suggests that acyl phenyl groups do not significantly stabilize amidinium ions by resonance. Inspection of molecular models indicates that this may be due to severe steric hindrance to formation of the coplanar conformation required for resonance between the acyl phenyl group and the carbonium system of the benzamidinium ion.

The rather imprecise Arrhenius activation energies and entropies of activation listed in Table IV suggest that differences in entropies of activation are more important than differences in enthalpies of activation in determining relative reactivities of amidinium ions toward base-catalyzed hydrolysis. The steric effect of acyl substituents appears to play an important role in determining the hydrolytic reactivity of N,N,N′,N′-tetrasubstituted amidinium salts. In contrast, the influence of acyl substituents on hydrolytic reactivity of N,N′-diarylformamidinium ions in acidic solution is due almost entirely to their effect on enthalpies of activation.[4] This is reasonable, since the transition states for hydrolysis of the N,N′-disubstituted amidinium ions should be relatively free of steric hindrance.

Comparison of reactivities of a series of *meta*-and *para*-substituted N,N′-dimethyl-N,N′-diphenylbenzamidinium salts, for which steric acyl substituent effects should be almost constant, permits evaluation of electronic effects of acyl substituents on reactivity (Table VI). The positive ρ value ($\rho = 1.57$) of a Hammett plot of these data (Figure 2) shows that electron withdrawal from the amidinium acyl carbon increases reactivity, as expected. (Electron-withdrawing substituents should raise the energy of the amidinium ion by their inductive effect more than they raise the energy of the transition state.) It is apparent from these data that resonance effects are relatively unimportant in determining reactivity of benzamidinium ions. If resonance interactions between the *p*-methyl and *p*-methoxy substituents and the acyl carbon of the amidinium ions significantly stabilized the cations, the *p*-toluamidinium and *p*-anisamidinium ions should be less reactive than would be predicted from a Hammett Plot drawn to fit the other substituents. This is

(16) S. M. McElvain, *Chem. Rev.*, **45**, 470 (1949).

(17) R. W. Taft, in M. S. Newman, "Steric Effects in Organic Chemistry", John Wiley & Sons, Inc., New York, N. Y., 1956, p. 601.

clearly not the case. Figure 2 shows also that the two *meta*-substituted benzamidinium salts are somewhat less reactive than predicted from the ρ value determined for the *para*-substituted compounds. This may be due to an appreciable steric effect of the *meta* substituents on this reaction.

Rates of hydroxide ion catalyzed hydrolysis of N,N′-dimethyl-N,N′-diphenylacetamidinium and -benzamidinium perchlorates were found not to be significantly influenced by the ionic strength of the reaction solutions in the range $\mu = 0.0075$ to $\mu = 0.055$. The two preequilibria of eq 3 should be influenced approximately equally but in opposite directions by changes in ionic strength of the medium, since the first involves ionic association and the second involves dissociation. In the rate-limiting step with hydroxide ion as a catalyst, there is a partial neutralization of charge, a process which should occur somewhat less readily at high than at low ionic strengths. The low Brønsted β value for the reaction indicates that proton transfer from the hydroxyl group of the tetrahedral intermediate to the catalyst is far from complete in the transition state, so that the charge distribution in the transition state is not greatly different from the charge distribution immediately preceding its formation. A large salt effect is therefore not anticipated, and is not observed.

The rate equation for hydroxide ion catalyzed hydrolysis of tetrasubstituted amidinium salts required by eq 3 is $k_{exp} = K_1K_2k_3[OH^-]$. The solvent deuterium isotope effect on the reaction is therefore a composite of the isotope effects on the two equilibria and the rate-limiting step of the reaction. That is,

$$k_{exp\,H}/k_{exp\,D} = (K_{1H}/K_{1D})\,(K_{2H}/K_{2D})\,(k_{3H}/k_{3D})\ (\text{if } [OH^-] = [OD^-])$$

The solvent isotope effects on the preequilibria and the rate-limiting step may be estimated by the method of Bunton and Shiner.[18,19] Application of this method yields $K_{1H}/K_{1D} = 0.65$, $K_{2H}/K_{2D} = 2.5$, and $k_{3H}/k_{3D} = 0.5$. The product of these three values is 0.8. This value, although only a rough approximation, is in reasonable agreement with experimental observation. $k_{exp\,H}/k_{exp\,D}$ was found to be 0.79 for N,N′-dimethyl-N,N′-diphenylacetamidinium perchlorate, and 0.56 for the analogous benzamidinium salt (see Table VII).

(18) C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, **83**, 42 (1961).
(19) C. A. Bunton and V. J. Shiner, *ibid.*, **83**, 3207 (1961).

Carbonium Ion Formation in Solvolysis of Phosphate Triesters

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The mechanisms of solvolysis of some triesters of phosphoric acid which might form carbonium ions have been investigated. Such a pathway is shown to be predominant in the solvolysis of tri-*t*-butyl and triisopropyl phosphates, but to be negligible in the case of triallyl phosphate. The solvolytic behavior of some five-membered cyclic tertiary alkyl esters is briefly discussed.

It has been known qualitatively for many years that triesters of phosphoric acid are hydrolyzed in basic solution rather readily to the corresponding diesters, but that subsequent stages of hydrolysis are relatively slow.[2] The behavior of trimethyl phosphate and of triphenyl phosphate, recently examined in detail by Barnard, Bunton, Llewellyn, Vernon, and Welch,[3] may probably be taken as characteristic of the reactions of the triesters of primary alcohols, phenols, and thiols with hydroxide ion.

The hydrolysis of trimethyl phosphate in aqueous base is first order in hydroxide ion and first order in the ester. Isotopic tracer experiments show that the phosphorus–oxygen bond is broken exclusively;[3,4] furthermore, within the limit of experimental error of the isotopic analysis, no isotopic exchange occurs prior to hydrolysis between the phosphoryl oxygen and the oxygen atoms of the solvent.[3] A small depression of rate is observed on changing the solvent from water to 75% dioxane–25% water. The few available data suggested that changes of neutral salt concentration do not noticeably affect the rate of saponification of the triesters. The hydrolysis of triphenyl phosphate in 75% dioxane–25% water was found also to be first order in both hydroxide ion and the ester.

The kinetic order of these hydrolyses, together with the position of bond fission, establishes that hydroxide ion attacks the phosphorus atom in the rate-controlling step of the sequence.

Corresponding data are very scanty for tertiary alcohol esters of phosphoric acid. The synthesis and qualitative observations concerning the hydrolysis of tri-*t*-butyl phosphate have been briefly reported.[5] The hydrolysis of mono-*t*-butyl phosphate has been studied in detail by Lapidot, Samuel, and Weiss-Broday;[6] the undissociated acid undergoes facile carbon–oxygen cleavage, with formation of the *t*-butyl carbonium ion. Evidence has been presented that the phosphate ester of the tertiary alcohol function of mevalonic acid pyrophosphate undergoes concerted decarboxylation and phosphate elimination to form isopentenyl pyrophosphate.[7]

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(2) G. Kosolapoff, "Organophosphorus Compounds," John Wiley & Sons, Inc., New York, N. Y., 1950.
(3) P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and J. A. Welch, *J. Chem. Soc.*, 2670 (1961).
(4) E. Blumenthal and J. B. M. Herbert, *Trans. Faraday Soc.*, **41**, 611 (1945).
(5) J. R. Cox, Jr., and F. H. Westheimer, *J. Amer. Chem. Soc.*, **80**, 5441 (1958).
(6) (a) A. Lapidot, D. Samuel, and M. Weiss-Broday, *J. Chem. Soc.*, 637 (1964); (b) L. Kugal and N. Halmann, *J. Org. Chem.*, **32**, 642 (1967).
(7) (a) G. Popjak and J. W. Cornforth, *Advan. Enzymol.*, **22**, 295 (1960); (b) C. A. Bunton and E. Humerer, *J. Org. Chem.*, **34**, 572 (1969).

In this paper we report the results of a study of the kinetics and mechanism of hydrolysis of tri-*t*-butyl phosphate, triisopropyl phosphate, and triallyl phosphate, and the synthesis and some studies of the hydrolysis of methyl pinacol phosphate and *t*-butyl pinacol phosphate.

Experimental Section

Materials.—Anhydrous pinacol (Fluka Chemical Co., purum) was dried by azeotropic distillation with benzene. After the benzene was removed, calcium hydride was added to the molten pinacol, and the pinacol was distilled *in vacuo* through a 2-ft Vigreux column.

Methanol and ethanol were dried by distillation from their magnesium salts[8] and stored in a tightly stoppered bottle.

Diethyl ether was dried over and distilled from lithium aluminum hydride immediately before use. Pentane, when used as a solvent in the chloridite preparation, was dried and stored over sodium metal wire.

Pyridine was boiled under reflux with calcium hydride, distilled, and stored over potassium hydroxide.

Triethylamine was dried by boiling under reflux with and distillation from BaO and then subjected to careful distillation through a 3-ft vacuum-jacketed column filled with glass helices. Cyclohexylamine was boiled under reflux with BaO and distilled.

Phosphorus trichloride was freshly distilled before its use in a reaction.

Dinitrogen tetroxide was synthesized by reaction of nitric oxide and oxygen. An evacuated gas manifold and an attached 12-l. flask were filled with nitric oxide to slightly less than 1-atm pressure. Oxygen was introduced into the system through another port in the manifold system. Oxygen was added until the pressure no longer decreased following its addition. One neck of a collection flask was attached to a part of the manifold system and another neck of the flask connected to a vacuum pump. The body of the flask was immersed in liquid nitrogen. The vacuum pump was started and the dinitrogen tetroxide collected and stored in the collection flask.

Other reagents were used without special purification. τ values in water are referred to DDS.

Tri-*t*-butyl Phosphite.—1.5 l. of petroleum ether (bp 30–60°) were placed in a 5-l., three-necked flask which was equipped with a dropping funnel, a mechanical stirrer, and a thermometer dipping below the surface of the petroleum ether. Triethylamine (315 g, 3.12 mol) and *t*-butyl alcohol (225 g, 3.04 mol) were then added to the flask. Stirring was begun and the flask and contents were cooled to below 0° (−10 to 0°) in an ice-salt mixture. Phosphorus trichloride (123 g, 0.895 mol) dissolved in 1 l. of petroleum ether was added dropwise to the cold mixture over a period of about 6 hr. During the addition of phosphorus trichloride, the temperature was maintained between −10° and 0°. After addition of phosphorus trichloride was complete, 1.5 l. of water was added to dissolve the precipitated amine hydrochloride. The aqueous layer was separated from the organic layer in a 6-l. separatory funnel. The organic phase, containing tri-*t*-butyl phosphite, was washed twice with approximately 500 ml of saturated aqueous sodium bicarbonate, then with about 500 ml of water. The organic layer was dried with anhydrous calcium chloride, and the petroleum ether solution was evaporated on a rotary evaporator under aspirator vacuum. After evaporation of the petroleum ether, about 220 g of crude tri-*t*-butyl phosphite was obtained.

The crude tri-*t*-butyl phosphite was distilled at 3-mm pressure, yielding approximately 160 g (71% of theory) of a liquid which boiled at 67–69°. Upon storage in a refrigerator, the liquid solidified (mp approximately 10°). An infrared spectrum of the material indicated *no* P–H stretch in the 4.5-μ region, and the nmr spectrum showed a single, sharp peak at τ 8.66 (neat liquid). The material was also converted in good yield to tri-*t*-butyl phosphate upon oxidation. Thus, the material was identified as pure tri-*t*-butyl phosphite. It is apparent that the difficulty encountered by previous workers (ref 17 and references therein) in distilling the product was occasioned by traces of acid, not by thermal instability of the compound.

(8) K. B. Wiberg, "Laboratory Techniques in Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1960, p 242.

Tri-*t*-butyl Phosphate.—Tri-*t*-butyl phosphite (50 g, 0.20 mol) dissolved in 100 ml of petroleum ether (bp 30–60°) in a 300-ml erlenmeyer flask was cooled in an ice bath. Dinitrogen tetroxide was passed into the cold mixture,[5] which was stirred on a magnetic stirrer. Addition of dinitrogen tetroxide was continued until the solution developed a green color (probably N_2O_3) or until unreacted NO_2 escaped from the reaction mixtures. The solution was washed with 100 ml of saturated sodium bicarbonate solution, then with water, and was dried over anhydrous calcium chloride. The dried solution was cooled in a Dry Ice–acetone bath, whereupon the tri-*t*-butyl phosphate (35 g, 66%, mp 67–70°) crystallized and was separated on a Büchner funnel. A second crop could be obtained by concentrating the mother liquor under vacuum and cooling. Recrystallization was effected by dissolving in petroleum ether at room temperature and cooling in Dry Ice–acetone. The mp after two such recrystallizations was 73–73.5° (lit.[5] mp 71–75°). The nmr spectrum showed a single absorption at 8.57 τ which under high resolution revealed coupling to phosphorus, $J \sim 0.5$ cps.

Cyclohexylammonium Di-*t*-butyl Phosphate.—Cyclohexylamine (0.8156 g, 8.24 mmol) was placed in a 50-ml volumetric flask and diluted to 50 ml with 50% v/v water–ethanol solution. The contents were transferred to a polyethylene bottle and thermostated at 60°. Tri-*t*-butyl phosphate (2.0069 g, 7.53 mmol) was then added to the solution. After 2 days, when the reaction was complete, the contents of the bottle were emptied into a 100-ml round-bottomed flask and the solvent distilled under aspirator vacuum. The solid remaining in the flask was dried under vacuum. The cyclohexylammonium di-*t*-butyl phosphate (2.287 g, 98% of theory) recrystallized from boiling 1,2-dimethoxethane (about 0.5 g salt / 25 ml of DME), as needles, mp after three recrystallizations 189.8–190.8° (dec), nmr sharp singlet at τ 8.38 under medium resolution and broad cyclohexylammonium absorption at $\tau \sim 8$–9.

Anal. Calcd for $C_{14}H_{32}PO_4N$: C, 54.35; H, 10.43; N, 4.53; P, 10.01. Found: C, 53.96; H, 10.34; N, 4.48; P, 10.00.

Solvolysis of Tri-*t*-butyl Phosphate in [^{18}O]H_2O–Ethanol.—Cyclohexylamine (0.8156 g) was weighed into a 50-ml volumetric flask. Tri-*t*-butyl phosphate (2.0069 g) was added and the flask was filled to the mark with a solvent prepared by mixing 25 ml of D_2O enriched in ^{18}O to 1.51 at. % (YEDA Research and Development Co., Ltd., Rehovoth, Israel) and 25 ml of absolute ethanol.

The contents of the volumetric flask were transferred to a polyethylene bottle and the bottle placed in a 60° temperature bath. The reaction was allowed to proceed for a week. After this time, the contents of the bottle were emptied into a round-bottomed flask and the solvent was removed under vacuum. The distillate was collected in a Dry Ice–acetone bath. When the distillation was completed, the solid remaining in the distilling flask was dried under vacuum for approximately 12 hr. The weight of solid was 2.2870 g. After two recrystallizations from 1,2-dimethoxyethane, the mp of the cyclohexylammonium di-*t*-butyl phosphate was 186.4–187.4° (dec).

The oxygen of this salt was converted to carbon dioxide by pyrolysis with mercuric cyanide and mercuric chloride.[9] The carbon dioxide was purified by the method of Haake and Westheimer,[10] and analyzed on a Consolidated–Nier 21-103C mass spectrometer.[11] Its isotopic content was identical with that of a sample of natural abundance.

Triisopropyl Phosphate.—Triisopropyl phosphite (Matheson Coleman and Bell) was oxidized with dinitrogen tetroxide while being cooled in an ice bath. The product, which distilled at 71–72° (1 mm), was a colorless liquid.

Pinacol Phosphorochloridite.—The method of Arbuzov and Azanovskaya[12] was followed with slight modification. Pentane as solvent in this reaction gave essentially the same results as diethyl ether and was more easily dried. Typically, pinacol (59.0 g, 0.50 mol) and pyridine (79.1 g, 1.00 mol) were dissolved in 400 ml of dry ether (or pentane) in a dry 1-l. three-necked flask equipped with a mechanical stirrer, a dropping funnel, and

(9) M. Anbar and S. Guttmann, *Intern. J. Appl. Radiation Isotopes*, **4**, 233 (1959).

(10) P. C. Haake and F. H. Westheimer, *J. Amer. Chem. Soc.*, **83**, 1102 (1961).

(11) We are grateful to Professor F. H. Westheimer for making this instrument available to us and to Dr. G. O. Dudek for aid in the determination.

(12) A. E. Arbuzov and M. M. Azanovskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 473 (1949).

a thermometer dipping below the surface of the solution. The flask was placed in an ice–salt bath, stirring was begun, and the contents were cooled below 0°. Phosphorus trichloride (69 g, 0.5 mol) was added dropwise to the cold mixture at a rate such that the temperature could be maintained below 0°. Addition required about 6 hr. After addition was completed, the mixture was boiled under reflux for 30 min. When the reaction mixture had cooled to room temperature, pyridine hydrochloride was removed by vacuum filtration. Usually, after filtering the pyridine hydrochloride, the filtrate was cloudy or contained a precipitate, which was probably due to formation of the hydrolysis product of the chloridite. Further filtrations only needlessly exposed the active chloridite to more atmospheric moisture. The solvent was removed by distillation or by use of a rotary evaporator. A yellow, fuming liquid (70–75 g) was obtained, which upon cooling in the refrigerator precipitated more pinacol phosphonate. Filtering the phosphonate and distilling the filtrate *in vacuo* [bp 53° (3 mm)] yielded a colorless, fuming liquid. Yields of pure chloridite were low, usually in the range of 25% of theory (20–25 g). A large amount of an orange, nonvolatile, tarry residue remained in the distilling flask.

Pinacol phosphonate, a by-product of this reaction, could be purified by sublimation at steam bath temperatures at 0.1–0.2 mm (mp 103–105°).

Methyl Pinacol Phosphite.—Pinacol phosphorochloridite (20.0 g, 0.11 mol) was dissolved in 30 ml of petroleum ether (bp 30–60°) in a 100-ml erlenmeyer flask stopper with a serum cap. A solution of dry methanol (3.60 g, 0.112 mol) and triethylamine (12.00 g, 0.119 mol) was injected into the solution through the serum cap with a hypodermic syringe. During the addition, the solution was cooled in an ice bath and stirring was maintained with a mechanical stirrer. After addition was completed, the triethylamine hydrochloride was filtered, the solvent removed on a rotary evaporator, and the concentrate distilled *in vacuo*, bp 24–28° (1 mm). In this manner, 9–10 g of methyl pinacol phosphite was obtained (about 50% of theory): nmr τ 6.61 (d, J = 24 cps), 8.82, 8.70.

Alternatively, for larger preparation, the reaction was performed in a three-necked, round-bottomed flask, adding the triethylamine–methanol mixture to the chloridite through a dropping funnel, while stirring with a mechanical stirrer and cooling in ice. Yields with this procedure were similar.

Methyl pinacol phosphite was extremely reactive toward water, producing pinacol phosphonate. Added to a small test tube containing water, it dissolved instantly with the liberation of heat. Care was required in the above reactions and in further handling of both the chloridite and phosphite to avoid exposure to moisture.

Methyl Pinacol Phosphate.—(a) Methyl pinacol phosphite (10.0 g, 0.056 mol) was dissolved in 50 ml of petroleum ether in a 100-ml flask. Dinitrogen tetroxide vapors were passed into the mixture, while the flask and contents were cooled in an ice bath. The mixture was stirred with a magnetic stirrer. Methyl pinacol phosphate soon precipitated from the mixture. The end of the reaction was indicated by the escaping of red vapors of NO_2 from the flask or by formation of a green color in the solution. The ether was removed, leaving a slightly yellow solid. Generally, 9.5–10.5 g of solid were obtained (90–95% of theory).

Purification of methyl pinacol phosphate could be effected by recrystallizations from benzene or petroleum ether (bp 90–120°) but a severe loss of material accompanied these methods. Purification by sublimation at steam-bath temperatures at 0.1–0.2 mm proved to be the best method. After one sublimation, the mp was 99.8–100.9°; nmr τ 6.20 (d, J = 24 cps), 8.56, 8.61.

Anal. Calcd for $C_7H_{15}PO_4$: C, 43.30; H, 7.79; P, 15.95. Found: C, 43.32; H, 8.05; P, 15.98.

(b) Pinacol phosphonate (5.89 g, 35.9 mmol) was dissolved in 25 ml of chloroform in a 50-ml flask. N-chlorosuccinimide (4.80 g, 36.0 mmol) was added in small portions while the flask was cooled in ice. After all the N-chlorosuccinimide had been added, the solution was boiled under reflux on the steam bath for 30 min. The solution was cooled and a mixture of methanol (1.2 g, 37.5 mmol) and triethylamine (4.0 g, 39.6 mmol) was added in small portions. Upon completion of the addition of methanol and triethylamine, the amine hydrochloride and succinimide were removed by filtration. The filtrate was concentrated on a rotary evaporator and a brown, oily mass resulted. The material was washed with water. The organic layer, dark brown in color, contained mostly chloroform. Evaporation of the chloroform in a watch glass by a stream of air left a dark brown solid. This solid was washed with petroleum ether, which removed much of the brown color but dissolved very little of the solid. The solid melted at 95–100° and gave nmr and ir spectra identical with those of methyl pinacol phosphate. After one sublimation, 2.04 g of purified methyl pinacol phosphate were obtained, mp 99.2–101°.

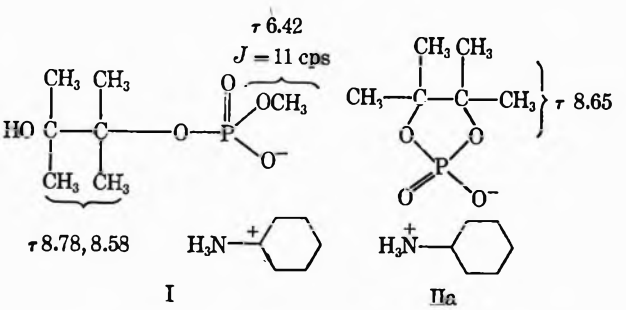
***t*-Butyl Pinacol Phosphite.**[12]—Pinacol phosphorochloridite was treated with an equivalent each of *t*-butyl alcohol and triethylamine in petroleum ether, as in the preparation of methyl pinacol phosphite. After the amine hydrochloride was filtered and the filtrate concentrated on a rotary evaporator, the concentrate was distilled *in vacuo:* nmr τ 8.68, 8.87, relative intensity 5:2.

***t*-Butyl Pinacol Phosphate.**[13]—Oxidation of *t*-butyl pinacol phosphite with dinitrogen tetroxide in petroleum ether yielded a white solid. Its mp after two sublimations at approximately 60–70° was 70.4–71.8° (0.1 mm).

Anal. Calcd for N $C_{10}H_{21}PO_4$: C, 50.80; H, 8.9; P, 13.15. Found: C, 50.60; H, 8.90; P, 13.25.

Hydrolysis of Methyl Pinacol Phosphate. Basic Solution.—An attempt to follow the kinetics of the basic hydrolysis of methyl pinacol phosphate revealed the extremely labile nature of this compound in basic solution. A solution approximately 0.08 *N* in NaOH in 50% 1,2-dimethoxyethane–water was made 0.5 in ionic strength with $NaClO_4$ and equilibrated at 30°. A 4.00 ml aliquot of the NaOH solution required 5.63 ml of 0.0495 *N* HCl for neutralization to pH 7. To 50 ml of the sodium hydroxide solution there was added methyl pinacol phosphate, 0.5831 g (3 mmol), and a 4.00 ml aliquot was withdrawn and titrated with 0.0495 *N* HCl as rapidly as possible. The sample required 0.80 ml of the hydrochloric acid solution; thus, since 0.240 mmol of the ester had consumed 0.239 mmol of the base, the hydrolysis of the phosphate was essentially complete at the end of about 60 sec, the time required to mix the solution, withdraw the aliquot, and titrate the sample.

To investigate the products of basic hydrolysis of methyl pinacol phosphate, 3.00 g (0.0154 mol) of the ester was dissolved in 100 ml of 50% 1,2-dimethoxyethane–water solution to which 2.00 ml (0.0165 mol) of cyclohexylamine had been added. After a few hours reaction time, the solvent and remaining cyclohexylamine were removed by vacuum distillation, leaving a brown solid, 3.81 g. After one recrystallization from 1,2-dimethoxyethane, the nmr spectrum of the reaction product in D_2O was obtained. Two peaks at τ 8.78 and 8.58 were attributed to the two different types of methyl groups in the ring-opened salt I. A doublet, centered at τ 6.43 (J = 11 cps), indicated a methyl group attached to a phosphate residue. A smaller peak at τ 8.65 was attributed to ring-retained salt II. Integration of the spectrum was obscured in the methyl region by the broad peak at τ 7.8–9.0 due to the cyclohexylammonium cation protons. However, there was approximately 80% ring-opened salt I and



20% ring-retained salt IIa. Repeated recrystallizations of the salt from 1,2-dimethoxyethane gave little separation of either reaction product, as indicated by nmr.

Acidic Solution.—Methyl pinacol phosphate (3.00 g, 0.0154 mol) was dissolved in 100 ml of 50% 1,2-dimethoxyethane–water. After a few hours of reaction, the solvent was removed by vacuum distillation. A white solid, 1.71 g, mp 191° (dec), was obtained. An nmr of this material showed two peaks, τ 8.66 (relative area = 12) and τ 0.54 (relative area = 1). The material was, therefore, formulated as pinacol phosphoric acid.

Anal. Calcd for $C_6H_{13}PO_4$: C, 40.00; H, 7.27; P, 17.19. Found: C, 39.44; H, 7.26; P, 17.34.

(13) We thank Mr. Kary Mullis for preparation of a sample of this compound.

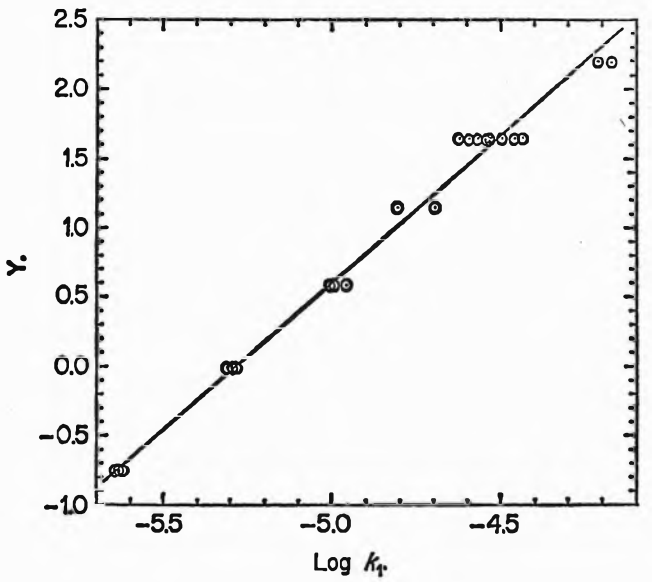


Figure 1.—Grunwald–Winstein correlation of the solvolysis rates of tri-*t*-butyl phosphate in 50% EtOH at 60°.

This is the only product of hydrolysis observed in initially neutral 1,2-dimethoxyethane–water solution.

Treating the acid with an equivalent of cyclohexylamine in 1,2-dimethoxyethane produced the cyclohexylammonium salt, which precipitated quantitatively. The single, sharp nmr peak of the salt in D_2O, other than those of cyclohexylammonium ion, was positioned at τ 8.63.

Hydrolysis of *t*-Butyl Pinacol Phosphate. Basic Solution.—Cyclohexylamine (17 ml, 0.014 mol) was dissolved in a solution of 50 ml of 1,2-dimethoxyethane and 50 ml of water. *t*-Butyl pinacol phosphate (3.00 g, 12.7 mmol) was added and allowed to react overnight. The solvent was removed by vacuum distillation, leaving 3.27 g of a white solid. An nmr spectrum in D_2O revealed a single methyl peak at τ 8.65, indicating that the only product of hydrolysis is the ring-retained salt.

Neutral Solution.—*t*-Butyl pinacol phosphate (3.00 g, 0.0127 mol) was dissolved in a solution of 50 ml of 1,2-dimethoxyethane and 50 ml of water. The reaction was allowed to proceed overnight. The solvent was removed by vacuum distillation. The solid obtained, 1.49 g, was identical in mp (191°), ir, and nmr with pinacol phosphoric acid obtained from neutral hydrolysis of methyl pinacol phosphate.

Conversion of the Hydrolysis Product into Methyl Pinacol Phosphate.—Pinacol phosphoric acid (1.605 g, 0.0892 mol) was placed in a 125-ml erlenmeyer flask and covered with 50 ml of diethyl ether. The solution was stirred on a magnetic stirrer. Small portions of diazomethane in ether solution were added to the acid until the pale yellow color of diazomethane persisted. During addition of diazomethane, vigorous gas evolution occurred and the solution remained colorless until excess diazomethane was added. The ether was removed on a rotary evaporator, whereupon a slightly discolored solid remained. Sublimation of the solid at steam-bath temperatures at 1-mm pressure gave 1.26 g (6.49 mmol, 73% of theory) of methyl pinacol phosphate, mp 99.8–101.0°. No depression of melting point occurred when it was mixed with a sample of the ester prepared by oxidation of methyl pinacol phosphite.

Solutions for basic solvolysis were prepared in each case by the following method. (Mixed solvent compositions refer to v/v per cent at room temperature.)

A quantity of a standard solution of sodium hydroxide was pipetted into a volumetric flask and a proportional quantity of the second solvent (ethanol or 1,2-dimethoxyethane) was then added with a pipet in order to achieve the desired solvent ratio. The calculated amount of sodium perchlorate was added in order to adjust the ionic strength to the desired value. The flask was then filled with solvent of the correct ratio. Except for the kinetic runs in 50% 1,2-dimethoxyethane–water, which were carried out in the volumetric flask, a quantity of the solution was pipetted into a bottle made of Teflon or of polyethylene. The containers were then equilibrated with a constant temperature bath. After temperature equilibration had been achieved, a quantity of the ester was added. The quantity of ester used was determined by the amount of base present; in most cases the concentration of ester was less than the concentration of base. A 4.00-ml aliquot was removed immediately after mixing, diluted with water, and titrated to neutrality with standard hydrochloric acid.

Data were analyzed by a least-squares treatment with the aid of the Burroughs B 5500 computer after the kinetic order had been established by preliminary fitting to standard rate expressions.

Results

The rate of consumption of base by tri-*t*-butyl phosphate (Table I) and by tri-*i*-propyl phosphate (Table II) was independent of the concentration of base as the base was varied from about 0.03 *N* to about 0.15 *N* but was clearly of the first order in ester concentration.

The variation of rate of solvolysis of tri-*t*-butyl phosphate as a function of ionizing power of the solvent in water–ethanol mixtures correlated with the Grunwald–Winstein *Y* values for these solvents[14] (Figure 1). The ^{18}O tracer experiments showed that in the solvolysis of tri-*t*-butyl bond is broken exclusively.

These results demonstrate that the solvolysis of tri-*t*-butyl phosphate under these reaction conditions has as the rate-limiting step the unimolecular ionization of the ester to the *t*-butyl carbonium ion and the di-*t*-butyl phosphate anion. The kinetic order suggests strongly that the hydrolysis of tri-*i*-propyl phosphate in water is also an ionization process, and such a process would accord with the behavior of isopropyl dihydrrogen phosphate (6b).

Triallyl phosphate, in contrast to the other two esters, solvolyzed at a rate proportional to the concentrations of both the ester and the base (Table III); the reaction is therefore, bimolecular, but since the point of bond cleavage has not been defined, it is not known whether attack of hydroxide ion is at phosphorus or at carbon.

Methyl pinacol phosphate solvolyzed in 50% water–dimethoxyethane in the presence of base to afford a mixture of about 80% methyl 3-hydroxy-2,3-dimethylbutyl-2 phosphate and about 20% pinacol cyclic phosphate, the ring-opened and ring-retained products, respectively. Based on the assumption that these reactions are bimolecular, it can be estimated that the rate constants for the two reactions of the esters with hydroxide ion at 30° are at least 2 $(mol/l.)^{-1}\,sec^{-1}$. These rates are, then, comparable to those observed by Covitz and Westheimer in the base-catalyzed hydrolysis of methyl ethylene phosphate.[15]

t-Butyl pinacol phosphate solvolyzed rapidly in 50% water–dimethoxyethane in initially neutral solution or in the presence of cyclohexylamine. A gas was evolved (presumably isobutylene), and from the solution pinacol cyclic phosphate was isolated quantitatively as its cyclohexylammonium salt.

Discussion

The establishment of the SN1 mechanism for solvolysis of tri-*t*-butyl phosphate in aqueous solvent mixtures

(14) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 43; K. B. Wiberg, "Physical Organic Chemistry," John Wiley & Sons, New York, N. Y., 1964, p 417; J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, New York, N. Y., 1963, p 297.

(15) F. Covitz and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 1773 (1963).

TABLE I

FIRST-ORDER RATE CONSTANTS FOR SOLVOLYSIS OF TRI-*t*-BUTYL PHOSPHATE IN VARIOUS SOLVENTS AT 60°

Solvent	Ester concn	Base concn	Half-life, hr	$k \times 10^5$ sec^{-1}	Ionic strength	Y[c]
50% DME H_2O	0.0764	0.1585	8.07	2.38	0.498	...
50% DME H_2O	0.0765	0.1551	9.06	2.13	0.195	...
40% EtOH H_2O	0.0358	0.1159	2.84	6.76	0.496	2.196
40% EtOH H_2O	0.0385	0.1140	3.14	6.13	0.0494	2.196
50% EtOH H_2O	0.0392	0.0926	6.73	2.86	0.492	1.655
50% EtOH H_2O	0.1732	0.1900	6.95	2.77	0.490	1.655
50% EtOH H_2O	0.0323	0.0337	6.01	3.20	0.494	1.655
50% EtOH H_2O	0.0312	0.0322	5.73	3.36	0.032[a]	1.655
50% EtOH H_2O	0.1388	0.1438	8.12	2.37	0.484[b]	1.655
70% EtOH H_2O	0.0478	0.0895	17.35	1.11	0.499	0.595
70% EtOH H_2O	0.0388	0.0860	18.85	1.02	0.496	0.595
80% EtOH H_2O	0.0388	0.0757	37.60	0.51	0.496	0.000
80% EtOH H_2O	0.0480	0.0756	36.95	0.52	0.496	0.000
90% EtOH H_2O	0.0526	0.0755	82.81	0.23	0.494	−0.747
90% EtOH H_2O	0.0442	0.0762	80.65	0.24	0.495	−0.747

[a] No ionic salt was added in this run; the base used was cyclohexylamine rather than sodium hydroxide. [b] Solution was made 0.14 *N* in cyclohexylammonium di-*t*-butyl phosphate. [c] Grunwald–Winstein *Y* value for these solvents taken from A. H. Feinberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2770 (1956).

TABLE II

FIRST-ORDER RATE CONSTANTS FOR SOLVOLYSIS OF TRIISOPROPYL PHOSPHATE IN WATER AT 90°

Ester concn	Base concn	Half-life, hr	$k \times 10^5$ sec^{-1}	Ionic strength
0.0678	0.0752	44.42	4.35	0.495
0.1462	0.1497	70.11	2.75	0.490
0.0177	0.0191	39.90	4.83	0.499
0.0632	0.1506	41.81	4.61	0.491

TABLE III

SECOND-ORDER RATE CONSTANTS FOR THE SOLVOLYSIS OF TRIALLYL PHOSPHATE IN 50% ETHANOL–WATER AT 60°

Ester concn	Base concn	$k \times 10^4$ (mol/l.)$^{-1}$ sec^{-1}	Ionic strength
0.0307	0.0374	3.24	0.497
0.0320	0.0766	2.61	0.497
0.1496	0.1502	3.49	0.490
0.1532	0.1897	3.32	0.490

suggests that under similar reaction conditions triesters of phosphoric acid containing one or more *t*-alkyl groups of un-ionized *t*-alkyl di- or monoesters of phosphoric acid may be expected to undergo rapid, heterolytic carbon–oxygen fission. This behavior is analogous to that of *t*-alkyl halides, although halide ions are much better leaving groups than is di-*t*-butyl phosphate anion.

Neither the di-*t*-butyl phosphate anion nor the monoanion of *t*-butyl phosphate[16] undergoes rapid carbon–oxygen fission, although the un-ionized acids of both these esters solvolyze rapidly.[6,16]

The rapid, clean removal of a single *t*-butyl group under neutral conditions makes attractive the possibility of employing it as a protective group during phosphorylation of alcohols sensitive to the conditions used to remove other protective groups. Unfortunately, our attempts to isolate di-*t*-butyl phosphorochloridate prepared by the method of Mark and Van Wazer[17] were frustrated by its rapid decomposition. By contrast, pinacolyl phosphorochloridate and pinacolyl phosphoric acid demonstrated a stability surprising in light of the above observations, the latter being isolable from aqueous solution. Although pinacolyl phosphorochloridate phosphorylates alcohols satisfactorily, solvolysis of methyl pinacol phosphate afforded a mixture of ring-opened and ring-retained phosphate diesters which appeared to have arisen by nucleophilic attack on phosphorus. The synthetic utility of the pinacolyl group as a protective group thus seems highly limited.

The complex solvolytic behavior of *t*-butyl pinacol phosphate will be the subject of another communication.

(16) M. G. Newton and J. R. Cox, Jr., unpublished results.
(17) V. Mark and J. R. Van Wazer, *J. Org. Chem.*, **29**, 1006 (1964).

Registry No.—Tri-*t*-butyl phosphate, 20224-50-4; cyclohexylammonium di-*t*-butyl phosphate, 20224-52-6; triisopropyl phosphate, 513-02-0; pinacol phosphonate, 16352-18-4; methyl pinacol phosphite, 14812-60-3; methylpinacol phosphate, 7443-26-7; *t*-butyl pinacol phosphate, 20224-35-5-; pinacol phosphoric acid, 13882-05-8; triallyl phosphate, 1623-19-4; tri-*t*-butyl phosphite, 15205-62-6.

Acknowledgment.—This work was generously supported by the National Institutes of Health under Grant 07965-03.

Pentacyclodecane Chemistry. V. The Synthesis and Acetolysis of *syn*- and *anti*-Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-yl *p*-Toluenesulfonate. Evidence Concerning the Intermediacy of Bridged Carbonium Ions[1]

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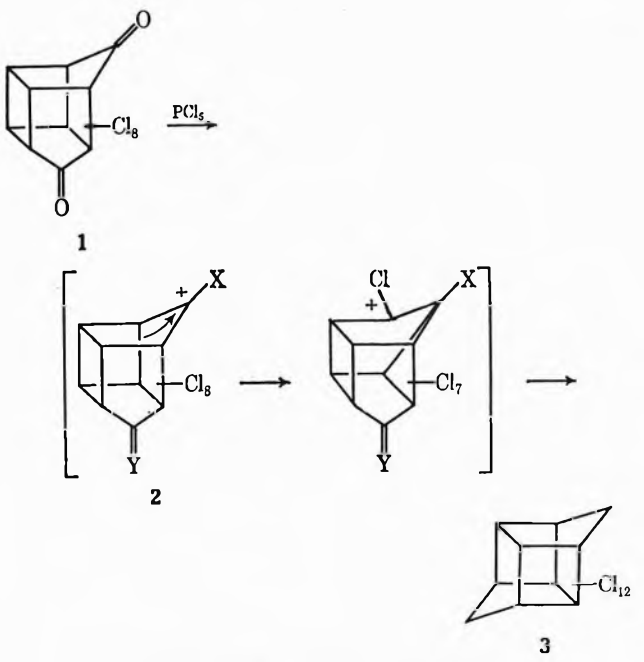
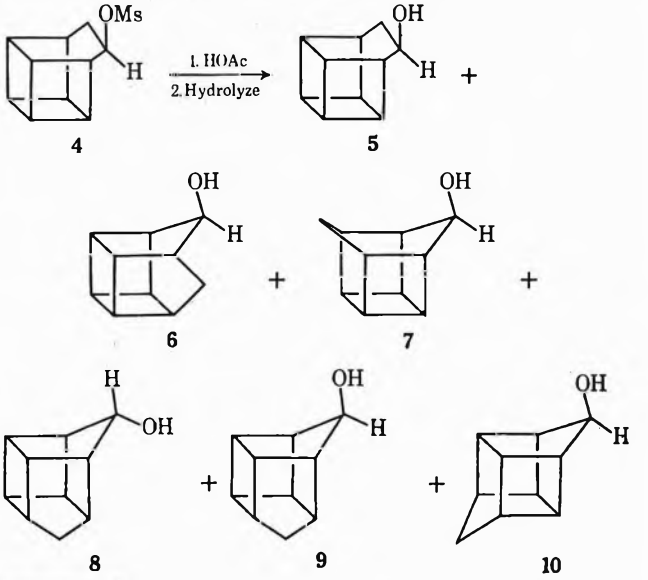
The *syn* and *anti* isomers of pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-ol were synthesized by irradiation of *syn*- and *anti,endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ol, respectively, in acetone solution. Solvolysis of the *syn*-pentacyclodecyl tosylate in unbuffered acetic acid gave almost exclusively the unrearranged *syn* acetate. Acetolysis of the *anti* tosylate gave mainly the rearranged pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]dec-6-yl acetate accompanied by 15% of unrearranged *anti* acetate. Internal return with rearrangement occurred with the *anti* tosylate. The rates of acetolysis of the *syn* and *anti* tosylates were measured; rate accelerations of 1.3×10^4 and 5×10^3, respectively, over those predicted for unassisted solvolysis were calculated from Schleyer's equation. Reduction of pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one with sodium borohydride, lithium aluminum hydride, and lithium tri-*t*-butoxyaluminum hydride gave 76–80:24–20 ratios of *syn* and *anti* alcohols, respectively. The rate of borohydride reduction was determined, and an attempted correlation with the solvolysis rates was made. Equilibration of the *syn* and *anti* alcohols with aluminum isopropoxide–acetone gave a 50:50 mixture. The solvolysis reactions are best interpreted in terms of bridged carbonium ion intermediates, although other explanations cannot be ruled out entirely.

The unsymmetrical perchloro diketone **1** has been reported to rearrange to the symmetrical chlorocarbon **3** on reaction with phosphorus pentachloride.[2] The



X = $OPCL_4$ or Cl, Y = 0 or Cl_2

most reasonable pathway for this 1,3- to 1,4-bishomocubyl[3] rearrangement involves a carbonium ion mechanism[4] in which a 1,2-alkyl migration occurs in one of the cations **2**. A related reaction involving the acetolysis of the 1,1-bishomocubyl mesylate **4** was also recently reported.[5] Interestingly, this reaction generates all of the five possible bishomocubyl carbon skeletons **5–10**,[3,6]



(1) Part IV: W. L. Dilling and C. E. Reineke, *Tetrahedron Lett.*, 2547 (1967). A preliminary account of this work is presented in this paper.

(2) (a) P. E. Eaton, Ph.D. Thesis, Harvard University, 1960; (b) G. W. Griffin and A. K. Price, *J. Org. Chem.*, **29**, 3192 (1964).

(3) The numbering for the bishomocubane system of nomenclature refers to the shortest path along the edges of a cube between the positions of the two methylene bridges. Thus the five possible bishomocubanes are as follows: pentacyclo[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]decane, 1,1-bishomocubane; pentacyclo[4.4.0.0^{2,5}.0^{3,9}.0^{4,7}]decane, 1,2-bishomocubane; pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane, 1,3-bishomocubane; pentacyclo[4.4.0.0^{2,5}.0^{3,9}.0^{4,8}]decane, 1,3′-bishomocubane; pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane, 1,4-bishomocubane.

(4) M. S. Newman and L. L. Wood, Jr., *J. Amer. Chem. Soc.*, **81**, 4300 (1959).

(5) W. G. Dauben and D. L. Whalen, *ibid.*, **88**, 4739 (1966).

(6) The stereoisomers **8** and **9** were only isolated as a mixture and were not identified individually.[5]

TABLE I

NMR DATA FOR PENTACYCLODECANOLS[a]

Alcohol	—CHOH—	—C—H	O—H	—CH₂—
syn **8**	−4.04[b] (1.0)[c]	−3.2 to −2.1 (−)[d]	−2.28 (−)[d]	−1.66,[e] −1.41[e] (2.0)
anti **9**	−4.28[f] (1.0)	−3.1 to −2.2 (7.9)	−2.08 (1.0)	−1.62[g] (1.0), −1.20[g] (1.0)
10	−4.08 (1.0)	−3.1 to −2.3 (8.0)	−2.15 (1.0)	−1.39 (2.0)

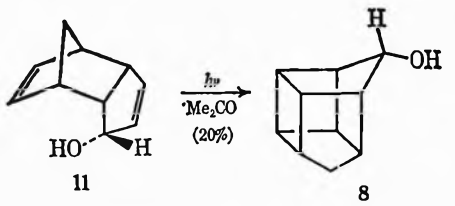
[a] $CDCl_3$ solution. [b] Ppm from internal TMS (δ). [c] Relative peak areas in parentheses. [d] Total relative area 9.0. [e] Doublet, J_{gem} = 10.8 cps, with further splitting evident. [f] Triplet, $J \sim 1.5$ cps. [g] Doublet, J_{gem} = 11.0 cps.

presumably *via* a series of carbonium ion rearrangements.[5]

The original purpose of the work described in this paper was the examination of the 1,3-bishomocubyl cation to 1,4-bishomocubyl cation rearrangement. The solvolysis of tosylate esters was chosen as the method for generating the 1,3-bishomocubyl cation. After this work was underway, it became apparent that this system was ideal for studying the possible intermediacy of bridged carbonium ions.

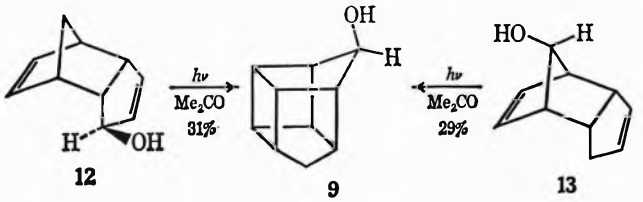
Results

syn-Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-ol[7] (**8**) was synthesized by the acetone photosensitized ring closure[8] of *endo,syn*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ol[9] (**11**).[10,11]



11 **8**

In a similar manner, the *anti* isomer **9** was prepared by irradiation of both the *anti*-3-dienol[9] **12** or the *syn*-10-dienol[9] **13** in acetone solution.

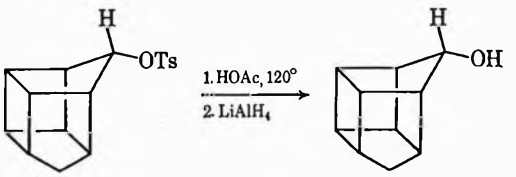


12 **9** **13**

The infrared, nuclear magnetic resonance (nmr), and mass spectra[13] (see Experimental Section) were entirely consistent with the assigned structures. All attempts to separate mixtures of the isomeric alcohols **8** and **9** were unsuccessful. Therefore, analyses of mixtures of these alcohols were made by nmr spectroscopy. The spectral data are given in Table I along with those for the symmetrical alcohol **10**. Of particular value for analysis were the signals for the proton on the hydroxyl-bearing carbon atoms (C-6). Also, the two isomers showed distinctly different AB quartet patterns for the methylene group.

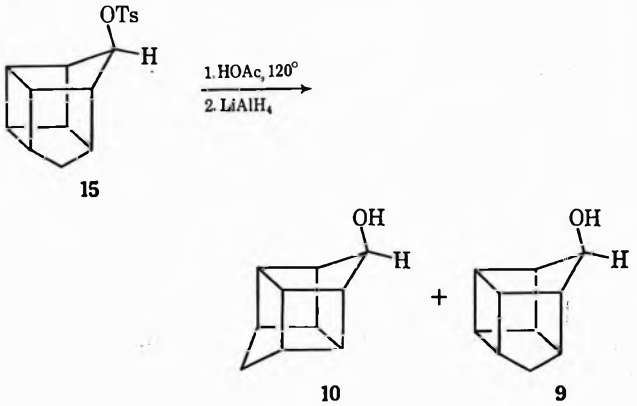
The acetates and tosylates of the alcohols **8** and **9** were prepared by standard procedures. The infrared, nmr, and mass spectra were consistent with the assigned structures. The differences in the nmr spectra of the alcohols **8** and **9** noted above were also observed in the spectra of the acetates and tosylates.

Preparative acetolysis of the *syn* tosylate **14** in unbuffered acetic acid at 120° for 10 half-lives, followed by lithium aluminum hydride reduction of the acetate product, gave the *syn* alcohol **8** in 94% over-all yield.



14 **8**

There could have been as much as 4% of both the *anti* alcohol **9** and the symmetrical alcohol **10** present in the *syn* alcohol **8** produced in this reaction. No concrete evidence for the formation of either **9** or **10** was obtained other than a gas chromatography (gc) peak with a retention time corresponding to the symmetrical alcohol **10**. The product from unbuffered acetolysis of the *anti* tosylate **15** at 120° for 10 half-lives was also reduced with lithium aluminum hydride. This product mixture consisted mainly (85%) of the rearranged symmetrical alcohol **10** and 15% unrearranged *anti* alcohol **9**. The presence of several per cent *syn* alcohol **8** would not have been detected in this product mixture. The over-all yield (75%) was not so high in this reaction as that described above from the *syn* tosylate **14**. Some black carbonaceous material was also formed in



15 **10** **9**

(7) The terms *syn* and *anti* refer to the position of the functional group with respect to the second methylene bridge (C-10).

(8) (a) G. O. Schenck and R. Steinmetz, *Chem. Ber.*, **96**, 520 (1963), have reported the acetone-sensitized ring closure of *endo*-dicyclopentadiene to pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane. (b) For other related ring closures see W. L. Dilling, *Chem. Rev.*, **66**, 384 (1966).

(9) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(10) Although the structural formulas in this paper show only one enantiomer, all the compounds capable of existing as optical isomers were actually racemic mixtures.

(11) The *syn* alcohol **8** has also been prepared by Cookson and coworkers[12] by the acetone-sensitized irradiation of *endo,anti*-tricyclo[5.2.1.0^{2,6}]deca-3,8-dien-10-ol.

(12) R. C. Cookson, J. Hudec, and R. O. Williams, *J. Chem. Soc., C*, 1382 (1967).

(13) See W. L. Dilling and M. L. Dilling, *Tetrahedron*, **23**, 1225 (1967), for the mass spectra of related compounds.

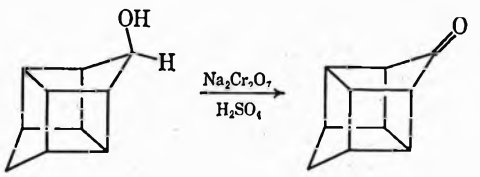
TABLE II

ACETOLYSIS RATES OF PENTACYCLODECYL TOSYLATES

Tosylate	Temp, °C	Rate constant (sec^{-1})[a]	$\Delta H^{\ddagger}$ (kcal/mol)[b]	$\Delta S^{\ddagger}$ (eu)[b]
syn **14**	120.0 ± 0.1	2.82 ± 0.04 × 10^{-4}	27.3 ± 1.0	−5.9 ± 1.6
	110.0 ± 0.1	1.10 ± 0.02 ± 10^{-4}		
	25	3.0 × 10^{-9}		
anti **15**	130.0 ± 0.1	1.18 ± 0.04 × 10^{-4}		
	120.0 ± 0.1	5.07 ± 0.21 × 10^{-5}	25.8 ± 2.4	−13.2 ± 4.1
	25	1.0 × 10^{-9}		

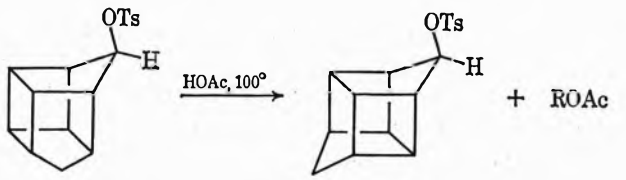
[a] Standard deviation given.[16] [b] Statistical error given.[17]

the acetolysis of the *anti* tosylate **15**. The symmetrical alcohol **10** was identified by spectral comparison with an authentic sample[5] as well as oxidation to the known ketone **16**.[2b,5] Acetolysis of the *anti* tosylate **15** at



10 **16**

100° for slightly less than 1 half-life (28% acetate isolated) gave approximately equal amounts of recovered *anti* tosylate **15** (30%) and rearranged symmetrical tosylate **17** (30%). The symmetrical tosylate



15 **17**

17 was identified by comparison of its nmr spectrum with that of an authentic sample.[14] No evidence (nmr, infrared) for any olefinic products was detected in the acetolysis of ether tosylate **14** or **15**.

The solvolysis rate data for tosylates **14** and **15** in unbuffered acetic acid are summarized in Table II.[15-17]

In order to use Schleyer's equation[18] relating the predicted unassisted solvolysis rate of secondary tosylates with strain effects, one needs an accurate measure of the carbonyl infrared stretching frequency of the corresponding ketone. The pertinent infrared absorption bands of ketone **18** are given in the Experimental Section. The splitting in the carbonyl region is assumed to be due to Fermi resonance.[19] Presumably the mode in resonance with $\nu_{C=O}$ is the first overtone of the band at 862 cm^{-1}. In order for a first overtone to be in Fermi resonance with a fundamental, two requirements must be met. One is that the first overtone must be of the same symmetry species as the fundamental with which it is in resonance. Since the ketone **18** has no formal symmetry elements, all modes belong to the same symmetry species. The second requirement is that the fundamental of the mode whose overtone is in Fermi resonance with $\nu_{C=O}$ must be a motion which has sizable components in a direction perpendicular to the motion of $\nu_{C=O}$. The fundamental at 862 cm^{-1} is likely to be a mode in which the carbon atoms adjacent to the carbonyl group expand symmetrically (ν "*sym* C–C–C"), thus fulfilling the second requirement. The frequency 862 cm^{-1} is reasonable for this vibration, although this assignment must be regarded as speculative. The band at 862 cm^{-1} has two satellites at 849 and 879 cm^{-1} which we assume make up a Fermi-resonance triplet. Therefore the two main Fermi-resonance hybrids near 1700 cm^{-1} will also be slplit into triplets. This is observed; the strongest component at 1763 cm^{-1} has reasonably spaced satellites at 1783 and 1742 cm^{-1}; the component at 1697 cm^{-1} has satellites at 1670 and 1720 cm^{-1} (shoulder ?). The first-order correction for Fermi resonance was made by using the approximation of Longseth and

$$\omega^0 = \frac{\omega_a + \omega_b}{2} \pm \frac{\omega_a - \omega_b}{2}\left(\frac{A_a - A_b}{A_a + A_b}\right)$$

Lord,[20] where the two values of ω^0 are the unperturbed frequencies, ω_a (1762.7 cm^{-1}) and ω_b (1697.2 cm^{-1}) are the observed frequencies, and A_a and A_b are the respective integrated band intensities (for which the peak-height intensities were substituted, A_a 1.15, A_b 0.05). The calculated values of ω^0 are 1729.9 ± 29.9 cm^{-1}. Therefore, $\nu_{C=O}$ (unperturbed) = 1759.8 cm^{-1} (or 1760 cm^{-1} to nearest cm^{-1}), and 2ν "*sym* C–C–C" (unperturbed) = 1700 cm^{-1}. The calculated frequency for the first overtone of the fundamental at 862 cm^{-1}, assuming a harmonic oscillator, is 1724 cm^{-1}. The anharmonicity is therefore 1.4%, an entirely reasonable amount. The values of the torsional angles, ϕ_i (both 60° in **14** and **15**), needed to use Schleyer's equation[18] were determined by examination of molecular models of the *syn* and *anti* tosylates **14** and **15**. The differences in the nonbonded ground-state and transition-state strain energies, GS-TS strain (**14** 0.4; **15**, 0.3), was estimated by a comparison of models of the tosylates **14** and **15** with models of various similar compounds for which Schleyer[18] has calculated strain energies.

Reduction of the pentacyclodecanone **18** with various hydride reducing agents gave primarily the *syn* alcohol **8** accompanied by smaller amounts of the *anti* epimer **9** in ratios of 3–4:1 (Table III).

(14) S. F. Brown, Senior Thesis, Princeton University, 1967.

(15) These data are slightly revised from those given in our original communication[1] owing to a different method of data treatment.

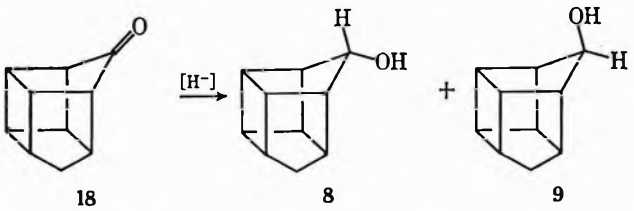
(16) E. L. Crow, F. A. Davis, and M. W. Maxfield, "Statistics Manual," Dover Publications, Inc., New York, N. Y., 1960, p 164.

(17) E. L. Purlee, R. W. Taft, Jr., and C. A. DeFazio, *J. Amer. Chem. Soc.*, **77**, 837 (1955).

(18) P. von R. Schleyer, *ibid.*, **86**, 1854 (1964).

(19) R. C. Cookson, E. Crundwell, R. R. Hill, and J. Hudec, *J. Chem. Soc.*, 3062 (1964).

(20) *Cf.* R. Ryason and M. K. Wilson, *J. Chem. Phys.*, **22**, 2000 (1954).



18 8 9

TABLE III

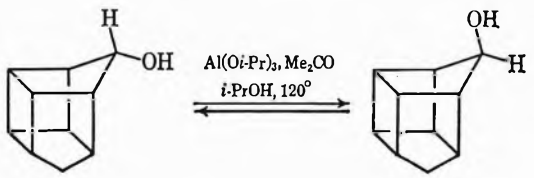
HYDRIDE REDUCTIONS OF PENTACYCLODECANONE 18

Reducting Agent	Solvent	Product distribution, % *syn* 8	*anti* 9
$NaBH_4$	MeOH	76 ± 1	24 ± 1
$LiAlH_4$[a]	Et_2O	80 ± 1	20 ± 1
$LiAl(O\text{-}t\text{-}Bu)_3H$	Et_2O	80 ± 1	20 ± 1

[a] Data from ref 13. Cookson and coworkers[12] also reported an 80:20 ratio for this reaction.

The rate of sodium borohydride reduction of the ketone **18** in 2-propanol at 0° was found to be 0.144 ± 0.007 M^{-1} sec^{-1}. Using the 76:24 ratio (Table III), one calculates partial rate factors of 11.0 × 10^{-2} M^{-1} sec^{-1} for hydride attack from the *anti* direction to produce the *syn* alcohol **8** and 3.5 × 10^{-2} M^{-1} sec^{-1} for attack from the *syn* direction to produce the *anti* alcohol **9**.

Equilibration of the epimeric alcohols **8** and **9** with aluminum isopropoxide and acetone in 2-propanol at 120° gave equal amounts of the two isomers within experimental error (50 ± 1:50 ± 1).[21]



8 9

Discussion

The skeletal rearrangement which occurs on solvolysis of the *anti* tosylate **15** shows that the 1,3-bishomocubyl cation can rearrange to the 1,4-bishomocubyl cation if the stereochemistry of the leaving group is appropriate. This observation lends support to the mechanism proposed above for the rearrangement which occurs on chlorination of the diketone **1**. Also, one step in the mechanism proposed by Dauben and Whalen[5] for the rearrangements occurring on solvolysis of the 1,1-bishomocubyl mesylate **4** is substantiated by this observation.

The fact that distinctly different products are formed on acetolysis of the *syn* and *anti* tosylates **14** and **15** shows that none or very little of a common intermediate is formed in the two reactions. This observation rules out any free or symmetrically solvated (*i.e.* free of leaving group effects) nonbridged carbonium ions as intermediates. A planar sp^2 carbonium ion carbon atom is assumed although a suggestion has been made that the structurally similar 7-norbornyl cation may be nonplanar.[22]

(21) Our previously reported[1] distribution for this equilibrium was in error.

The products from acetolysis of the tosylates **14** and **15** are easily rationalized on the basis of stereospecific rearrangements dictated by the stereochemistry of the tosylate group; *i.e.*, only rear-side 1,2-alkyl migrations are permitted (Scheme I). It is also clear that combination of the cation with the nucleophile must occur from the front side. The 1,3-bishomocubyl acetates **19** and **21** and the 1,4-bishomocubyl acetate **22** are not the only products which could conceivably be formed under the above specified requirements (Scheme I). Rearrangement *via* path b would lead to a 1,2-bishomocubyl derivative **20** while path d would lead to a 1,3′ derivative **23**. No evidence for the formation of any products other than **19**, **21**, and **22** was obtained. This lack of rearrangement to products having the carbon skeletons of **20** and **23** (and to the 1,1-bishomocubyl skeleton as in **5**) is entirely reasonable when one considers the relative amounts of strain present in these systems as judged by an examination of molecular models. The order of decreasing strain in the bishomocubyl carbon skeletons is probably 1,1 > 1,2 > 1,3′ > 1,3 > 1,4 owing to the 1,1 system having four cyclobutane rings fused together, the 1,2 system having three cyclobutane rings fused about a single carbon atom, the 1,3′ system having three cyclobutane rings fused in a linear arrangement, the 1,3 system having two cyclobutane rings fused, and the 1,4 system having two isolated cyclobutane rings. Dauben and Whalen's[5] results starting from the 1,1-bishomocubyl system are thus entirely reasonable.

With the data at hand, we have no evidence concerning the rearrangement of the *syn* tosylate **14** to the enantiomeric carbon skeleton (Scheme I). Work is currently under way to test this point. It is conceivable that the *syn* acetate **19** formed in this reaction arises simply by a substitution reaction proceeding with retention of configuration without any skeletal rearrangement, although we favor a reaction involving rearrangement (see below). Solvolysis of 7-norbornyl tosylate or brosylate leads to a high degree of retention without skeletal rearrangement in the formation of the 7-norbornyl product.[22,23]

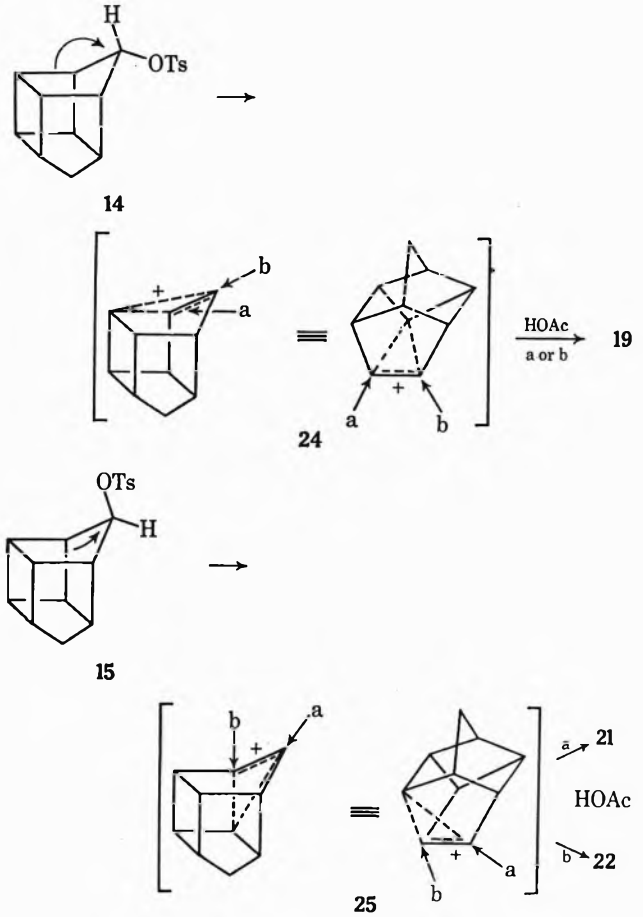
Reasonably good first-order kinetics were obtained for the acetolysis of the *anti* tosylate **15** up to 80–90% completion of the reaction, even though considerable rearrangement to the 1,4-bishomocubyl tosylate **17** occurred during acetolysis. The infinity titrations were also in good agreement with the theoretical values. These results imply that the acetolysis rate for the 1,4-tosylate **17** is nearly the same as that for the *anti* 1,3-tosylate **15**. Unpublished work by Schleyer and Brown shows this to be true; $k_{1,4}^{120°}$ = 6.86 × 10^{-5} sec^{-1}.[14] The low material balance (75%) and blackening of the reaction mixture on acetolysis of the *anti* tosylate **15** may indicate some ring opening to olefinic products followed by polymerization or decomposition.

The simplest and most consistent explanation for the stereochemical results of the solvolyses of the

(22) (a) F. B. Miles, *J. Amer. Chem. Soc.*, **90**, 1265 (1968); (b) P. G. Gassman, J. M. Hornback, and J. L. Marshall, *ibid.*, **90**, 6238 (1968). See however (e) J. E. Williams, Jr., R. Sustmann, L. C. Allen, and P. von R. Schleyer, *ibid.*, **91**, 1037 (1969).

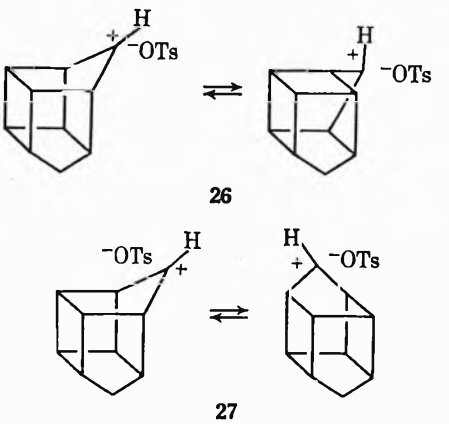
(23) (a) P. G. Gassman and J. M. Hornback, *ibid.*, **89**, 2487 (1967); (b) F. B. Miles, *ibid.*, **89**, 2488 (1967).

epimeric tosylates **14** and **15** is the intermediacy of the bridged ions **24** and **25**.[24]



The observed stereochemical retention in these substitution reactions could not have been due to S–O bond cleavage,[25] as evidenced by the fact that the acetates **19**, **21**, and **22** were the primary reaction products, not the alcohols **8**, **9**, and **10**. The concept of rapidly equilibrating nonbridged ions[26] (free or symmetrically solvated) does not appear to give a reasonable explanation, since one of the nonbridged ions (Scheme I) from both tosylates is the same (assuming a planar sp^2 carbonium ion); thus the same products would be expected from either tosylate, and such is not the case. The only apparent way for this explanation to be valid is for the equilibration between the two nonbridged cations to be faster than the C-6 carbon–hydrogen bending vibration, a situation which for all practical purposes would be the same as a vibrating bridged ion. A steric effect cannot be invoked in these bishomocubyl cations as the reason for the observed stereochemistry, as has been done for the 2-norbornyl system.[24f] Studies on hydride reduction of 1,3-bishomocubanone **18** and equilibration of the *syn* and *anti* alcohols **8** and **9** (see below) show that both faces of the carbonium ion at C-6 should be readily accessible to approach by a nucleophile.

An alternative explanation, which is not so easily dismissed, is the intermediacy of two sets of rapidly equilibrating nonbridged ion pairs **26** and **27**, which could be generated from the tosylates **14** and **15** respectively. Thus no common intermediate would be



formed from the two tosylates **14** and **15** if these ion pairs were the intermediates. One must still have some mechanism to account for the almost exclusive retention of configuration in these reactions, results which are opposite to those usually observed for SN1 reactions where complete racemization does not occur. Even with the α-phenylneopentyl system, where one might expect some net retention due to steric hindrance to rearside attack, the stereochemical result is 10% net inversion.[27] Two phenomena are possible to account for the observed retention. One involves rearrangements which are so rapid that solvent molecules are not able to attack the cation center on the side opposite the tosylate anion.[28,29] The second explanation for retention involves assistance by the anion to the acetic acid molecule attacking from the front side. This type of explanation has been offered for the net retention observed with several arylmethyl *p*-nitrobenzoates;[30] a process approximating an SNi reaction is apparently responsible for this retention.[31] However, the stereospecificity was much lower in these reactions than that which we observed, even though the *p*-nitrobenzoate anion is a stronger base than the tosylate anion.

Another criterion usually employed in elucidating the mechanism of reactions involving σ participation is rate enhancement.[32] The major problem encountered in these arguments, as well as in the present study, is trying to decide what the rate would be in the absence of participation or anchimeric assistance. Since the

(24) For reviews of the bridged-ion problem, see (a) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 126; (b) J. A. Berson, "Molecular Rearrangements," Part 1, P. deMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 111; (c) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965; (d) G. D. Sargent, *Quart. Rev.*, **20**, 301 (1966); (e) B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms, 1965," Interscience Publishers, New York, N. Y., 1966, p 1; "Organic Reaction Mechanisms, 1966," Interscience Publishers, New York, N. Y., 1967, p 1; (f) H. C. Brown, *Chem. Brit.*, 199 (1966); *Chem. Eng. News*, **45**, No. 7 86 (1967); (g) G. A. Olah, *ibid.*, **45**, No. 14, 77(1967); (h) H. L. Goering and G. N. Fickes, *J. Amer. Chem. Soc.*, **90**, 2848, 2856, 2862 (1968).

(25) See (a) C. W. Shoppee and G. A. R. Johnston, *J. Chem. Soc*, 3261 (1961), (b) C. A. Bunton and Y. F. Frei, *ibid.*, 1872 (1951).

(26) (a) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *J. Amer. Chem. Soc.*, **87**, 2137 (1965); (b) H. C. Brown, R. Bernheimer, C. J. Kim, and S. E. Scheppele, *ibid.*, **89**, 370 (1967).

(27) S. Winstein and B. K. Morse, *ibid.*, **74**, 1133 (1952).

(28) (a) P. S. Skell and R. J. Maxwell, *ibid.*, **84**, 3963 (1962); (b) G. J. Karabatsos, R. A. Mount, D. O. Rickter, and S. Meyerson, *ibid.*, **88**, 5651 (1966); (c) H. C. Brown and M. H. Rei, *ibid.*, **86**, 5008 (1964).

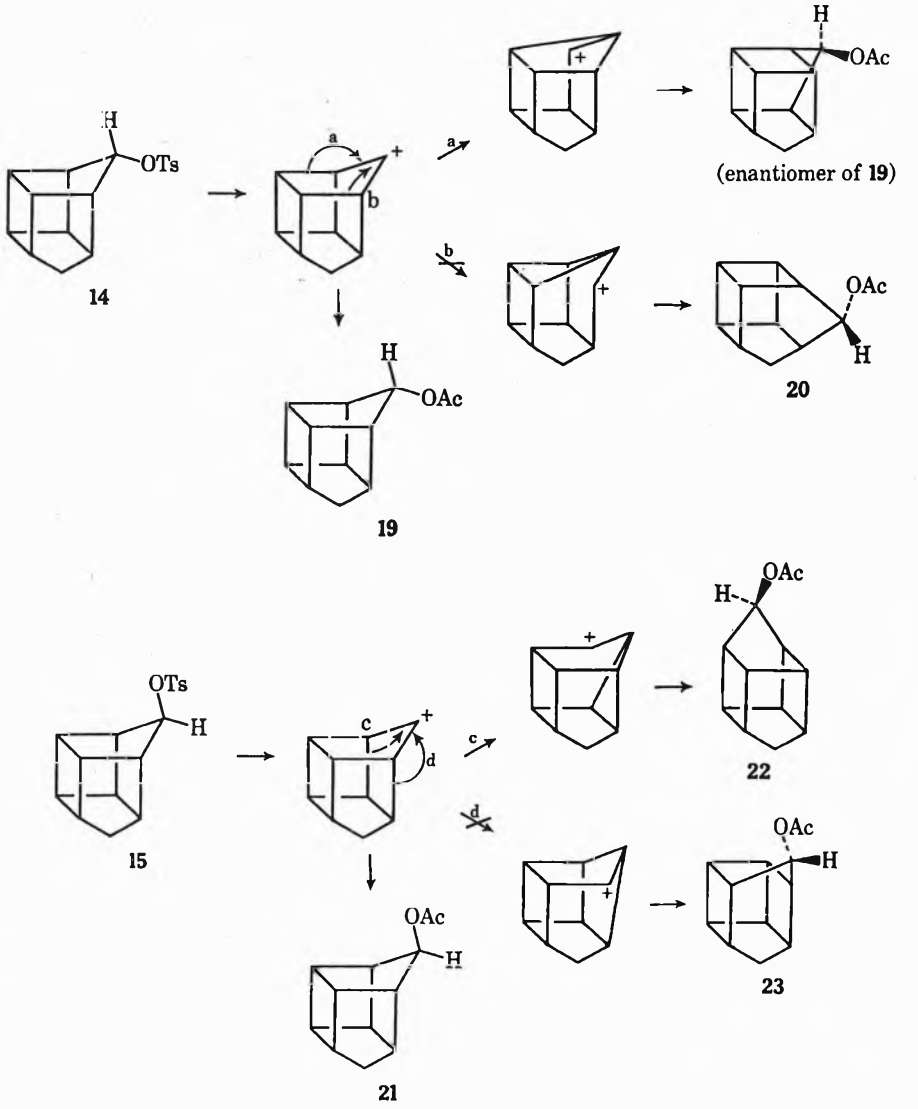
(29) If the rearrangement is truly this fast, it would appear that the ions involved would be essentially single vibrating bridged ions.

(30) (a) H. L. Goering and S. Chang, *Tetrahedron Lett.*, 3607 (1965); (b) H. L. Goering, R. G. Briody, and J. F. Levy, *J. Amer. Chem. Soc.*, **85**, 3059 (1963).

(31) H. Hart and H. S. Eleuterio, *ibid.*, **76**, 1379 (1954).

(32) P. von R. Schleyer, *ibid.*, **86**, 1856 (1964).

SCHEME I



6-pentacyclodecyl system contains the 7-norbornyl nucleus, one might choose the latter as a model[18,33] for predicting the unassisted rate for the former. On this basis, the rate accelerations for both the *syn* and *anti* tosylates **14** and **15** at 25° are *ca.* 10^5–10^6.[34] However, the carbonyl stretching frequency of 7-norbornanone is 1773 cm^{-1} [33] while that for 6-pentacyclodecanone **18** is only 1760 cm^{-1}. Because the carbonyl stretching frequency is sensitive to and reflects the C–CO–C bond angle, and ionization of the corresponding tosylate system is inhibited by a small C–C–C angle, the 7-norbornyl system may not be a good model. Schleyer[18] has developed an equation which utilized the carbonyl frequency of the ketone corresponding to the secondary tosylate in question as well as several other strain factors for calculating unassisted solvolysis rates. The calculated unassisted solvolysis rate constants at 25° for the *syn* and *anti* tosylates **14** and **15** are 2.3×10^{-13} sec^{-1} and 1.9×10^{-13} sec^{-1}, respectively, which correspond to rate acceleration factors of 1.3×10^4 and 5×10^3, respectively. It appears to us that Schleyer's equation is the best model for estimating unassisted solvolysis rates at the present time, although the use of this correlation has come under attack.[36]

Another means of detecting unexpectedly high solvolysis rates is a correlation between these rates and the rates of sodium borohydride reduction of the corresponding ketones.[37] Such a correlation is shown in Figure 1. All of the data except those for the two pentacyclodecyl systems are taken from Brown and Muzzio's paper.[37] This series of bicyclic compounds, excluding the pentacyclodecyl systems and those for which anchimeric assistance is believed to be operative in solvolysis, such as *anti*-7-norbornenyl, show at best a qualitative relationship between the rates of solvolysis and borohydride reduction as pointed out by these authors. The correlation line drawn between the cyclopentyl and 7-norbornyl compounds, as suggested by these authors, is one which gives a reasonable locus for the remaining points. Using this correlation line, one calculates rate accelerations of 320 and 1300 respectively for acetolysis of the *syn* and *anti* tosylates

(33) C. S. Foote, *J. Amer. Chem. Soc.*, **86**, 1853 (1964).

(34) The rate of acetolysis of 7-norbornyl tosylate at 25° is 6.4×10^{-15} sec^{-1}.[35]

(35) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Amer. Chem. Soc.*, **77**, 4183 (1955).

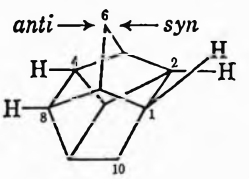
(36) H. C. Brown, I. Rothberg, P. von R. Schleyer, M. M. Donaldson, and J. J. Harper, *Proc. Nat. Acad. Sci.*, **56**, 1653 (1966).

(37) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966).

14 and **15**. However, owing to the poor correlation in general for the points in Figure 1, we cannot state unequivocally, based on this correlation, whether or not there is anchimeric assistance to ionization in the solvolysis of the 1,3-bishomocubyl systems.

It appears to us that the kinetic data indicates the possibility of anchimeric acceleration in the solvolyses of the tosylates **14** and **15**, but that an unambiguous answer cannot be given at the present time. The stereochemical results appear to us to be most consistent with and most simply explained by the intermediacy of bridged cations. However we cannot rule out certain other possibilities such as two noninterconverting sets of rapidly equilibrating non-bridged ion pairs.

The predominance of *anti* attack in the hydride reductions of the ketone **18** can be rationalized by an examination of molecular models. Due to the methylene group at C-10, the hydrogen atom on C-1 projects upward toward the methylene bridge at C-6. The other three hydrogen atoms at C-2, -4, and -8 lie essentially in the plane described by C-2, -4, and -8.



This steric approach control[38] in these reductions is expected because of the strained nature of the sp^2 carbon atom (C-6) in the ketone **18**, which would lead to a transition state similar to the reactants. On the other hand, the 50:50 distribution obtained on equilibration of the alcohols **8** and **9** indicates equal thermodynamic stability for the two isomers, *i.e.*, very little or no effect of the C-1 hydrogen atom. The hydride reductions are expected to be more sensitive to steric effects than the equilibration, owing to a perpendicular attack of the reducing agent on the carbonyl carbon atom. The actual energy differences ($\Delta\Delta F^{\ddagger}$) in the two modes of reduction are not great, *ca.* 0.7–0.8 kcal/mol.

Experimental Section

Melting points were determined in capillary tubes and are corrected. Boiling points are not corrected. Infrared spectra were recorded using a Perkin-Elmer 337 double grating spectrometer by Mr. F. L. Beman and coworkers. The precision infrared carbonyl frequencies of the ketone **18** were measured directly with the optical read-out on a Beckman IR-9 spectrometer by Dr. W. J. Potts, Jr., and coworkers. Nuclear magnetic resonance (nmr) spectra were obtained by Mr. Beman and coworkers with a Varian A-60 spectrometer. The chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane. Mass spectral analyses were performed by Mrs. W. L. Dilling and coworkers with a magnetically scanning 90° sector spectrometer using an electron ionizing voltage of 75 eV and a vaporizer temperature of 200° unless specified otherwise. High resolution mass spectra were obtained by Dr. L. A. Shadoff with a Consolidated Electrodynamics 21-110B spectrometer. Microanalyses were determined by Mr. L. E. Swim and coworkers. Gas chromatographic (gc) analyses were performed with a F & M 500 gas chromatograph. Thin layer chromatographic analyses were performed by Dr. N. E. Skelly.

(38) *Cf.* H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 28–32.

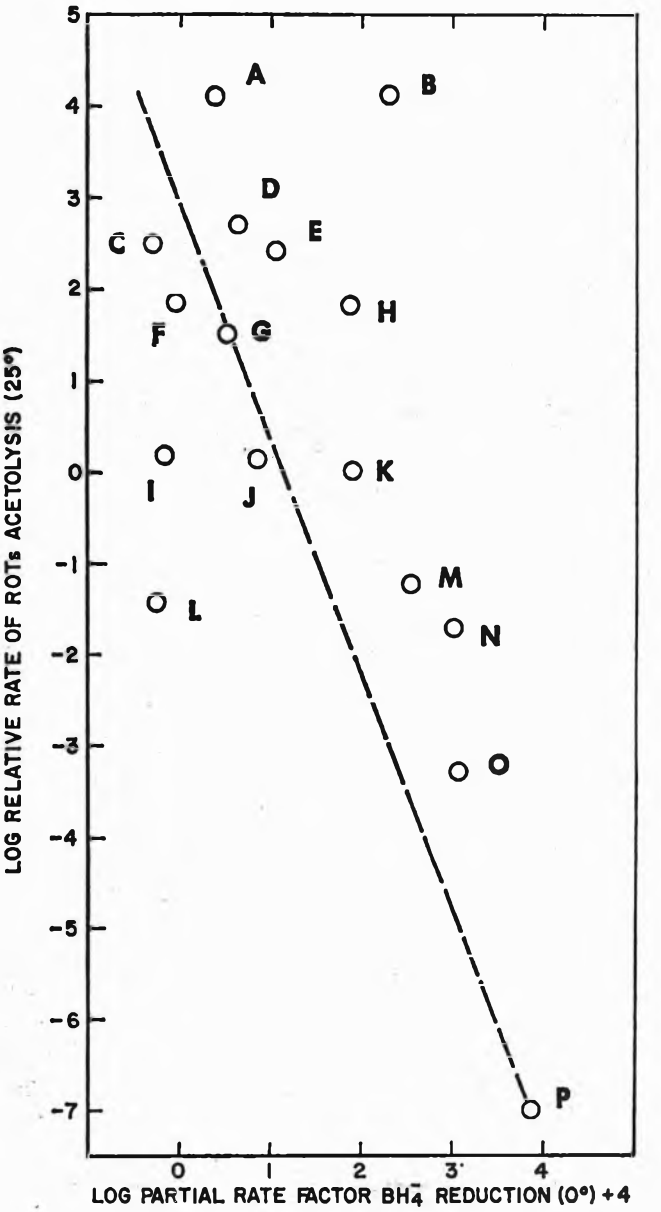
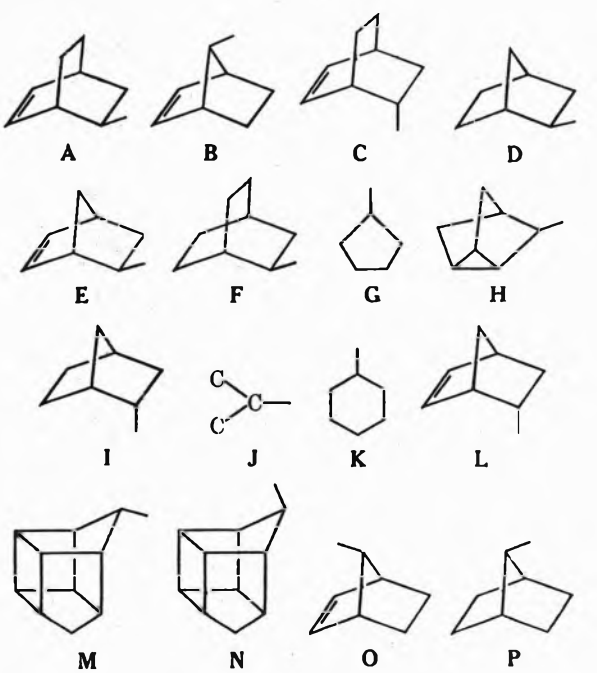


Figure 1.—Plot of logarithms of the relative rates of tosylate acetolysis *vs.* the logarithms of the partial rate factors for borohydride reduction.



endo,syn-Tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-ol (11).—The first preparations of this material were made by the lithium aluminum hydride reduction of *endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one (28).[9] In some cases products resulting from reduction of the conjugated double bond occurred. These side products could be eliminated by using aluminum hydride in place of lithium aluminum hydride.

A slurry of aluminum hydride[39] in ether was prepared by adding aluminum chloride (0.4 g, 3 mmol) in small portions to a stirred mixture of lithium aluminum hydride (0.38 g, 10 mmol) in 50 ml of dry ether.

To this stirred slurry of aluminum hydride and lithium chloride, a solution of the ketone 28 (0.50 g, 3.4 mmol) in 10 ml of ether was added dropwise. The reaction mixture was stirred for 0.5 hr at room temperature and hydrolyzed by the cautious addition of 5 ml of water followed by 15 ml of 5 *N* hydrochloric acid. The ether layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of the solvent and sublimation of the residue at 100° (0.5 mm) afforded 0.38 g (76%) of dienol 11. Analysis by gc (column A, 10-ft × 0.25-in. 20% Apiezon L on 60–80 mesh Chromosorb WAW, 150°, helium flow rate 150 ml/min) showed only one peak for the alcohol 11. The infrared and nmr spectra were identical wth those of a sample prepared by the lithium aluminum hydride reduction; the mixture melting point was not depressed.

syn-Pentacyclo[5.3.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]decan-6-ol (8).—A solution of the *syn* dienol 11 (3.8 g, 26 mmol) in 140 ml of redistilled acetone was purged with a slow stream of purified nitrogen for 1.5 hr. The solution was irradiated with a 450-W Hanovia medium pressure mercury arc lamp (type 679 A) through a 9700 Corex filter. The reaction was followed by gc analysis (column A, 225°, 40 ml/min): 11, R_t 7.7 min; 8, R_t 9.7 min. After irradiation for 1.5 hr, the conversion of 11 to 8 was essentially complete. An additional 6.3 g (43 mmol) of the alcohol 11 was completely reacted after 2 hr of similar treatment. The acetone was removed *in vacuo* from the combined reaction mixtures to give 10.7 g of a viscous yellow oil. This crude product was sublimed twice at 110° (0.5 mm) and recrystallized once from hexane to give 2.0 g (20%) of crystalline product 8. Further recrystallization gave a sample: mp 175–176° (lit.[12] mp 180–181°); $\nu_{max}^{CCl_4}$ 3640 (w), 3340 (m, br), 2975 (s), 2860 (m), 1455 (w), 1340 (m) cm^{-1}; $\nu_{max}^{CS_2}$ 1290 (m), 1264 (m), 1245 (m), 1206 (w), 1196 (m), 1162 (m), 1129 (m), 1080 (s), 1047 (s), 1030 (m), 1018 (m), 951 (w), 941 (m), 889 (w), 878 (w), 846 (w), 835 (m), 800 (w), 789 (w), 768 (w), 698 (m), 619 (w), 547 (w), 520 (w), 481 (w) cm^{-1}. Nmr spectral data are given in Table I. The mass spectrum was consistent with that reported previously.[13]

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16; mol wt, 148. Found: C, 81.4; H, 8.09; mol wt, 148 (mass spectroscopy).

anti-Pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]decan-6-ol (9).—A solution of *endo,anti*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-ol[9] (12) (10.0 g, 67.6 mmol) in 150 ml of acetone was irradiated as described above for the *syn* isomer. The reaction was also followed by gc analysis as described for the *syn* isomer: 12, R_t 8.2 min; 9, 9.7 min. After irradiation for 6.5 hr, the conversion of 12 to 9 was essentially complete. The acetone was removed to give 12.8 g of viscous yellow oil containing some crystalline material. Sublimation twice at 100° (0.5 mm) gave 5.1 g of soft white crystals. Recrystallization once from hexane gave 3.1 g (31%) of the alcohol 9, mp 145–155°. Additional recrystallization gave a sample: mp 164–166° (lit.[12] mp 171–172°); $\nu_{max}^{CCl_4}$ 3640 (w), 3340 (m, br), 2975 (s), 2860 (m), 1455 (w), 1340 (m) cm^{-1}; $\nu_{max}^{CS_2}$ 1297 (m), 1245 (m), 1202 (m), 1185 (m), 1090 (s), 1078 (s), 1052 (s), 1031 (m), 1010 (w), 980 (w), 953 (w), 948 (m), 926 (m), 899 (w), 879 (w), 847 (w), 806 (w), 779 (w), 768 (w), 708 (m), 636 (w), 553 (w), 502 (w), 462 (w) cm^{-1}. Nmr spectral data are given in Table I. The mass spectrum was consistent with that reported previously.[13]

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16; mol wt, 148. Found: C, 81.2; H, 8.15; mol wt, 148 (mass spectrometry).

By the procedure described above, a solution of *endo,syn*-tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-10-ol[9] (13) (6.2 g, 42 mmol) in 150 ml of acetone was irradiated for 2 hr. The gc retention time of 13 under conditions described in the preceding section was 8.2 min. Removal of the acetone gave 7.0 g of a yellow oil which partially crystallized on cooling. Sublimation at 80–90° (0.5–1.0 mm) and crystallization from pentane gave 1.81 g (29%) of crystals. Three additional recrystallizations of this material gave a sample of the alcohol 9, mp 160–164°, showing infrared and nmr spectra identical with those reported above for 9.

All attempts to separate mixtures of the isomeric alcohols 8 and 9 were unsuccessful. Crystallization from heptane and sublimation of an 80:20 mixture of 5 and 6 did not result in any fractionation.[13] The two alcohols had the same retention time on 17 different packed gc columns.[13] A mixture of 8 and 9 emerged as a single peak, R_t 28 min, from a 100 ft × 0.01 in. capillary column coated with 1,2,3-tris(2-cyanoethoxy)propane operated at 100°. Thin layer chromatography of the alcohol mixture on silica gel G with chloroform produced only one spot on development.

syn-Pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]dec-6-yl Acetate (19).—A 0.50-g (3.4 mmol) sample of the mixture of alcohols (80% 8, 20% 9) obtained from the lithium aluminum hydride reduction of the corresponding ketone 18[13] was converted to the acetate mixture by stirring with 2 ml of acetic anhydride in 5 ml of pyridine at room temperature for 24 hr. The mixture was treated with 20 ml of water and extracted six times with 10 ml portions of pentane. The combined extracts were washed once with water, once with 10% hydrochloric acid, and again with water. After drying over anhydrous sodium sulfate, the pentane solution was decanted from the drying agent, and the pentane was removed under vacuum to give 0.58 g (90%) of acetates (80% 19, 20% 21): ν_{max}^{neat} 2980 (s), 2865 (w), 1740 (s), 1460 (w), 1380 (m), 1360 (w), 1277 (s), 1251 (s), 1231 (s), 1071 (m), 1042 (s) cm^{-1}; nmr spectrum (CCl_4), a broad singlet at −4.96 (0.21 H, –CHOAc– of 21), a broad singlet at −4.70 (0.84 H, –CHOAc– of 19), a broad multiplet at −3.1 to −2.3 with maximum intensity at −2.68 (8.0 H, –C(H)–), a singlet at −1.97 (2.4 H, CH_3CO_2– of 19), a singlet at −1.87 (0.6 H, CH_3CO_2– of 21), and a pair of unsymmetrical doublets (with further ill-defined splitting) centered at −1.66 and −1.39 ppm (1.9 H, $-CH_2-$ of 19, J_{gem} = 11.0 cps, minor absorption for $-CH_2-$ of 21 also visible, see following); mass spectrum, *m/e* 190 (M^+), 82 ($C_5H_6O^+$, base peak). Gc analysis (column A, 200°, 40 ml/min) showed a single peak, R_t 23.4 min.

anti-Pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]dec-6-yl Acetate (21).—As described above for the *syn* isomer, a solution of the *anti* alcohol 9 (0.50 g, 3.4 mmol) and 2 ml of acetic anhydride in 5 ml of pyridine was converted to 0.66 g (103%) of the *anti* acetate 21: ν_{max}^{neat} 2980 (s), 2865 (w), 1740 (s), 1460 (w), 1380 (m), 1360 (w), 1298 (m), 1268 (s), 1251 (s), 1230 (m) 1219 (m), 1204 (m), 1077 (m), 1045 (s), 936 (m) cm^{-1}; nmr spectrum ($CDCl_3$), a broad singlet at −5.06 (0.9 H, –CHOAc–), a broad multiplet at −3.0 to −2.4 with maximum intensity at −2.79 and −2.65 (7.9 H, —C(H)–), a singlet at −1.94 (3.1 H, CH_3CO_2), and a pair of unsymmetrical doublets (with further ill-defined splitting) centered at −1.66 and −1.25 ppm (2.1 H, $-CH_2-$, j_{gem} 11.0 cps); mass spectrum, *m/e* 82 ($C_5H_6O^+$, base peak).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; mol wt, 190. Found: C, 75.6; H, 7.16; mol wt, 190 (mass spectroscopy).

Gc analysis showed *ca.* 2% lower-boiling impurity.

syn-Pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]dec-6-yl *p*-Toluenesulfonate (14).—According to the method of Tipson,[40] the *syn* alcohol 8 (0.76 g, 5.1 mmol) and *p*-toluenesulfonyl chloride (1.0 g, 5.2 mmol) in 5 ml of pyridine were mixed at 0° and stirred at 0° for 1 hr. The mixture was stirred at room temperature for 2 hr, and then, while cooling in an ice bath, treated with 30 ml of water. The resulting milky mixture was extracted three times with 20-ml portions of methylene chloride, and the combined organic extracts were washed once with water, twice with 20-ml portions of 10% hydrochloric acid solution, and again with water. After drying over anhydrous sodium sulfate, the drying agent was removed by filtration, and the methylene chloride was removed *in vacuo* to give 1.35 g (87%) of crude *syn* tosylate 14. Four recrystallizations from hexane gave a sample for analysis and kinetic studies: mp 64.5–65.5°; $\nu_{max}^{CCl_4}$ 2990 (m), 2940 (w), 2870 (w), 1375 (m), cm^{-1}; $\nu_{max}^{CS_2}$ 1192 (s), 1180 (s), 988 (s), 962 (m), 939 (m), 918 (m), 890 (m), 857 (s), 815 (m), 669 (s), 563 (s) cm^{-1}; nmr spectrum (CCl_4), a pair of unsymmetrial doublets centered at −7.74 and −7.28 (3.7 H, Ar–H, J_{vic} = 8.2 cps), a broad singlet at −4.50 (1.0 H, –CHOTs–), a singlet at −2.45 (Ar–CH_3) superimposed on a broad multiplet at −3.1 to −2.3

(39) M. J. Jorgenson, *Tetrahedron Lett.*, 559 (1962).

(40) R. S. Tipson, *J. Org. Chem.*, 9, 235 (1944).

with maximum intensity at −2.65 (10.9 H total, —C–H), and a pair of unsymmetrical doublets (with further ill-defined splitting) centered at −1.65 and −1.37 ppm (2.4 H, $-CH_2-$, J_{gem} = 11 cps); mass spectrum (*ca.* 40°, direct probe sample introduction), *m/e* 130.0781 ($C_{10}H_{10}^+$, *m/e* calcd 130.0783, base peak).

Anal. Calcd for $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00; S, 10.60; nuclidic mass, 302.0977. Found: C, 67.2; H, 5.88; nuclidic mass, 302.0980.

***anti*-Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-yl *p*-Toluenesulfonate (15).**—As described above for the *syn* isomer, 1.96 g (13.2 mmol) of the *anti* alcohol 9 and *p*-toluenesulfonyl chloride (2.7 g, 14 mmol) in 10 ml of pyridine were converted to 4.0 g of tosylate, obtained as a brown oil. Crystallization from hexane gave 3.6 g (90%) of crystalline tosylate, **15**, mp 61–70°. A sample was recrystallized for analysis and kinetic acetolysis: mp 78–78.5°; $\nu_{max}^{CCl_4}$ 2990 (m), 2740 (w), 2870 (w), 1375 (m) cm^{-1}; $\nu_{max}^{CS_2}$ 1190 (s), 1179 (s), 989 (s), 974 (m), 923 (s), 900 (m), 859 (m), 833 (m), 814 (m), 669 (m), 563 (s), cm^{-1}; nmr spectrum ($CDCl_3$), a pair of unsymmetrical doublets centered at −7.76 and −7.32 (3.9 H, Ar–H, J_{vic} 8.3 cps), a broad singlet at −4.85 (1.0 H, –CHOTs–), a singlet at −2.44 (Ar–CH_3) superimposed on a broad multiplet at −3.0 to −2.2 with maximum intensity at −2.68 and −2.56 (10.9 H total, —C–H), and a pair of unsymmetrical doublets centered at −1.60 and −1.19 ppm (2.2 H, $-CH_2-$, J_{gem} 11.0 cps); mass spectrum (*ca.* 40°, direct probe sample introduction), *m/e* 130 ($C_{10}H_{10}^+$, base peak).

Anal. Calcd for $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00; S, 10.60; nuclidic mass, 302.0977. Found: C, 67.6; H, 5.80; nuclidic mass, 302.0983.

Preparative Acetolysis of *syn* Tosylate 14.—A solution of the *syn* tosylate 14 (0.89 g, 2.9 mmol) in 50 ml of glacial acetic acid was heated at 120° in a constant temperature bath for 7 hr (10 half-lives). After cooling to room temperature, the mixture was poured into 300 ml of water, and the cloudy mixture was extracted with methylene chloride (2 × 100 ml, 3 × 50 ml). This reaction was much cleaner, giving less insoluble material than was observed in the solvolysis of the isomeric *anti* tosylate **12** (see below). The combined extracts were washed with 5% sodium bicarbonate solution (100 ml, 50 ml) until the aqueous layer remained basic to bromophenol blue indicator, washed once with water (100 ml), and dried over anhydrous sodium sulfate. Removal of the drying agent by filtration and evaportion of the methylene chloride under vacuum gave 0.62 g of crude product. Infrared and nmr spectral analyses showed only acetate absorption; no tosylate or alcohol was detected. Gc analysis (column A, 175°, 40 ml/min) showed one major peak, R_t 37.4 min, with a slight shoulder, R_t *ca.* 34.5 min. Injection of a mixture of the crude solvolysis product and an authentic sample of the *syn* acetate **19** showed only one peak.

A sample, 0.58 g (3.1 mmol) of the crude solvolysis product, dissolved in 5 ml of dry ether, was added dropwise to a stirred slurry of 0.23 g (6 mmol) of lithium aluminum hydride in 10 ml of ether. After reaction for 16 hr at room temperature, the mixture was hydrolyzed with 0.5 ml of water and 1 ml of 5% sodium hydroxide solution. The insoluble salts were removed by filtration, and the filtrate was dried over anhydrous sodium sulfate. Removal of the ether under vacuum gave 0.41 g (94% from tosylate) of the *syn* alcohol **8** as shown by comparison of the infrared and nmr spectra with those of an authentic sample. The nmr spectrum indicated the possibility of the presence of up to 3–4% of the *anti* alcohol **9** by weak absorption at *ca.* −4.3 ppm. Gc analysis of the alcohol (column A, 175°, 40 ml/min) showed one major component corresponding by retention time (25.2 min) to the *syn* alcohol **8** and a minor component (*ca.* 4% of the total area) corresponding by retention time (23.2 min) to pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-ol (**10**) (see below). The spectra of the crude product gave no indication of the identity of this minor component, and no further attempt at its identification was made.

Preparative Acetolysis of *anti* Tosylate 15. A. At 120° for 11 Half-lives. Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-ol (10).—A solution of 1.86 g (6.15 mmol) of the *anti* tosylate **15** in 100 ml of glacial acetic acid was heated in a constant temperature bath at 120° for 42 hr (11 half-lives). The dark reaction mixture was poured into 600 ml of water through a cotton filter to remove some of the black insoluble material present. The cloudy mixture was extracted with methylene chloride, and the combined organic extracts were washed with saturated sodium bicarbonate solution and with water, and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the methylene chloride removed under vacuum to give 0.93 g (80% yield) of an acetate as shown by the infrared spectrum. No tosylate or alcohol bands were observed in the infrared spectrum.

A sample of the product acetates (0.80 g, 4.2 mmol) in 5 ml of dry ether was added dropwise to a stirred slurry of 0.23 g (6 mmol) of lithium aluminum hydride in 15 ml of ether. After stirring at room temperature for 15 hr, the reaction mixture was hydrolyzed by the addition of 1 ml of 5% sodium hydroxide solution followed by 0.5 ml of water. The insoluble salts were removed by filtration, and the ether filtrate was dried over anhydrous sodium sulfate. The ether was removed by distillation to give 0.58 g (94% yield from acetate, 75% from tosylate) of crystalline alcohol product, mp 115–135°. Nmr analysis of this product showed it to be a mixture of 15% *anti* alcohol **9** and 85% pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-ol (**10**) based on the resonances at −4.28 and −4.07 ppm, respectively. Gc analysis under conditions described in the preceding experiment showed two overlapping peaks with retention times of 23.6 min (**10**) and 25.2 min (**9**). The relative amounts were approximately the same as those shown by nmr analysis. Injection of a mixture of the reduction product and a known sample of the *anti* alcohol **9** caused enhancement of the minor peak. On a 10 ft × 0.25 in. Ucon Polar column at 200°, thered uction mixture showed two peaks with retention times of 44.7 and about 46.0 min. The retention time of the *anti* alcohol **9** was 46.1 min under identical conditions. The presence of several per cent *syn* alcohol **8** would not have been detected by nmr or gc.

Recrystallization of the alcohol mixture twice from pentane gave 0.23 g of alcohol **10** (containing 10% of the *anti* alcohol **9**): mp 143–144° (lit.[5] mp 137–140°); $\nu_{max}^{CCl_4}$ 3640 (w), 3330 (m, br), 2970 (s), 2920 (m), 2850 (m) cm^{-1}; $\nu_{max}^{CS_2}$ 1300 (m), 1272 (m), 1250 (m), 1085 (s), 1074 (s), 1050 (s), 1012 (m), 922 (m) cm^{-1}; nmr spectrum ($CDCl_3$), a broad singlet at −4.08 (0.90 H, –CHOH–) (0.10 H also appeared at −4.28 for **9**), broad multiplet at −3.1 to −2.3 with maximum intensity at −2.91, −2.70, and −2.51 (8.0 H, –C–H), a singlet at −2.15 (1.0 H, O–H), and a singlet at −1.39 ppm (2.0 H, $-CH_2-$) (minor absorption at −1.7 to −1.1 also appeared for **9**); mass spectrum, *m/e* 148 (M^+), 66 ($C_5H_6^+$, base peak). The infrared and nmr spectra were in agreement with the spectra of the symmetrical alcohol **10** provided by Professor W. G. Dauben.[5]

B. At 100° for One Half-life. Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]-dec-6-yl *p*-Toluenesulfonate (17).—A solution of the *anti* tosylate **15** (1.0 g, 3.3 mmol) in 40 ml of acetic acid was heated at 100° for 22.5 hr. Work-up as in part A gave 0.80 g of a partially crystalline product mixture of tosylate and acetate as indicated by the infrared spectrum. The nmr spectrum ($CDCl_3$) if the mixture indicated the presence of both acetate and tosylate products and both the pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane and pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane skeletal systems. The relative peak areas were −7.9 to −7.2 ppm, 46.2 (due to 4 H), *anti* tosylate **15** and rearranged tosylate **17**; −4.85 ppm, 11.2 (1 H), *anti* tosylate **15** and rearranged acetate **22**; −4.64 ppm, 5.8 (1 H), rearranged tosylate **17**; −2.07 ppm, 8.0 (6 H), acetic anhydride; −1.97 ppm, 16.0 (3 H), rearranged acetate **22**; −1.8 to −1.5 and −1.3 to −1.1 ppm, ~15.8 (2 H), *anti* tosylate **15**; −1.5 to −1.3 ppm, ~19.2 (2 H), rearranged acetate **22** and rearranged tosylate **17**. The composition of this material was calculated from this data to be 32% (mol) *anti* tosylate **15**; 32% rearranged tosylate **17**; 29% rearranged acetate **22**; and 7% acetic anhydride. This material accounts for 89% of the starting tosylate **15**; yields are 30% recovered *anti* tosylate **15**, 30% rearranged tosylate **17**, and 28% rearranged acetate **22**. Based on unrecovered tosylates, these data indicate 40% acetolysis; the calculated value is *ca.* 48% based on an estimated rate constant of 8.2×10^{-6} sec^{-1} at 100°. The source of the acetic anhydride was the acetic acid solvent.

Recrystallization of the tosylate–acetate mixture three times from pentane gave a sample of crystalline tosylate, mp 59–62° (lit.[14] mp for **17**, 74–74.7°). The nmr spectrum ($CDCl_3$) indicated a 54:46 mixture of symmetrical tosylate **17** [broad singlets at −4.64, –CHOTs–, and −1.40 ppm, $-CH_2-$ (lit.[14] nmr in CCl_4, −4.58, −1.40 ppm)] and *anti* tosylate **15**. Infrared bands due to **17** not appearing in the spectrum of **15** were at 965 and 687 cm^{-1} (CS_2).

Oxidation of Alcohol 10. Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-one (16).—The alcohol **10** (0.23 g, 1.6 mmol), obtained above (90% pure), in 3 ml of ether was stirred for 2 hr at room temperature with 1 ml of a solution prepared by adding 5.0 g (16.8 mmol) of sodium dichromate dihydrate and 3.75 ml of 96% sulfuric acid to water to make a total volume of 25 ml.[41] The layers were separated, and the aqueous layer was extracted four times with 5-ml portions of ether. The combined ether extracts were washed once with saturated sodium bicarbonate solution, once with water, and dried over anhydrous sodium sulfate. Removal of the ether gave 0.15 g (63%) of crude product. Recrystallization from pentane gave light yellow crystals of the ketone **16**, mp 119–122° (lit. mp 120–122°,[5] 123°,[2b] 124.5–125.5°[14]); $\nu_{max}^{CCl_4}$ 2985 (m), 2930 (w), 2855 (w), 1755 (s) cm^{-1}; $\nu_{max}^{CS_2}$ 1260 (m), 1164 (m), 1156 (m), 1015 (w), 972 (w), 557 (m) cm^{-1}. The nmr spectrum was in good agreement with data reported in the literature.[5,42] The infrared and nmr spectra were in agreement with the spectra of the symmetrical ketone **16** provided by Professor W. G. Dauben.[5]

Procedure for Kinetic Acetolysis Runs.—The rates of acetolysis were determined titrimetrically by a procedure similar to that used by previous workers.[43] The acetic acid used for all kinetic work was prepared by refluxing with twice the calculate amount of acetic anhydride needed to react with the specified amount of water in the starting acid for 24 hr, and then distilling at a 10:1 reflux ratio through a 3-ft vacuum-jacketed Vigreux column. The middle cut, bp 115°, with 1% by weight added acetic anhydride, was used. The standard sodium acetate solution (4.03×10^{-3} *M*) was prepared by refluxing 106.7 mg of primary standard sodium carbonate in about 200 ml of the dry acetic acid and then diluting the resulting solution to 500 ml at room temperature in a volumetric flask. Ampoules were prepared for use by soaking them overnight in chromic acid cleaning solution. After being rinsed well with water, the ampoules were soaked in 10% aqueous ammonia solution, again rinsed well with water, and finally dried in an oven at 130° for several hours. The bromophenol blue indicator was used as a saturated solution in acetic acid. Tosylate samples were weighed into tared 25-ml volumetric flasks and diluted to volume with acetic acid. The samples were dissolved by shaking, and 2-ml aliquots were dispensed from a burette into 3-ml ampoules. The ampcules were sealed and placed in an oil bath maintained at the desired temperature (± 0.1°). After a temperature equilibration period of 5–10 min, the first ampoule was withdrawn at zero time, and succeeding ampoules were withdrawn at appropriate times. The withdrawn ampoules were allowed to cool to room temperature and opened. The contents were titrated to the yellow bromophenol blue end point with the standard sodium acetate solution. The tosylate concentrations and other pertinent data for the kinetic runs are presented in Table IV.

TABLE IV

SUMMARY OF KINETIC ACETOLYSIS[a] DATA FOR *syn* TOSYLATE **14** AND *anti* TOSYLATE **15**

Run	Tosylate	Temp, °C	Initial concn, *M*	No. of points taken	% reaction followed	Infinity titration, % of theory
1	14	110	0.0164	8	76	97.4
2	14	110	0.0149	9	77	97.8
3	14	120	0.0159	10	79	95.8
4	14	120	0.0133	10	80	94.0
5	15	120	0.0194	6	53	90.4
6	15	120	0.0250	9	87	98.5
7	15	130	0.0216	10	88	101.8
8	15	130	0.0193	10	79	103.2

[a] Typical experimental data are presented in Table V.

The rate constants were obtained by the infinity titer method using the equation

$$2.303 \log \frac{A_\infty - A_0}{A_\infty - A_t} = k_t$$

TABLE V

KINETICS OF ACETOLYSIS OF *syn* TOSYLATE **14** AT 110.0 ± 0.1°

Run 1		Run 2	
Time, sec	Log $\frac{A_\infty - A_0}{A_\infty - A_t}$	Time, sec	Log $\frac{A_\infty - A_0}{A_\infty - A_t}$
556	0.0228	613	0.0342
929	0.0481	1262	0.0674
1485	0.0748	1781	0.0896
2576	0.1281	2423	0.1268
4341	0.2146	4105	0.2103
5991	0.3109	5514	0.2835
12400	0.5644	8701	0.4333
		12088	0.5962

where A_∞, A_0, and A_t are the number of milliliters of standard sodium acetate solution required for the titration of the aliquots after 10 half-lives (average of 2), at time zero, and at time t, respectively. The data from the duplicate runs were combined in a least squares analysis[16] to evaluate the rate constants (Table II).

Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-6-one (18).—Material for the infrared measurements was prepared by irradiation of *endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**1**)[9] as described by Cookson and coworkers.[12,44] Purification was achieved by column chromatography on Woelm acid-washed alumina, activity grade I, using hexane–ether as the eluent, followed by sublimation at 70° (9 mm), mp 126.5–127.5° (lit. mp 122–126°,[12] 124–126°,[44] 124.5–125.5°[2b]). Infrared spectra were recorded with 1.5% and 10% (wt/vol.) solutions: partial spectrum, $\nu_{max}^{CCl_4}$ (log I_0/I for 1.5% solutions), 1783.3 (0.50), 1762.7 (1.15) 1742.2 (0.30), ~1720 (0.04, shoulder), 1697.2 (0.05), 1670 cm^{-1} (0.007); $\nu_{max}^{CS_2}$ 879 (0.03), 862 (0.08), 849 cm^{-1} (0.03).

Lithium Tri-*t*-butoxyaluminum Hydride Reduction of Ketone 18.—A slurry of lithium tri-*t*-butoxyaluminum hydride was prepared by adding 1.90 g (25.6 mmol) of *t*-butanol to a mixture of 0.30 g (7.9 mmol) of lithium aluminum hydride in 100 ml of ether. To this stirred mixture there was added 0.50 g (3.4 mmol) of ketone **18** as a solution in 5 ml of ether. The reaction mixture was stirred at room temperature for 1 hr and then hydrolyzed by adding 5 *N* hydrochloric acid until the solids dissolved. The ether layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of the solvent and sublimation of the residue afforded 0.25 g (50%) of a mixture of alcohols, mp 168–172°. Analysis by nmr indicated the composition to be 80 ± 1% *syn* isomer **8** and 20 ± 1% of the *anti* isomer **9**.

Sodium Borohydride Reduction of Ketone 18.—A solution of sodium borohydride (0.20 g, 5.3 mmol) in 10 ml of methanol was stirred in an ice bath at 0–5°. Over a period of 5 min, a solution of 0.50 g (3.4 mmol) of ketone **18** in 3 ml of methanol was added dropwise such that the temperature did not rise above 15°. The reaction mixture was warmed to room temperature and stirred overnight. Decomposition of the borates was accomplished by adding dilute hydrochloric acid. The alcohols were precipitated by dilution with water. The products were extracted with ether, washed with water, and dried. Evaporation of the solvent and sublimation at 100° (0.5 mm) afforded 0.30 g (60%) of a mixture of alcohols, mp 166–171°. Analysis by nmr indicated 76 ± 1% alcohol **8** and 24 ± 1% alcohol **9**.

Procedure for Sodium Borohydride Reduction Kinetics of Ketone 18.—The rate of reduction of this ketone was obtained relative to that of cyclohexanone. A solution was made up containing 0.381 g (3.93 mmol) of cyclohexanone, 0.490 g (3.36 mmol) of ketone **18**, and 0.187 g of *o*-dichlorobenzene (internal standard), and diluted to 10 ml with 2-propanol. This solution was cooled for 15 min in an ice–water bath and added quickly to a cold (0°), stirred solution of 0.045 g (1.2 mmol) of sodium borohydride in 10 ml of 2-propanol. At intervals of 1, 2, and 10 min, 0.3-ml aliquots were removed and quenched by placing in vials containing 3 drops of 5 *N* hydrochloric acid. The ketone–alcohol ratios were determined by gc (10 ft × 0.25 in. 20% Carbowax 20M on Chromosorb WAW, 175° isothermal for 21 min, then programmed at 11°/min to 225°, finally isothermal at 225°, 40 ml/min): R_t cyclohexanone, 11.0 min; cyclohexanol, 12.8 min; *o*-dichlorobenzene, 20.0 min; ketone

(41) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).
(42) R. J. Stedman and L. D. Davis, *Tetrahedron Lett.*, 1871 (1968).
(43) (a) S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, **70**, 821 (1948); (b) H. Tanida, T. Tsuji, and H. Ishitobi, *ibid.*, **86**, 4904 (1964).
(44) R. C. Cookson, J. Hudec, and R. O. Williams, *Tetrahedron Lett.*, No. 22, 29 (1960).

18, 37.0 min; alcohols 8 and 9, 42.4 min. None of the starting materials or products were lost by other reactions to give nonvolatile products.

After a 1-min reaction, the ratio of cyclohexanone to cyclohexanol was 82.9:17.1, respectively. At the same time, the ratio of ketone 18 to the mixture of alcohols 8 and 9 was 18.5:81.5, respectively. After 2 min, the above ratios were 78.8:21.2 and 13.1:86.9. After 10 min, these ratios were 68.8:31.2 and 3.1:96.9. The relative rates were calculated by the equation below[45]

$$\frac{k_x}{k_y} = \frac{\log \frac{[X]_f}{[X]_i}}{\log \frac{[Y]_f}{[Y]_i}}$$

where i and f indicate initial and final. The relative rates were 8.97 after 1 min, 8.53 after 2 min, and 9.38 after 10 min.

The average relative rate for reduction of pentacyclodecanone 14 to cyclohexanone was 8.96 ± 0.43. Since the absolute rate for reduction of cyclohexanone at 0° is $1.61 \times 10^{-2}\ M^{-1}\ \text{sec}^{-1}$,[37] the calculated rate for 18 is $0.144 \pm 0.007\ M^{-1}\ \text{sec}^{-1}$.

Equilibration of *syn* 8 and *anti* 9 Alcohols.—According to the procedure of Wilcox and coworkers,[46] the reaction mixtures were made up in heavy-walled Pyrex tubes which were then frozen at −196° and sealed *in vacuo*. Each tube contained 100 mg (0.68 mmol) of alcohol, 300 mg (1.47 mmol) of aluminum isopropoxide, 20 μl (0.27 mmol) of acetone, and 2 ml of 2-propanol. The tubes were placed in a constant temperature oil bath at 120° and removed for analysis after the appropriate intervals. The reactions were worked up by pouring the contents of the tube into 5 ml of 5 *N* hydrochloric acid. This mixture was then diluted with water and the alcohols were extracted with two 20-ml portions of ether. The combined ether extracts were washed with water and dried ($MgSO_4$). The alcohols were recovered by evaporation of the ether and sublimation of the residue at 100° (0.5 mm). The recovery of the alcohols was *ca.* 75% in each run. The sublimate was analyzed by nmr. The two carbinol C–H (C-6) absorption peaks for 8 and 9 at −4.04 and −4.28 ppm, respectively, were recorded six times for each equilibration sample. The areas of the peaks were obtained by plainmeter integration and averaged. The results of these analyses are given in Table VI.

TABLE VI

ALUMINUM ISOPROPOXIDE EQUILIBRATION OF *syn* ALCOHOL 8 AND *anti* ALCOHOL 9

Starting alcohol	Equilibration time, hr	Distribution (%)[a] *syn* 8	*anti* 9
syn 8	95	51.2	48.8
	137	50.0	50.0
	169	50.3	49.7
anti 9	95	50.5	49.5
	168	50.0	50.0

[a] The range of precision in these values is ± 1%.

Registry No.—**8**, 20446-30-4; **9**, 20446-31-5; **10**, 20446-32-6; **14**, 20446-33-7; **15**, 20446-34-8; **18**, 20446-29-1; **19**, 20446-35-9; **21**, 20440-15-7.

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(45) G. A. Russell, "Technique of Organic Chemistry," Vol. VIII, Part I, 2nd ed, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p 343.

(46) C. F. Wilcox, Jr., M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).

Equilibration of *p*-Menthadienes in Acid and Base[1]

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Conditions are described for equilibrating the *p*-menthadienes with acid or base without getting appreciable amounts of the aromatization product, *p*-cymene. The equilibrium composition is given, and rate constants for the interconversions observed in acid and base are recorded and compared.

A great many studies have been reported involving acid-[3] and base-catalyzed[4] isomerizations of various substances to mixtures containing *p*-menthadienes. However, due to complicating side reactions, especially aromatization, equilibrium among the *p*-menthadienes appears to have been reached only in one case, involving potassium *t*-butoxide in dimethyl sulfoxide at 50°, which gave a 5:3:1 ratio of II, III, and V, respectively.[4c] In this study, only the three main constituents were identified, and the only rate constants given are for disappearance of starting materials. We wish to report a fuller analysis of the equilibrium composition, conditions for achieving it in acid and base with <10% of side reactions, and rate constants for many of the possible interconversions of the isomers.

Equilibrium was first reached with potassium *t*-butoxide in *t*-butanol at 200° for 8 hr. Starting from α-terpinene (II), 3,8-*p*-menthadiene (IV), or γ-terpinene (V), gas phase chromatography (gpc) gave virtually the same trace. Preparative gpc of the mixture in one case followed by spectral analysis and derivatization of the components showed the equilibrium mixture at 200° to contain the six isomers shown in Scheme I in the percentages indicated (relative to total diene = 100%; in a typical case, 1% of menthenes and 7% of *p*-cymene were also present). The stability order observed for the *p*-menthadienes can be rationalized in terms of the intrinsic stabilities of double bonds in various menthenes (Δ3 > 1Δ > Δ8 > the other three

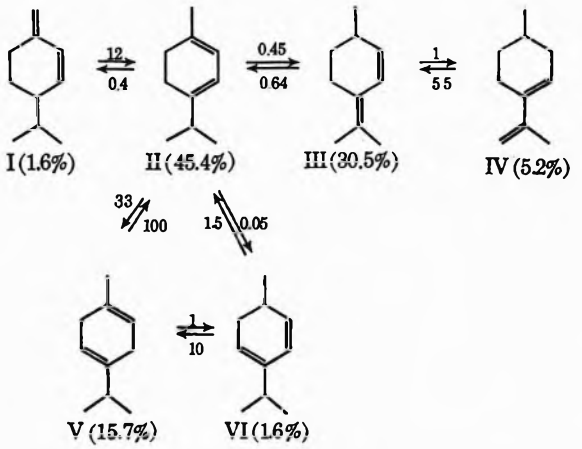
(1) Taken in part from the B.S. Thesis of H. P. Klein, University of Illinois, 1963, and the M.S. Thesis of E. J. Salacinski, University of Arizona, 1966; presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(2) Alfred P. Sloan Fellow, 1967–1969.

(3) For example, (a) O. Wallach, *Ann.*, **239**, 34 (1887); (b) W. A. Mosher, *J. Amer. Chem. Soc.*, **69**, 2139 (1947); (c) R. C. Palmer and A. F. Wicke, Jr., U. S. Patent 2,799,717; (d) J. Vergese, *J. Sci. Ind. Res.* (India), **18B**, 263 (1959); (e) E. von Rudloff, *Can. J. Chem.*, **39**, 1 (1961); (f) Y. Watanabe, *Kogyo Kagaku Zasshi*, **65**, 1573 (1962); (g) G. L. K. Hunter and W. B. Brogden, Jr., *J. Org. Chem.*, **28**, 1679 (1963); (h) M. I. Goryaev, V. I. Shabalina, and A. D. Dembitskii, *Dokl. Akad. Nauk SSSR*, **158**, 155 (1964); (i) G. Valkanas and N. Iconomou, *Pharm. Acta Helv.*, **39**, 441 (1964); (j) R. E. Wrolstad and W. G. Jennings, *J. Chromatog.*, **18**, 318 (1965).

(4) (a) H. Pines and H. E. Eschinazi, *J. Amer. Chem. Soc.*, **77**, 6314 (1955); (b) H. Pines and L. Schaap, *ibid.*, **79**, 2956 (1957); (c) S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Naslund, *J. Org. Chem.*, **33**, 221 (1968).

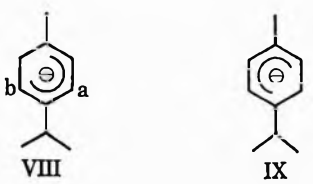
SCHEME I[a]



[a] Equilibrium percentages and rate constants (relative to V → II = 100; the absolute value for this rate constant was 4.5 ± 0.5 × 10^{-2} sec^{-1}) for isomerization of *p*-menthadienes at 200° with potassium *t*-butoxide in *t*-butanol.

positions[5]) coupled with small resonance energies for the cisoid conjugated dienes and *larger* resonance energies for the transoid conjugated dienes I and III.[6] Especially noteworthy is III, which in spite of having both double bonds in unfavorable positions on the menthane carbon skeleton, possesses sufficient resonance energy to be the second most stable isomer.

Rate constants for many of the interconversions were obtained by matching concentration *vs.* time curves for the observed dienes in kinetic runs starting from II, IV, and V, using an analog computer. Scheme I is based on the assumption that all the interconversions proceeded *via* pentadienyl carbanion intermediates. The rate constants for reactions leading to and from VI are considerably less certain than the others; since II and V equilibrate much more rapidly than VI forms, it is not clear how much VI is coming from each. The values given in Scheme I for the rate constants involving VI were based on the assumption that the pentadienyl carbanion VIII would protonate about eight times as



VIII

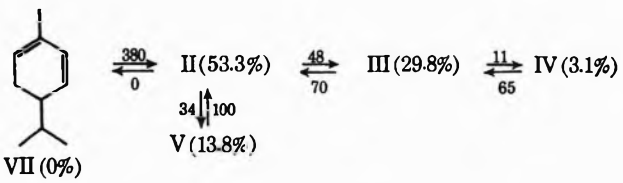
IX

fast at a as at b;[7] they gave a satisfactory fit. The largest rate constants, for the interconversion of II with V, are large partly because U-shaped pentadienyl anions are involved rather than the other shapes,[8] and partly because there are *two* good routes, one involving deprotonation at a secondary site to VIII and reprotonation at another secondary site, and the other involving similar reactions with IX as the intermediate.

Having thus learned the equilibrium composition from experiments in base, and noting that none of the many final compositions reported from acid-catalyzed isomerizations[3] comes very close to the equilibrium composition, it was decided to see if conditions could be found for equilibrating in acid without extensive side reactions. In addition, the rate constants for approach to equilibrium, which could be very different since the intermediates were now carbonium ions instead of carbanions, were of interest.

After trying several other conditions, essentially those of Palmer and Wicke[3c] were used. α-Phellandrene (VII) was stirred vigorously under nitrogen at 67° with twice its weight of 50% aqueous sulfuric acid, and samples were withdrawn occasionally for analysis. After 32 hr, the values in Scheme II, quite close to those in Scheme I, had been obtained. The minor components I and VI were undoubtedly present again in amounts under 2%, but were ignored in the acid study. The percentages of the four major components were approaching values close to the limiting values found in base (*e.g.*, the concentration of II was decreasing from its maximum value of 72.4% at 7 hr). The reaction was worked up at this point and the identities of the major products verified by preparative gas chromatography and spectral analysis. *p*-Menthadienes still comprised 93% of the mixture; 5% *p*-cymene and 2% menthenes had also been formed. For the determination of the rate constants in Scheme II, with an analog computer, the equilibrium values obtained at 200° were used; though the equilibrium values at 67° no doubt differ from those at 200° owing to entropy differences, they may not differ by much more than the experimental error in the values.

SCHEME II[a]



[a] 32-hr percentages and rate constants (relative to V → II = 100; the absolute value for this rate constant was 2.0 ± 0.3 × 10^{-5} sec^{-1}) for isomerization of *p*-menthadienes at 67° with 50% aqueous sulfuric acid.

Although it was originally hoped that, under mild acidic conditions starting with a conjugated *p*-menthadiene, other conjugated dienes (formed *via* allylic carbonium ion intermediates) would be formed much faster than unconjugated dienes, it is readily seen from Scheme II that the unconjugated diene V is formed from II almost as rapidly as the conjugated diene III is formed from II. Thus, unlike the situation in base, in which there is a rate difference of about 10^6 between isomerizations proceeding *via* allylic anions and pentadienyl anions,[8,9] there must be a small difference

(5) H. Pines and H. E. Eschinazi, *J. Amer. Chem. Soc.*, **78**, 1178 (1956).

(6) R. B. Bates, R. H. Carnighan, and C. E. Staples, *ibid.*, **85**, 3030 (1963).

(7) Cyclohexadienyl anion protonates 8 times as fast at the central carbon as at each end: R. B. Bates, R. H. Carnighan, and C. E. Staples, *ibid.*, **85**, 3032 (1963).

(8) R. B. Bates, R. H. Carnighan, and C. E. Staples, *ibid.*, **85**, 3031 (1963); this extra stability is probably due to homoconjugation, since the alternative explanation involving better chelation of the U shape seems to be ruled out by kinetic studies showing that KO*t*-Bu and LiO*t*-Bu give the same relative rate constants for the interconversions of the hexalins (S. S. Bratcher, M.S. Thesis, University of Arizona, 1967).

(9) A. Schriesheim, C. A. Rowe, Jr., and L. Naslund, *J. Amer. Chem. Soc.*, **85**, 2111 (1963).

between the allylic carbonium ion intermediates and the tertiary homoallylic carbonium ions X and XI.

X XI

As expected, the relative rate constants in acid and base differ considerably. Using the analog computer and the rate constants in Scheme I and II, curves for approach to equilibrium in acid and base from each of the dienes were drawn. The major differences result from the very rapid equilibration between II and V in base (*via* a U-shaped pentadienyl anion); if II were desired from V, for example, base would be chosen since with it a mixture containing 74% V and 26% II can be obtained, whereas in acid, V never gets appreciably above its equilibrium value of 45%, and by the time it is close to that value, 10% of III has formed.

A general advantage of base for diene isomerizations, that of fewer and slower side reactions, holds to some extent for the *p*-menthadienes, since aromatization is faster relative to isomerization in acid, at least under our conditions. A big advantage of acid in the *p*-menthadiene case is that the system can be entered from alcohols such as α-terpineol[3e] and isomeric hydrocarbons such as the readily available pinenes.[3a-d,f,i]

Experimental Section

The α-phellandrene (VII) used was Eastman practical grade, purified by preparative gas phase chromatography (gpc) on Carbowax 20M to 98% purity, contaminated with 2% α-terpinene (II). Samples of α-terpinene (II) and γ-terpinene (V) obtained from the Glidden Co. contained several per cent *p*-cymene as the only noticeable impurity and were used without purification, as was the 3,8-*p*-menthadiene (IV) obtained from the Hercules Powder Co.

For gpc analyses, Carbowax 20M on water- or base-washed firebrick at 110–140° was used unless otherwise stated.

Equilibration in Base.—A mixture of 6% potassium in *t*-butanol under nitrogen was stirred until all of the metal had reacted, and to 10 g of this solution was added 9 g of the diene to be equilibrated. The equilibrations were performed by heating sealed tubes (nitrogen atmosphere) containing 1-cm³ portions of these solutions to 200° for 8 hr. The tubes were quenched in ice water, opened, and the contents poured into sodium chloride solution. The hydrocarbons were extracted with ether, and the ether solution was washed twice with salt water to remove *t*-butanol. After drying over potassium carbonate, the ether was allowed to evaporate at room temperature under a nitrogen stream and the residual oil was analyzed. The equilibrated samples starting from II, IV, V, VII, and a 3:1 mixture of VII and I had virtually the same nmr spectra and gpc patterns. Even after 30 hr, menthadienes still comprised 96% of the hydrocarbon mixture; the remainder consisted of *p*-cymene (3%) and menthenes (1%). The equilibrium menthadiene composition given in Scheme I was determined by integration of the gpc curve obtained by equilibrating VII for 30 hr. Several equilibrated samples were put through a preparative gpc column and all hydrocarbon fractions were collected and analyzed by nmr and uv. Maleic anhydride adducts were prepared from the cisoid dienes II and VI. Retention times in minutes were as follows: a menthene, 8.8; VI, 10.4; another menthene, 13.2; II, 16.8; I, 19.8; V, 23.4; IV and *p*-cymene, 27; III, 30.3. The relative amounts of IV and *p*-cymene were determined from the intensity of the absorption at 233.5 mμ in the sample collected at 27 min; *p*-cymene does not absorb there, but it was necessary to correct for the absorption due to III, a contaminant in the collected sample.

Kinetic runs were made at 200 ± 0.1° starting from II, IV, and V. Tubes were removed and analyzed at various time intervals, and the resulting composition–time curves were matched as well as possible on an analog computer using Scheme I. The best rate constants thus obtained are given in Scheme I.

Equilibration in Acid.—To 8.0 g of α-phellandrene (VI) under nitrogen in a bath maintained at 67.0 ± 0.03° was added 15.3 g of 50% sulfuric acid, and the paddle stirrer was started. When a sample was to be removed for analysis, the stirrer was momentarily stopped and the sample was taken with a syringe from the upper layer. The sample was squirted into 10% sodium hydroxide solution and the hydrocarbons were extracted by washing three times with ether. The ether solution was washed twice with water and the ether was evaporated.

After 32 hr, the relative amounts of the various *p*-menthadienes were changing very little, although the *p*-cymene and menthene concentrations continued to rise from their values of 5% and 2%, respectively. The gpc trace looked strikingly similar to that obtained from the base equilibrations, and mixed gpc confirmed the correspondence in retention times for the components of the two samples. Samples of the equilibrium mixture (composition given in Scheme II) were put through the preparative gpc as before; various spectral methods confirmed the similarity in composition of the equilibrium mixtures obtained in acid and in base.

A kinetic study of this reaction gave the rate constants in Scheme II. The concentration of IV, the only menthadiene which was not well separated on Carbowax, was determined by gpc on a second packing, silicone rubber, rather than by the uv method mentioned above. VII had a retention time of 16.1 on Carbowax. The retention times in minutes for the major components on silicone rubber at 150° were VII, 10.3; II and *p*-cymene, 10.6; IV and V, 12.5; III, 14.4.

Registry No.—I, 555-10-2; II, 99-86-5; III, 586-63-0; IV, 586-67-4; V, 99-85-4; VI, 586-68-5; VII, 99-83-2.

Acknowledgment.—We thank the Glidden Co. for generous gifts of α- and γ-terpinenes, the Hercules Powder Co. for 3,8-*p*-menthadiene, and the Petroleum Research Fund and National Science Foundation for financial support.

Long-Range Effects in the Alkylation of Benzene with Polyhalooctanes

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The pseudo-first-order rate constants for the hydrogen fluoride–boron trifluoride catalyzed reaction of benzene with three different series of polyhalooctanes were measured. Each series of polyhalooctanes is comprised of isomers which differ only in the position of attachment of the reactive secondary chloro group relative to the unreactive primary substituents. The 1-bromo, 1,1-dichloro, and 1,1,1-trichloro groups are shown to decrease the rate of reaction of a secondary chloro group, relative to the unsubstituted case, even when separated by seven methylene units. The influence of these primary substituents is shown to decrease by a constant attenuation factor of 0.59 per methylene unit.

We previously described our investigation of the alkylation of benzene with a series of dichlorooctane isomers which contained both primary and secondary chloro groups.[1] The hydrogen fluoride–boron trifluoride catalyst system permitted reaction of the secondary chloro group, leaving the primary chloro group unchanged. We now wish to report our results of alkylations with three other series of polyhaloalkane isomers. These are the 1-bromo-X-chlorooctane, 1,1,X-trichlorooctane, and 1,1,1,X-tetrachlorooctane series.[2] In each series the substituents at C-1 were shown to be unreactive under the conditions used.

1-Bromo-X-Chlorooctanes.—This series of isomers was prepared by radical chlorination of 1-bromooctane to about 20% conversion. The dihalooctane fraction was shown by vapor phase chromatography (vpc) to be comprised of eight isomers. These were assumed to be the 1-bromo-1-chloro-, 1-bromo-2-chloro-, through 1-bromo-8-chlorooctane isomers in "numerical order"[3] of elution. A rigorous identification of the isomers was not attempted, although there are excellent grounds for the above assignments. Thus, chlorination of 1-chlorooctane yielded eight isomers which eluted from the same vpc column in "numerical order";[1] by analogy, 1-bromo-X-chlorooctane would be expected to behave in the same manner. In the 1,X-dichlorooctane series, each isomer was found to be present in greater quantity than the preceding isomer in the "numerical order" of elution;[4] the same pattern was found for 1-bromo-X-chlorooctane. The 1-bromo-3-chloro- and 1-bromo-8-chlorooctane isomers were isolated and identified as the third and eighth peaks, respectively.

The alkylation procedure was identical with that used in previously described work with 1,X-dichlorooctane.[1] Boron trifluoride was passed slowly into a stirred solution of the mixed dihalooctanes in excess benzene and liquid hydrogen fluoride at 0°.

The reaction was followed by vpc as a function of time. The 1-bromo-1-chloro-, 1-bromo-2-chloro-, and 1-bromo-8-chlorooctane isomers were unchanged after 6 hr, as shown by vpc analysis using an internal standard. The reaction was found to be pseudo first order in each of the alkylating agents. The results of the kinetic treatment are shown in Table I.

The products were identified as the 7-, 6-, 5-, and 4-phenyl-1-bromooctanes, and were formed in the proportions shown in Table II. These products were identical and in the same proportion in each sample regardless of the time of sampling.

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE REACTIONS OF BENZENE WITH POLYHALOOCTANES USING HF/BF_3 AS CATALYST AT 0°

	$k \times 10^4$, sec^{-1}				
Compd	X = 3	X = 4	X = 5	X = 6	X = 7
X-Chlorooctane	58	58	58	58	58
1,X-Dichlorooctane	0.71	8.0	17	26	35
1,1,X-Trichlorooctane	···	2.1	7.5	18	28
1,1,1,X-Tetrachlorooctane	···	0.8	4.8	14	25
1-Bromo-X-chlorooctane	1.0	9.7	21	33	42

TABLE II

WEIGHT PER CENT PRODUCTS FROM REACTIONS OF BENZENE WITH POLYHALOOCTANES USING HF/BF_3 AT 0°

	Phenyl position			
1-substituent	7	6	5	4
Cl	53	29	14	4
Cl_2	62	29	8	1
Cl_3	58	34	6	2
Br	50	31	15	4

1,1,X-Trichlorooctanes.—Treatment of octanal with phosphorus pentachloride yielded 1,1-dichlorooctane, which, upon free-radical-catalyzed chlorination, gave the 1,1,X-trichlorooctane series of isomers. By analogy with the 1,X-dichlorooctane series, it was assumed that these isomers eluted in "numerical order."[5] Furthermore, the 1,1,1 isomer was synthesized; and the 1,1,2, 1,1,3, and 1,1,8 isomers were trapped from a vpc column and identified spectroscopically.

The alkylation procedure was identical with that previously described. The 1,1,1, 1,1,2, 1,1,3, and 1,1,8 isomers were unchanged. The pseudo-first-order rate constants for the reaction of the remaining isomers are shown in Table I.

The products did not vary as a function of time, nor did their relative proportions. The products were 7-, 6-, 5-, and 4-phenyl-1,1-dichlorooctanes in the relative amounts shown in Table II.

1,1,1,X-Tetrachlorooctanes.—The radical-catalyzed addition of chloroform to 1-heptene gave 1,1,1-trichlorooctane,[6] which, upon radical chlorination, gave the 1,1,1,X-tetrachlorooctane isomer series. Seven

(1) D. L. Ransley, *J. Org. Chem.*, **33**, 1517 (1968).

(2) X represents the position of chloro group attachment to each available carbon atom in turn; *e.g.*, 1,1,X-trichlorooctane represents the 1,1,1-, 1,1,2-, 1,1,3-, 1,1,4-, 1,1,5-, 1,1,6-, 1,1,7-, and 1,1,8-trichlorooctane mixture.

(3) "Numerical order" is the order shown in the example in ref 2.

(4) With the exception of the isomer with longest retention time, *i.e.*, when X = 8.

(5) The 1,1,3 isomer eluted before the 1,1,2 isomer in this series. However, the 1,1,3 isomer was present in greater quantities than the 1,1,2 isomer; hence, the relative amounts of the isomers is probably a better indication that the remaining isomers eluted in "numerical order."

(6) M. S. Kharasch, E. V. Jensen, and W. H. Urry, *J. Amer. Chem. Soc.*, **69**, 1100 (1947).

peaks were evident in the chromatogram of this isomer mixture. There were increasing proportions of the isomers with increasing retention time,[4] and once more its was assumed that elution was in "numerical order." Supporting evidence for this assumption was provided by synthesis of the 1,1,1,3 isomer and recognition of distinctive spectroscopic features of the 1,1,1,6, 1,1,1,7, and 1,1,1,8 isomers in fractions concentrated by vpc.

The kinetic data for the alkylation reactions run under the previously described conditions are shown in Table I. The proportions of the products, 7-, 6-, 5-, and 4-phenyl-1,1,1-trichlorooctanes, were the same in each sample and are shown in Table II.

Discussion

The use of liquid hydrogen fluoride and boron trifluoride as a catalyst system for the alkylation of benzene provides a unique opportunity to study the influence of several unreactive groups on the reaction at the site of the secondary chloro group. The alkylation reactions under consideration involve ionization of a secondary chloro group to produce a carbonium ion. Any electron-withdrawing influence of the unreactive groups at the reaction site would increase the energy requirements of this process and thereby decrease the rate of reaction.

We have demonstrated that the 1-bromo, 1,1-dichloro, and 1,1,1-trichloro groups do not react under the conditions used. By running competition rate experiments within each isomeric series, the change of the influence of the unreactive group with distance from the reaction site may be observed. By running each series of reactions under identical conditions, the relative influence of the unreactive groups may be compared.

The reactions were shown to be pseudo first order in each alkylating agent. The observed first-order rate constants are shown in Table I and are compared with the data for the similar reactions of 1,X-dichlorooctane and secondary monochlorooctane obtained in previous work.[1]

In qualitative terms we see that the reaction rate increases as the distance between the secondary chloro group and the unreactive, electron-withdrawing group increases. However, in each series the 7-chloro isomer reacts more slowly than the unsubstituted monochlorooctanes. This indicates that the influence of the substituents at C-1 is still appreciable at C-7.

Peterson and coworkers have recently demonstrated that the influence of remote substituents, varying by a constant factor per methylene unit, on the addition of trifluoroacetic acid to olefins, can extend over 11 methylene units.[7] From a familiar[8] empirical treatment, log (log k_H − log k_X)[9] was successfully plotted as a linear function *vs.* the number of methylene units separating the substituent and the site at which the charge was generated.

Figure 1 shows the result of treating the data of Table I in this manner. Remarkably good linear plots are obtained for the four cases under consideration.

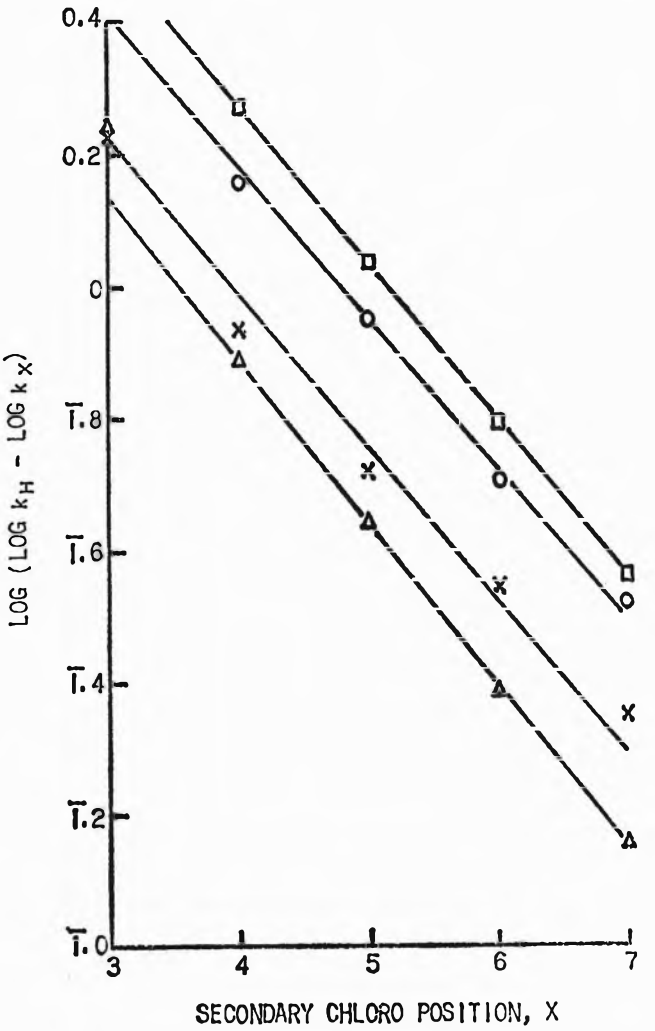

Figure 1.—Plot of rate data for alkylations with polyhalooctanes, assuming the substituent effect falls off by a constant factor per methylene unit: ×, 1,X-dichlorooctanes; ○, 1,1,X-trichlorooctanes; □, 1,1,1,X-tetrachlorooctanes; △, 1-bromo-X-chlorooctanes.

The slope of the lines is the log of the attenuation factor.[7] The average value for the attenuation factor from our four systems is 0.59. This compares with 0.65 obtained by Peterson[7] and 0.53 by Stevenson and Williamson[10] in correlating pK values for a series of ω-cyanoamines.

The relative proportions of the reaction products are shown in Table II. There is a greater tendency for phenyl attachment at positions remote from the unreactive, electron-withdrawing group. Within each series, ionization of the secondary chloro group is the slow step. The carbonium ion rapidly isomerizes, presumably by a series of 1,2 hydride shifts. Thus, within each series, there is a common intermediate. The product proportions are dependent on the substituents at C-1. The tendency is for the groups with the strongest electron-withdrawing influence to favor phenyl attachment at the most remote secondary carbon atoms. Alkylation on benzene is a rapid and irreversible[1] process under the conditions used.

We had planned to include the reaction of 1-fluoro-X-chlorooctane with benzene in our study. However, the 1-fluoro group appears to react somewhat faster

(7) P. E. Peterson, C. Casey, E. V. P. Tao, A Agtarap, and G. Thompson, *J. Amer. Chem. Soc.*, **87**, 5163 (1965).

(8) See ref 1 and 7 and references therein.

(9) k_H = rate constant for the unsubstituted reaction; k_X = rate constant for the substituted case.

(10) G. W. Stevenson and D. Williamson, *J. Amer. Chem. Soc.*, **80**, 5943 (1958).

than secondary chloro compounds. The reaction products, 1-fluorophenyl-, chlorophenyl-, and diphenyloctanes, were not investigated in detail.

At this point we should add a note concerning the catalyst system. To the best of our knowledge the combination of hydrogen fluoride and boron trifluoride as a catalyst system for the alkylation of aromatic compounds with alkyl halides has not been used previously.[11] The rapid rates at ambient temperatures, excellent yields, and high degree of selectivity between primary and secondary substituents make this a most interesting system. However, there are some unusual features of this system.

Reaction did not start as soon as boron trifluoride was passed into the system, but did so quite abruptly after boron trifluoride has passed for about 20 min in our work with 0.1 mol of alkylating agent.[12] In our competition reactions, each isomer started to react at about the same time.

Experimental Section

1-Bromo-X-Chlorooctane.—Into a 1-l. turbomixer, with an internal cooling coil and gas inlet at the bottom, was placed 499 g (2.58 mol) of 1-bromooctane. Nitrogen was bubbled through the mixture for 30 min. Chlorine was then passed with rapid stirring at about 25° for 1 hr at 258 ml/min with a GE sun lamp to initiate the reaction. Nitrogen was then bubbled through the mixture for 1 hr and the reaction mixture washed with water, twice with 10% sodium bicarbonate, and finally with water. The mixture was dried ($MgSO_4$) and distilled. The fraction boiling at 124–144° (10 mm), 103 g, was used in the alkylation studies. The assigned composition of this fraction was 1-bromo-1-chloro- (trace), 1-bromo-2-chloro- (0.4%), 1-bromo-3-chloro (3.4%), 1-bromo-4-chloro- (14.7%), 1-bromo-5 chloro- (23.6%), 1-bromo-6-chloro-, and 1-bromo-7-chloro- (54.2%), and 1-bromo-8-chlorooctane (3.4%).

After the alkylation reaction was terminated, the unreacted 1-bromo-3-chloro- and 1-bromo-8-chlorooctane isomers were trapped from a 10 ft × 0.25 in. 20% Carbowax on Chromosorb W column. The nmr[13] of the former showed two overlapping triplets centered at 3.36 (CH_2Cl) and 3.23 ppm (CH_2Br) and chain methylene groups. The 1-bromo-3-chlorooctane showed nmr bands at 4.00 (t, CHCl), 3.48 (t, $BrCH_2$), 2.1 (q, $BrCH_2$-CCl-), and 1.7 ppm (m, CH_2CCl), and methylene and terminal methyl protons.

1,1-Dichlorooctane.—Into a 5-l., 3-neck flask was placed 1115 g (5.350 mol) of phosphorus pentachloride and 500 g of benzene. To the stirred slurry was added 600 g (4.7 mol) of octanal over a 5-hr period at no more than 10°. After standing overnight, ice and water were added slowly with cooling. The product was washed with sodium bicarbonate and water and then dried ($MgSO_4$). The product was distilled; the fraction boiling at 95–99° was found to be 97% pure 1,1-dichlorooctane contaminated with octanal. Since the removal of octanal by sodium bisulfite washes was not successful, the product was redistilled to give 98.6% pure material.

1,1,X-Trichlorooctane.—The chlorination of 1,1-dichlorooctane was performed in the same manner as that used for the preparation of 1-bromo-X-chlorooctane. The fraction boiling at 117–130° (15 mm) was used in the alkylation studies. The composition of this fraction was 1,1,1- (trace), 1,1,2- (2%), 1,1,3- (10.5%), 1,1,4- (16.1%), 1,1,5- (17.9%), 1,1,6- (21.0%), 1,1,7- (23.8%), and 1,1,8-trichlorooctane (10.3%).

After the alkylation reaction was complete, the 1,1,8 isomer and a mixture of the 1,1,2 and 1,1,3 isomers were trapped from a 10 ft × 0.25 in. 20% Carbowax on Chromosorb W column. The nmr of the 1,1,8 isomer showed a triplet at 5.56 ($CHCl_2$), a triplet at 3.38 (CH_2Cl), a crude quartet at 2.16 (CH_2CCl_2), and methylene protons at 1.37 ppm.

The mixture of 1,1,2 and 1,1,3 isomers, the latter being predominant, showed a pair of overlapping doublets at 5.8, a smaller doublet at 5.71, a complex peak at 3.96, a pair of overlapping doublets at 2.42, methylene protons at 1.3, and terminal methyl at 0.89 ppm. The mixture was then subjected to spin–spin decoupling treatment. Irradiation at 3.9 ppm (a) collapsed the 5.8 ppm band to a triplet, (b) collapsed the 5.71 ppm doublet to a singlet, thereby giving a good indication that the minor constituent was the 1,1,2 isomer, and (c) collapsed the 2.42 ppm doublet pair to one doublet. Irradiation at 2.5 ppm reduced the 5.8 ppm doublets to a singlet and the complex group at 3.96 ppm to a crude triplet. Irradiation at 5.8 ppm did not affect the 3.96 ppm group but reduced the bands at 2.42 ppm to a doublet. C-3 of the 1,1,3 isomer is asymmetric; hence the protons on C-2 are not magnetically equivalent. The assignment of the bands at 5.8 (Cl_2CH), 3.96 (CHCl), and 2.42 ppm (Cl_2CCH_2CCl), and the behavior in the spin–spin decoupling treatment are consistent with that for the 1,1,3 isomer.

1,1,1-Trichlorooctane.—Into a 1-l., stainless steel, stirred autoclave was placed 186 g (1.90 mol) of 1-heptene, 900 g (6.56 mol) of chloroform, and 4.0 g of benzoyl peroxide. The sealed bomb was heated at 80° for 4 hr and a further 8 g of benzoyl peroxide added. The bomb was then heated for another 6 hr at 90°.

This procedure was repeated; the two products were combined. The unreacted chloroform and 1-heptene were removed by distillation, and the bulk of the product distilled at 84–86° (6 mm). More careful fractionation of the 240 g of product so obtained gave a product of 98.5% purity boiling at 85° (6 mm).

1,1,1,X-Tetrachlorooctane.—The chlorination of 1,1,1-trichlorooctane used the previously described procedure. The fraction boiling at 115–123° (6 mm) was used in the alkylation studies. The composition of this fraction was 1,1,1,3- (3.2%), 1,1,1,4- (19.7%), 1,1,1,5- (22.9%), 1,1,1,6- and 1,1,1,7- (46.7%), and 1,1,1,8-tetrachlorooctane (6.3%). The impurities plus the 1,1,1,2 isomer constituted 1.2% of the mixture. Concentration of various isomers, either from distillation cuts before reaction or by trapping the unreactive isomers after reaction, permitted spectroscopic methods to substantiate the assignments. Further, the 1,1,1,3 isomer was synthesized by the addition of carbon tetrachloride to 1-heptene [bp 105–106° (6 mm)].

The nmr of the 1,1,1,3 isomer showed peaks at 4.2 (m, CHCl), 3.18 (eight line distinctive multiplet), 1.82 (m, $CClCH_2$), 1.4 (methylene protons), and 0.99 ppm (terminal methyl).

The most distinctive feature from the nmr of the 1,1,1,6 isomer was the triplet methyl group at 1.14 ppm. The doublet methyl group of the 1,1,1,7 isomer was observed in the nmr at 1.6 ppm. The nmr of the 1,1,1,8 isomer showed a band at 3.4 ppm (t, $ClCH_2$) and was distinctive because of the absence of the terminal methyl group.

Alkylation of Benzene with Polyhalooctanes.—Into a 1-l. polyethylene bottle fitted with a stirrer, a gas inlet near the bottom, and a copper condenser, was placed 0.1 mol of the mixed polyhalooctane isomers and 312 g (4 mol) of benzene, and the mixture was cooled to 0°. Liquid hydrogen fluoride, 40 g (2 mol) was added to the stirred, cooled mixture. Boron trifluoride was passed into the stirred mixture throughout the reaction at 4 ml/min. Samples were taken at intervals, at which time the stirring was interrupted. The sample was washed with water, 5% sodium bicarbonate, and water and then dried ($MgSO_4$).

Samples were analyzed on a 200 ft × $^1/_{16}$ in. SF 96 coated capillary column. In each series the reactants were analyzed at 140–160° and the column then rapidly heated to 180–200° to permit analysis of the products. The area under the peaks was considered as proportional to weight for isomeric products.

Products. Phenyl-1-bromooctanes.—7-Phenyl-1-bromooctane was trapped from a 10 ft × 0.25 in. 20% Carbowax on Chromosorb W column. The nmr showed aromatic protons at 7.0, a triplet at 3.2 (CH_2Br), a sextuplet at 2.58 (benzylic methine), and methylene protons at 1.2 ppm. The doublet methyl group β to the phenyl group could also be observed at 1.2 ppm but was not separable from the methylene proton signal. The mass spectrum

(11) G. F. Hennion and R. A. Kurtz, [*J. Amer. Chem. Soc.*, **65**, 1001 (1943)] describe the alkylation of benzene with alkyl halides using boron trifluoride and water, alcohol, "or other polar compounds reactive to boron trifluoride" as the catalyst system. The selectivity of primary *vs.* secondary halides was noted, though yields were less than 70% and reflux temperatures were required.

(12) The effect of variables in the HF/BF_3 system is currently under investigation. Results to date indicate that a certain BF_3 concentration is required before reaction starts.

(13) Nuclear magnetic resonance (nmr) integrals were correct within 5% for assigned structures: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet.

showed the parent peak at m/e 268, a small peak at 253 ($-CH_3$), and major peaks at 188 (-HBr), 173 (-HBr, $-CH_3$), 131 ($C_{10}H_{11}^+$), and 105 [$-(CH_2)_6Br$].

The phenyl-1-bromooctanes undergo three major modes of cleavage in the mass spectrograph. These are loss of either the alkyl or bromoalkyl group to yield the corresponding benzylic carbonium ions and the loss of both the alkyl group and HBr. Hence there are three distinctive mass spectral peaks associated with each isomer. Those observed are for the 4-phenyl isomer (m/e 211, 131, and 147), the 5-phenyl isomer (225, 145, and 133), the 6-phenyl isomer (239, 159, and 119), and the 7-phenyl isomer. The intensities of the observed peaks were qualitatively appropriate to the assignments made.

The peaks corresponding to the 3-phenyl isomer (m/e 197, 117, and 171) and the 2-phenyl isomer (183, 103, and 185) were not detected by this method or by vpc which would detect 0.1%.

Phenyl-1,1-dichlorooctanes.—7-Phenyl-1,1-dichlorooctane was trapped from the previously described Carbowax column. The nmr showed aromatic protons at 7.0, a triplet at 5.5 ($CHCl_2$), a sextuplet at 2.58 (benzylic methine), a multiplet at 2.04 (CH_2CCl_2), methylene protons at 1.5, and a doublet at 1.19 ppm (methyl β to phenyl).

The 6-phenyl-1,1-dichlorooctane was concentrated by vpc. The nmr showed aromatic protons at 7.0, a triplet at 5.5 ($CHCl_2$), a sextuplet at 2.58 (benzylic methine), a multiplet at 2.04 (CH_2CCl_2), methylene protons at 1.5, and a triplet at 0.75 ppm (methyl γ to phenyl).

The mass spectrum of the phenyldichlorooctane mixture showed peaks corresponding to alkyl or alkyldichloro group loss to form the corresponding benzylic carbonium ions and loss of both alkyl group and HCl. The observed peaks corresponded to the 4-phenyl isomer (m/e 201, 147, and 165), the 5-phenyl isomer (215, 133, and 179), the 6-phenyl isomer (229, 119, and 193), and the 7-phenylisomer (243, 105, and 207).

Phenyl-1,1,1-trichlorooctane.—The 7-phenyl isomer was recognized by the characteristic doublet at 1.15 ppm in the nmr. The mass spectrum showed the parent peak at m/e 292 and peaks at 256 (-HCl), 241 (-HCl, $-CH_3$), 131 ($C_{10}H_{11}^+$), and 105 [$-(CH_2)_5CCl_3$].

The 6-phenyl isomer showed a triplet in the nmr at 0.7 ppm characteristic of a methyl group γ to phenyl. The mass spectrum showed the parent peak at m/e 292 and peaks at 256 (-HCl), 227 (-HCl, $-C_2H_5$), 145 ($C_{11}H_{13}^+$), and 119 [$-(CH_2)_4CCl_3$].

The mass spectrum of the phenyl-1,1,1-trichlorooctane mixture showed peaks corresponding to the 5-phenyl isomer (m/e 249, 133, and 213) and the 4-phenyl isomer (235, 147, and 199).

The nmr of all isomers showed the $-CH_2CCl_3$ peak overlapping with the methine hydrogen.

Registry No.—Benzene, 71-43-2; 1,1-dichlorooctane, 20395-24-8; 1,1,1-trichlorooctane, 4905-79-7; 1,1,1,3-tetrachlorooctane, 18088-13-6; 1,1,1,6-tetrachlorooctane, 20414-34-0; 1,1,1,7-tetrachlorooctane, 20414-35-1; 1,1,1,8-tetrachlorooctane, 10311-13-4; 7-phenyl-1,1-dichlorooctane, 20414-37-3; 6-phenyl-1,1-dichlorooctane, 20414-38-4; 7-phenyl-1,1,1-trichlorooctane, 20414-39-5; 6-phenyl-1,1,1-trichlorooctane, 20414-40-8; 1,1,8-trichlorooctane, 20414-41-9; 1,1,3 trichlorooctane, 4905-80-0.

Application of the Linnett Electronic Theory to Organic Chemistry. II. Introduction

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The double-quartet theory of Linnett is shown to account for a wide variety of typical organic structural phenomena. The concept of L strain, a unique corollary of the Linnett theory, is discussed and put on a semiquantitative basis. Examples of problems in geometry, stabilization, hyperconjugation, and configurational inversion are provided from among the classes alkanes, alkenes, alkynes, amines, carbanions, carbonium ions, radicals, and carbenes, and certain predictions are made.

In the past few years there has appeared a modified theory of chemical binding, developed by Linnett.[1,2] Based on the principles of quantum mechanics, Linnett's theory nevertheless differs drastically in many cases from that held in recent decades by most chemists (the Lewis–Langmuir octet rule),[3-5] while in other cases it agrees. Heretofore the chief area of application has been in inorganic chemistry with a few ventures into organic territory.

We have found that a detailed examination of structure and mechanism throughout organic chemistry in the light of the Linnett concepts can provide increased understanding. A portion of this work has already been presented in preliminary form.[6] In this paper, which is intended as the introduction to a series of detailed surveys of mechanism, Linnett's structural concepts are extended, in the simplest possible way, to typical organic molecules and intermediates. For the most part, discussions will be limited to elements of atomic number below neon in the periodic table.

The Linnett Theory.—Inasmuch as a complete description has been published,[1,2] only a few points will be repeated here. The principal innovation is the treatment of the outermost shell of electrons around the nucleus of an atom as an array, not of pairs with perhaps an odd electron, but of two spin sets, one of each spin. The disposition of the electrons in each spin set toward each other is rather firmly fixed, owing both to the Pauli principle and their mutual electrostatic repulsion, at that with the maximum mutual distance within the radius of the shell. (By the "position" of an electron, of course, "most probable position" is meant throughout.) Thus, a quartet occupies the corners of a regular tetrahedron, a trio the corners of an equilateral triangle, and a duo the ends of a straight line, all centered on the nucleus. The relative positions of the two spin sets are the most staggered possible (consistent with the maximization of binding energy), to minimize interelectronic repulsion. The second restriction is weaker than the first, however, because the Pauli principle is not involved.

(1) J. W. Linnett, *J. Amer. Chem. Soc.*, **83**, 2643 (1961).
(2) J. W. Linnett, "The Electronic Structure of Molecules," Methuen & Co. Ltd., London, 1964.
(3) G. N. Lewis, *J. Amer. Chem. Soc.*, **38**, 762 (1916).
(4) G. N. Lewis, "Valence and the Structure of Atoms and Molecules," The Chemical Catalog Co., New York, N. Y., 1923.
(5) I. Langmuir, *J. Amer. Chem. Soc.*, **38**, 2221 (1916).
(6) R. A. Firestone, *Tetrahedron Lett.*, 971 (1968).

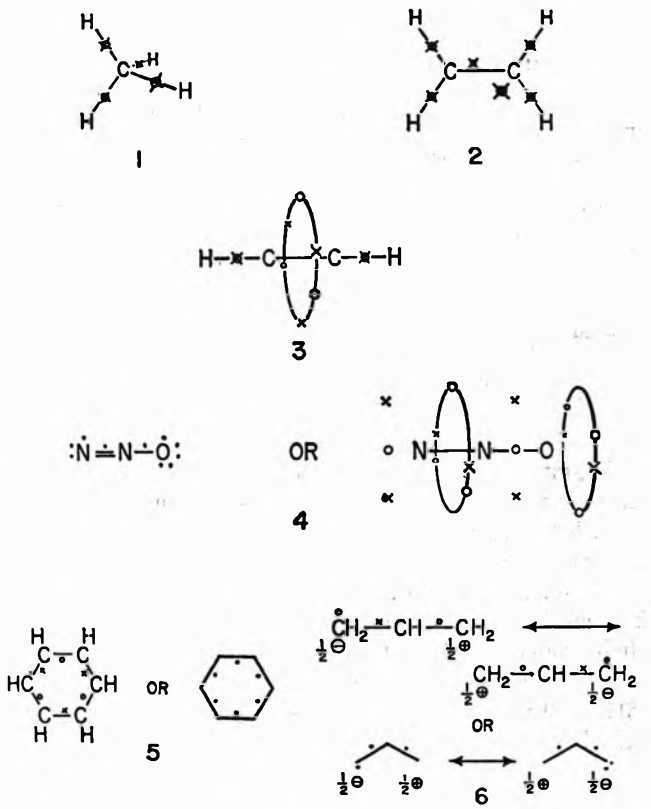


Figure 1.—1, methane; 2, ethylene; 3, acetylene; 4, nitrous acid; 5, benzene; 6, allyl radical.

A chemical bond between two atoms consists of one or more electrons between the nuclei, shared by both and as close to both as possible, allowing for the electrons' mutual repulsion and the Pauli principle. Thus a single bond has the two electrons close paired on the line connecting the two nuclei; their positions need not coincide, however. A double bond has four electrons which may or may not be close paired, and a triple bond has six electrons not close paired. Bonds with odd numbers of electrons are also permitted. The more electrons involved, the stronger the bond, although not necessarily in direct proportion. For nonbonding electrons, on the other hand (those not shared by more than one atom), the energy of the molecule is greater, the closer they lie to the internuclear line.

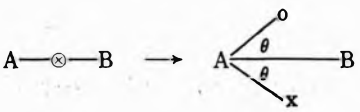
The chief innovation here is the deemphasis on the pair; a bond may contain any number of electrons, even or odd, up to six. In addition, great stress is laid upon the advantage of structures that have as few close pairs as possible, consonant with the other limitations. The relative ease with which the various types of atoms assume formal charges is also taken into account.

Another feature of Linnett's theory, though not a novelty, is that double bonds are seen as two-membered rings with bent bonds. The history and advantages of the bent-bond theory, particularly from the standpoint of rotational isomerism, have been adequately reviewed.[7] It should be noted that triple bonds, while bent, are not simply two-membered bicyclic systems since they contain no close pairs.

A few structures are depicted in Figure 1 for illustration. We have adopted Linnett's convention of representing the two types of electrons by o's and x's, with simplified diagrams where possible, in which — represents a pair of electrons, one of each spin, without regard to whether or not they are close paired, and · represents one electron of either spin. Enough perspective drawings have been provided to illustrate at least one each of two-, three-, four-, five-, and six-electron bonds; in these particular illustrations, the lines connecting atoms, and some connecting electrons (*viz.*, five- and six-electron bonds), are there solely as aids to visualization. Space limitations preclude further discussion of Linnett's theory; ref 1 and 2 can be consulted for a full exposition.

L Strain.—One of the consequences of the double-quartet theory is that any event, at a given point in the valence shell of an atom, which alters the relative disposition of the two spin sets at that point will alter it at all other points as well, in a definite way. Thus all the bonds to that atom play a role in the reaction whether they appear to or not. This factor is distinct from the usual steric and electronic effects, and supplements but does not replace them.

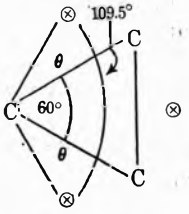
During a reaction, it is sometimes found that the two electrons in a single bond not directly involved are forced apart and off the internuclear line. This will



weaken the bond and, therefore, raise the activation energy, even though the bond may be intact and unstrained in both the reactants and the products. Bond weakening of this type constitutes a type of strain which we believe has not been invoked before and which we propose to call L strain. It may be exhibited by stable species as well as by transition states. Several examples of L strain have already been described.[6]

It is obvious that the strain energy will increase with θ, slowly at first and then more rapidly. An empirical relationship can be worked out using data from the literature.

(1) Cyclopropane suffers from L strain at each carbon atom. If we momentarily assume that all spin



sets are completely undistorted, the amount of L strain is seen to be 49.5°; θ = *ca.* 25°. The angle strain in cyclopropane has been estimated to be about 21 kcal/mol,[8] which provides a figure of 7 kcal/mol per C—C bond. Of course, the ring bonds will be stronger if the tetrahedra bend slightly so that the electrons can move a little inward.[9] Thus 2θ in cyclopropane must be less

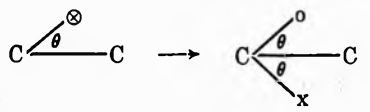
(7) E. A. Walters, *J. Chem. Educ.*, **43**, 134 (1966); E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, N. Y., 1965, pp 19–22.

(8) K. W. Egger, D. M. Golden, and S. W. Benson, *J. Amer. Chem. Soc.*, **86**, 5420 (1964).

(9) That this is likely is indicated by the observed H–C–H angle in cyclopropane of 113.6 ± 2°: O. Bastiensen and P. N. Skancke, *Advan. Chem. Phys.*, **3**, 323 (1960), p 349.

than 49.5°, and our estimated strain energy for 49.5° somewhat low.

A correction must now be made for electron correlation, because the hypothetical reaction



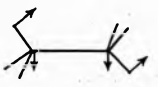
is exothermic, owing to the increase in interelectronic distance, even though the sum of the electronic deflections from the internuclear line is unchanged. A simple calculation of this correction can be made by setting the correlation energy proportional to sin θ. Perfect correlation (*i.e.*, maximum separation of electrons) is achieved at $2\theta = 70.5°$, for a first-row atom whose valence shell is filled, because any further increase in θ necessarily involves the nearer approach of other electrons of the valence shell.[10] From the "resonance energies" of benzene and carbon dioxide,[2] the approximate figure of 4 kcal/mol per electron pair can be derived for the maximum electron correlation energy, which is assigned to $2\theta = 70.5°$. The correlation correction for cyclopropane, then, is about 3 kcal/mol per bond and the corrected L-strain energy for $2\theta = 49.5°$ is 4 kcal/mol per electron pair.

(2) The strain energy of cyclobutane is almost the same as that of cyclopropane.[11] If the two also have similar total angle-strain energies, the L-strain energy for $2\theta \leqq 19.5°$ comes approximately to 4 kcal/mol per electron pair (21 ÷ 4 − 1.2 kcal).

(3) Ethylene can be looked upon as a strained two-membered ring with its four bonding electrons ideally 55° off the internuclear line but actually <55°. The difference in bond energy between two single C–C bonds and one double bond is 19.4 kcal/mol.[12] If there is no correlation correction for $2\theta = 109.5°$, the L-strain energy comes to 9.7 kcal/mol per electron pair; one could, however, assign up to half the maximum correction, or 2 kcal/mol, which would bring the L-strain energy to 7.7 kcal/mol.

(4) Acetylene has six well-correlated electrons in the C–C bond, each with $\theta \leqq 70.5°$. The difference in bond energy between three single bonds and one triple bond is 48.2 kcal/mol.[12] It is not clear whether a correlation correction should be made here; the figure would be 0.7 kcal/mol for an angular separation of 56°. With the correction, the L strain is 48.2 ÷ 3 − 0.7, or 15.4 kcal/mol per electron pair and, without it, 16.1 kcal/mol.

(5) Certain molecular vibration modes can yield L-strain data. For the vibration of ethane depicted in **7**, the energy required for a 10° distortion is 3.1 kcal/



7

mol.[13] This corresponds to a bent bond, as in cyclopropane and cyclobutane, with $\theta = 10°$. The L-strain energy, then, comes to 3.1 − 1.2 = 1.9 kcal/mol per electron pair.

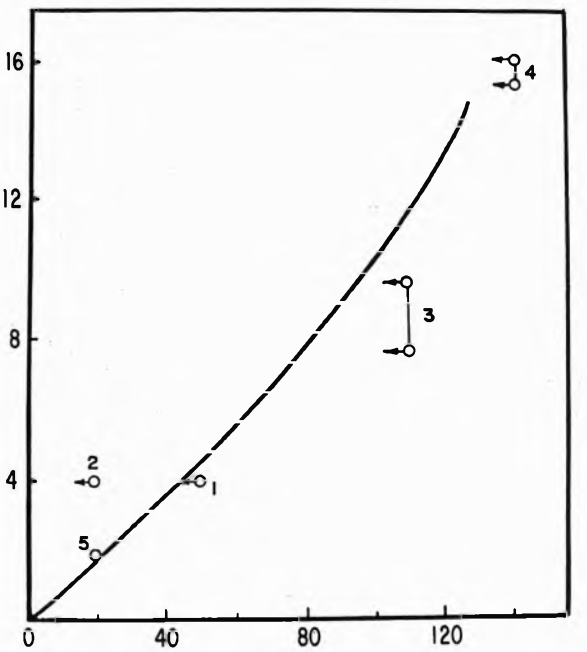
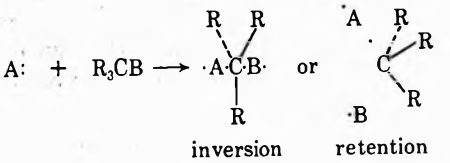


Figure 2.—L-Strain energies *vs.* angles for C–C bonds. Ordinate in kilocalories per mole; abcissa in degrees. For numbering of points, see text.

These numbers are plotted in Figure 2. The arrows next to some of the points indicate that the actual L-strain angles must be smaller than the calculated ones by some unknown amount. Where the data permitted the adoption of two different L-strain energies, both are depicted. The line was sketched visually as the best smooth approximation to all the points except that for cyclobutane whose angle strain is unaccountably high. Although the curve is a crude one, it is good enough to use for the estimation of approximate L-strain energies.

Among the uses to which Figure 2 may be put is the estimation of the difference in L strain in the transition states of the SN2 reaction for inversion and retention, according to the mechanism proposed in ref 6. For



inversion, the three C–R bonds suffer from 40° of L strain each and, for retention, 70.5°. The difference in L strain per C–R bond is 6.8 − 3.6 or *ca.* 3.2 kcal/mol, so that inversion should be preferred to retention by *ca.* 10 kcal/mol. If R = H, this becomes *ca.* 11 kcal/mol after correcting for the difference between C–C and C–H bond energies.[12] If R = CH_3, secondary L strain within the CH_3 groups will raise the base figure still further, to an estimated 14 kcal/mol, based on the data[14] for the successive replacement of H by CH_3 on carbon atoms undergoing SN2 displacement.

For SE2 reactions of the type $A^+ + CH_3B \rightarrow ACH_3 + B^+$, and for radical displacements $A\cdot + CH_3B \rightarrow ACH_3$

(10) This point can be clarified if necessary by referring to the cubical array suggested by W. F. Luder, *J. Chem. Educ.*, **44**, 206 (1967) as a pictorial aid to the visualization of Linnett's structure for the neon configuration.

(11) J. D. Dunitz and V. Schomaker, *J. Chem. Phys.*, **20**, 1703 (1952).

(12) T. L. Cottrell, "The Strength of Chemical Bonds," 2nd Ed., Butterworth & Co. Ltd., London, 1958.

(13) J. W. Linnett, personal communication.

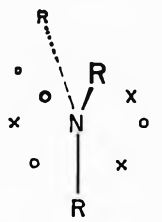
(14) D. Cook and A. J. Parker, *J. Chem. Soc.*, *B* 142 (1968).

+ B·, inversion should also be preferred.[15] The effect of charge type on the energies of these transition states, which is expected to be significant, has been neglected in this discussion but will be taken up at a later time.

Typical Organic Structures. Tetravalent Saturated Carbon.—Methane (1) is depicted above. The two spin sets, both tetrahedra, coincide despite the creation of four close pairs because considerations of bond strength outweigh those of electron correlation.

Trivalent Saturated Nitrogen.—The two spin sets are anchored together at three points, leaving the fourth electrons a rather close pair also. Thus, amines are pyramidal in shape, equivalent to sp^3 hybridization.

The easy inversion of amines occurs through the transition state **8**. The three bonds suffer from L



strain (2θ) of 40° each and the lone pair is now well correlated. The estimated activation energy from L strain considerations alone comes to approximately 7 kcal/mol.[16] The experimental value is *ca.* 6 kcal/mol for NH_3.[17] The activation energy is expected to increase with methylation owing to secondary L strain in the methyl groups.[18]

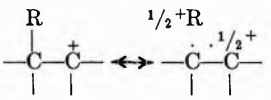
Divalent Saturated Oxygen.—Here the two tetrahedra are fastened together at only two corners. The four nonbonded electrons are still, therefore, formally close paired, but with considerably more freedom to spread than those in amines.[19]

Alkyl Halides.—The two spin sets around the halogen atom are now joined at only one point and the nonbonded electrons are well correlated. The noble gas configuration, with its optimal electron correlation, is nevertheless not attainable.

Carbanions.—These are isoelectronic with amines and the same considerations apply.

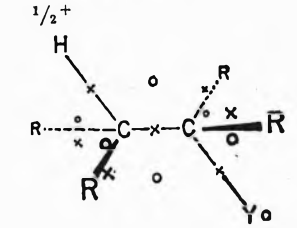
Carbonium Ions.—The structures should be planar, with R–C–R angles of 120°, since both spin sets are equilateral triangles centered on the nucleus. This agrees with current thinking, based mainly on the slow rate of formation of carbonium ions at bridgeheads.[20,21] The degree of rigidity with which carbonium ions apparently adhere to planarity[21] is not so easily accounted for, however; distortion of a spin set would be expected to be easier the fewer electrons it contains, because severe Pauli "repulsion" ought to come into play only as the interelectronic angle gets down near 109.5°.

Hyperconjugation.—This is a stabilizing factor in carbonium ions[22] which can be depicted in the following way. It is apparent from this picture why C–H

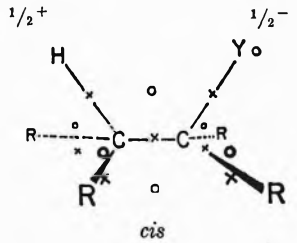


hyperconjugates better than C–C,[23] since not only does hydrogen bear a positive charge more easily than carbon, but also there is a certain amount of L strain associated with a carbon atom that has only seven valence electrons, *e.g.*, when R = CH_3 (*vide infra*), but absent when R = H.

Another phenomenon can also be rationalized. Shiner and coworkers have shown that the secondary β-deuterium isotope effect on solvolysis is subject to a steric restriction, with the *trans*-coplanar conformation apparently preferred[24,25]; yet, in the solvolysis of cyclopentyl tosylate, a *β-cis* deuterium has a larger retarding effect (k_H/k_D = 1.22) than a *trans* (k_H/k_D = 1.16).[26] The situation is reminiscent of the observation by dePuy's group that, in cyclopentyl systems, E2 eliminations also exhibit larger *cis/trans* ratios than normal.[27] From these and other data, Shiner and Humphrey[25] conclude that hyperconjugative assistance to solvolysis is maximized in both *cis*- and *trans*-coplanar arrange-



trans



cis

(15) There are few examples of S_E2 reactions not involving heavy atoms or small rings. Of particular interest is the formation of *t*-butyl cation from both neopentane and 2,2,3,3-tetramethylbutane in super acids, reported by H. Hogeveen and A. F. Bickel, *Chem. Comm.*, 635 (1967), and by G. A. Olah and R. H. Schlosberg, *J. Amer. Chem. Soc.*, **90**, 2726 (1968). Taking into account both the steric inaccessibility of neopentyl carbon and the fact that free protons cannot exist even in super acids, one is forced to conclude that these S_E2 reactions occur with inversion. Whether this is a general rule remains to be seen.

(16) Calculated from Figure 2, allowing 4 kcal/mol for the lone pair. Since N–H bonds are somewhat stronger and N–C bonds somewhat weaker than C–C bonds,[12] no bond strength correction was made in this case.

(17) G. Herzberg, "Infrared and Raman Spectra," D. Van Nostrand Co., Inc., New York, N. Y., 1945; D. M. Dennison and G. E. Uhlenbeck, *Phys. Rev.*, **41**, 313 (1932); C. H. Townes and A. L. Schawlow, "Microwave Spectroscopy," McGraw-Hill, Book Co., Inc., N. Y., 1955.

(18) In this example, and others like it to follow, it should not be inferred that L strain alone is responsible for the activation energy. The intention is simply to show that the energetics of many phenomena are commensurate with those anticipated from L strain and, therefore, that it must be reckoned an important factor in these cases.

(19) The deviations of bond angles from 109.5° in many compounds are ascribed, in large part, to this "spreading" tendency of unshared valence electrons: C. E. Mellish and J. W. Linnett, *Trans. Faraday Soc.*, **50**, 657 (1954).

(20) P. D. Bartlett and L. H. Knox, *J. Amer. Chem. Soc.*, **61**, 3184 (1939).

(21) W. von E. Doering, M. Levitz, A. Sayigh, M. Sprecher, and W. P. Whelan, Jr., *ibid.*, **75**, 1008 (1953).

(22) See, *inter alia*, (a) V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *ibid.*, **90**, 418 (1968), and earlier papers; (b) H. C. Brown and R. A. Wirkkala, *ibid.*, **88**, 1453 (1966); (c) K. L. Servis, S. Borcic and D. E. Sunko, *Tetrahedron*, **24**, 1247 (1968); (d) T. Yonezawa, H. Nakatsuji and H. Kato, *J. Amer. Chem. Soc.*, **90**, 1239 (1968).

(23) M. Ballester and J. Riera, *Tetrahedron*, **20**, 2217 (1964), and references contained therein.

(24) V. J. Shiner, Jr., B. L. Murr, and G. Heinemann, *J. Amer. Chem. Soc.*, **85**, 2413 (1963).

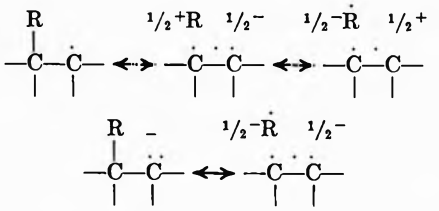
(25) V. J. Shiner, Jr., and J. S. Humphrey, Jr., *ibid.*, **85**, 2416 (1963).

(26) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *ibid.*, **80**, 2326 (1958).

(27) C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Smat, *ibid.*, **87**, 2421 (1965).

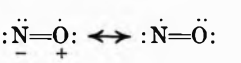
ments, and absent at 90°. In conformity with these ideas, our transition state for hyperconjugation-assisted solvolysis, like that for the E2 reaction,[6] has two preferred planar conformations, of which the *trans* is slightly better with respect to electron correlation.

Hyperconjugation of radicals and anions is also ex-



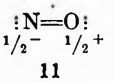
pected. There is evidence for the former,[28a] but the latter goes counter to the general belief that anion stability decreases in the order primary, secondary, tertiary. We suggest that this order, if correct, is a solution phase phenomenon, and predict that in the gas phase it will be reversed.[28b]

Organic Radicals.—Molecules such as $CH_3\cdot$ and *t*-BuO· are generally treated as *unsaturated* structures containing at least one atom with an incomplete valence shell. The low activation energies for dimerization of methyl and *t*-butoxy radicals[29] fit this description. However, by abandoning the fixed idea that electrons must be paired whenever possible, Linnett has shown that many radicals can be written with *saturated* structures, in particular those whose formally unsaturated atom is directly bonded to one possessing unshared electrons. Although these molecules still have an odd electron, they contain no atoms with incomplete valence shells. A good example is nitric oxide, NO.[30] Two canonical Lewis forms can be written, **9** and **10**, each



9 **10**

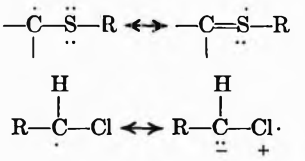
with the odd electron on an unsaturated atom. Since dimerization, for example, to O=N—N=O, would create a new bond without cost to the existing ones, the failure of NO to dimerize is difficult to understand. In the Linnett structure **11**, on the other hand, the mole-



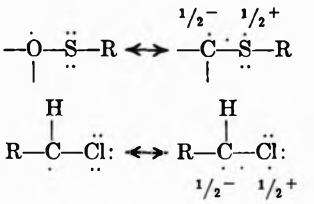
11

cule as a whole is saturated because both atoms have filled valence shells; dimerization would consequently lead to no increase in the number of bonding electrons, but would lead to increased interelectronic repulsion owing to the creation of close pairs. Many other examples of this type have also been discussed.[1,2]

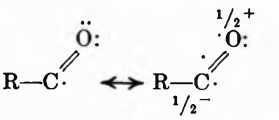
Formally unsaturated organic radicals are stabilized by adjacent sulfur[31] or chlorine.[32] The resonance forms depicted below were proposed to account for this stabilization. We now suggest that these are actually ex-



amples of saturated radicals, shown below. The stabili-



zation of acyl radicals[32] can be explained similarly. By this reasoning, one would expect that any atom bearing unshared electrons could stabilize an adjacent radical in



the same way. In the case of oxygen, there is ample evidence for such stabilization.[33] Many studies have shown that the α C–H bond in ethers is especially activated to attack by oxygen,[33-35] nitrogen,[36] and carbon[37] radicals. The α C–H bond in amines is similarly activated.[38,39] While it could be argued that these are all kinetic effects arising from the attacking radicals' being of the acceptor type, the reduced dissociation energies of C–H bonds next to oxygen,[40] and the large stabilization energies of $XCH_2\cdot$ radicals compared with $CH_3\cdot$, when X bears unshared valence electrons,[41] support our interpretation. For example, these comparisons among bond dissociation energies (in kilocalories/mole) may be made[40]: H–CH_2OH, 92; and H–CH_3, 104; H–$CH(CH_3)OH$, 90; and H–Et, 98. For radicals $XCH_2\cdot$, the following stabilization energies, in kilocalories/mole relative to $CH_3\cdot$, are reported[41]: X = F, 13; Cl, 14; Br, 19; OCH_3, 20. In comparison, the value for X = CN is only 11.

The transfer of formal charge implied in the preceding description of radical stabilization manifests itself in the increased acidity of OH bonds next to radical centers. In general, $R_2\dot{C}OH$ is much more acidic than R_2-CHOH.[42]

(28) (a) B. Mile, *Angew. Chem. Intern. Ed. Engl.*, **7**, 507 (1968). (b) Anionic hyperconjugation has been discussed by R. A. Mulliken, *Tetrahedron* **5**, 253 (1959), and draws possible experimental support from the report by W. M. Schubert, R. B. Murphy, and J. Robins, *ibid.*, **17**, 199 (1962), that *p*-alkyl groups lower the energies of the uv transitions of both anilines and nitrobenzenes.

(29) R. Gomer and G. B. Kistiakowsky, *J. Chem. Phys.*, **19**, 85 (1951); D. J. Carlsson, J. A. Howard and K. U. Ingold, *J. Amer. Chem. Soc.*, **88**, 4725 (1966).

(30) Reference 2, pp 43, 58.

(31) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, p 27.

(32) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 51; J. S. Shirk and G. C. Pimentel, *J. Amer. Chem. Soc.*, **90**, 3349 (1968).

(33) R. S. Davidson, *Quart. Rev.*, **21**, 249 (1967).

(34) M. L. Mihailovic and M. Miloradovic, *Tetrahedron*, **22**, 723 (1966).

(35) C. Walling and M. J. Mintz, *J. Amer. Chem. Soc.*, **89**, 1515 (1967).

(36) R. Partch, *Tetrahedron Lett.*, 1361 (1966).

(37) A. Ledwith and M. Sambhi, *J. Chem. Soc., B*, 670 (1966).

(38) W. H. Urry, O. O. Juveland, and F. W. Stacey, *J. Amer. Chem. Soc.*, **74**, 6155 (1952).

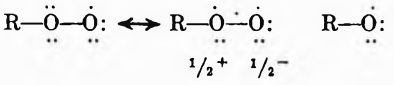
(39) M. M. Nazarova and L. K. Freidlin, *Bull. Acad. Sci. USSR, Div. Chem. Sci., Engl. Transl.*, 1754 (1966).

(40) J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966).

(41) R. H. Martin, F. W. Lampe, and R. W. Taft, *J. Amer. Chem. Soc.*, **88**, 1353 (1966).

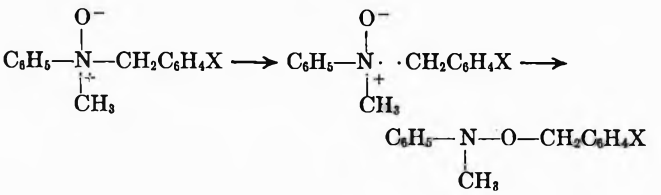
(42) G. Porter and F. Wilkinson, *Trans. Faraday Soc.*, **57**, 1686 (1961); R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1964, p 66.

In like manner, peroxy radicals can be pictured as saturated, in contrast with alkoxy radicals, which are unsaturated.[2] It is thus understandable why peroxy

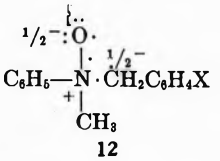


radicals are much less reactive than alkoxy toward dimerization[43] and hydrogen abstraction.[44]

A number of 1,2 rearrangements, formerly thought to be heterolytic in nature, are now recognized as proceeding *via* radical cleavage–recombination. It is difficult to rationalize these homolyses on conventional grounds. For example, the following reaction[45] proceeds readily at 30–45° which, as the authors point out, is a surprisingly low temperature for homolysis of a C–N bond.



Electron-withdrawing substituents in the benzyl ring increase the reaction rate. These facts can be accommodated with the three-electron bonded structures **12** and **13** for the transition state and nitroxyl intermediate, respectively. In a parallel investigation, another



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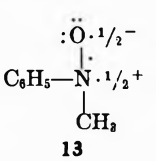
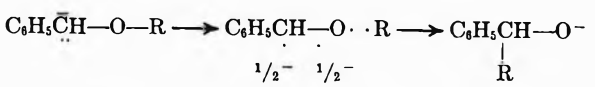


13

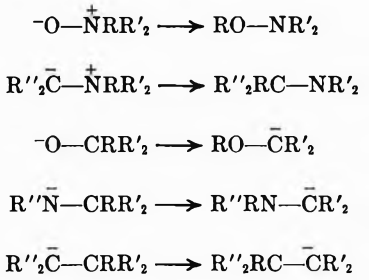
example of the same type has also been shown to have the same mechanism.[46]

Radicals may be stabilized not only by hetero atoms, but also by carbon if it possesses unshared electrons. Thus, removal of a proton from carbon facilitates homolysis at neighboring oxygen, as in the Wittig rearrangement.[47]



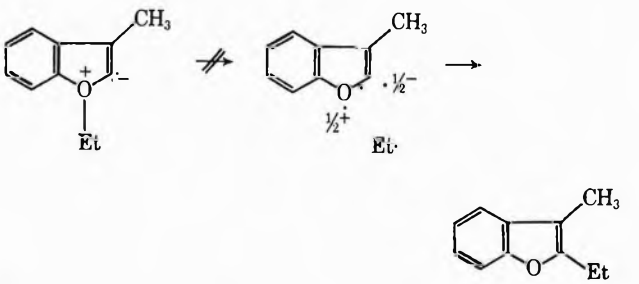
A similar mechanism has also been proposed by Schöllkopf, *et al.*,[45] for the related Stevens rearrangement.[48]

It can be predicted, then, that an important factor in the ease with which this sort of rearrangement will take place is the increase in binding energy of the AB bond which accompanies the change $\ddot{A}—B—C \rightarrow \dot{A} \doteq \dot{B} + \dot{C}$. For each AB combination, this increase can be estimated by interpolating on the smooth plot of bond energy *vs.* multiplicity for two-, four-, and six-electron bonds. After minor corrections for differences in electron correlation and L strain have been made, it should be possible to calculate the activation energy differences within series such as the following. Within each series,

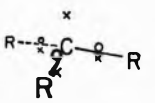


groups R and R′ must be chosen so that R· is a good radical and the reactions are thermodynamically favorable.

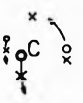
It is significant that $R''\bar{N}—\overset{+}{N}RR'_2 \rightarrow R''RN—NR'_2$ does not occur readily,[49] since the difference between the energies of N–N and $N \doteq N$ bonds is particularly small, only 27 kcal/mol, *vs.* C–C, 33, C–N, 34, or C–O, 45. Steric inhibition of assisted homolysis is also possible, as illustrated below.[50] Although the zwitterionic intermediate seems exceptionally well suited for Wittig rearrangement, none of the normal Wittig product was observed.[51] This is expected because the intermediate radical is highly strained; the $\dot{O} \doteq \dot{C}=C$ angle must be *ca.* 108° but wants to be *ca.* 152°.



The geometry of trivalent carbon with a septet of electrons can be predicted in simple terms from the Linnett structure 14. Since one spin set is a triangle and the other a tetrahedron, both centered on the nucleus, all three bonds are L strained by *ca.* 19.5°. The



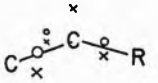
14



15

molecule will be a flattened pyramid, not quite planar, but easily inverted by rotating one spin set as in **15**. This picture agrees with current opinion.[52]

Vinyl radicals are described by a similar picture, **16**.

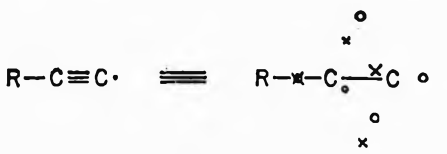


16

(43) P. D. Bartlett and G. Guaraldi, *J. Amer. Chem. Soc.*, **89**, 4799 (1967).
(44) C. Walling and V. P. Kurkov, *ibid.*, **89**, 4895 (1967).
(45) U. Schöllkopf, U. Ludwig, M. Patsch, and W. Franken, *Ann.*, **703**, 77 (1967).
(46) E. J. Grubbs, J. A. Villareal, J. D. McCullough, and J. S. Vincent, *J. Amer. Chem. Soc.*, **89**, 2234 (1967).
(47) P. T. Lansbury, V. A. Pattison, J. D. Sidler, and J. B. Bieber, *ibid.*, **88**, 78 (1966).
(48) H. E. Zimmerman, "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, p 345.
(49) R. C. Slagel, *J. Org. Chem.*, **33**, 1374 (1968); W. S. Wadsworth and W. Bruxvoort, *Chem. Comm.*, 542 (1968).
(50) H. H. Wasserman and J. M. Fernandez, *J. Amer. Chem. Soc.*, **90**, 5322 (1968).
(51) H. H. Wasserman, personal communication.
(52) W. A. Pryor, *Chem. Eng. News*, **46** [3], 74 (1968).

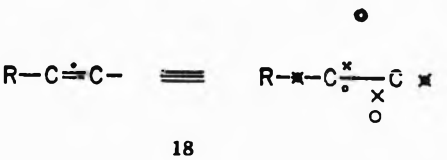
They should be slightly bent, but easily inverted. This geometry is known to be correct.[53] The estimated C–C–R angle is 152°, close to the experimental value.[28a]

Acetylenic radicals are unusual in that the simple structure **17** is a poor one according to the Linnett



17

theory, because the triangular spin set on the right-hand carbon atom is centered far off the nucleus. While this is not forbidden for a trio, it must increase the energy of the radical considerably. An alternative formulation is **18**, in which the trio is now centered properly, but the carbon-carbon bond has lost one bonding electron. This too must increase the energy; and, in fact, acetylenic radicals are destabilized relative to their alkyl and vinyl counterparts, as shown by the data in Table I.[40,54]



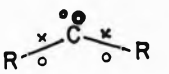
18

Carbenes.—For singlet carbenes, the idealized representation is that of two coincident triangular spin sets; the R–C–R angle is 120°. Allowing for the tendency of the unshared electrons to "spread,"[19] one expects a somewhat smaller angle. The experimental value is *ca.* 103°.[55] Triplet carbenes, on the other hand, have one quartet and one duo. If these are arranged to minimize L strain in the two C—R bonds, as in **19**, an R–C–R angle of about 145° is predicted with undistorted spin sets; slightly less when the greater flexibility of a duo, compared with a quartet, is taken into account. This rather peculiar angle is not far from the latest experimental figure of about 150°.[56]

TABLE I

BOND DISSOCIATION ENERGIES IN KILOCALORIES/MOLE

Bond	D	Ref
H—CH_3	104	40
H—Et	98	40
H—$CHCH_2$	104	40
H—CCH	~125	54
H—CN	129	40
CH_3—CH_3	88	40
Et—Et	87	40
CH_2CH—$CHCH_2$	100	54
CHC—CCH	150	54
CN—CN	145	40
CH_3—Et	85	40
CH_3—CCH	117	54
CH_3—CN	122	54
Et—CN	128	54



19

This brief survey of organic structural types demonstrates the power of the Linnett theory to correlate a large body of diverse facts by means of a relatively small number of very simple concepts. In future papers of the series, the ideas presented here will be applied in depth to problems in organic reaction mechanisms.

Acknowledgment.—The advice and encouragement of Professor Linnett have been of great assistance in this work.

(53) W. G. Bentrude, *Ann. Rev. Phys. Chem.*, **18**, 300 (1967).
(54) S. W. Benson, *J. Chem. Educ.*, **42**, 502 (1965).
(55) G. Herzberg, *Proc. Roy. Soc.* (London), **A262**, 291 (1961).
(56) I. Moritani, S-I. Murahashi, M. Nashino, Y. Yamamoto, K. Itoh, and N. Magata, *J. Amer. Chem. Soc.*, **89**, 1259 (1967).

Addition of Nitryl Iodide to Olefins[1]

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The reaction of silver nitrite with iodine in the presence of olefins was studied and was found to lead to nitro–iodo adducts. The reaction has the characteristics of a nitryl iodide addition and appears to proceed by a free-radical attack of an NO_2 species on the double bond. Stereochemical and regiochemical considerations are discussed. The method provides a selective synthesis of β-iodonitro-, vinylnitro-, and nitroalkanes under mild reaction conditions.

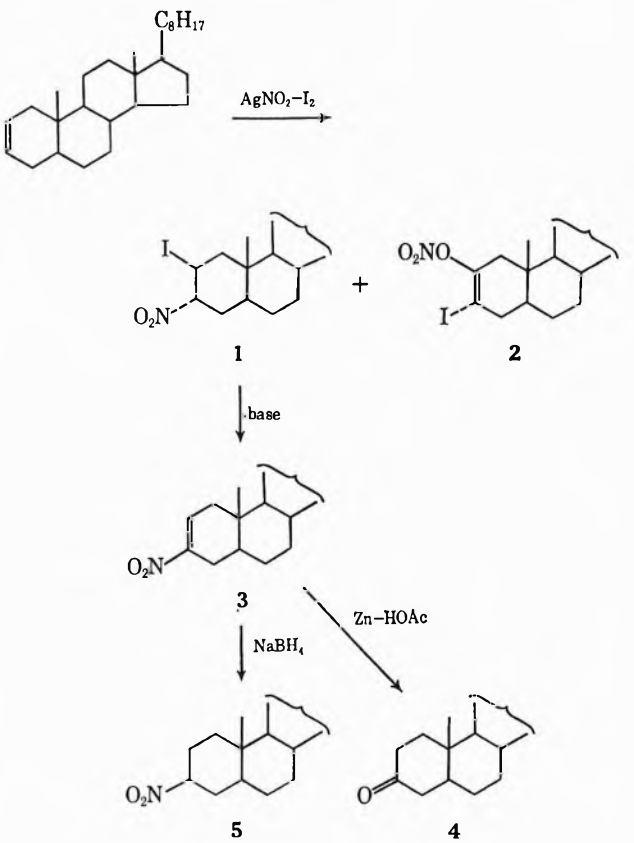
Addition reactions of pseudohalogens to olefins have recently gained in importance through their synthetic and mechanistic applications.[3] In extending pseudohalogen chemistry, this paper describes the reaction of nitryl iodide with olefins and illustrates the reaction pathway, stereochemistry, regiochemistry,[4] and products.

The reaction of silver nitrite and iodine in the presence of cyclohexene was first reported by Birchenbach to give dinitro– and iodo–nitro adducts.[5] This reaction was disregarded until 1964 when its synthetic utility and mild conditions were initially described.[1a] More recently, the mild reaction conditions of the nitryl iodide reaction have been emphasized by its use in the nitration of sugars.[6] An alternate means to synthesize nitro iodides *via* the strong oxidizing agent, dinitrogen tetroxide, has been described by Stevens and Emmons.[7]

In analogy with other pseudohalogens,[3] the reaction of silver nitrite with iodine is expected to lead to INO_2. This reagent is theoretically capable of dual heterolysis to NO_2^+ and I^- or to I^+ and NO_2^- as well as to homolysis into free radicals; hence it can function as nitryl iodide or as iodine nitrite and either ionically or free radically.

To gain information on the stereochemistry and regiochemistry of the addition of NO_2I to olefins, the reaction of silver nitrite and iodine was studied in ether in the presence of 2-cholestene. The major product (51%) was 2β-iodo-3α-nitrocholestane (**1**) together with 26% unreacted 2-cholestene and 5% 3α-iodo-2β-cholestanyl nitrate (**2**) (Scheme I). The position of the NO_2 function in **1** was proven by elimination to 3-nitrocholest-2-ene (**3**), and subsequent reduction to the known 3-cholestanone (**4**). Sodium borohydride reduction of the vinyl nitro compound (**3**) led to the known 3β-nitrocholestane (**5**).[8]

SCHEME I



Attempted conversion of **1** to a steroidal aziridine was unsuccessful; treatment with zinc or with $LiAlH_4$ led to 2-cholestene by diaxial elimination of INO_2, whereas ferrous sulfate and HCl led to recovery of starting material.

The nmr spectrum of the nitro iodide **1** indicates secondary protons at τ 4.79 and 5.16 geminal to a nitro and an iodine function, respectively. Both signals have half-widths of 8 Hz indicative of equatorial protons[9] and hence of *trans* diaxially oriented NO_2 and I groups. The nmr of the nitro iodide **1** also indicates a C-19 methyl signal at τ 8.83, a shift of 0.40 ppm from the signal in cholestane. Although this is a large shift, it is not surprising since most of the 2-axial groups cause a significant shift of the C-19 methyl group.[3b,10,11] Of the many functionalities considered, iodine has been reported to have a particularly strong anistropic effect increasing in the order chloride > bromide > iodide.[12] This progression fits the observed chemical shifts for the 2-axial halides noted in Table I.

(1) (a) Presented in part before the Symposium on Electrophilic Additions to Olefins, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964. (b) A. Hassner in L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 757. (c) Stereochemistry. XLIII. For paper XLII, see A. Hassner, R. J. Isbister, and A. Friederang, *Tetrahedron Lett.*, in press.

(2) (a) The work described was taken from the thesis submitted by J. E. Kropp in partial fulfillment of the requirements for the Ph.D. degree from the University of Colorado (1965). (b) Participant, NSF Summer Research Program for College Teachers.

(3) For instance (a) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, **90**, 2869 (1968); (b) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967), and references cited therein.

(4) Regio is used to describe directional effects in bond making or breaking: A. Hassner, *ibid.*, **33**, 2684 (1968).

(5) L. Birchenbach, J. Goubeau, and E. Berniger, *Ber.*, **65**, 1339 (1932).

(6) W. A. Szarek, D. G. Lance, and R. L. Beach, *Chem. Commun.*, 356 (1968).

(7) T. E. Stevens and W. D. Emmons, *J. Amer. Chem. Soc.*, **80**, 338 (1958).

(8) J. R. Bull, E. R. H. Jones, and G. D. Meakins, *J. Chem. Soc.*, 2601 (1965). We are greatful to Dr. Meakins for a sample of **5**.

(9) A. Hassner and C. H. Heathcock, *J. Org. Chem.* **30**, 1748 (1965).

(10) K. Tori and T. Komeno, *Tetrahedron*, **21**, No. 2, 309 (1965).

(11) A. Hassner and F. Boerwinkle, *J. Amer. Chem. Soc.*, **90**, 216 (1968).

(12) G. S. Reddy and J. H. Goldstein, *J. Chem. Phys.*, **38**, 2736 (1936).

TABLE I
NMR SHIFTS OF STEROIDAL C-19 PROTONS

2 substituent	3 substituent	C-19 methyl, τ	Shift, ppm, from cholestane
H	H	9.23	0.00
2β-I	3α-NO_2	8.83	−0.40
2β-Br	3α-Br	8.86	−0.37
2β-Br	3α-N_3	8.91	−0.32[a]
2β-Cl	3α-I	8.89	−0.34[a]
2β-NO_2	H	9.32	+0.12[b]
H	3β-NO_2	9.13	−0.10
2β-OH	3α-SH	9.00	−0.23[c]
2β-OH	H	8.98	−0.25[c]
H	3α-SH	9.22	−0.01[c]
2β-SH or SCOMe	H	8.95	−0.28[c]
2α-SH	H	9.17	−0.06[c]
2β-N_3	3α-Br	9.01	−0.22[a]
2β-N_3	3α-I	9.02	−0.21[d]
2β-NCO	3α-I	8.98	−0.25[e]
2β-ONO_2	3α-I	9.10	−0.13

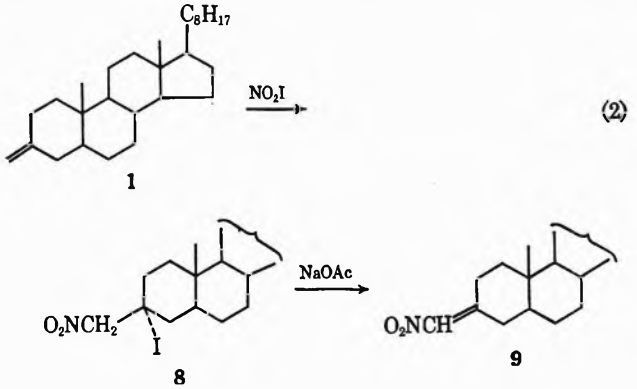
[a] See ref 11. [b] A. Hassner, J. M. Larkin, and J. E. Dowd, *J. Org. Chem.*, **33**, 1733 (1968). [c] See ref 10. [d] See ref 3a. [e] See ref 3b.

It is clear from the shifts of the C-19 protons in Table I that 2β-hydroxy-3α-cholestanethiol (0.18 ppm) and 2β-hydroxycholestane (0.20 ppm) show almost the same shift of the C-19 methyl signal; hence the 3α substituent has only a slight effect upon the C-19 absorption. Analogously the large shift of the C-19 protons in 2β-iodo-3α-nitrocholestane (**1**) would appear to be due mainly to the 2β-iodo group with only slight influence by the 3α-nitro function.

The fact that the nitro group in **1** occupies the 3α position suggested that the pseudohalogen was not reacting as iodonium nitrite (INO_2) through a three-membered iodonium ion intermediate,[3b] but instead had behaved as nitryl iodide (NO_2I). This conclusion was confirmed by the regiochemistry of the reaction of silver nitrite and iodine in the presence of styrene. The unstable nitro iodide **6** on treatment with pyridine produced the known β-nitrostyrene (**7**) (eq 1).

$$\mathrm{PhCH{=}CH_2 + AgNO_2 + I_2 \longrightarrow \underset{\displaystyle I}{\overset{\displaystyle |}{\mathrm{PhCHCH_2NO_2}}} \longrightarrow \underset{\mathbf{6}}{} \mathrm{PhCH{=}CHNO_2} \quad (1)}$$
7

The regioselectivity of NO_2I additions was further demonstrated by the formation of 3-iodo-3-(nitromethyl)cholestane (**8**) from the addition to 3-methyleenecholestane (eq 2). The structure of **8** was apparent



(2)

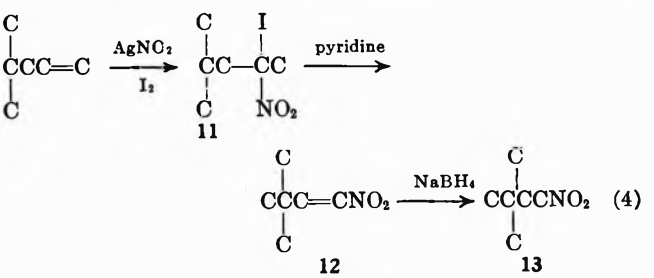
from HI elimination with sodium acetate to 3-(nitromethylene)cholestane (**9**).

The above results do not differentiate between attack by NO_2^+ or $NO_2\cdot$ on the terminal carbon of the olefin. Substantiation for the free-radical pathway was obtained by studying the NO_2I addition to an unsaturated ester substrate, since the creation of a positive charge, but not of a free radical, next to a carbonyl group is very unfavorable.[13,14] The product from reaction of methyl acrylate with nitryl iodide and subsequent elimination with sodium acetate was methyl 3-nitroacrylate (**10**) (eq 3), identical with **10** obtained by Shechter, *et al.*,[15]

$$\mathrm{CH_2{=}CHCOOCH_3 \xrightarrow[I_2]{AgNO_2} O_2NCH_2\underset{\displaystyle I}{\overset{\displaystyle |}{C}}HCOOCH_3 \xrightarrow{NaOAc} O_2NCH{=}CHCOOCH_3} \quad (3)$$
10

in the free-radical addition of nitryl chloride (NO_2Cl) to methyl acrylate. A free-radical addition is also consistent with the fact that the formation of **1** is greatly inhibited in the presence of oxygen.

In studying the effect of bulky groups upon the addition reaction of bromine in methanol, Newman, *et al.*,[16] found that the direction of addition allowed a differentiation between a free carbonium ion pathway and one involving a cyclic intermediate. When *t*-butylethylene was treated with silver nitrite and iodine, the crude adduct **11** was obtained which on elimination of HI with pyridine led to vinylnitro compound **12**. The nmr spectrum of this compound shows doublets at τ 2.87 (J = 13.5 Hz) and 3.28 (J = 13.5 Hz) indicative of a *trans* olefin and ruling out the possibility of a terminal C=CH_2. Reduction of **12** by sodium borohydride gave the saturated nitro compound **13** (eq 4) that showed a classical A_2X_2 absorption in the nmr spectrum.



(4)

Since the nitro group is the attacking species and it becomes bonded to the terminal carbon, the intermediate radical or ion was probably not bridged; otherwise opening by INO_2 should have led to the opposite regioisomer.

The diaxial iodo–nitro adduct **1** provides a good testing ground to show whether participation by a neighboring NO_2 group is possible in solvolysis reactions. Though Jeffery, *et al.*,[17] found no assistance by an NO_2 group in the solvolysis of benzyl halides, neighboring-group participation was reported for *o*-

(13) A. M. Mattocks and W. H. Hartung, *J. Biol. Chem.*, **165**, 501 (1946).
(14) H. Shechter and F. Conrad, *J. Amer. Chem. Soc.*, **75**, 5610 (1953).
(15) H. Shechter, F. Conrad, A. L. Daulton, and R. E. Kaplin, *ibid.*, **74**, 3052 (1952).
(16) W. H. Puterbaush and M. S. Newman, *ibid.*, **79**, 3469 (1957).
(17) E. A. Jeffery, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **29**, 3365 (1964).

nitrobenzyl tosylates.[13] When **1** was refluxed with silver sulfate, nitrate, or perchlorate in alcohol it was recovered essentially unchanged; a small amount of nitro olefin was formed but no methyl ethers were detectable by nmr. On the refluxing of **1** in absolute methanol in the presence of silver oxide, 3-nitro-2-cholestene (**3**) was obtained in 99% yield.

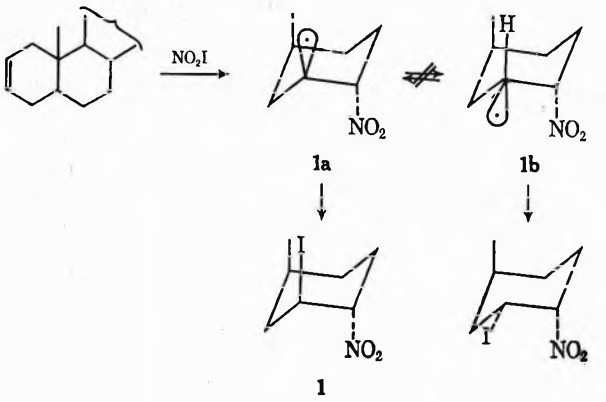
The reaction of $AgNO_2$ and I_2 with olefins does not involve the initial formation of diiodide followed by reaction with silver nitrite since no nitro compounds were obtained upon treating an equilibrated solution of 2-cholestene and its diiodide (obtained from 2-cholestene and iodine) with $AgNO_2$. Further evidence for the formation of an NO_2I species[19] was obtained by filtering the solids from the reaction mixture of silver nitrite and iodine before the addition of the olefin. Upon addition of 2-cholestene the nitro iodide **1** was produced, albeit in very poor yield.

The nitro iodide **1** was also obtained in good yield by slow addition of dinitrogen tetroxide to a solution of 2-cholestene and iodine in nonpolar solvents. This reaction also proceeds through attack of NO_2 on the double bond followed by quenching of the radical with iodine.

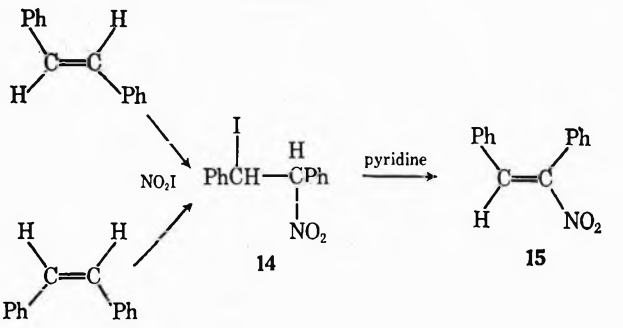
The *trans* stereochemistry in adduct **1** suggests that either a stable pyramidal radical is produced or the quenching reaction is more rapid than inversion of the radical formed. Since Brand and Stevens[20] have shown that 2-nitrocyclohexyl radicals lead to a great deal of epimerization, the *trans* diaxial NO_2I addition to 2-cholestene warrants an explanation. Approach from the α side in steroids occurs for steric reasons. In the *trans* fused decalin system stereoelectronic factors are responsible for the preferred axial attack by the NO_2 radical with simultaneous development of an axial radical. The resulting adduct radical will prefer to have a chair rather than a twist–boat conformation thus giving rise to **1a**. Using the propositions of Brand and Stevens, radical **1a** must be short lived and not allow for the epimerization that takes place in the case of nitryl chloride, dinitrogen tetroxide, or dinitrogen pentoxide additions to cyclohexene. Instead the intermediate nitroalkyl radical (**1a**) is apparently trapped very rapidly and efficiently by iodine before it can invert to **1b** (Scheme II). In this fashion the product is kinetically controlled giving rise to the sterically unfavored 1,3-diaxial arrangement of iodine and C-19 methyl. Other examples of stereoselective radical addition to a cyclohexene system such as the thiol addition to *t*-butylcyclohexene[21] or diaxial radical additions to steroid 5-enes can be similarly explained.[22]

When nitryl iodide was added to *cis*- and *trans*-stilbene, the resulting product appeared to be a diastereoisomeric mixture (**14**) with an nmr doublet at τ 3.43 (1 H) and two doublets at 3.74 ($^1/_2$ H) and 3.86 ($^1/_2$ H). This mixture was dehydrohalogenated to give the same *cis*-1,2-diphenyl-1-nitrostilbene (**15**) (Scheme III) as that obtained by Stevens and Emmons.[7]

SCHEME II

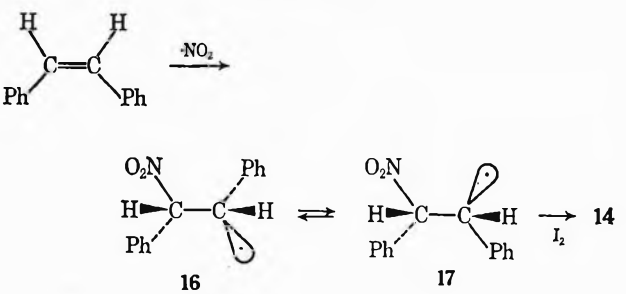


SCHEME III



After treating an excess of *cis*-stilbene with nitryl iodide, the nmr of the crude product indicated the unreacted stilbene to be solely the *cis* isomer, suggesting that the formation of the nitro radical is nonreversible. Since no *cis–trans*-stilbene isomerization had occurred, yet a diastereoisomeric mixture of products was obtained, a long-lived pyramidal structure (**16**) must not be formed. Instead, the phenyl stabilized radical **16** is interconverted to **17** before it is quenched by iodine (Scheme IV).

SCHEME IV



Unlike nitryl fluoroborate, NO_2I does not serve as an efficient source of positive nitrylium ions as evidenced by its failure to nitrate toluene or methyl benzoate. With phenol, *o*- and *p*-nitrophenols as well as iodophenols were obtained.

Experimental Section

Preparation of 2β-Iodo-3α-nitrocholestane (1). A. General Procedure. Reaction with $AgNO_2$–I_2 in Ether.—Silver nitrite, 1.16 g (7.55 mmol), and iodine, 3.85 g (15.1 mmol), were stirred in 75 ml of ether for 30 min and 2-cholestene, 2.79 g (7.55 mmol), was added while the headspace of the reaction flask was flushed with dry nitrogen (if the headspace was not flushed with nitrogen

(18) W. B. Dickinson, *J. Amer. Chem. Soc.*, **86**, 3580 (1964).

(19) NO_2I is easily oxidized in polar solvents to INO_3. The addition of this species to olefins will be discussed in a subsequent publication.

(20) J. C. D. Brand and I. D. R. Stevens, *J. Chem. Soc.*, 629 (1958); *Chem. Ind.* (London), 1742 (1955).

(21) (a) E. S. Huyser and J. R. Jeffrey, *Tetrahedron*, **21**, 3083 (1965); (b) F. G. Bordwell, P. S. Landis, and G. S. Whitney, *J. Org. Chem.*, **30**, 3764 (1965).

(22) C. W. Shoppee and R. Lack, *J. Chem. Soc.*, 4864 (1960).

during the reaction, the yield of the isolated nitro compound dropped to less than 30%). The mixture was stirred for 4 hr and filtered and the solids were washed with ether. The ether was washed with a solution of $NaHSO_3$ and 100 ml of saturated sodium chloride solution and dried ($MgSO_4$). The ethereal solution was then evaporated under a stream of nitrogen until the orange-brown residue was dry.

A portion (0.1013 g) of the crude material was dissolved in 4.9868 g of Spectro Grade chloroform. Infrared spectral analysis, using calibrations by means of the hill and valley technique for the transmittance at 1630 cm^{-1} for **2**, indicated the presence of 5% 3α-iodo-2β-cholestanyl nitrate (**2**).

The orange-brown solids were triturated with 5 ml of hexane and cooled in an ice chest. The solids were filtered off and washed with a small amount of cold hexane. After the mixture was dried, 2.033 g (51%), mp 127–135°, of a white solid was obtained. Several recrystallizations from ethyl acetate gave an analytical sample of **1**: mp 141–143°; ir (KBr) 1548, 1367, and 870 cm^{-1} (nitrate); nmr peaks at τ 4.79 (m, 1, $W_{1/2}$ = 8 Hz), 5.16 (m, 1, $W_{1/2}$ = 8 Hz), and 8.83 (s, 3). The hexane mother liquor was chromatographed on alumina to give 0.732 g (26%) of 2-cholestene, mp 70–72°.

Anal. Calcd for $C_{27}H_{46}NO_2I$: C, 59.65; H, 8.53; N, 2.58. Found: C, 59.54; H, 8.59; N, 2.47.

B. Reaction with N_2O_4–I_2.—A solution of 1.5 g (4.06 mmol) of 2-cholestene and 2.05 g (8.12 mmol) of iodine were stirred in 75 ml of dry ether and approximately 0.46 g (5.0 mmol) of dinitrogen tetroxide in 5 ml of hexane was added dropwise over a period of 0.5 hr. This solution was stirred for an additional 2 hr and then worked up as usual. Upon evaporation, 1.272 g of a tan product was obtained. The crude infrared spectrum showed nitro absorption at 1545 cm^{-1}, and no absorption characteristic of nitrate or of 2-cholestene. This crude product was recrystallized once from ethyl acetate to give **1**, melting at 138–140°, and identical by infrared spectra with material obtained under procedure A.

Preparation of 3-Nitro-2-cholestene (3).—A mixture of 0.250 g (0.46 mmol) of 2β-iodo-3α-nitrocholestane (**1**) and 0.109 g (0.92 mmol) of silver oxide (dried in a vacuum oven) was refluxed for 4 hr in 100 ml of methanol. The solution was cooled to room temperature, filtered through a sintered-glass funnel, and evaporated to give 0.188 g (99%) of white solid: mp 90–100°; ir 1509 and 1339 cm^{-1} (NO_2); nmr τ 2.90 (br, 1, C=H). This material was recrystallized from ether–methanol to give **3**, mp 122–124°.

Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found: C, 77.34; H, 10.78; N, 3.67.

Zinc Reduction of 3-Nitro-2-cholestene (3).—Zinc dust (800 mg) was added in portions during 1 hr to a stirred warm (40°) suspension of 250 mg of 3-nitro-2-cholestene (**3**) in 15 ml of acetic acid and 0.5 ml of water. After 4 hr of reflux, the mixture was filtered hot and the zinc was washed well with hot HOAc. Addition of water and extraction with ether gave 116 mg of product which on crystallization from methanol (86 mg) melted at 124–127° and was identical by ir, mixture melting point, and 2,4-dinitrophenylhydrazone formation with 3-cholestanone.

3β-Nitrocholestane (5).—A mixture of 400 mg (0.965 mmol) of nitro olefin **3**, 14 ml of ethanol, and 70 mg (2 mmol) of $NaBH_4$ was stirred at room temperature for 3 hr and allowed to stand for an additional 14 hr. Work-up with water and 0.1 *N* HCl and ether extraction yielded 343 mg of **5**, mp 90–98°; recrystallization from methanol gave a product of mp 94–96.5°, identical with an authentic sample.[8]

Preparation of β-Nitrostyrene (7).—The general procedure was used incorporating 2.96 g (19.2 mmol) of silver nitrite, 9.75 g (38.4 mmol) of iodine, and 2.00 g (19.2 mmol) of styrene in 75 ml of dry ether. Upon evaporation the oil was taken up in 10 ml of ether and 10 ml of pyridine was added. This mixture was stirred for 2 hr at room temperature and then extracted with a large volume of pentane and water. The pentane was repeatedly washed with water, then dried ($MgSO_4$), and distilled at 0.5-mm pressure. Material boiling 80–120° was collected and recrystallized from methanol to give two crops: 0.618 g, mp 54–55°; and 0.770 g, mp 35–42°. The total yield was 49%. The infrared spectra of these products were identical with those of a known sample of β-nitrostyrene (lit.[23] mp 54°).

3-Methylenecholestane was obtained as described[24] by heating 5.0 (13.0 mmol) of cholestan-3-one in 30 ml of tetrahydrofuran with triphenylphosphinemethylene prepared from 6.62 g (16.4 mmol) of triphenylmethylphosphonium iodide and 17.7 mmol of NaH in dimethyl sulfoxide at 55° for 20 hr. Chromatography on alumina gave 3.925 g (78%) of 3-methylenecholestane. Recrystallization from ether–methanol gave a product of mp 62–64° (lit.[24] mp 64–65°); ir 3045, 1751, 1641, and 881 cm^{-1}.

3-Iodo-3-(nitromethyl)cholestane (8). A. Using Silver Nitrite and Iodine.—The general procedure was used incorporating 0.832 g of silver nitrite (5.42 mmol), 2.76 g of iodine (10.84 mmol), and 2.00 g of 3-methylenecholestane (5.25 mmol). After evaporation with nitrogen and trituration with hexane, two crops of a light brown solid were obtained: 0.875 g, mp 131–136°; and 0.100 g, mp 125–131°. The total yield was 34%. This material was recrystallized from acetone to give an analytical sample, mp 142–144°. The unstable nitroiodocholestane **8** turned brown and lost iodine upon standing, even in the dark. Infrared showed peaks at 1548, 1368, and 646 cm^{-1}; nmr showed τ 5.05 (s, 1). The hexane mother liquor was chromatographed to give 0.440 g (53%) of starting olefin.

Anal. Calcd for $C_{28}H_{48}NO_2I$: C, 60.31; H, 8.68; N, 2.51. Found: C, 61.01; H, 9.14; N, 2.12.

B. Using Dinitrogen Tetroxide and Iodine.—A solution of 5.0 g (17.6 mmol) of 3-methylenecholestane and 2.4 g (18.0 mmol) of iodine were stirred together at room temperature in 150 ml of dry ether and 1.4 g (36.0 mmol) of dinitrogen tetroxide in 5 ml of hexane was added dropwise over a period of 1 hr. This solution was stirred for an additional 2 hr and worked up as usual to give 7.485 g (77% yield), mp 123–134°. The product was recrystallized from acetone to give **8**, an unstable white solid, mp 142–143°, which was identical with **8** obtained by method A. Upon standing at room temperature and in the dark for 2 days this material turned a light brown.

3-(Nitromethylene)cholestane (9).—A solution of 2.5 g of 3-iodo-3-(nitromethyl)cholestane **8** was dissolved in 150 ml of dry ether and 2.50 g of freshly fused sodium acetate was added. This mixture was refluxed for 17 hr and allowed to cool to room temperature. After the solids were filtered, the filtrate was evaporated to give 1.927 g of crude product in 99% yield. The infrared spectrum of the crude product showed only a trace of saturated nitro compounds with absorption at 1548 cm^{-1}. Recrystallization of this product from ether–methanol gave an analytical sample of **9**: mp 97–98°; ir 3160, 1630, 1511, 822, and 761 cm^{-1}; nmr signals at τ 3.30 (s, 1) and 9.09 (s).

Methyl 3-Nitroacrylate (10).—A mixture of 2.0 g (23.2 mmol) of freshly distilled methyl acrylate, 3.58 g (23.2 mmol) of silver nitrite, and 11.7 g (46.4 mmol) of iodine in 100 ml of ether was allowed to react as in the general procedure to give a brown oil. This oil was stirred with 2.0 g (27.8 mmol) of anhydrous sodium acetate for 3 hr at room temperature. Vacuum distillation gave 0.240 g of methyl 3-nitroacrylate (higher yields of elimination products are achieved if freshly fused sodium acetate is refluxed with the product for 17 hr[16]): mp 36–37° (lit.[16] mp 38°); infrared absorption at 1720, 1522 cm^{-1}; nmr peaks at τ 2.35 (1 H, J = 13 Hz) and 2.99 (1 H, J = 13 Hz).

3,3-Dimethyl-1-nitro-1-butene (12).—The general procedure was used incorporating 5.5 g (35.7 mmol) of silver nitrite, 18.0 g (71.4 mmol) of iodine, 3.00 g (35.7 mmol) of 3,3-dimethylbutene, and 200 ml of dry ether to give 4.29 g (45%) of an inseparable mixture of 3,3-dimethyl-2-iodo-1-nitrobutane and 3,3-dimethyl-2-iodobutyl nitrate upon evaporation: infrared absorption at 1638, 1558, 1372, and 1279 cm^{-1}; nmr peaks at τ 4.80 (t, 1), 4.56 (d, 2), and minor signals at 4.72 (d) and 4.22 (t).

The crude product mixture of 5.4 g of 3,3-dimethyl-2-iodo-1-nitrobutane and 3,3-dimethyl-2-iodobutyl nitrate was dissolved in 10 ml of ether and treated with 10 ml of pyridine. After 15 min a solid precipitated out. The mixture was stirred for an additional 4 hr, poured into ice water, and extracted with pentane. The pentane was dried over anhydrous magnesium sulfate and evaporated to give 2.83 g (98%) of a yellow oil. This material was distilled on a spinning-band column to give an analytical sample: bp 30° (1 mm); $n^{24}D$ 1.4546; infrared absorption at 3123, 1641, 1529, 1349, 967, 842, and 719 cm^{-1}; nmr peaks at τ 2.87 (d, 1, J = 13.5 Hz), 3.28 (d, 1, J = 13.5 Hz).

Anal. Calcd for $C_6H_{11}NO_2$: C, 55.79; H, 8.59; N, 10.85. Found: C, 55.80; H, 8.59; N, 10.89.

(23) I. M. Heilbron, Ed., "Dictionary of Organic Compounds," Oxford Press, New York, N. Y., 1938.

(24) F. Sondheimer and R. Mechoulom, *J. Amer. Chem. Soc.*, **89**, 5029 (1957).

3,3-Dimethyl-1-nitrobutane (13).—3,3-Dimethyl-1-nitrobut-1-ene (2.83 g) was dissolved in 50 ml of methanol and 1.00 g of sodium borohydride was added. This mixture was stirred for 24 hr at room temperature, poured into water, made acidic with dilute hydrochloric acid, and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to give 0.483 g (17%) of 3,3-dimethyl-1-nitrobutane: nmr peaks at τ 5.54 (t, 2), 8.04 (t, 2).

A. Reaction of *trans*-Stilbene with Silver Nitrite and Iodine.—The general procedure was used incorporating 5.85 g (32.5 mmol) of *trans*-stilbene, 2.50 g (16.3 mmol) of silver nitrite, and 8.25 g (32.5 mmol) of iodine in 75 ml of ether. After reaction the mixture was filtered and the solids were washed free of iodine color with ether. The solids were heated on a steam bath with 150 ml of benzene and filtered while hot. The combined filtrates were worked up as usual. Recrystallization from benzene gave 4.232 g of product **14**: mp 167–169°; infrared absorption at 1540, 1352, and 723 cm^{-1}; nmr peaks at τ 3.43 (d, 1, J = 12 Hz), 3.74 (d, $W_{1/2}$ = 12 Hz), and 3.86 (d, $W_{1/2}$ = 12 Hz). The analytical sample melted at 172–173°.

Anal. Calcd for $C_{14}H_{12}NO_2I$: C, 47.61; H, 3.43; I, 35.94. Found: C, 47.81; H, 3.67; I, 36.24.

The mother liquor gave 4.087 g of unreacted olefin which was found to be only *trans*-stilbene by nmr with a signal at τ 2.9.

B. Reaction of *cis*-Stilbene with Silver Nitrite and Iodine.—The previous reaction was repeated incorporating 2.56 g of silver nitrite, 16.5 g of iodine, and 3.0 g of *cis*-stilbene. After work-up 2.40 g of crude **14**, mp 167–169°, was obtained. The infrared and nmr spectra were identical with those of the analyzed sample. The nmr of the mother liquor indicated that the recovered olefin consisted solely of *cis*-stilbene with a signal at τ 3.45.

***cis*-α-Nitrostilbene (15).**—A solution of 1.50 g of 1,2-diphenyl-1-iodo-2-nitroethane (**14**) was dissolved in 10 ml of ether and 10 ml of pyridine and allowed to stand at room temperature for 2 hr. This mixture was extracted with pentane–water and the pentane was repeatedly washed with water. After drying ($MgSO_4$) and evaporation 1.132 g of a dark brown solid was obtained. Chromatography on silica gel gave 0.812 g of **15** as a bright yellow solid, mp 72–73° (89%) (lit.[7] mp 74–75°).

Registry No.—Nitryl iodide, 15465-40-4; **1**, 20429-43-0; **3**, 13643-70-4; **8**, 20429-45-2; **9**, 20429-46-3; **12**, 20429-42-9; **14**, 20429-47-4.

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Nucleosides. LX.[1a] Fluorocarbohydrates. XXII.[1b] Synthesis of 2-Deoxy-2-fluoro-D-arabinose and 9-(2-Deoxy-2-fluoro-α- and -β-D-arabinofuranosyl)adenines[2]

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Nucleophilic attack of KHF_2 on methyl 2,3-anhydro-5-*O*-benzyl-α-D-riboside is shown to occur largely at the 2 position (in contrast to the β-D anomer) and leads to methyl 5-*O*-benzyl-2-deoxy-2-fluoro-α-D-arabinoside (**4b**), thus achieving the first *direct* synthesis of a 2-fluoropentose derivative. From **4b**, 2-deoxy-2-fluoro-D-arabinose (**6**) is obtained. Fusion of 1,3-di-*O*-acetyl-5-*O*-benzyl-2-deoxy-2-fluoro-D-arabinose with 2,6-dichloropurine affords a readily resolved α–β mixture of 9-glycosylpurine nucleosides, which are converted into 9-(2-deoxy-2-fluoro-α- and -β-D-arabinofuranosyl)adenines (**14** and **15**). Confirmation of the anomeric configuration of these nucleosides is obtained by conversion into their 5′-tosylates (**16** and **17**) and by cyclization of the β anomer to its 3,5′-cyclo nucleoside (**18**).

9-β-D-Arabinofuranosyladenine[3] (Ara-A) is an effective inhibitor of the growth of several mouse tumors.[4,5] However, the efficacy of this drug is reduced by the conversion of Ara-A *in vivo* into the inactive inosine analog by adenosine deaminase.[5] These results suggest that an analog of Ara-A which would maintain its chemotherapeutic effect without undergoing enzymatic degradation would be desirable. Toward this end, the synthesis of the 2′-fluoro analog of Ara-A was undertaken. Such a nucleoside may also be regarded as a 2′-fluoro analog of 2′-deoxyadenosine occurring in DNA.

In previous studies we reported the synthesis of 2′-deoxy-2′-fluoro analogs of uridine,[6a] 5-fluorouridine,[6a] ribothymidine,[6a] and cytidine[6b] by treatment of 2,2′-anhydro nucleosides with hydrogen fluoride. By glycosyl cleavage of the 5,6-dihydro derivative of 2′-deoxy-2′-fluorouridine, 2-deoxy-2-fluoro-D-ribose[6c] was obtained. We now report the first synthesis of a 2-fluoropentose from a pentoside precursor and its conversion into 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (**10b**).

It was demonstrated[7] that treatment of the β-epoxide (**1**) with KHF_2 in ethylene glycol gave the 3-fluoro xyloside (**2**) as the only isolable product (Scheme I). That the 3-fluoro isomer was the predominant product from this reaction may be due to steric factors related to the methoxy group in the β configuration. It may be expected, particularly in view of previous results with

(1) For previous papers in these series see (a) Nucleosides. LIX: K. A. Watanabe, M. P. Kotick and J. J. Fox, *Chem. Pharm. Bull.*, **17**, 416 (1969). (b) Fluorocarbohydrates. XXI: R. C. Young, R. A. Dwek, and P. W. Kent, *Carbohyd. Res.*, in press.

(2) This work was supported in part by funds from British Scientific Research Council (J. A. W.), the British Medical Research Council (N. F. T.) and the National Cancer Institute, National Institutes of Health, U. S. Public Health Service Grant 08748 (J. J. F. and J. A. W.).

(3) W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 2648 (1960); E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3247 (1962); C. P. J. Glaudemans and H. G. Fletcher, Jr., *ibid.*, **28**, 3004 (1963); E. J. Reist, V. J. Bartuska, and L. Goodman, *ibid.*, **29**, 3725 (1964).

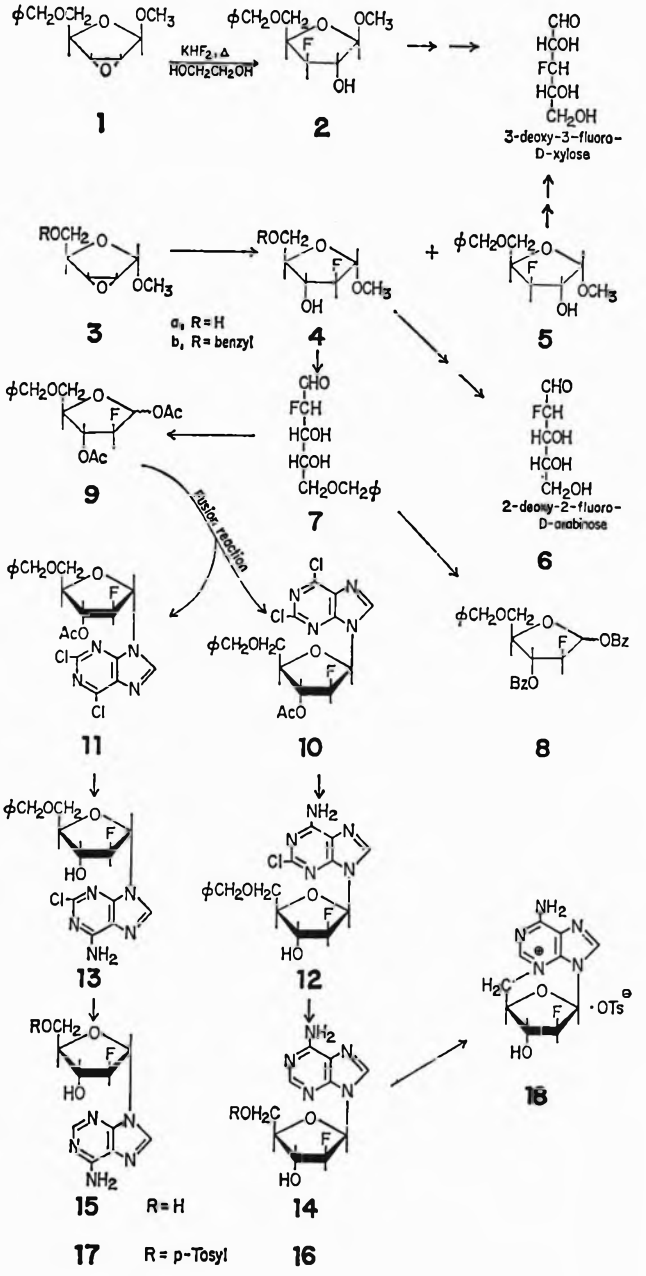
(4) R. Koshiura and G. A. LePage, *Cancer Res.*, **28**, 1014 (1968) and leading references therein.

(5) For a review of the biochemistry of arabinosyl nucleosides see S. S. Cohen, *Progr. Nucleic Acid Res. Mol. Biol.*, **5**, 1 (1966).

(6) (a) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964); (b) I. L. Doerr and J. J. Fox, *ibid.*, **32**, 1462 (1967); (c) J. F. Codington, I. L. Doerr, and J. J. Fox, *Carbohyd. Res.*, **1**, 455 (1966).

(7) J. A. Wright and N. F. Taylor, *ibid.*, **6**, 347 (1968).

SCHEME I



other nucleophiles,[8] that the α-epoxide (**3**)—where this steric inhibition to attack on C2 is not present—would react with KHF_2 to give a significant proportion of the 2-fluoro isomer. Accordingly, the known[9] methyl 2,3-anhydro-α-D-ribofuranoside (**3a**) was converted into the 5-*O*-benzyl ether (**3b**) and treated with KHF_2 in refluxing ethylene glycol to give a mixture of fluoro sugars **4b** and **5b**. The former (**4b**) was obtained in 40% yield, whereas the *xylo* isomer (**5b**) was present in only small amounts. Separation of the isomers was achieved by short column chromatography on silica gel. The identity of the 3-fluoro *xylo* isomer was established by debenzylation (hydrogenolysis) followed by acid hydrolysis to give 3-deoxy-3-fluoro-D-xylose, identical with that previously reported.[7]

Compound **4b** was isolated as a pure syrup which gave satisfactory elemental analyses (C, H, F) and showed the presence of the methoxyl and benzyl groups in its nmr spectrum. Assuming a normal *trans* opening of epoxide **3b**, it is clear that **4b** must be the 2-deoxy-2-fluoroarabinofuranoside. Final confirmation of the position of the fluoro atom in **4b** is given later in the proof of the structure of nucleoside **10**.

Catalytic hydrogenolysis of **4b** using 5% Pd/C proceeded readily, giving rise to glycoside **4a** as a colorless syrup, whose nmr and ir spectra showed the absence of the benzyl substituent. Acid hydrolysis of **4a**, using conditions similar to those employed for hydrolysis of the methyl 3-deoxy-3-fluoro-D-*xylo*- and -*arabino*-furanosides previously reported,[7,10] was much slower. Thus, while methyl 3-deoxy-3-fluoro-α-D-arabinofuranoside was completely hydrolyzed in 1 hr in refluxing 0.05 *M* H_2SO_4, compound **4a** required 5 hr under similar conditions. This finding is in agreement with others attesting to the influence of electronegative substituents[11] at C-2 upon the rate of hydrolysis of glycosides.

The hydrolysis product **6** was isolated as a viscous, colorless, analytically pure syrup which reduced Fehling's solution and which differed chromatographically from 3-deoxy-3-fluoro-D-xylose and -arabinose and from 2-deoxy-2-fluoro-D-ribose. These data allow the structural assignment of 2-deoxy-2-fluoro-D-arabinose to **6**. The 60-MHz nmr spectrum of **6** was very complex, and no first-order analysis was attempted.

Acid hydrolysis of methyl 5-*O*-benzyl-2-deoxy-2-fluoroarabinoside (**4b**) using conditions similar to those employed with 3-deoxy-3-fluoro analogs[7,10] was also slow, requiring 4 hr for completion. From this reaction 5-*O*-benzyl-2-deoxy-2-fluoro-D-arabinose (**7**) was obtained as a chromatographically pure syrup which reduced Fehling's solution. Periodate oxidation of **7** proceeded slowly, and in 100 hr the consumption of 3.2 mol of oxidant per mol was observed with the liberation of 1.5 mol of formic acid and 0.5 mol of fluoride ion. These results contrast with those obtained from the isomeric 3-deoxy-3-fluoro analogs[7,10] and are in keeping with the behavior of methyl 2-deoxy-2-fluoro-D-ribopyranoside[6c] and of malondialdehydes[12] toward this oxidant. Compound **7**[13] was characterized as the crystalline 1,3-di-*O*-benzoyl derivative (**8**).

Acetylation of **7** gave the 1,3-di-*O*-acetyl derivative **9** which was chromatographically homogeneous on tlc and gave satisfactory elemental analyses. Condensation of **9** with 2,6-dichloropurine at 160° using *p*-toluenesulfonic acid as catalyst (fusion procedure)[14] gave an anomeric mixture[15] which was readily resolved by short column chromatography[16] on silica gel G into the β nucleoside **10** (30%), the α nucleoside **11** (29%), and unreacted sugar **9** (15%). The β anomer **10** crystallized

(8) G. Casini and L. Goodman, *J. Amer. Chem. Soc.*, **85**, 235 (1963); L. Goodman, *ibid.*, **86**, 4167 (1964); P. W. Austin, J. G. Buchanan, and E. M. Oakes, *Chem. Commun.*, 374 (1965).

(9) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 5247 (1958).

(10) J. A. Wright and N. F. Taylor, *Carbohyd. Res.*, **3**, 333 (1967).

(11) J. N. BeMiller, *Advan. Carbohy. Chem.*, **22**, 25 (1967).

(12) C. F. Huebner, S. R. Ames, and E. C. Bubl, *J. Amer. Chem. Soc.*, **68**, 1621 (1946).

(13) Compounds **7** and **6** are depicted in the aldehydo form for convenience only.

(14) B. Helferich and E. S. Hillebrecht, *Chem. Ber.*, **66**, 378 (1933); T. Sato, T. Shimadate, and Y. Ishodo, *Nippon Kagaku Zasshi*, **81**, 1440 (1960); M. J. Robins, W. A. Bowles, and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 1251 (1964).

(15) This result was expected in view of the absence of a substituent at C-2 capable of neighboring-group participation.

(16) B. J. Hunt and W. Rigby, *Chem. Ind.* (London), 1868 (1967).

readily, but the α anomer was isolated only as a glass, although chromatographically pure. The site of glycosylation in both anomers was shown to be on position 9 by comparison of their ultraviolet spectra with those of the 7- and 9-methyl-2,6-dichlorpurines.[17] The benzyl substituent in **10** and **11** is an isolated chromophore absorbing only weakly in the 250–300-mμ region and thus does not interfere significantly with λ_{max} values. Thus, compounds **10**, **11**, and 2,6-dichloro-9-methylpurine exhibit λ_{max} at 274 mμ, whereas the λ_{max} of 2,6-dichloro-7-methylpurine is at 278–284 mμ.

The nmr spectra of **10** and **11** furnished clear proof that the fluorine atom is at carbon 2 of the sugar. Thus, the anomeric proton in each isomer appeared as a quartet at about δ 6.5 ppm, displaying the characteristically large vicinal H–F coupling; H-1′ of **11** possessed $J_{1'\text{-F}}$ of 14.5 Hz, and $J_{1',2'}$ of 2.0 Hz, while for **10** the comparable values were 17.3 Hz and 4.0 Hz, respectively, measured in acetone-d_6. It was also noted that in the spectrum of **10** the signal at δ 8.55 assigned to H-8 was split into a doublet with a coupling constant of 2.6 Hz. This splitting, also observed in compounds **12** and **14** (see below), is believed to be long-range (^5J) coupling to the 2′-fluoro substituent, since spin-decoupling experiments ruled out H-8–H-1′ coupling. In addition, a fine-splitting of about 1 Hz in the signals assigned to the 5′ protons in **10**, **11**, and some of the other compounds described herein was attributed to long-range coupling with the fluorine atom, since the ring proton signals showed no such splitting. Fluorine nmr spectra should provide confirmation of these extra couplings. The rest of the signals in the spectra of **10** and **11** were well-resolved, including those assigned to H-2′, which showed geminal H–F couplings of 50.5 Hz in agreement with the assigned structures.

Treatment of **10** and **11** with alcoholic ammonia at room temperature resulted in hydrolysis of the 3′-*O*-acetyl esters and replacement of the 6-chloro substituent by amino groups, to give **12** and **13** in 85–90% yields. Conversion into the fully deblocked nucleosides was effected by hydrogenolysis in the presence of Pd/C catalyst. Tlc showed this reaction to proceed stepwise, with rapid removal of the 5′-*O*-benzyl group followed by slow replacement of the 2-chloro substituent by hydrogen, to give 80–85% yields of **14**, mp 232–234°, and **15**, mp 209–210°. The uv spectra of **14** and **15** closely resembled that of adenosine in water and at pH 1, providing further confirmation of the 9-substituted adenine structure. In the nmr spectra, signals at δ ~8.2 (sharp singlet) and ~7,3 ppm (broad singlet) were assigned to H-2 and NH_2 respectively.

Chemical confirmation of the configurational assignments at the anomeric center of **14** and **15** was obtained from their 5′-*O*-tosyl esters **16** and **17** using the method originated by Todd, *et al.*[18] The position of the tosyl substituents in **16** and **17** was indicated in their nmr spectra by a downfield shift of ~0.7 ppm in the signals assigned to the 5′ protons. Compound **17** remained unchanged after 5-hr reflux in dioxane, whereas **16** underwent complete conversion into the 3,5′-cyclo nucleoside **18**. The conversion of **16** into **18** was accompanied by a bathochromic shift in the uv spectrum from 262 to 274 mμ, by the appearance of new absorption bands at 685, 1010, and 1210 cm^{-1} in the ir spectrum characteristic of the tosylate anion, by loss of solubility in nonaqueous solvents, and by a large reduction in chromatographic mobility.

(17) A. G. Beaman and R. K. Robins, *J. Org. Chem.*, **28**, 2310 (1963).
(18) V. M. Clark, A. R. Todd and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

Experimental Section

General Procedures.—Melting points were determined using a Hoover–Thomas capillary apparatus, and are corrected. Thin layer chromatography (tlc) was performed on microscope slides coated with silica gel GF 254 (Merck), using ethyl acetate–benzene (1:3) (solvent A) and methanol–chloroform (1:5) (solvent B) as eluting solvents. Compounds were detected by viewing under uv light and by spraying with 20% (v/v) H_2SO_4 in ethanol followed by heating to 130°. Reducing sugars were detected using aniline hydrogen phthalate reagent. All evaporations were carried out *in vacuo*.

Nmr spectra were measured on a Varian A-60 instrument, using TMS as internal standard. Chemical shifts are reported in ppm (δ), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (complex multiplet). Coupling constants are first order. Uv spectra were measured using a Unicam Model SP 800, and ir spectra on a Perkin-Elmer Model 221 spectrophotometer. Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Methyl 2,3-Anhydro-5-*O*-benzyl-α-D-ribofuranoside (3b).—To a solution of **3a**[9] (10 g, 0.068 mol) in anhydrous DMF (50 ml), silver oxide (14 g) and benzyl bromide (12 ml, 0.10 mol) were added. The mixture was shaken 24 hr at room temperature, then diluted with chloroform (500 ml) and water (500 ml). The chloroform layer was separated and filtered, pyridine (50 ml) was added, and the solution was washed successively with water (six times, 200 ml), 2 *N* HCl (thrice, 200 ml), and saturated $NaHCO_3$ (200 ml), then dried ($MgSO_4$) and evaporated. The resulting oil was distilled *in vacuo* to give colorless **3b** (13.4 g): bp 110–115° (0.02 Torr); $[\alpha]^{22}D$ −18.1° (c 1.3, ethanol); nmr (acetone-d_6) signals at δ 7.34 (s 5, aromatic), 5.17 (s 1, H-1), 4.55 (s 2, benzyl CH_2), 4.25 (t 1, H-4, $J_{4,5}$ 3.9 Hz), 3.71 (s 2, H-2, H-3), 3.60 (d 2, H-5), and 3.38 (s 3, OCH_3).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.18; H, 6.68.

Methyl 5-*O*-Benzyl-2-deoxy-2-fluoro-α-D-arabinofuranoside (4b).—A solution of **3b** (7 g) and KHF_2 (10 g) in ethylene glycol (140 ml) was refluxed gently for 1 hr. A further charge of KHF_2 (5 g) was added, and reflux continued another 0.5 hr. The cooled mixture was poured into saturated $NaHCO_3$ (500 ml) and extracted with chloroform (thrice, 200 ml). The dried ($MgSO_4$) chloroform layers were evaporated and the syrupy residue was chromatographed on a large diameter column of silica gel G (200 g), eluting with ethyl acetate–petroleum ether (bp 30–60°) (1:3). Fractions were collected containing **4b** (3.2 g), unreacted **3b** (1.1 g), and methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-xylofuranoside (**5**) (1.0 g), identified by hydrogenolysis and acid hydrolysis to 3-deoxy-3-fluoro-D-xylose, identical (ir and nmr spectra and chromatography) with an authentic sample.

4b had $[\alpha]^{22}D$ 94.3 (c 0.5, ethanol); nmr ($CDCl_3$) signals at δ 7.36 (s 5, aromatic), 5.06 (d 1, H-1, $J_{1,F}$ 10.3 Hz), 4.82 (q 1, H-2, $J_{2,F}$ 51, $J_{2,3}$ 1.6 Hz), 4.62 (s 2, benzyl CH_2), 4.1 (m 2, H-3, H-4), 3.92 (s 1, OH-3), 3.64 (d 2, H-5, $J_{4,5}$ 5.5 Hz), and 3.40 ppm (s 3, OCH_3).

Anal. Calcd for $C_{13}H_{17}O_4F$: C, 60.92; H, 6.69; F, 7.41. Found: C, 61.06; H, 6.88; F, 7.37.

Methyl 2-Deoxy-2-fluoro-α-D-arabinofuranoside (4a).—A solution of **4b** (510 mg) in ethanol (50 ml) containing 5% Pd/C (100 mg) was shaken in an atmosphere of hydrogen until uptake ceased (3 hr, 1 mol). The filtered solution was evaporated, leaving the product **4a** as a viscous syrup with a characteristic sweet odor, $[\alpha]^{21}D$ 141° (c 0.7, ethanol). The nmr spectrum in acetone-d_6 was rather complex, but signals could be observed at δ 4.96 (d 1, H-1, $J_{1,F}$ 12.0 Hz), 4.85 (octet 1, H-2, $J_{2,F}$ 52.0, $J_{2,3}$ 2.6, $J_{2,1}$ 1.0 Hz), and 3.7–4.5 (m 6, H-3, H-4, H-5, OH-3 and OH-5).

Anal. Calcd for $C_6H_{11}O_4F$: C, 43.37; H, 6.67; F, 11.44. Found: C, 43.47; H, 6.64; F, 11.46.

2-Deoxy-2-fluoro-D-arabinose (6).—A solution of **4a** (218 mg) in 0.1 *N* aqueous sulfuric acid (20 ml) was refluxed until tlc monitoring (solvent B) showed the hydrolysis to be complete (5 hr). The solution was cooled to room temperature and neutralized with barium carbonate. After filtration, the aqueous solution

was evaporated to dryness, and the residue extracted with absolute ethanol (twice, 5 ml). Evaporation to dryness gave **6** as a pale yellow syrup, which reduced Fehling's solution, $[\alpha]^{21}D$ −72.4° (*c* 1.0, water).

Anal. Calcd for $C_5H_9O_4F$: C, 39.48; H, 5.96; F, 12.49. Found: C, 39.80; H, 6.10; F, 12.08.

5-*O*-Benzyl-2-deoxy-2-fluoro-D-arabinose (7).—A solution of **4b** (5.0 g) in dioxane (250 ml) and 2 *N* H_2SO_4 (250 ml) was refluxed 5 hr, cooled to 0–5°, and neutralized by careful addition of concentrated ammonia. The solution was evaporated, and the residue extracted with chloroform (twice, 100 ml). The dried ($MgSO_4$) chloroform solution was evaporated, leaving **7** as a syrup (4.5 g) which reduced Fehling's solution and on tlc (solvent B) showed slight contamination with slower moving components. An analytical sample was obtained by preparative tlc on silica gel PF_{254} (Merck), eluting twice with solvent A, $[\alpha]^{23}D$ (after 1.5 hr equilibration) 37.2° (*c* 0.6, ethanol). The nmr spectrum ($CDCl_3$) contained signals at δ 7.37 (s 5, aromatic), 5.42 (d 1, H-1, $J_{1,F}$ 9.7 Hz), 4.87 (q 1, H-2, $J_{2,F}$ 50, $J_{2,3}$ 1.6 Hz), 4.54 (s 2, benzyl CH_2), 4.23 (m 1, H-3), 3.86 (m 1, H-4), 3.81 (s 2, OH) and 3.56 (d 2, H-5, $J_{4,5}$ 6 Hz).

Anal. Calcd for $C_{12}H_{15}O_4F$: C, 59.49; H, 6.24; F, 7.84. Found: C, 59.34; H, 6.25; F, 7.52.

Benzoylation of **7** using a two fold excess of benzoyl chloride in pyridine gave a 70% yield of the 1,3-di-*O*-benzoyl ester **8**, mp 53–56° after two recrystallizations from methanol. Nmr had signals ($CDCl_3$) at δ 7.0–8.3 (m 15, aromatic), 6.75 (d 1, H-1, $J_{1,F}$ 9 Hz), 5.60 (q 1, H-3, $J_{3,F}$ 19.5, $J_{3,4}$ 3.4 Hz), 5.50 (d 1, H-2, $J_{2,F}$ 49 Hz), 4.67 (m 3, H-4 + benzyl CH_2), and 3.86 ppm (d 2, H-5, $J_{4,5}$ 5.0 Hz).

Anal. Calcd for $C_{26}H_{23}O_6F$: C, 69.32; H, 5.15; F, 4.21. Found: C, 69.49; H, 5.29; F, 3.27.

1,3-Di-*O*-acetyl-5-*O*-benzyl-2-deoxy-2-fluoro-D-arabinose (9).—Acetylation of **7** (1.43 g, 0.0059 mol) using acetic anhydride (1.74 ml, 0.0185 mol) in pyridine (15 ml) at room temperature for 18 hr gave a syrup **9** (1.85 g), which failed to reduce Fehling's solution and showed no hydroxyl absorption in the ir spectrum. **9** had $[\alpha]^{22}D$ 53.1° (*c* 0.6, ethanol). The nmr spectrum (acetone-d_6) contained signals centered at δ 7.33 (s 5, aromatic), 6.26 (q 1, H-1, $J_{1,F}$ 10.5, $J_{1,2}$ 0.7 Hz), 5.25 (q 1, H-3, $J_{3,F}$ 22.8, $J_{3,4}$ 4.5 Hz), 5.10 (q 1, H-2, $J_{2,F}$ 49.0), 4.60 (s 2, benzyl CH_2), 4.47 (q, 1, H-4, $J_{4,5}$ 4.5), 3.74 (d 2, H-5), 2.09 and 2.06 ppm (each s, 3, acetyls).

Anal. Calcd for $C_{16}H_{19}O_6F$: C, 58.89; H, 5.87; F, 5.82. Found: C, 59.03; H, 5.99; F, 5.87.

2,6-Dichloro-9-(3-*O*-acetyl-5-*O*-benzyl-2-deoxy-2-fluoro-α-and -β-D-arabinofuranosyl)purines (10 and 11).—A mixture of **9** (950 mg, 2.92 mmol) and 2,6-dichloropurine (500 mg, 2.64 mmol) in a round-bottomed flask was placed in an oil bath preheated to 160°, and stirred. Within 1 min the mixture became homogeneous. Toluene-*p*-sulfonic acid (10 mg) was added, and heating and stirring maintained under reduced pressure for a further 20 min. After cooling, the gummy residue was dissolved in ethyl acetate (10 ml) and chromatographed on a large-diameter column of silica gel G (100 g), eluting with solvent A. Fractions containing unreacted **9** (129 mg), **11** (344 mg), and **10** (357 mg) were collected.

11 was obtained as a colorless gum, $[\alpha]^{22}D$ 8.6° (*c* 1.3, ethanol). Nmr signals (in acetone-d_6) were assigned as follows: δ 8.31 (s 1, H-8), 7.42 (s 5, benzyl aromatic), 6.70 (q 1, H-1′, $J_{1,F}$ 14.5, $J_{1,2}$ 2.0 Hz), 5.96 (sextet 1, H-2′, $J_{2,F}$ 50.5, $J_{2,3}$ 2.0 Hz), 5.69 (octet 1, H-3′, $J_{3,F}$ 13.5, $J_{3,4}$ 4.0 Hz), 4.92 (quartet 1, H-4′ $J_{4,5}$ 5.0 Hz), 4.25 (s 2, benzyl CH_2), 3.93 (q 2, H-5′, $J_{5,F}$ 1.0 Hz), and 2.12 ppm (s 3, acetyl). The uv spectrum showed λ_{max} (ethanol) 274.5, 254 (shoulder) mμ (ε 7780, 4780).

Anal. Calcd for $C_{19}H_{17}N_4O_4Cl_2F$: C, 50.12; H, 3.76; N, 12.30; Cl, 15.58; F, 4.17. Found: C, 50.28; H, 3.84; N, 12.19; Cl, 15.67; F, 4.16.

10 crystallized on evaporation of the appropriate fraction. Recrystallization from ether–petroleum ether afforded colorless needles, mp 115–117°, $[\alpha]^{22}D$ 23.5° (*c* 0.9, ethanol). Nmr signals (in acetone-d_6) were centered at δ 8.35 (d 1, H-8, $J_{8,F}$ 2.6 Hz), 7.35 (s 5, benzyl aromatic), 6.54 (q 1, H-1′, $J_{1,F}$ 17.3, $J_{1,2}$ 4.0 Hz), 5.62 (octet 1, H-3′, $J_{3,F}$ 17.5, $J_{3,2}$ 2.0, $J_{3,4}$ 3.9 Hz), 5.5 (octet 1, H-2′, $J_{2,F}$ 50.5 Hz), 4.67 (s 2, benzyl CH_2), 4.42 (q 1, H-4′, $J_{4,5}$ 4.8 Hz), 3.93 (q 2, H-5′, $J_{5,F}$ 0.8 Hz), and 2.15 ppm (s 3, acetyl). The uv spectrum showed λ_{max} (ethanol) 273.5, 253 (shoulder) mμ (ε 8930, 5300).

Anal. Found: C, 49.88; H, 3.76; N, 12.18; Cl, 15.68; F, 4.15.

6-Amino-2-chloro-9-(5-*O*-benzyl-2-deoxy 2-fluoro-α- and -β-D-arabinofuranosyl)purines (12 and 13).—The same procedure was used for both anomers. A solution of **10** (623.3 mg) in ethanol (50 ml) previously saturated with ammonia at −5° was kept in a bomb at room temperature for 1 week. Evaporation produced a pale yellow amorphous residue which could be crystallized from aqueous ethanol to give clusters of needles, **12** (468.3 mg), mp 163–166°. Recrystallization from ethanol afforded pure material, mp 169–171, $[\alpha]^{22}D$ 29.8° (*c* 0.7 ethanol). The uv spectrum showed λ_{max}^{EtOH} 264 mμ (ε 15,200).

Anal. Calcd for $C_{17}H_{17}N_5O_3ClF$: C, 51.84; H, 4.35; N, 17.78; Cl, 9.00; F, 4.82. Found: C, 51.77; H, 4.39; N, 17.65; Cl, 9.10; F, 4.84.

Similar treatment of **11** gave a similar yield of **13**, mp 149–155°. Recrystallization from ethanol gave colorless needles: mp 158–160°; $[\alpha]^{22}D$ 34.4° (*c* 0.4, ethanol); nmr spectrum (acetone-d_6) δ 8.32 (s 1, H-8), 7.37 (s 5, benzyl aromatic), 7.42 (broad 2, NH_2), 6.36 (q 1, H-1′, $J_{1',F}$ 17.0, $J_{1,2}$ 2.1 Hz), 5.76 (sextet 1, H-2′, $J_{2',F}$ 51, $J_{2',3'}$ 2.1 Hz), 5.54 (d 1, OH-3′), *J* 6.3 Hz), 4.64 (s 2, benzyl CH_2), 4.2–4.9 (m 2, H-3′, H-4′), 3.77 (q 2, H-5′, $J_{4',5'}$ 5.0, $J_{F,5'}$ 1.0 Hz); uv spectrum λ_{max}^{EtOH} 265 mμ (ε 14,400).

Anal. Found: C, 51.72; H, 4.19; N, 17.30; Cl, 8.79; F, 4.77.

9-(2-Deoxy-2-fluoro-α- and -β-D-arabinofuranosyl)adenines (14 and 15).—The same procedure was used for both anomers. To a previously hydrogenated suspension of 5% Pd/C (1.5 g) in 50% aqueous ethanol (100 ml), a solution of **12** (827.7 mg, 2.10 mmol) in ethanol (50 ml) containing NaOH (2.1 ml, 1.0 *N*) was added, and the mixture hydrogenated in a Parr apparatus. When uptake ceased (30 hr), the mixture was filtered (Whatman No. 42) and the catalyst was thoroughly washed with boiling aqueous ethanol. Filtrate and washings were evaporated to small volume, whereupon the product **14** crystallized as clusters of needles (475.4 mg). Recrystallization from ethanol gave a product of mp 232–234°, $[\alpha]^{24}D$ 22.6° (*c* 0.7, water). The nmr spectrum (DMSO-d_6) contained signals at δ 8.35 (d 1, H-8, $J_{8,F}$ 2.0 Hz), 8.19 (s 1, H-2), 7.32 (1 broad, NH_2), 6.33 (q 1, H-1′, $J_{1',F}$ 14.7, $J_{1',2'}$ 4.2 Hz), 5.95 (broad 1, OH-3′), 5.70 (sextet 1, H-2′, $J_{2,F}$ 53 Hz, $J_{2',3'}$ 4.2 Hz), 5.08 (1 broad, OH-5′), 3.6–4.8 (m 4, H-3′, H-4′, H-5′). The uv spectrum showed $\lambda_{max}^{H_2O}$ 259 mμ (ε 14,970); $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 14,800).

Anal. Calcd for $C_{10}H_{12}N_5O_3F$: C, 44.61; H, 4.49; N, 26.01; F, 7.05. Found: C, 44.42; H, 4.46; N, 25.77; F, 7.00.

15 had mp 209–210°, $[\alpha]D$ 62.0° (*c* 0.5, water). The nmr spectrum (DMSO-d_6) contained signals at δ 8.35 (s 1, H-8), 8.22 (s 1, H-2), 7.36 (broad s 2, NH_2), 6.33 (q 1, H-1′, $J_{1',F}$ 16.3, $J_{1',2'}$ 3.4 Hz), 5.76 (sextet 1, H-2′, $J_{2',F}$ 52.0, $J_{2',3'}$ 3.4 Hz), 5.0 (broad 1, OH-3′), 4.2–4.8 (m 2, H-3′, H-4′), 3.62 (q 2, H-5′, $J_{4',5'}$ 4.1, $J_{F,5'}$ 1.0 Hz), and 3.36 ppm (s 1, OH-5′); uv spectrum $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,400); $\lambda_{max}^{pH\ 1}$ 257.5 mμ (ε 14,300).

Anal. Found: C, 44.79; H, 4.48; N, 25.96; F, 7.05.

9-(2-Deoxy-2-fluoro-5-*O*-tosyl-α- and -β-D-arabinofuranosyl)-adenines (16 and 17).—Toluene-*p*-sulfonylation of **14** (78.1 mg, 0.29 mmol) was carried out in anhydrous pyridine (4 ml) using toluene-*p*-sulfonyl chloride (130 mg, 0.67 mmol). Tlc (solvent B) showed complete disappearance of **14** (R_f 0.22) after 24 hr, with a major new spot of R_f 0.55 and a trace component of R_f 0.75. The mixture was poured into water (40 ml) and extracted with chloroform (six times, 15 ml). After two washings with saturated $NaHCO_3$ (20 ml), the dried ($MgSO_4$) chloroform extract was evaporated, leaving a gummy residue. Reevaporation from aqueous ethanol gave a colorless foam (50.0 mg) which on tlc (solvent B) was seen to contain one major component, R_f 0.55, and trace spots, R_f 0.04 and 0.75. No further purification was carried out. The compound possessed uv spectrum with λ_{max}^{EtOH} 262 mμ (ε 13,700). In the ir spectrum, strong absorption bands at 1170 and 1350 cm^{-1} indicated the presence of the sulfonoxy substituent. Similarly, **15** gave the 5′-tosyl derivative **17**, λ_{max}^{EtOH} 259 mμ (ε 14,600); in the ir spectrum new bands at 1175 and 1360 cm^{-1} indicated the presence of the sulfonoxy substituent.

Anal. Calcd for $C_{17}H_{18}N_5O_5FS$: C, 48.22; H, 4.28; N, 16.54; F, 4.49; S, 7.57. Found: C, 48.05; H, 4.38; N, 16.45; F, 4.25; S, 7.50.

3,5′-Cyclo-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine toluene-*p*-sulfonate (18).—A solution of **16** (11.6 mg) in anhydrous dioxane (1 ml) was refluxed until the uv spectrum became constant (80 min) with λ_{max} 274 mμ. Tlc of the mixture at this point showed complete disappearance of the spot R_f 0.55 (sol-

vent B), leaving only the spot R_f 0.04, which was the cyclic tosylate. Evaporation to dryness gave a colorless foam. This had, in the uv spectrum, $\lambda_{max}^{H_2O}$ 274 mμ (ε 12,300). In the ir spectrum, new bands at 685, 1010, and 1210 cm^{-1} indicated the presence of the tosylate anion.

Anal. Calcd for $C_{17}H_{18}N_5O_5FS$: C, 48.22; H, 4.28; N, 16.54; F, 4.49; S, 7.57. Found: C, 48.20; H, 4.51; N, 16.38; F, 4.35; S, 7.55.

Registry No.—**3b**, 20187-72-8; **4a**, 20187-73-9; **4b**, 20187-74-0; **6**, 20187-75-1; **7**, 20187-76-2; **8**, 20187-77-3; **9**, 20187-78-4; **10**, 20187-79-5; **11**, 20187-80-8; **12**, 20227-40-1; **13**, 20187-81-9; **14**, 20227-41-2; **15**, 20187-82-0; **16**, 20187-83-1; **17**, 20187-84-2; **18**, 20187-85-3.

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Nucleosides. LXI. Transformations of Pyrimidine Nucleosides in Alkaline Media. IV. The Conversion of 5-Hydroxyuridines into Imidazoline Nucleosides[1,2]

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Isopropylidene-5-hydroxyuridine (2) and 1-methyl-5-hydroxyuracil (8) undergo a benzilic acid type of rearrangement and dehydration in 0.1 *N* NaOH at 100° to give the corresponding 1-substituted 2-oxo-4-imidazoline-4-carboxylic acids 5 and 9. 1,3-Dimethyl-5-hydroxyuracil (10a) and 1-methyl-3-benzyl-5-hydroxyuracil (10b) are converted under these conditions into the corresponding 1,3-disubstituted 4-hydroxy-2-oxoimidazolidine-4-carboxylic acids 11a and b. Compound 11b was converted into the crystalline methyl ester 14 by treatment with diazomethane. The 4-hydroxyimidazolidines 11a and b undergo acid-catalyzed dehydration to give the 1,3-disubstituted 2-oxo-4-imidazoline-4-carboxylic acids 12a and b. Evidence for the existence of the tautomeric 5-keto forms of the 5-hydroxyuracil derivatives necessary for benzilic acid rearrangement is presented. The 5-hydroxyuracil derivatives are prepared by treatment of the corresponding 5-bromouracils with CO_2-buffered sodium bicarbonate solution at 100°. In unbuffered sodium bicarbonate solution, isopropylidene-5-bromouridine (1) and 2′-deoxy-5-bromouridine are converted *via* their 5-hydroxy derivatives into the 2-oxo-4-imidazoline-4-carboxylic acid nucleosides. The potential application of this rearrangement to DNAs containing 2′-deoxy-5-bromouridine instead of thymidine is discussed. An *in situ* method for the conversion of uridine into the imidazoline nucleoside 6 is described. Ultraviolet spectral and pK_a data for the 5-hydroxyuracil derivatives are given.

We have previously reported[3] that 5-halogeno derivatives of isopropylideneuridine (1, X = F, Br, I) undergo rearrangement in 1 *N* sodium hydroxide to give the 2-oxo-4-imidazoline-4-carboxylic acid nucleoside **5** in varying yield. This rearrangement involves participation of the 5′-hydroxyl group, and it was suggested that the reaction proceeds *via* the 5′,6-anhydro acyclic ureide **4** (X = F, Br, I). We now wish to report that certain derivatives of 5-hydroxyuracil (isobarbituric acid) also undergo base-catalyzed rearrangement to 2-oxo-4-imidazoline-4-carboxylic acids. This new rearrangement does not involve participation of a sugar hydroxyl group and proceeds by a mechanism different from that of the rearrangement **1** → **4** → **5** in 1 *N* sodium hydroxide (Scheme I).

Our interest in the alkaline stability of 5-hydroxyuracil derivatives resulted from experiments which indicate that isopropylidene-5-hydroxyuridine (2) is stable in 1 *N* sodium hydroxide but unstable in 0.1 *N* sodium hydroxide. First, compound **2** was formed along with the imidazoline nucleoside **5** (20% yield) when a 0.1 *M* solution of the 5-bromo nucleoside **1** in 1 *N* sodium hydroxide was heated at 55° for 20 hr.[3] Moreover, compound **2** appeared to be stable under these reaction conditions, as shown by a gradual increase in the intensity of the uv absorption maximum of **2** at ~305 mμ. Secondly, isopropylidene-5-hydroxyuridine (2) was also formed when a 0.02 *M* solution of **1** (X = Br) in 0.1 *N* sodium hydroxide was heated at 100°. In this case, however, the concentration of **2** as monitored spectrally first increased and then gradually decreased with the concomitant formation of the imidazoline nucleoside **5**. After acidic hydrolysis of the isopropylidene group, the known[3] 1-(β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid (**6**) was obtained in 45% yield. This finding suggests the possibility that isopropylidene-5-hydroxyuridine (2) is an intermediate in the formation of **5** from **1** (X = Br) in 0.1 *N* sodium hydroxide. Evidence supporting the intermediacy of **2** was obtained when an attempt was made to synthesize this compound by using the procedure of Wang.[4] Accordingly, when **1** (X = Br) was heated under nitrogen in dilute sodium bicarbonate solution, the formation of **2** was indicated by the appearance of an absorption peak at 305 mμ. During the 22-hr reaction period, however, the pH of the reaction mixture increased from ~8.3 to ~10 and the slow disappearance of **2** and concomitant formation of **5** was again noted. The unblocked nucleoside **6** was isolated in 54% yield. Formation of **5** was considerably reduced when the reaction mixture of **1** (X = Br) with sodium bicarbonate was buffered (~ pH 8.3) with carbon dioxide gas. After a reaction period of 5 hr, crystalline **2** was isolated in 46% yield and characterized by conversion into the known 5-hydroxy-

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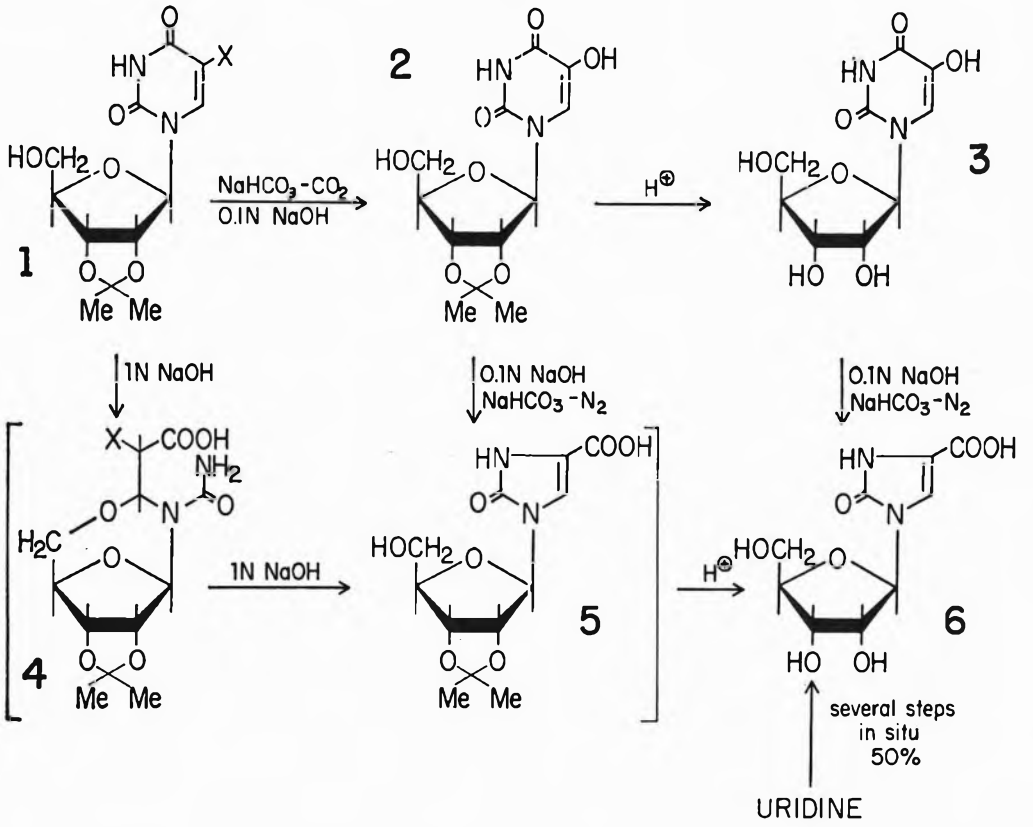
(2) A preliminary account of part of this work has been published: B. A. Otter, E. A. Falco, and J. J. Fox, *Tetrahedron Lett.*, 2967 (1968).

(3) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 1390 (1969).

(4) S. Y. Wang, *J. Amer. Chem. Soc.*, **74**, 668 (1952).

SCHEME I



uridine (**3**).[5] Treatment of **2** with either 0.1 *N* sodium hydroxide or unbuffered sodium bicarbonate solution at 100° resulted in smooth conversion into the imidazoline **5**, which was isolated as the unblocked nucleoside **6** in good yield. Similar treatment of 5-hydroxyuridine (**3**) afforded **6** directly. Moreover, the rearrangement **3** → **6** proceeds at the same rate as that of the rearrangement **2** → **5**, indicating that neighboring-group participation of the 5′-hydroxyl group is not involved in these reactions.[6] However, isopropylidene-5-hydroxyuridine (**2**, 0.02 and 0.1 *M*) proved to be stable in 1 *N* sodium hydroxide at 55° as shown by the constancy of the uv spectrum over a 24-hr period. These data show that the imidazoline nucleoside **5** can be formed from **1** (X = Br) *via* two routes. One pathway, operating in 1 *N* sodium hydroxide, does not involve **2** as an intermediate but probably proceeds *via* the acyclic ureide **4** as suggested previously.[3] The other pathway, operating in 0.1 *N* sodium hydroxide[7] or unbuffered sodium bicarbonate solution, proceeds *via* **2** which is itself converted into **5**. Based on these considerations, we devised a simple *in situ* synthesis of the imidazoline nucleoside **6** directly from uridine in 50% yield. Treatment of uridine with bromine water afforded 5-bromo-6-hydroxy-5,6-dihydrouridine, which on treatment with sodium bicarbonate[4] was converted into 5-hydroxyuridine (**3**) and thence to imidazoline **6**.

The ring contraction of 5-hydroxyuracil derivatives is not restricted to the nucleoside series, but can be used for the preparation of a variety of 1-substituted and 1,3-disubstituted-2-oxo-4-imidazoline-4-carboxylic acids. Thus, treatment of 1-methyl-5-hydroxyuracil (**8**, Scheme II) with refluxing 0.1 *N* sodium hydroxide afforded the known[8] 1-methylimidazoline **9** in 80% yield. However, the reactions of 1,3-disubstituted 5-hydroxyuracils in sodium hydroxide differ from those of the 1-substituted compounds (**2**, **3**, and **8**) in that only small amounts of the corresponding imidazolines are formed directly. Instead, the 1,3-disubstituted compounds are slowly converted into non-uv-absorbing intermediates (**11**) which afford the imidazolines after treatment with acid. Thus, uv spectral examination (pH ~10) of the reaction of 1,3-dimethyl-5-hydroxyuracil (**10a**) with refluxing 0.1 *N* sodium hydroxide revealed an 80% decrease in the intensity of the peaks at 242 and 310 mμ over a 19-hr period. Only a small increase in absorption at 255 mμ, attributable to the formation of **12a**, was noted. Acidification of the solution, however, resulted in the rapid formation of a large peak at 269 mμ, a value corresponding to the known[8] absorption of **12a** in acid solution. On a preparative scale, compound **12a** was isolated in 71% yield.

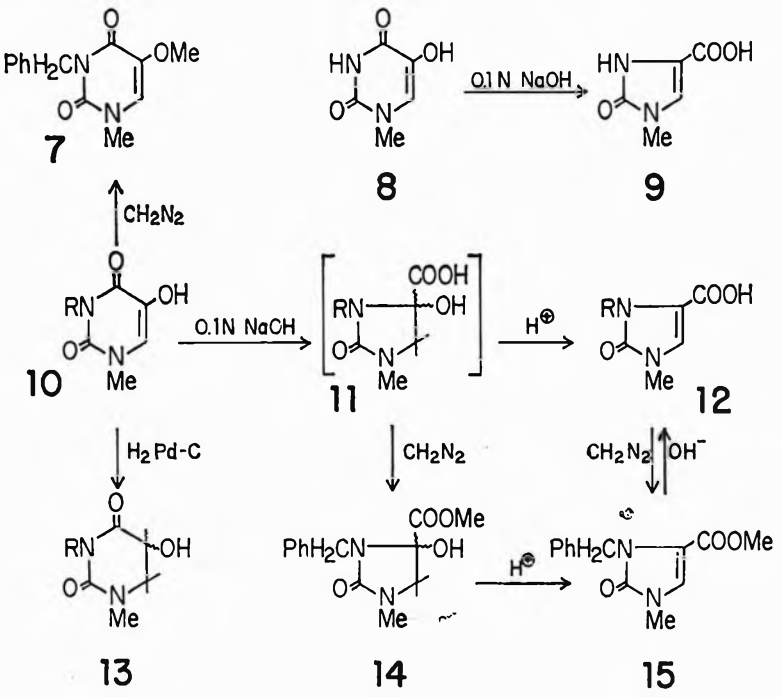
(5) Further study of the formation of 5-hydroxyuridine (**3**) from 5-bromouridine in $NaHCO_3$–CO_2 has shown, contrary to our previous report,[2] that this reaction and the analogous conversion of isopropylidene-5-bromouridine (**1**) into isopropylidene-5-hydroxyuridine (**2**) proceed at similar rates. These reactions do not, therefore, involve participation of the 5′-hydroxy group[6] (formation of a 5-bromo-5′,6-anhydro-5,6-dihydro intermediate) but probably proceed *via* 5-bromo-6-hydroxy-5,6-dihydrouridines. The latter intermediates are analogous to those suggested by Wang[4] for the conversion of 5-bromouracil and 1,3-dimethyl-5-bromouracil into their corresponding 5-hydroxy compounds.

(6) It has been demonstrated previously that reactions involving interaction between the 5′-hydroxyl group and the aglycon of uridine derivatives are greatly facilitated by the presence of a 2′,3′-*O*-isopropylidene group. For a discussion of this point, see ref 3 and other citations therein.

(7) It is possible that the formation of **5** from **1** (X = Br) in 0.1 *N* NaOH involves both routes (**1** → **4** → **5**) and (**1** → **2** → **5**). It should be noted that in aqueous alkali (0.1 → 1*N* hydroxide) a competing reaction involving direct attack by hydroxide on C-6 leading to barbituric acid nucleosides is also operative. This affects the over-all yields of imidazoline nucleoside from **1**. As mentioned previously,[3] such barbituric acid nucleosides are unstable under these reaction conditions, leading to nonchromophoric degradation products.

(8) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **33**, 3573 (1968).

SCHEME II



a series, R=Me

b series, R=Ch_2Ph

Similar results were obtained with 3-benzyl-1-methyl-5-hydroxyuracil (**10b**) which gave the corresponding imidazoline (**12b**) in 74% yield. The intermediate (**11a**) in the formation of **12a** from **10a** proved to be unstable and attempts to isolate it resulted in formation of a considerable amount of **12a**. The analogous intermediate (**11b**) was more stable and was isolated as a crude, amorphous sodium salt which was contaminated with small amounts of starting material **10b** and imidazoline **12b**. Careful neutralization of this material with acetic acid and methylation with a large excess of diazomethane afforded a mixture containing the methyl ether **7**, the methyl ester **15**, and a crystalline, non-uv-absorbing compound which was shown to be 3-benzyl-4-hydroxy-1-methyl-2-oxoimidazolidine-4-carboxylic acid methyl ester (**14**). The intermediates **11a** and **11b** are therefore the corresponding 1,3-dimethyl- and 3-benzyl-1-methyl-carboxylic acids, respectively. The structure of **14** was established from the combustion analysis ($C_{13}H_{15}N_2O_4$); from the infrared spectrum, which shows peaks at 3400 (hydroxyl), 1750 (ester carbonyl), and 1680 cm^{-1} (ureide carbonyl); and from the nmr spectrum in DMSO-d_6. In addition to the expected 1-methyl and 3-benzyl resonances, the nmr spectrum of **14** shows an additional methyl signal at δ 3.30 (CO_2Me) and an exchangeable proton (OH) at δ 7.0 which is not coupled to either of two protons (H-5, H-5) appearing as an AB system at δ 3.31 and 3.79. The lack of coupling of the hydroxyl proton indicates the tertiary alcohol structure; for secondary alcohols, such as **13a** and **13b**, coupling (~5 Hz) is observed. The chemical shifts of the geminal protons of **13a** and **13b** are similar to those of the C-5 protons of **14**. Treatment of an aqueous solution of **14** with dilute hydrochloric acid resulted in the rapid formation of the imidazoline ester **15** which could be converted into the imidazoline carboxylic acid **12b** by alkaline hydrolysis.

Neither 5-hydroxyuracil nor 3-methyl-5-hydroxyuracil is converted into the corresponding imidazoline when treated with 0.1 *N* sodium hydroxide at 100°. In both cases, ultraviolet absorption was lost over a 24-hr period but no indication of imidazoline formation was obtained, either before or after acidification of the solutions. The instability of 5-hydroxyuracil in alkali has been reported previously.[4,9]

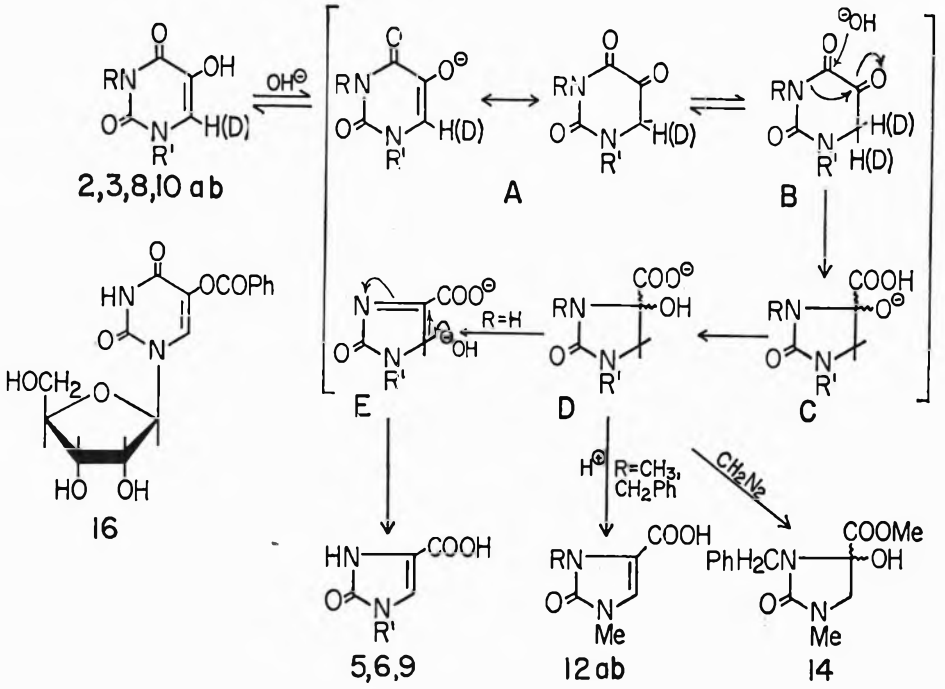
Identification of the intermediates **11a** and **11b** as α-hydroxy acids allows the formulation (Scheme III) of the ring contraction of 5-hydroxyuracil derivatives as a benzilic acid type of rearrangement. A requirement of this rearrangement is that the 5-hydroxyuracils exist partly in the tautomeric 5-keto form (**B**). Attack of hydroxide ion on C-4 of **B** and subsequent migration of the C–N bond[10] would give intermediate **C**, which would undergo a proton shift to give the imidazolidine **D**. In the 1,3-disubstituted series, intermediate **D** (corresponding to **11a** and **b**) is stable in base but undergoes rapid acid-catalyzed dehydration to the imidazolines **12a** and **12b**. Base-catalyzed dehydration of 1,3-disubstituted **D** takes place only to a small extent. In the 1-substituted series (**D**, R = H), however, base-catalyzed dehydration involving abstraction of the labile N-3 protons would give the 2 oxoisoimidazolines

(9) E. R. Garrett, H. J. Nestler, and A. Somodi, *J. Org. Chem.*, **33**, 3460 (1968).

(10) This process could take place in either the concerted manner shown or stepwise with the formation of a ureido α-keto acid which would then undergo ring closure to **C**. Attack of hydroxide ion on C-5 of **B** followed by migration of the 5,6 bond would also give **C**, but this is considered to be unlikely because the benzilic acid rearrangement of isotopically labeled alloxan to alloxanic acid has been shown[11] to involve exclusive C–N bond cleavage.

(11) H. Kwart, R. W. Spayd and C. J. Collins, *J. Amer. Chem. Soc.*, **83**, 2579 (1961). See also P. A. S. Smith and R. O. Kan. *ibid.*, **83**, 2580 (1961).

SCHEME III



E. Rearrangement of **E** would then give the 1-substituted imidazolines **5**, **6** and **9**.

Although 5-hydroxyuracil derivatives exist in solution predominately in the 5-enol form (see later discussion of uv spectra), the presence of the 5-keto tautomers (**B**) is indicated by the following data. Treatment of isopropylidene-5-hydroxyuridine (**2**) with refluxing deuterium oxide results in exchange of H-6 for deuterium, as shown by a gradual decrease in the intensity of the H-6 resonance relative to the nmr signals of protons which did not undergo exchange. This exchange reaction involves ionization of the 5-hydroxyl group ($pK_a = 7.7$) of **2** to give the mesomeric anion **A**. Deuteration of **A** at the C-6 position gives **B**, which then reverts to isopropylidene-5-hydroxyuridine-6-*d*. Evidence supporting this mechanism is that deuterium exchange does not take place when the enolate ion–keto equilibrium **A** ⇌ **B** is precluded by substitution of the 5-hydroxyl group. Thus, 5-benzoyloxyuridine (**16**) does not incorporate deuterium at C-6 when treated with refluxing deuterium oxide. Rapid deuterium exchange of isopropylidene-5-hydroxyuridine (**2**), and hence formation of the 5-keto tautomer **B**, takes place under the alkaline conditions which lead to the formation of the imidazoline nucleoside **5**. Thus, when the reaction of **2** (0.02 *M*) in 0.1 *N* sodium deuterioxide at 100° was stopped after 30 min, the remaining starting material had undergone complete exchange of H-6 for deuterium. Under identical conditions the 1,3-dimethyl-5-hydroxyuracil (**10a**) remaining after 2 hr had undergone ~30% exchange. The slower rate of exchange observed for **10a**, compared with **2**, is consistent with the slower rate at which **10a** undergoes ring contraction.

As mentioned proviously, isopropylidene-5-hydroxyuridine (**2**, 0.1 *M*) is stable in 1 *N* sodium hydroxide at 55°. The rate of deuterium incorporation into **2** is low under these conditions; over a 24-hr period in 1 *N* sodium deuterioxide, only 80% exchange of H-6 was observed. The lack of formation of the imidazoline nucleoside **5** from **2** in 1 *N* sodium hydroxide is therefore a reflection of the very low concentration of the 5-keto tautomer **B**. Similarly, 1,3-dimethyl-5-hydroxyuracil (**10a**, 0.1 *M*) is stable in 1 *N* sodium hydroxide as 55°, and the extent of deuterium incorporation (~10% in 24 hr) is again smaller than that observed for isopropylidene-5-hydroxyuridine (**2**) under these conditions. The slower rates of exchange of **10a** may be due to a decrease in the carbanion character of the mesomeric ion **A** caused by the inductive effect of the methyl substituents. Substituent effects on the enol–keto equilibria of 5-hydroxyuracils, together with studies of electrophilic substitution of the C-6 position, are currently under investigation in this laboratory.

The ultraviolet absorption and apparent pK_a data of the 5-hydroxyuracils used in this study are listed in Table I. The similarity of the spectrum of 1,3-dimethyl-5-hydroxyuracil to those of 5-hydroxyuracil and its mono-N-methyl derivatives in the pH range of 1–10 (neutral to monoanion) show conclusively, as would be expected, that the first dissociation of all these compounds is due to ionization of the 5-hydroxyl group. The similarity of the spectrum of 1-methyl-3-benzyl-5-methoxyuracil (pH 1–14) to those of the other 5-hydroxyuracils (at pH 1) in Table I shows that the neutral species of all these compounds exist predominantly in the 2,4-dicarbonyl-5-hydroxy form (due allowance given to the effects of alkylation at N-1 and N-3). The bathochromic shifts produced by N-1 substitution (*vs.* N-3 substitution) are similar to effects noted previously[12] with uracil and its N-methyl derivatives. As expected, the substitution of a sugar moiety on N-1 in place of a methyl group exerts an acid-strengthening effect.

General Considerations.—5-Hydroxyuridine is a normal component of the ribonucleic acids of yeast (*Torula utilis*).[13] In this regard, the chemistry of 5-

(12) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).
(13) A. W. Lis and W. E. Passarge, *Arch. Biochem. Biophys.*, **114**, 593 (1966).

TABLE I

ULTRAVIOLET AND APPARENT pK_a DATA[a] FOR 5-HYDROXYURACIL AND DERIVATIVES

	Neutral species				Monoanion				Dianion				
	pH 1				pH 10				pH 14				
Compd	λ_{max}, mμ	ε × 10^{-3}	λ_{min}, mμ	ε × 10^{-3}	λ_{max}, mμ	ε × 10^{-3}	λ_{min}, mμ	ε × 10^{-3}	λ_{max}, mμ	ε × 10^{-3}	λ_{min}, mμ	ε × 10^{-3}	pK_{a_1}
5-Hydroxyuracil	277	7.10	245	2.24	305	6.12	272	3.04	302	~5.25[b]	270	~2.52[b]	8.09[c]
					240	7.62	220	4.86	sh 240	~7.29[b]			
1-Methyl-5-hydroxyuracil	284	7.90	247	1.73	310	6.75	272	2.55	304	6.03	269	2.54	7.94[d]
					240	7.38	220	4.74	sh 240	6.95			
Isopropylidene-5-hydroxyuridine	280	8.67	244	2.40	306	7.50	270	3.50	303	7.10	268	2.87	7.72[e,f]
					247	6.40	224	5.10					
3-Methyl-5-hydroxyuracil	277	6.70	245	2.23	304	6.13	272	3.15	322	~7.90[b]	275	~1.65[b]	8.22
					242	7.19	222	4.71	242	~7.77[b]	222	~4.24[b]	
1,3-Dimethyl-5-hydroxyuracil	283	7.35	247	1.83	310	6.73	273	2.55	...	...	...	...	8.18
					242	6.90	225	5.17					
1-Methyl-3-benzyl-5-hydroxyuracil	286	7.22	249	1.93	312	6.66	275	2.54	...	...	...	...	8.06
					243	7.01	228	6.18					
1-Methyl-3-benzyl-5-methoxyuracil	283[g]	7.13	249[g]	2.07	...	...	...	...	...	...	...	...	...

[a] Determined spectrophotometrically by methods previously described [J. J. Fox and D. Shugar, *Bull. Soc. Chim. Belges*, 61, 44 (1952)]. pK_{a_1} values refer to ionization of the 5-hydroxyl group and are accurate to ±0.05 pH unit. Accurate pK_a values (ionization of N–H groups) were not determined. [b] Compound unstable in 1 *N* NaOH making pK_{a_2} determination impossible. [c] pK_{a_1} 8.11 and pK_{a_2} 11.48 (potentiometric titration) previously reported [A. Albert and J. N. Phillips, *J. Chem. Soc.* 1294 (1956)]. [d] pK_{a_2} ~ 12. [e] pK_{a_2} ~ 11.5. [f] pK_{a_1} 7.8 (potentiometric titration) previously reported for 5-hydroxy-2′-deoxyuridine [T. Y. Shen, J. F. McPherson, and B. O. Linn, *J. Med. Chem.*, 9, 366 (1966)]. [g] pH 1–14.

hydroxyuridine described herein should be taken into account in studies on the alkaline degradation of ribonucleic acids containing 5-hydroxyuridine or of 5-hydroxyuridylic acids.[13,14]

We also find that 5-bromo-2′-deoxyuridine is converted in dilute alkali (*via* its 5-hydroxy derivative) into the 2′-deoxy analog of **6**. This finding suggests that the over-all conversion may be applicable under mild conditions to known[15] deoxyribonucleic acids in which 2′-deoxy-5-bromouridine replaces some of the thymidine residues. Such a chemical rearrangement may alter the base pairing and, conceivably, the biological properties of the deoxyribonucleic acid.

Experimental Section

General Procedures.—Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are uncorrected. The nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference. Chemical shifts are reported in parts per million (δ) and signals are expressed as s (singlet), d (doublet), t (triplet), or m (complex multiplet). Values given for coupling constants (hertz) and chemical shifts are first order unless the spin system is designated AB or ABX. Thin layer chromatography was performed on silica gel GF_{254} (Merck); separated materials were detected with ultraviolet light and by spraying with 10% v/v sulfuric acid in ethanol followed by heating at 110°. Evaporations were carried out *in vacuo* with bath temperatures kept below 45°. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, and by Spang Microanalytical Laboratory, Ann Arbor, Michigan. For reactions that were monitored by changes in the uv spectra, 0.1-ml aliquots were diluted with water to give a concentration of 1 × 10^{-4} *M* in starting material; uv spectra were then recorded at pH ~ 10 on a Cary Model 15 spectrometer.

1-(β-D-Ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid (6) from Isopropylidene-5-bromouridine[16] (1). Method A.—A solution of 363 mg (1 mmol) of 1 (X = Br) in 50 ml of 0.1 *N* NaOH was refluxed for 6 hr. A rapid decrease in the uv absorption of 1 at 275 mμ was followed by the appearance of peaks at ~305 (**2**) and 253 mμ (**5**). The 305-mμ peak reached a maximum value of OD 0.11 at 90 min and then decreased, while the 252-mμ peak increased to a maximum OD of 0.53. Hydrolysis of the isopropylidene group of **5** to give **6** took place during the isolation procedure. The dark yellow solution was cooled and passed through a column containing an excess of Dowex AG-50W-X8 (H^+). The colorless, acidic effluent and washings were concentrated to ~2 ml. Acetone was added and the solution cooled to give crystals of the dihydrate of **6** (135 mg, 45%), mp and mmp 107–110° (resolidifies and melts at 195–200°, eff, dec). The uv and ir spectra of this material were identical with those of **6** prepared previously.[3]

Method B.—Isopropylidene-5-bromouridine (**1**) (18.15 g, 0.05 mol) was added to a solution of sodium bicarbonate (0.15 mmol) in 1 l. of water. The solution was refluxed under nitrogen for 22 hr. Uv spectral examination revealed a gradual loss of **1** (λ_{max} 275 mμ) and formation of **2** (λ_{max} 305 mμ) which reached a maximum concentration (OD 0.21) at ~3 hr. During this time the pH of cooled samples of the reaction mixture increased from 8.5 to 10. After 3 hr, the 305-mμ peak (**2**) gradually decreased with the concomitant formation of a peak at 252 mμ (**5**) which reached a maximum value of OD 0.72 at 22 hr. The brown reaction mixture was cooled and deionized by passage through a column containing ~200 ml of Dowex AG 50W-X8 (H^+). The effluent and washings were concentrated to ~100 ml; acetone (50 ml) was added and the solution was cooled, whereupon crystalline material separated. The product (8.0 g, 54%) had mp and mmp 107–110° (resolidifies and melts at 195–200°, eff, dec) and gave ir and uv spectra identical with those of **6** prepared *via* method A.

2′,3′-O-Isopropylidene-5-hydroxyuridine (2).—Carbon dioxide gas was bubbled into a suspension of 5.45 g (0.015 mol) of **1** (X = Br) in 300 ml of water containing 3.78 g (0.045 mmol) of sodium bicarbonate. The mixture was heated to reflux temperature, whereupon **1** dissolved. Heating was continued for 6 hr, at which time the absorption of **2** at 305 mμ reached a maximum value of OD 0.45. The pH of the cooled reaction mixture was ~8.5. The solution was passed through a column (3 × 30 cm) containing Dowex AG1, X-8 (OH^-, 100–200 mesh) and the column was washed with water until the effluent was neutral. The column was then eluted with 0.05 *M* NH_4HCO_3, and 25-ml fractions were collected. Fractions 50–100, which gave a positive ferric chloride test, were combined and concentrated to 30 ml. Crystallization of **2** (1.80 g, 40%) commenced on cooling. A second crop of 280 mg, 6% (total yield 46%), was obtained by concentration of the filtrate. Both crops gave only a single spot on tlc (MeOH–$CHCl_3$, 1:4 v/v). A sample recrystallized from water for analysis had mp 215–217°; nmr δ 11.43 broad s (1, NH), 8.64 s (1, 5-OH), 7.32 s (1, H-6), 5.89 d (1, H-1′, $J_{1',2'}$ = 2.2), 5.06 broad t (1, 5′-OH), 4.84 m (2, H-2′, H-3′),

(14) D. A. Smith and D. W. Visser, *J. Biol. Chem.*, **240**, 446 (1965).

(15) For a discussion of DNAs containing 5-bromouracil see review by R. E. Handschumacher and A. D. Welch, "The Nucleic Acids," E. Chargaff and J. N. Davidson, Ed., Academic Press Inc., New York, N. Y., 1960, Vol. 3, p 453.

(16) Purchased from Zellstoff-fabrik Waldhof, Mannheim, W. Germany.

4.07 m, (1, H-4'), 3.61 m (2, H-5', H-5'), 1.50 and 1.31 ppm s (2, 6-H, isopropylidene methyls).

Anal. Calcd for $C_{12}H_{16}N_2O_7$: C, 48.00; H, 5.37; N, 9.33. Found: C, 47.90; H, 5.40; N, 9.19.

Compound **2** was converted into 5-hydroxyuridine (mp 238–240°, lit.[17] mp 238–240°) by treatment with 80% acetic acid at 100° for 1 hr.

1-(β-D-Ribofuranosyl)-2-oxo-4-imidazoline-4 carboxylic Acid (6) from Isopropylidene-5-hydroxyuridine (2). Method A.—A solution of 300 mg (1 mmol) of **2** in 50 ml of 0.1 *N* NaOH was refluxed for 6 hr, at which time the absorption peak at 252 mμ (**5**) reached a maximum value of OD 0.90. The cooled solution was passed through a column containing an excess of Dowex AG-50W-X8 (H^+), and the neutral eluate was acidified (to pH ~1) with HCl to ensure complete hydrolysis of the isopropylidene group. Concentration of the solution to ~1 ml and addition of acetone afforded crystals (213 mg, 72%) of **6**, mp and mmp 107–110° (resolidifies and remelts at 195–200° eff, dec).

Treatment of 5-hydroxyuridine (**3**, 1 mmol) with 0.1 *N* NaOH (50 ml) at 100° results in formation of **6**. Uv spectral examination showed that the rearrangements **3** → **6** and **2** → **5** proceed at the same rate and give similar yields of imidazoline.

Method B.—A sample of **2** (300 mg, 1 mmol) was added to a solution of sodium bicarbonate (252 mg, 3 mmol) in 20 ml of water. The solution was refluxed for 22 hr, cooled, and processed as described in method A above. The yield of pure **6** was 207 mg (70%).

1-(2-Deoxy-β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic Acid.—2'-Deoxy-5-bromouridine (3 g, 0.01 mol) was dissolved in a solution of sodium bicarbonate (2.52 g, 0.03 mol) in 200 ml of water. The solution was buffered with CO_2 gas (pH ~8.5) and refluxed for 9 hr. During this time, the conversion of starting material into 2'-deoxy-5-hydroxyuridine was monitored by the increase in absorption at ~302 mμ. The flow of CO_2 was stopped after 9 hr, and refluxing continued for a further 12 hr. Spectral examination of the black reaction mixture (pH ~10) showed the presence of the 2'-deoxy-imidazoline nucleoside together with some 2'-deoxy-5-hydroxyuridine. The cooled solution was passed through an excess of Dowex AG-50W-X8 (H^+) and the eluate and washings were concentrated almost to dryness. Most of the water was removed by codistillation with ethanol, and the product was precipitated by addition of ether. The dried precipitate was crystallized with difficulty from 95% methanol–ether to give 610 mg (40%) of the hemihydrate, mp 187–190°.

Anal. Calcd for $C_9H_{12}N_2O_6 \cdot {}^1/_2H_2O$: C, 42.68; H, 5.13; N, 11.06. Found: C, 42.97; H, 4.91; N, 11.14.

1-Methyl-2-oxo-4-imidazoline-4-carboxylic Acid (9).—1-Methyl-5-hydroxyuracil[18] (**8**) (1.42 mg, 1 mmol) was dissolved in 50 ml of 0.1 *N* NaOH and the solution was refluxed. Uv spectral examination showed that the product (**9**) reached a maximum concentration (OD = 0.85) at ~23 hr. The solution was acidified with HCl, concentrated to 25 ml, and cooled. The resulting precipitate was recrystsllized from water to give 114 mg (80%) of pure **9**, mp and mmp 274–276° eff, dec (but dependent on rate of heating). The uv, nmr, and ir spectra of this material were identical with those of authentic[8] **9**.

1,3-Dimethyl-2-oxo-4-imidazoline-4-carboxylic Acid (12a).—A solution of 780 mg (5 mmol) of **10a**[4] in 250 ml of 0.1 *N* NaCH was refluxed for 19 hr. During this time, the uv absorption max of **10a** (~310 mμ) decreased by 84%. Acidification (to pH 3) of the 1×10^{-4} solution used for following uv changes resulted in the appearance of a peak at 269 mμ which increased to OD 0.95 in 10 min. Acidification of the cooled reaction mixture with HCl (to pH ~1) and concentration to ~50 ml afforded **12a** (550 mg, 71%) in two crops, mp and mmp 230–232°. The uv and ir spectra were identical with those of authentic[8,19] **12a**.

1-Methyl-3-benzyluracil.—1-Methyluracil (7.2 g, 5.7 mmol) was added to a solution of KOH (6.4 g, 11.4 mmol) in 150 ml of ethanol. Benzyl bromide (9.7 g, 5.7 mmol) was added and the mixture was refluxed for 7 hr. The cooled solution was concentrated almost to dryness, diluted with 100 ml of water, and neutralized with acetic acid. The solution was extracted with ether (thrice, 100 ml); the ether extracts were dried and concentrated to dryness. Recrystallization of the residue from 50% ethanol afforded pure material (9 g, 73%), mp 105–106°.

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.66; H, 5.55; N, 12.96. Found: C, 66.72; H, 5.56; N, 12.93.

1-Methyl-3-benzyl-5-bromouracil.—Bromine (6.6 g, 4.1 mmol) was added to a solution of 1-methyl-3-benzyluracil (9.0 g, 4.2 mmol) in 175 ml of glacial acetic acid. The pale yellow solution was heated on a steam bath for 30 min, concentrated to ~50 ml, and then poured into 500 ml of water. The resulting precipitate was recrystallized from 50% ethanol to give pure material (12 g, 97%), mp 124–125°.

Anal. Calcd for $C_{12}H_{11}BrN_2O_2$: C, 48.81; H, 3.73; N, 9.49. Found: C, 48.82; H, 3.68; N, 9.39.

1-Methyl-3-benzyl-5-hydroxyuracil (10b).—Carbon dioxide gas was bubbled through a solution of 9 g (0.033 mol) of 1-methyl-3-benzyl-5-bromouracil in 600 ml of 50% ethanol containing 7.5 g (0.09 mol) of sodium bicarbonate. The solution was refluxed for 22 hr, at which time the absorption of **10b** at 312 mμ reached a maximum value. The solution was cooled, neutralized with 1 *N* HCl, and concentrated to remove the ethanol. The product crystallized when the aqueous solution was acidified with 1 *N* HCl. Recrystallization from 50% ethanol afforded pure **10b** (5.7 g, 80%): mp 163–164°; nmr δ 8.66 s (1, OH), 7.33 and 7.31 two barely resolved singlets (6, phenyl and H-6), 5.07 s (2, CH_2), and 3.29 ppm s (3, CH_3).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.17; N, 12.07. Found: C, 62.21; H, 5.09; N, 11.96.

1-Methyl-3-benzyl-2-oxo-4-imidazoline-4-carboxylic acid (12b) was prepared from 1.26 g (5 mmol) of **10b** as described for the preparation of **12a**. The yield of pure **12b** (recrystallized from water), mp 224–226°, was 74%; nmr δ ~12.5 broad s (1, COOH), 7.30 s (5, phenyl), 7.55 s (1, H-5), 5.16 s (2, CH_2), and 3.28 ppm s (3, NCH_3).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.17; N, 12.07. Found: C, 62.03; H, 5.14; N, 11.99.

3-Benzyl-4-hydroxy-1-methyl-2-oxoimidazolidine-4-carboxylic Acid Methyl Ester (14).—A solution of 2.32 g (10 mmol) of **10b** in 300 ml of 0.1 *N* NaOH was refluxed for 17 hr. The uv absorption maximum of **10b** (312 mμ) decreased by 85% during this period. The cooled solution was passed through a column (2.5 cm diameter) containing 16 g of Amberlite IRC-50. The eluate was made weakly alkaline by the addition of 1.5 ml of 1 *N* NaOH. The eluate and washings (100 ml) were concentrated to dryness (with the bath temperature kept below 20°) and the residue was dried *in vacuo* over KOH pellets. The amorphous material (2.3 g) was suspended in 10 ml of methnol and 400 mg of unidentified gelatinous material removed by filtration. To the methanol solution (5°) was added three charges of diazomethane (~30 mmol each in 50 ml of ether) at 4 hr intervals after just neutralizing the reaction mixture each time with glacial acetic acid. The solution was stored at 5° for 4 hr after the final addition of diazomethane, and then concentrated to 10 ml, whereupon **14** (250 mg) crystallized. Concentration of the methanol filtrate to dryness and suspension of the residue (800 mg) in cold methanol afforded a second crop (400 mg) of insoluble **14**. Recrystallization of the combined crops from boiling methanol gave 460 mg of pure **14**: mp 169–170°; ir ν_{max} (KBr) 3400 (OH), 1750 (ester carbonyl), 1680 cm^{-1} (ureide carbonyl). The nmr spectrum of **14** showed an AB subspectrum for the C-5 protons (δ 3.79, 3.31; $J_{5,5}$ = 10.5 Hz) and another AB system for the benzyl methylene protons (δ 4.44, 4.24; J_{gem} = 16.0 Hz). Other nmr signals were at δ 7.28 s (5, phenyl), 7.0 s (1, OH, exchanges on addition of D_2O), 3.30 s (3, ester methyl), and 2.78 ppm s (3, NCH_3).

Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.09; H, 6.06; N, 10.65. Found: C, 59.16; H, 6.01; N, 10.55.

Tlc (MeOH–$CHCl_3$, 1:30 v/v) showed that the combined mother liquors from above contained mostly **14** and small amounts of **7** and **15**. These compounds were not isolated, but their identities were established by comparison of chromatographic mobility and uv spectra of eluted materials with those of **7** and **15** described below. A 1×10^{-4} *M* solution of **14** in water showed only end absorption (below 220 mμ) in the uv. Acidification of this solution resulted in formation of the imidazoline ester **15** ($\lambda_{max}^{pH\ 1}$ 271 mμ) which underwent hydrolysis to **12b** (shift of λ_{max} to 258 mμ) on treatment with alkali.

1-Methyl-3-benzyl-5-hydroxy-5,6-dihydrouracil (13b).—A sample of **10b** (1 g, 4.3 mmol) was dissolved in a suspension of 10% Pd–C (~50 mg) in 200 ml of ethanol, and the mixture was hydrogenated on a Parr apparatus for 6 hr. The catalyst was removed and the filtrate concentrated to a colorless syrup which

(17) D. W. Visser, "Synthetic Procedures in Nucleic Acid Chemistry," W. W. Zorbach and R. S. Tipson, Ed., Interscience Publishers, New York, N. Y., 1968, Vol. 1, p 428.

(18) Prepared from 1-methyluracil as described by Z. Budesinsky, J. Prikryl, and E. Svatek, *Coll. Czech. Chem. Commun.*, **29**, 2980 (1964).

(19) G. E. Hilbert, *J. Amer. Chem. Soc.*, **54**, 3413 (1932).

crystallized spontaneously to give pure **13b**, mp 75–78°. The nmr spectrum of **13b** contained peaks at 7.25 (5, s, phenyl), 6.09 (1 broad peak, OH) and 4.82 (2, s, benzyl CH_2). The geminal H-6 and H-5 protons appeared as an ABX subspectrum (after removal of the H-5, OH coupling by addition of D_2O) with H-5, δ_X 4.32; H-6, δ_A 3.29; H-6, δ_B 3.51 (J_{AB} = 12.5; J_{AX} = 9.7; J_{BX} = 5.1 Hz). The 5-OH group in the spectrum of 1,3-dimethyl-5-hydroxy-5,6-dihydrouracil[20] (**13a**) appeared as a doublet (δ 5.97, $J_{5,OH}$ = 5.5 Hz).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 5.98; N, 11.97. Found: C, 61.29; H, 6.03; N, 11.96.

1-Methyl-3-benzyl-5-methoxyuracil (**7**).—A solution of **10b** (232 mg, 1 mmol) in methanol (20 ml) was treated with an excess of diazomethane in ether. The solution was concentrated to dryness after 12 hr, and the residue was crystallized from ethyl acetate to give 210 mg (85%) of **7**: mp 146–147°; nmr δ 7.45 s (1, H-6), 7.28 s (5, phenyl), 5.01 s (2, CH_2), 3.65 s (3, OCH_3), and 3.30 ppm s (3, NCH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.37. Found: C, 63.42; H, 5.72; N, 11.21.

1-Methyl-3-benzyl-2-oxo-4 imidazoline-4-carboxylic acid methyl ester (**15**) was prepared by methylation of 232 mg (1 mmol) of **12b** with an excess of diazomethane. The yield of pure material (from ethyl acetate–30–60° petroleum ether) was 220 mg (90%), mp 147–149°; nmr δ 7.61 s (1, H-5), 7.25 s (5, phenyl), 5.10 s (2, CH_2), 3.70 s (3, $COOCH_3$), and 3.27 ppm s (3, NCH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.37. Found: C, 63.44; H, 5.68; N, 11.26.

5-Benzoyloxyuridine (**16**).—Benzoic anhydride (226 mg, 1 mmol) was added to a refluxing solution of **3** (260 mg, 1 mmol) in 25 ml of methanol. Heating was continued for 1 hr and then a further charge of benzoic anhydride (1 mmol) was added. This procedure was repeated; after a reaction period of 3 hr, tlc ($CHCl_3$–MeOH, 5:1 v/v) showed only a trace of starting material. Concentration of the solution afforded a colorless syrup which crystallized after addition of ether. The solid was washed liberally with ether and the dried residue was dissolved in 10 ml of 50% ethanol. Crystallization commenced during concentration of the solution to 5 ml, and was completed by cooling. The yield of pure material, mp 218–220°, was 197 mg (54%) [crystallization of **16** remaining in the mother liquor was inhibited by the presence of a small amount of starting material (**3**)]: uv $\lambda_{max}^{H_2O}$ 237, 270 mμ; $\lambda_{min}^{H_2O}$ 214, 252 mμ; nmr δ 11.8 s (1, NH), 8.30 s (1, H-6), 8.2–7.4 m (5, phenyl), 5.83 d (1, H-1′, $J_{1',2'}$ = 4.5 Hz), ~5.0 broad peak (3, hydroxyls), 4.0 m (3, H-2′, H-3′, H-4′), 3.6 broad s (2, H-5′, H-5′).

Anal. Calcd for $C_{16}H_{16}N_2O_8$: C, 52.75; H, 4.43; N, 7.69. Found: C, 52.96; H, 4.46; N, 7.66.

Stability of Isopropylidene-5-hydroxyuridine (**2**) **and 1,3-Dimethyl-5-hydroxyuracil** (**10a**) **in 1 *N* NaOH.**—Solutions of **2** (0.1 and 0.02 *M*) and **10a** (0.1 *M*) in 1 *N* NaOH were heated at 55°. Aliquots (0.1 ml) taken immediatedly and at 24 hr were diluted with water to 1×10^{-4} *M*. In each case, the uv absorption maxima decreased by less than 5% in 24 hr.

(20) S. Y. Wang, *J. Amer. Chem. Soc.*, **80**, 6196 (1958).

Deuterium Exchange of Isopropylidene-5-hydroxyuridine (**2**) **and 1,3-Dimethyl-5-hydroxyuridine** (**10a**). **A. In D_2O.**—A solution of 60 mg of **2** in 2 m lof D_2O was heated under reflux at 100°. Integration of the H-6 and H-1′ signals in the nmr spectrum of **2** revealed that 75% and 100% exchange of H-6 for deuterium had taken place at 2 and 4 hr respectively. 5-Benzoyloxyuridine (**16**, 30 mg) showed no decrease of the H-6 signal, relative to the H-1′ resonance, when refluxed in D_2O (1 ml) for 2 hr.

B. In 0.1 *N* NaOD.—A solution of **2** (30 mg, 0.1 mmol) in 5 ml of 0.1 *N* NaOD in D_2O was refluxed for 30 min. The solution was cooled and concentrated to 0.5 ml. Integration of the nmr spectrum showed that complete exchange of H-6 had taken place. When 15.6 mg (0.1 mmol) or **10a** was refluxed in 5 ml of 0.1 *N* NaOD for 2 hr, the nmr spectrum of the concentrated solution showed that ~30% exchange of H-6 had taken place. In this case, the intensity of the H-6 signal was compared to those of the N-1 and N-3 methyl groups.

C. In 1 *N* NaOD.—A solution of **2** (15 mg, 0.05 mmol) in 0.5 ml of 1 *N* NaOD in D_2O was heated at 55° for 23 hr. Integration of the nmr spectrum at 5 and 23 hr showed that 36% and 80% exchange, respectively, of H-6 had taken place. 1,3-Dimethyl-5-hydroxyuracil (**10a**), 15.6 mg (0.1 mmol), was heated at 55° in 1 ml of 1 *N* NaOD for 23 hr. The solution was concentrated to 0.3 ml; integration of the nmr spectrum indicated ~10% exchange of H-6.

Conversion of Uridine into 1-(β-D-Ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic Acid (**6**).—A small excess of bromine was dissolved in a solution of uridine (4.84 g, 20 mmol) in 300 ml of water. The excess bromine was removed by aeration, and sodium bicarbonate 6.7 g (80 mmol) was added in portions. The solution was diluted to 400 ml and refluxed for 20 hr. The brown solution was deionized by passage through a column containing ~100 ml of Dowex AG 50W-X8 (H^+). The effluent and washings were concentrated to 30 ml; acetone was added and the solution was cooled. The resulting crystals (2.3 g, 39%), mp 107–110° (resolidifies and melts 195–200°, eff, dec), gave ir and uv spectra identical with those of dihydrated **6** prepared as above. A second crop was obtained as follows. The filtrate was neutralized with acetic acid and the solution was passed through a column containing 50 ml of Dowex AG1-X8 (OAc^-). The column was eluted with 0.1 *N* HOAc until the effluent was free of uv absorbing material; nucleoside **6** was then obtained by elution with 0.1 *N* HCl. Concentration of the appropriate fractions afforded crystalline **6** dihydrate (600 mg, total yield 49%).

Registry No.—**2**, 20406-82-0; 1-(2-deoxy-β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid, 20406-83-1; 1-methyl-3-benzyluracil, 20406-84-2; 1-methyl-3-benzyl-5-bromouracil, 20406-85-3; **7**, 20462-27-5; **8**, 15585-47-4; **10a**, 20406-86-4; **10b**, 20406-87-5; **12b**, 20406-88-6; **13b**, 20406-89-7; **14**, 20406-90-0; **15**, 20407-04-9; **16**, 20407-06-1; 5-hydroxyuracil, 4628-37-9; 3-methyl-5-hydroxyuracil, 1671-14-3.

Synthesis of Ethyl 4-Thio-α-D-lyxofuranoside and Related Compounds

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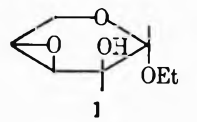
The reaction of ethyl 3,4-anhydro-β-L-ribopyranoside (1) with sodium benzyl mercaptide at −20° leads selectively to the formation of crystalline ethyl *S*-benzyl-4-thio-α-D-lyxopyranoside (2) in high yield. Small amounts of ethyl *S*-benzyl-3-thio-β-L-xylopyranoside (3) are formed in comparable reactions at room temperature or above. Desulfurization of 2 gave ethyl 4-deoxy-β-L-*erythro*-pentoside (5), acid hydrolysis of which gave 4-deoxy-L-*erythro*-pentose which was characterized by reduction and benzoylation giving crystalline 1,3,5,6-tetra-*O*-benzoyl-2-deoxy-D-*erythro*-pentitol. Treatment of 2 with sodium in liquid ammonia followed by immediate equilibration with methanolic hydrogen chloride gave a mixture of the the α and β forms of methyl 4-thio-D-lyxofuranoside (8a) from which a crystalline tri-*O*-*p*-nitrobenzoate was obtained. Treatment of 2 with sodium in ammonia alone gave crystalline ethyl 4-thio-α-D-lyxopyranoside (9) which upon subsequent equilibration with ethanolic hydrogen chloride gave a low yield of crystalline ethyl 4-thio-α-D-lyxofuranoside (11). Crystalline ethyl 4-thio-β-D-ribofuranoside (13) has also been prepared by treatment of 1,2,3,5-tetra-*O*-acetyl-4-thio-D-ribofuranose (12) with ethanolic hydrogen chloride.

Recently syntheses of a number of sugars containing sulfur as part of a furanose or pyranose ring have been described.[1] These syntheses involve the preparation of appropriately substituted 4-thio or 5-thio sugars which show a strong tendency toward glycoside formation with inclusion of the sulfur in the acetal ring. Since conversion of a primary hydroxyl group into a suitable sulfur-containing substituent is relatively straightforward, a number of 5-thiopentopyranosides are now known.[1] The corresponding 5-thiohexoses are, however, less accessible and only syntheses of 5-thio-D-glucopyranose[2] and 5-thio-L-idopyranose[3] derivatives have been achieved, both *via* the appropriate 5,6-dideoxy-5,6-episulfides. Other methods have led to 6-acetamido-6-deoxy-5-thio-L-idopyranose[4] and 6-deoxy-5-thio-L-talopyranose.[5]

As part of another study in this institute we were stimulated to attempt the synthesis of a 5-thio-β-D-galactopyranoside for evaluation as an inducer of the enzyme β-galactosidase. Since preparation of a suitable derivative of 5-thiogalactose would appear to require either a lengthy sequence from D-galactose *via* the episulfide route or use of an inaccessible L sugar we have examined an alternative route *via* homologation of a more easily prepared 4-thiopentose. In this paper we describe the synthesis of a suitable 4-thio-D-lyxose derivative and its conversion into ethyl 4-thio-α-D-lyxofuranoside. Our studies on the homologation reaction will be reported separately.[6]

The known ethyl 3,4-anhydro-β-L-ribopyranoside (1) appeared to be a suitable precursor of 4-thio-D-lyxose derivatives and its synthesis was achieved in an over-all yield of 42% from ethyl α-D-lyxopyranoside *via* modifications of the four-step route previously described.[7] Reaction of 1 with sodium benzyl mercaptide at −20° led to apparently completely specific diaxial opening with formation of crystalline ethyl *S*-benzyl-4-thio-α-D-lyxopyranoside (2) in 83% yield.[8] Similar reactions at room temperature or above were less specific and a small amount of ethyl *S*-benzyl-3-thio-β-L-xylopyranoside (3) was detected by thin layer chromatography. Isolation of this minor product in crystalline form was facilitated by conversion of the major product (2) into its isopropylidene derivative (4) followed by chromatography on silicic acid.



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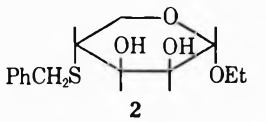

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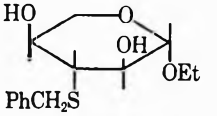

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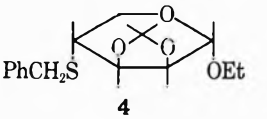

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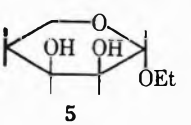
Treatment of 2 with an excess of a sponge nickel catalyst[9] led to very rapid desulfurization and formation of ethyl 4-deoxy-β-L-*erythro*-pentopyranoside (5) as an analytically pure, distillable syrup. Hydrolysis of the glycoside gave 4-deoxy-L-*erythro*-pentose (6) as a homogeneous reducing syrup with an optical rotation very similar to that reported earlier by a different route.[8a] Reduction of 6 with sodium borohydride followed by benzoylation gave crystalline 1,3,4,5-tetra-*O*-benzoyl-2-deoxy-D-*erythro*-pentitol (7) which was identical in every way with a sample of the same product obtained by reduction and benzoylation of 2-deoxy-D-ribose.[10]



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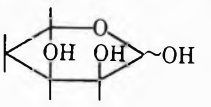

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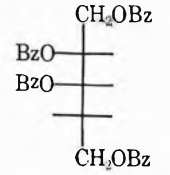


7

The availability of 2 made the synthesis of 4-thio-D-lyxofuranosides an attractive goal. Removal of the benzyl group from 2 was achieved by treatment with sodium in liquid ammonia, and, in view of the known

(1) H. Paulsen, *Angew. Chem. Intern. Ed. Engl.*, **5**, 495 (1966).

(2) (a) M. S. Feather and R. L. Whistler, *Tetrahedron Lett.*, 667 (1962); (b) R. M. Rowell and R. L. Whistler, *J. Org. Chem.*, **31**, 1515 (1966).

(3) T. J. Adley and L. N. Owen, *Proc. Chem. Soc.*, 418 (1961).

(4) L. Goodman and J. E. Christensen, *J. Org. Chem.*, **29**, 1787 (1964).

(5) C. L. Stevens, R. P. Glinski, G. E. Gutowski, and J. P. Dickerson, *Tetrahedron Lett.*, 649 (1967).

(6) J. P. H. Verheyden and J. G. Moffatt, unpublished results.

(7) J. Piotrovsky, J. P. H. Verheyden, and P. J. Stoffyn, *Bull. Soc. Chim. Belges*, **73**, 969 (1964).

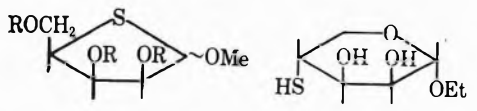
(8) The related methyl 3,4-anhydro-β-L-ribopyranoside has been opened by hydrogen bromide, amines, and sodium methyl mercaptide: (a) P. W. Kent and P. F. V. Ward, *J. Chem. Soc.*, 416 (1953); (b) W. G. Overend, A. C. White, and N. R. Williams, *Chem. Ind.*, 1840 (1963); (c) N. A. Hughes, R. Robson, and S. A. Saeed, *Chem. Commun.*, 1381 (1968).

(9) Davidson Chemical Division, W. R. Grace and Co., Cincinnati, Ohio.

(10) S. David and P. Jaymond, *Bull. Soc. Chim. Fr.*, 157 (1959).

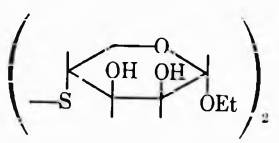
ease of disulfide formation from thio sugars,[11] the crude product was directly treated with 6% methanolic hydrogen chloride for 24 hr. These conditions would be expected to lead to equilibration of the glycosidic grouping with selective formation of the thiofuranosides as has been previously demonstrated in the D-ribothiofuranose[12a,b] and D-arabinothiofuranose[12c] series. The reaction mixture contained at least five components by thin layer chromatography and the three major ones have been isolated. The most abundant of these (27%) was a syrup containing two products with very similar thin layer chromatographic mobilities. These gave negative nitroprusside tests for thiols[13] and were shown by nmr spectroscopy to be a roughly 2:1 mixture of the desired anomeric methyl 4-thio-D-lyxofuranosides (**8a**). The methyl glycosides appeared as two sharp singlets at 3.36 and 3.40 ppm and the anomeric proton as a pair of overlapping doublets at 4.88–4.97 ppm. All other protons were in an unresolved envelope at 3.59–4.67 ppm. Upon addition of trichloroacetylisocyanate[14] the spectrum was simplified, the methyl groups now appearing as a broadened singlet at 3.41 ppm and the anomeric protons as well-resolved doublets at 5.35 ppm (J = 2 Hz) and 5.21 ppm (J = 3 Hz). The C_2 and C_3 protons were shifted downfield roughly 1.2 ppm, but the C_5 methylene group, being associated with a primary alcohol, shifted much less and appeared as a multiplet at 4.63 ppm. *p*-Nitrobenzoylation of the mixture gave a crystalline triester (**8b**) which appeared to be a single anomer, the anomeric proton appearing as a sharp doublet (J = 2.8 Hz) at 5.35 ppm. The magnitude of this coupling constant does not permit definitive assignment of anomeric configuration.[15]

The other major products were obtained in crystalline form and proved to be ethyl 4-thio-α-D-lyxopyranoside (**9**) and the corresponding disulfide (**10**) in yields of 11 and 14%. The thiol (**9**) showed unexpected stability (see later) and was unchanged after prolonged storage. The small coupling constant (2 Hz) of the anomeric proton of **9** indicates that the molecule exists in a conformation with both the 1-OEt and 2-OH groups axial, as does the *S*-benzyl derivative (**2**). The disulfide (**10**) gave a negative thiol test and its dimeric structure was confirmed by mass spectrometry.



8 a, R = H
b, R = *p*-NO_2Bz

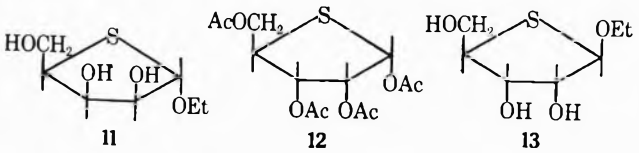
9



10

The above experiment indicates that acid-catalyzed equilibration of the glycoside does not very readily occur with these compounds and this stability is also reflected in the unusual difficulties encountered during hydrolysis of **2**.[6] Treatment of **2** with sodium in liquid ammonia without subsequent acidic treatment led to isolation of the crystalline thiol **9** in quantitative yield. Subsequent treatment of **9** with 1% ethanolic hydrogen chloride led to very slow disappearance of the thiol group, 50% being still present by colorimetric assay[16] after 4 days at room temperature. Even brief reactions at 80°, however, led to a plethora of products. Treatment of **9** with ethanolic hydrogen chloride under a variety of conditions led to the isolation of crystalline ethyl 4-thio-α-D-lyxofuranoside (**11**) but only in yields of 7–8%. The assigned structure is based upon elemental analysis, the absence of a free thiol grouping, and nmr spectroscopy. The coupling constant of the anomeric proton (4 Hz) does not permit assignment of configuration but the large positive optical rotation (+331°) strongly suggests it to be α.

For purposes of comparison we have also prepared crystalline ethyl 4-thio-β-D-ribofuranoside (**13**) in 45% yield by methanolysis of 1,2,3,5-tetra-*O*-acetyl-4-thio-β-D-ribofuranose[12b] (**12**) under conditions similar to those above. The β configuration for **13** is confirmed by both the small coupling constant (1 Hz) of the anomeric proton and the large negative rotation of −144°. The related methyl β-glycoside has been obtained as a syrup by Whistler.[12a]



11 **12** **13**

Experimental Section

General Methods.—Thin layer chromatography (tlc) was performed using 0.25-mm layers of Merck silica gel GF and preparative tlc on 20 × 100 cm glass plates coated with 1.3-mm layers of Merck silica gel HF. Column chromatography was done using 100–200 mesh Davidson grade 923 silica gel or Merck silica gel with 0.05–0.20-mm particles, Nuclear magnetic resonance (nmr) spectra were obtained using Varian A-60 or HA-100 spectrometers and mass spectra using an Atlas CH-4 instrument with a direct inlet system and an ionizing voltage of 70 eV. Optical rotatory dispersion (ORD) spectra were determined using a JASCO ORD/UV-5 instrument. Elemental analyses were performed by Dr. A. Bernhardt, Mülheim, Germany. We are grateful to Mr. John Murphy and Miss Janice Tremble, and to Dr. Laszlo Tökes for their assistance in obtaining nmr and mass spectra, respectively.

Ethyl 3,4-Anhydro-β-L-ribopyranoside (**1**).—This compound was prepared in an over-all yield of 42% from ethyl α-D-lyxopyranoside by modifications of a reported procedure.[7] The main improvements were in the use of perchloric acid for preparing the acetonide, and not purifying any of the intermediates. The final distilled product had mp 49–50°; $[\alpha]^{21}D$ +148° (c 1.0, MeOH); nmr (DMSO-d_6) 4.20 ppm (d, 1, $J_{1,2}$ = 4.6 Hz, C_1-H), 1.08 ppm (t, 3, J = 7 Hz, CH_3CH_2), 5.05 ppm (d, 1, J = 5 Hz, OH).

Ethyl *S*-Benzyl-4-thio-α-D-lyxopyranoside (**2**).—Benzyl mercaptan (17 ml, 145 mmol) and **1** (17.0 g, 106 mmol) were dissolved in cold 1.25 *M* methanolic sodium methoxide (100 ml) and the solution was immediately cooled to −20° and stored for 5 days. Aqueous acetic acid (200 ml of 1.75 *M*) was added followed by water (250 ml) and the white crystalline product was collected

(11) R. L. Whistler and R. M. Rowell, *J. Org. Chem.*, **29**, 1259 (1964).

(12) (a) R. L. Whistler, W. E. Dick, T. R. Ingle, R. M. Rowell, and B. Urbuss, *ibid.*, **29**, 3723 (1964); (b) E. J. Reist, D. E. Gueffroy, and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 5658 (1964); (c) R. L. Whistler, U. G. Nayak, and A. W. Perkins. *Chem. Commun.*, 1339 (1968).

(13) G. Toennies and J. J. Kolb, *Anal. Chem.*, **23**, 823 (1951).

(14) V. W. Goodlett, *ibid.*, **37**, 431 (1965).

(15) R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **4**, 230 (1967).

(16) R. E. Basford and F. M. Huennekens, *J. Amer. Chem. Soc.*, **77**, 3873 (1955).

and washed with water giving 25 g (83%) of **2** with mp 134–136°, unchanged upon recrystallization from aqueous methanol; λ_{max}^{MeOH} 261 mμ sh (ε 3400) and 267 sh (2200); $[\alpha]^{21}D$ +84° (*c* 0.33, MeOH); ORD (MeOH) plain positive ; nmr ($CDCl_3$) 4.80 (d, 1, $J_{1,2}$ = 1.5 Hz, C_1-H), 7.30 (s, 5, Ar), 1.19 (t, 3, *J* = 7 Hz, CH_3CH_2), 2.5–2.7 ppm (br, s, 2, two OH).

Anal. Calcd for $C_{14}H_{20}O_4S$: C, 59.14; H, 7.09; S, 11.25. Found: C, 59.31; H, 7.31; S, 11.45.

Ethyl *S*-Benzyl-2,3-*O*-isopropylidene-4-thio-α-D-lyxopyranoside (4).—Phosphorus pentoxide (100 mg) was added with shaking to a solution of **2** (284 mg, 1 mmol) in anhydrous acetone (10 ml). After 3 min the mixture was filtered and the filtrate shaken with an excess of $BaCO_3$. After filtration the solution was evaporated to dryness and the residue (335 mg) was chromatographed on a column of Davidson silica gel using a gradient of chloroform in benzene. Homogeneous **4** (250 mg, 75%) was distilled in a Kugelrohr apparatus[17] at 125° (10^{-3} mm): nmr ($CDCl_3$) 1.32 (s, 6, CMe_2), 4.92 (d, 1, $J_{1,2}$ = 1 Hz, C_1-H), 7.33 (br, s, 5, C_6H_5), 3.84 (s, 2, SCH_2), 1.19 (t, 3, *J* = 7 Hz, CH_3CH_2); λ_{max}^{MeOH} 260 mμ (ε 3100), 265 (2200); $[\alpha]^{21}D$ +7° (*c* 0.1, MeOH); ORD $[\alpha]_{255}$ +208° (pk), $[\alpha]_{240}$ 0°, $[\alpha]_{224}$ −2200° (tr).

Anal. Calcd for $C_{17}H_{24}O_4S$: C, 62.95; H, 7.46; S, 9.87. Found: C, 63.15; H, 7.30; S, 9.75.

Ethyl *S*-Benzyl-3-thio-β-L-xylopyranoside (3).—Benzyl mercaptan (2.6 ml, 6.3 mmol) and **1** (900 mg, 5.6 mmol) were heated overnight under reflux in 5 ml of 1.25 *M* methanolic sodium methoxide. After neutralization with acetic acid the mixture was evaporated and the residue partitioned between chloroform and water giving an organic phase which contained two close moving spots by tlc using $CHCl_3$–EtOAc (1:1). After evaporation of the solvent 400 mg of pure **2** was obtained by crystallization from chloroform–hexane. The mother liquors were evaporated and the partially crystalline residue (1.19 g) was treated with acetone (5 ml), 2,2-dimethoxypropane (0.5 ml), and $HClO_4$ (20 μl). After 15 min, NH_4OH (0.1 ml) was added and the solvent was evaporated. The residue was dissolved in benzene, extracted with water, and chromatographed on a column of Davidson silica gel (120 g). Elution with benzene gave 650 mg of pure **4** and elution with chloroform and crystallization from benzene–hexane gave 60 mg of **3** with mp 86–87°; λ_{max}^{MeOH} 265 mμ (ε 2100), 260 (3100); $[\alpha]^{21}D$ +41° (c 0.33, MeOH); nmr 4.27 (d, 1, $J_{1,2}$ = 6.5 Hz, C_1-H), 7.30 (s, 5, C_6H_5), 3.88 (s, 2, SCH_2), 1.24 (t, 3, *J* = 7 Hz, CH_3CH_2).

Anal. Calcd for $C_{14}H_{20}O_4S$: C, 59.14; H, 7.09. Found: C, 59.23; H, 7.01.

Ethyl 4-Deoxy-β-L-erythro-pentoside (5).—A mixture of Davidson sponge nickel (5 g) and **2** (0.50 g) were stirred in methanol for 30 min and then filtered through Celite. Evaporation of the filtrates and short-path distillation at 90° (10^{-3} mm) gave 140 mg (50%) of **5** as a clear syrup: $[\alpha]^{21}D$ +104°; nmr (DMSO-d_6) 4.59 (d, 1, $J_{1,2}$ = 3 Hz, C_1-H), 4.50 (d, 1, *J* = 5 Hz, OH), 4.37 (d, 1, *J* = 6 Hz, OH), 1.6 (m, 2, C_4-H_2), 1.12 ppm (t, 3, *J* = 7 Hz, CH_3CH_2).

Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, Found: C, 52.08; H, 8.81.

4-Deoxy-L-*erythro*-pentose (6).—A solution of **5** (100 mg) in 1 *N* H_2SO_4 (20 ml) was heated at 100° for 4 hr. After neutralization with $Ba(OH)_2$, treatment with CO_2 and evaporation the residue was extracted with hot acetone giving 70 mg (85%) of pure **6** as a colorless syrup: $[\alpha]^{21}D$ +28.5° (*c* 0.2 H_2O) (lit.[8a] $[\alpha]^{21}D$ −23.1°); nmr (DMSO-d_6) 4.77 (t, 1, $J_{1,2}$ = 4 Hz, $J_{H,OH}$ = 5 Hz giving d, $J_{1,2}$ = 4 Hz with D_2O, C_1-H), 6.05 (d, 1, $J_{H,OH}$ = 5 Hz, C_1-OH), 4.37 ppm [br, s, 2, $(OH)_2$].

1,3,4,5-Tetra-*O*-benzoyl-2-deoxy-D-*erythro*-pentitol (7).—Sodium borohydride (15 mg) and **6** (60 mg) were dissolved in water (4 ml) and after 30 min at 25° Dowex 50 (H^+) resin (2 ml) was added. After filtration, evaporation of the solvent, and several evaporations with methanol, the residue was treated with benzoyl chloride (0.25 ml) in pyridine (0.5 ml) at 100° for 10 min. Addition of water gave crystalline **7** (213 mg, 86%) that was recrystallized from ethanol with mp 129–130°, $[\alpha]^{21}D$ −14.5° (*c* 1.8, $CHCl_3$), both identical with those of **7** prepared by reduction and benzoylation of 2-deoxyribose:[10] nmr ($CDCl_3$) 7.5 (br, s, 12, C_6H_5), 8.0 (br, s, 8, C_6H_5), 2.43 (m, 2, C_2-H_2), 2.43 (m, 4, CH_2O), 5.9 ppm (m, 2, C_3-H, C_4-H).

Debenzylation and Equilibration of 2.—Sodium chips (230 mg, 10 mg-atoms) were slowly added to a stirred solution of **2** (710 mg, 2.5 mmol) in anhydrous NH_3 (50 ml). NH_4Cl (600 mg) was then added and after careful evaporation of the solvent the residue was dissolved in 6% methanolic hydrogen chloride (50 ml). After 24 hr the solution was neutralized with $PbCO_3$, filtered, evaporated, and chromatographed on a column of 100 g of Davidson silicic acid using CH_2Cl_2–CH_3OH (19:1). The first peak contained 55 mg (11%) of **9** with mp 103.5–105° (see below). The second peak contained 120 mg (27%) of a syrup showing two close spots on tlc with $CHCl_3$–MeOH (9:1) and shown by nmr (see text) to be a 2:1 mixture of the anomers of **8a**. Reaction with *p*-nitrobenzoyl chloride in pyridine followed by preparative tlc using three consecutive developments with chloroform–hexane (2:1) separated two close bands. Elution and crystallization from aqueous acetone of the more intense, faster band gave pure **8b** of mp 76–78°; $[\alpha]^{21}D$ +13° (*c* 0.1, $CHCl_3$); nmr 5.35 (d, 1, $J_{1,2}$ = 2.8 Hz, C_1-H), 3.47 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{27}H_{21}N_3O_{13}S$: C, 51.67; H, 3.37. Found: C, 52.16; H, 3.35.

The third major peak contained 68 mg (14%) of disulfide **10** of mp 130–135° after crystallization from acetone–hexane; nmr pyridine-d_5) 5.52 (d, 2, $J_{1,2}$ = 2.5 Hz, 1-H, 1′-H), 4.35 (t, 2, $J_{1,2}$ = $J_{2,3}$ = 2.5 Hz, 2-H, 2′-H), 1.14 ppm (t, 6, *J* = 7 Hz, OCH_3); mass spectrum *m/e* 386 (M^+), 341 (M^+ − OEt), 193 ($M^+/2$), 148 ($M^+/2$ − OEt).

Anal. Calcd for $C_{14}H_{26}O_8S_2$: C, 43.52; H, 6.78; S, 16.57. Found: C, 43.31; H, 6.64; S, 16.78.

Ethyl 4-Thio-α-D-lyxopyranoside (9).—Sodium chips (690 mg, 30 mg-atoms) were added slowly to a solution of **2** (2.13 g, 7.5 mmol) in anhydrous NH_3 (500 ml) until a blue solution persisted. After addition of NH_4Cl (1.8 g) the NH_3 was evaporated and the residue extracted with acetone. Evaporation of the extracts left 1.46 g (100%) of white, crystalline **9** of mp 108–109°. Two recrystallizations from acetone–hexane gave mp 109.5–110.5°; ir (KBr) 2575 cm^{-1} (SH); $[\alpha]^{21}D$ +53° (*c* 0.1, H_2O); ORD (plain positive) $[\alpha]_{300}$ +265°, $[\alpha]_{240}$ +730°, $[\alpha]_{218}$ +1920°; nmr (DMSO-d_6) 4.69 (d, 1, $J_{1,2}$ = 2 Hz, C_1-H), 2.10 (s, 1, SH), 4.73 (d, 1, $J_{H,OH}$ = 5 Hz, OH), 4.67 (d, 1, $J_{H,OH}$ = 3 Hz, OH), 1.13 ppm (t, 3, *J* = 7 Hz, CH_3CH_2).

Anal. Calcd for $C_7H_{14}O_4S$: C, 43.29; H, 7.27; S, 16.48. Found: C, 43.41; H, 7.08; S, 16.61.

Ethyl 4-Thio-α-D-lyxofuranoside (11).—A solution of **9** (500 mg) in 6% ethanolic hydrogen chloride (17 ml) was kept at room temperature for 21 hr, then diluted with ethanol and neutralized with $PbCO_3$. Evaporation of the filtrate left a brown syrup (460 mg) that was purified by preparative tlc using chloroform–acetone (2:1). The product bands were detected with a heated wire[18] and eluted with ethanol. The fastest band gave 70 mg (14%) of starting material and was followed by 50 mg (10%) of **11**. Crystallization from acetone–ethyl acetate gave 40 mg (8%) of pure **11** of mp 95–96°; $[\alpha]^{21}D$ +331° (*c* 2.8, MeOH); nmr (pyridine-d_5) 5.48 (d, 1, $J_{1,2}$ = 4 Hz, C_1-H), 4.63 (t, 1, $J_{1,2}$ = $J_{2,3}$ = 4 Hz, C_2-H), 4.94 (q, 1, $J_{2,3}$ = 4 Hz, $J_{3,4}$ = 6 Hz, C_3-H), 4.10 (br, q, 1, $J_{3,4}$ = 6 Hz, $J_{4,5}$ = 5 Hz, C_4-H), 4.30 (d, 2, $J_{4,5}$ = 5 Hz, C_5-H_2), 1.11 (t, 3, *J* = 7 Hz, CH_3CH_2), 3.6 ppm (m, 2, CH_3CH_2); mass spectrum *m/e* 176 (M^+ − H_2O), 159, 146, 131, 117.

Anal. Calcd for $C_7H_{14}O_4S$: C, 43.29; H, 7.27; S, 16.48. Found: C, 43.39; H, 7.12; S, 16.25.

The slowest band contained 200 mg (40%) of **10**.

Ethyl 4-Thio-β-D-ribofuranoside (13).—A solution of 12[19] (85 mg) in 6% ethanolic hydrogen chloride (3 ml) was kept under nitrogen for 17 hr, neutralized with $PbCO_3$, and evaporated to dryness giving 36 mg of a brown syrup. This was decolorized with carbon and crystallized from acetone giving 22 mg (45%) of **13** with mp 92–93°; $[\alpha]^{21}D$ −144° (*c* 2.5, EtOH); nmr (pyridine-d_5) 5.29 (d, 1, $J_{1,2}$ = 1 Hz, C_1-H), 1.08 (t, 3, *J* = 7 Hz, CH_3CH_2), 3.55 ppm (m, 2, CH_2CH_3); mass spectrum *m/e* 194 (M^+), 176 (M^+ − H_2O), 159, 146, 131, 117, 91.

Anal. Calcd for $C_7H_{14}O_4S$: C, 43.29; H, 7.27. Found: C, 43.54; H, 6.92.

Registry No.—**1**, 2773-65-1; **2**, 20072-93-9; **3**, 20072-94-0; **4**, 20072-95-1; **5**, 20072-96-2; **6**, 20072-97-3; **7**, 20072-98-4; **8b**, 20072-99-5; **9**, 20073-00-1; **10**, 20073-01-2; **11**, 20073-02-3; **13**, 20073-03-4.

(17) R. Graeve and G. H. Wahl, *J. Chem. Educ.*, **41**, 279 (1964).

(18) J. L. Bloomer and W. R. Eder, *J. Chromatogr.*, **34**, 548 (1968).

(19) We are grateful to Dr. Leon Goodman for a sample of this compound.[12b]

Ribosyl Derivatives of Hypoxanthine[1]

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The preparation of 7-α- and 7-β-D-ribofuranosylhypoxanthines (α- and β-**5c**) from 9-propenylhypoxanthine (**10**) is described. β-**5c** was also prepared from the chloromercuri derivative of 3-benzylhypoxanthine (**1**), but the chloromercuri derivative of 3-benzhydrylhpyoxanthine (**2**) gave, after removal of the protective groups, not 7- but 1-β-D-ribofuranosylhypoxanthine (β-**13c**) resulting presumably from a rearrangement of the benzhydryl group to N-9. β-**13c** was also prepared from 3-benzhydrylhypoxanthine (**3**) and the mercuri derivative of 9-propenylhypoxanthine. The 7 isomer of 6-mercaptopurine ribonucleoside was prepared from β-**5a**.

We have been engaged in the synthesis of the nucleoside components of the family of B_{12} vitamins, and one of the objectives of the present work was to prepare the nucleoside component of factor *G*, 7-α-D-ribofuranosylhypoxanthine, and congeners thereof.[1] Previously we found that the chloromercuri derivative of 3-benzylhypoxanthine (**1**) reacts with acylglycosyl halides at N-7 to give, for example, 7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3-benzylhypoxanthine (β-**4b**), which, on treatment with sodium methoxide in methanol, gave 3-benzyl-7-β-D-ribofuranosylhypoxanthine (β-**4c**).[2,3] Catalytic hydrogenolysis of β-**4c** gave some of the desired 7-β-D-ribofuranosylhypoxanthine (β-**5c**), but the major product was 3-benzyl-1,2-dihydro-7-β-D-ribofuranosylhypoxanthine.[2,3] In the present work this procedure was improved by reversing the latter two steps and using benzoyl blocking groups: thus β-**4a** was hydrogenolyzed to β-**5a**, which was then debenzoylated to β-**5c**. The benzoylated nucleoside β-**5a** was also thiated to give 7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)purine-6(1*H*)-thione (β-**6a**), which was debenzoylated to 7-β-D-ribofuranosylpurine-6(1*H*)-thione (β-**6c**), an isomer of the anticancer agent 6-mercaptopurine ribonucleoside.

Even though the route β-**4a** to β-**5a** to β-**5c** is an improvement over the original procedure,[3] a large amount of the unwanted 7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-benzyl-1,2-dihydrohypoxanthine is still obtained. In an effort to improve the yield of β-**5c** by reducing the amount of dihydro compound formed, the more readily hydrogenolyzed benzhydryl group was substituted for the benzyl group of **1**. Contrary to the previous report,[3] however, the reaction of chloromercuri 3-benzhydrylhypoxanthine (**2**) with 2,3,5-tri-*O*-acetylribofuranosyl chloride did not give 7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3-benzhydrylhypoxanthine (β-**4b**). Removal of the blocking groups of the product gave what appeared to be a 1-ribosylhypoxanthine (**13c**). Furthermore, no ring-reduced material was formed. Thus, it would seem that **2** rearranged to the mercuri derivative of 9-benzhydrylhypoxanthine (**8**),[4] which reacted with the halo sugar at N-1 to give 9-benzhydryl-1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)hypoxanthine (**14b**)[5] (Scheme I).

Since 3-benzylhypoxanthine is known to be alkylated at N-1 in dipolar aprotic solvents,[6,7] 3-benzhydrylhypoxanthine (**3**) was allowed to react with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in N,N-dimethylacetamide (DMA). From this reaction was isolated 1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)-3-benzhydrylhypoxanthinium bromide (**7b**), identified by its elemental analyses and spectra. Initial attempts to purify **7b** by recrystallization from boiling ethanol resulted, in part, in loss[7] of the labile 3-benzhydryl group to give **13b** and, in part, in migration of this group from N-3 to N-9[6,7] to give **14b**. Removal of the acetyl groups of **13b** gave **13c**, identical with that obtained from **2**. In both cases only one anomer was obtained, and its anomeric configuration was established as β in two ways. First, **13c** was converted into its 2′,3′-isopropylidene derivative **12**, the pmr spectrum of which showed a coupling constant of 2.2 Hz from the $H_{1'}$–$H_{2'}$ coupling, precluding the α, or *cis*, configuration.[8] Second, 1-β-D-ribofuranosylhypoxanthine (β-**13c**) was also synthesized from 9-propenylhypoxanthine[9] (**10**) *via* its mercuri derivative **9**.[10] 1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-9-propenylhypoxanthine (β-**15b**) was deacetylated, and the propenyl group of β-**15c** was removed by oxidation in neutral solution[9] to give β-**13c**. Although this method of synthesis of β-**13c** is definitely inferior to its preparation from **3**, it does constitute a proof of structure of β-**13c** based on the *trans* rule.[11]

In still another approach to the synthesis of 7-ribosylhypoxanthine (**5c**), 9-propenylhypoxanthine (**10**) was allowed to react with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in N,N-dimethylacetamide at room temperature. Under these conditions 7-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)-9-propenylhypoxanthinium bromide (**11a**) was formed.[7,12] Oxidative removal of the propenyl group of **11a** gave 7-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)hypoxanthine (**5a**), which was purified by chromatography on a silica gel column before debenzoylation to 7-D-ribofuranosylhypoxanthine (**5c**). Examination of the nmr spectrum of **5c** indicated that it was an approximately 1:1 mixture of the α and β anomers.[13] The formation of equal quantities of α and β anomers of

(1) This work was supported by funds from the Southern Research Institute, the C. F. Kettering Foundation, and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51. Preliminary communications describing part of this work have appeared: J. A. Montgomery and H. J. Thomas, *J. Heterocycl. Chem.*, **5**, 303, 741 (1968).

(2) J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, **28**, 2304 (1963).

(3) H. J. Thomas and J. A. Montgomery, *ibid.*, **31**, 1413 (1966).

(4) The exact nature of this proposed intermediate (**8**) is obviously not known.

(5) The migration of the benzyl group from the 3 to the 9 position of hypoxanthines is known.[6,7]

(6) J. A. Montgomery and H. J. Thomas, *Chem. Ind.* (London), 1596 (1965).

(7) J. A. Montgomery, K. Hewson, S. J. Clayton, and H. J. Thomas, *J. Org. Chem.*, **31**, 2202 (1966).

(8) N. J. Leonard and R. A. Laursen, *J. Amer. Chem. Soc.*, **85**, 2026 (1963).

(9) J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, **30**, 3235 (1965).

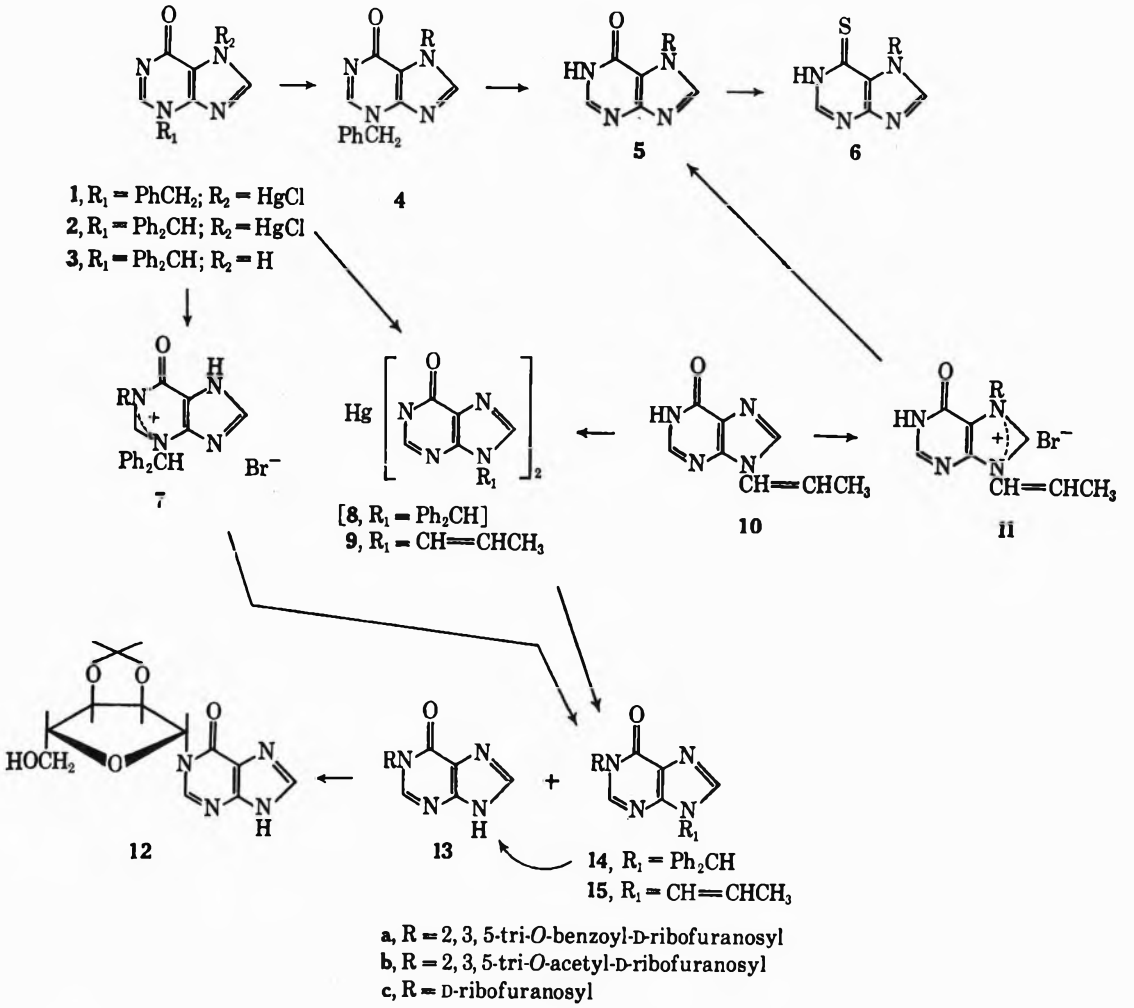
(10) See also T. H. Hashizume and H. Yamazaki, *Tetrahedron Lett.*, 3839 (1967).

(11) B. R. Baker, *Ciba Found. Symp. Chem. Biol. Purines*, 120 (1957).

(12) J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, **84**, 1914 (1962).

(13) J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **11**, 48 (1968).

SCHEME I



a glycosylpurine from the reaction of a purine with a glycosyl halide containing a participating acyloxy group at C-2 has not been previously reported. The amount of α anomer obtained from **10** could be increased by allowing it to react with 5-*O*-benzoyl-D-ribofuranosyl bromide 2,3-cyclic carbonate,[14-17] which gave an anomer ratio of about 2α to 1β. Separation of these anomers was achieved by chromatography on a cellulose column. The β anomer was identical with that prepared from **1**. The identity of the *cis* or α anomer was established by analysis and by its ultraviolet and pmr spectra. The signal due to $H_{1'}$ of α-**5c** (*cis* anomer) occurs downfield from the signal due to $H_{1'}$ of β-**5c** (*trans* anomer), as is the case in all reported instances of anomeric purine nucleoside pairs.[13,15,18,19] Yet another exception to Hudson's rules, however, is presented by this anomeric pair (α- and β-**5c**). It is probably significant that the 7-D-ribofuranosyladenines obey Hudson's rules, whereas the 7-D-ribofuranosylguanines[19] and hypoxanthines, both of which have an oxo function at C-6, do not.

In an effort to better understand the reaction of 9-propenylhypoxanthine (**10**) with these glycosyl halides, their anomeric configurations were determined by means of nmr spectrometry. 2,3,5-Tri-*O*-acetylribofuranosyl bromide (and also the chloride) was shown to be a 3:2 mixture of β to α anomer, the 5-benzoylribofuranosyl bromide 2,3-cyclic carbonate was found to be 2:1 β to α mixture, but the 2,3,5-tri-*O*-benzoylribofuranosyl bromide was a 1:2 β to α mixture.[20,21] Based on these analyses the anomeric mixtures of nucleosides formed could be explained by postulating an SN2-type reaction. The reaction of 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide[22] with **10**, however, gave, after removal of the protective groups, 7-α-D-arabinofuranosylhypoxanthine,[3] with at most a trace of the β anomer. This result requires the complete anomerization of the α-bromide, which is highly unlikely, or the intervention of the 1,2 ortho ester ion. Why ortho ester ion interven-

(14) R. S. Wright, G. M. Tener, and H. G. Khorana, *J. Amer. Chem. Soc.*, **80**, 2004 (1958).

(15) J. A. Montgomery and H. J. Thomas, *ibid.*, **87**, 5442 (1965).

(16) Reaction of this glycosyl halide with the mercuri derivative of *N*-benzoyl-3-benzyladenine gave an anomeric mixture which after removal of the blocking groups gave a 14% yield of 7-α-D-ribofuranosyladenine and an 8% yield of the β anomer.[15] Wright, *et al.*,[14] similarly obtained a 24% yield of 9-α-D-ribofuranosyladenine and a 15% yield of adenosine. This halo sugar probably reacts by direct displacement of the bromo group with Walden inversion, and evidence has been presented to support the contention that the sugar is an anomeric mixture with the β anomer predominating[17] (prior to pmr work reported herein).

(17) G. M. Tener and H. G. Khorana, *J. Amer. Chem. Soc.*, **79**, 437 (1957).

(18) T. Nishimura and B. Shimuzu, *Chem. Pharm. Bull.* (Tokyo), **13**, 803 (1965).

(19) K. Imai, A. Nohara, and M. Honjo, *ibid.*, **14**, 1378 (1966).

(20) Other investigators have also reported that this sugar is richer in the α anomer.[21]

(21) J. D. Stevens, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1806 (1968).

(22) R. K. Ness and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **80**, 2007 (1958).

tion occurs with the *arabino* and apparently does not with the *ribo* sugar is not easily explained.

Stevens, Ness, and Fletcher have observed that the reaction of 2,3,5-tri-*O*-benzoylribofuranosyl bromide with 5,6-dimethylbenzimidazole in dioxane gave a 1.8 β to 1 α anomer ratio.[21] In the related Hilbert–Johnson reaction of 5-benzoyloxymethyl-2,4-dimethoxypyrimidine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in *acetonitrile*, a *polar solvent*, both α and β anomers are formed also,[23] although with other sugars and other pyrimidines only the β anomer is produced (in the *nonpolar solvents benzene, toluene, and xylene*, a number of instances have been reported in which both anomers are formed).[24] Prystas and Sorm have suggested that the stronger nucleophiles (among the 2,4-dialkoxypyrimidines) can react with the *trans* halogenoses by direct displacement, thus successfully competing with ortho ester ion formation, which would give rise to *trans* (or in this case β) nucleosides only.[25] This explanation obviously cannot, without modification, be applied to the present case.

Experimental Section

The melting points reported were determined with a Mel-Temp apparatus and are not corrected. The optical rotations were determined in the solvents specified with a Rudolph Model 80 polarimeter. The uv spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer (Table I). The ir spectra of the compounds were determined in pressed KBr disks with a Perkin-Elmer Model 521 spectrophotometer, but the data are not presented. The nmr spectra were determined in DMSO-d_6 containing TMS as internal reference with a Varian A-60A spectrometer. Chromatographic analyses were carried out on thin layer plates of silica gel H (Brinkmann). The plates were developed using mixtures of $CHCl_3$ and MeOH in various proportions. The spots were detected by uv light after spraying the plates with Ultraphor (WT, highly concentrated) (BASF Colors & Chemicals, Inc., Charlotte, N. C.). Most of the chromatographic purifications were carried out on Mallinckordt SilicAR-7 with the solvents indicated; exceptions are noted. The analytical samples were dried over P_2O_5 at 0.07 mm for 16–20 hr at the temperatures given.

7-α- and 7-β-D-Ribofuranosylhypoxanthine (α- and β-5c). A.—A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide, prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (8.43 g, 16.7 mmol) and 9-propenylhypoxanthine (2.68 g, 15.2 mmol) in DMA (200 ml) was left for 4.5 days at room temperature and then evaporated to dryness *in vacuo*. The gummy residue became a solid upon trituration with Et_2O. A solution of the solid in MeOH (500 ml) was stirred and cooled in an ice bath while 4% aqueous $KMnO_4$ (100 ml) was added slowly. The resulting brown solid was filtered off and washed with MeOH. The combined filtrate and washings were evaporated to dryness *in vacuo*, and the residue was triturated with $CHCl_3$ (200 ml). The $CHCl_3$-insoluble material was removed by filtration, and the filtrate was dried over $MgSO_4$ and evaporated to dryness. The residue obtained was a white glass weighing 5.14 g. Purification was effected by column chromatography (4 cm × 20 cm) with $CHCl_3$–MeOH (97:3) as the eluent. The product, a mixture of 7-α- and 7-β-D-(2,3,5-tri-*O*-benzoyl)ribofuranosylhypoxanthines, was obtained as a white glass weighing 3.12 g.

A solution of the blocked nucleosides in MeOH (61 ml) containing NaOMe (581 mg, 10.8 mmol) was refluxed for 45 min, chilled in an ice bath, stirred with Amberlite IR-120 (H) ion-exchange resin to remove Na^+ ions, and then evaporated to dryness *in vacuo*. An aqueous solution of the residue was washed with $CHCl_3$ to remove methyl benzoate, and, after treatment with charcoal, was evaporated to dryness. The residue, a mixture of 7-α- and 7-β-D-ribofuranosylhypoxanthines, became a white solid after trituration with EtOH: yield 1.04 g (35%). This solid was found by nmr spectrometry to be a 1:1 mixture of α and β anomers.

The anomers were separated by chromatographing 953 mg of the mixture on an Avicel[26] column (3.5 cm × 45 cm) using H_2O as the eluent and collecting fractions of 5 ml. The fractions were examined by tlc on Avicel plates developed in H_2O; fractions rich in the faster moving α anomer were combined and evaporated to dryness. The residual white solid weighed 470 mg. There was also obtained, by combining the other fractions, 376 mg of a 1:1 mixture and 92 mg of a mixture rich in β anomer.

The mixture rich in α anomer was rechromatographed on an Avicel column, and 127 mg of nearly pure α anomer was obtained. Pure α-5c was precipitated as a gel, first from H_2O, and then from aqueous EtOH. It was dried at 100°: yield 35 mg; $[\alpha]^{25}D$ −78.1 ± 0.3 (*c* 0.99, H_2O); δ (ppm) 3.57 (m, C_5'-H_2), 4.20 (m, C_2'-H, C_3'-H, and C_4'-H), 5.37 (m, OH, NH), 6.66 (d, $J_{1'2'}$ = 4.4 Hz, C_1'-H), 8.00 and 8.39 (C_2-H and C_8-H).

Anal. Calcd for $C_{10}H_{12}N_4O_5$: C, 44.79; H, 4.51; N, 20.90. Found: C, 45.04; H, 4.67; N, 20.98.

B.—A solution of 5-*O*-benzoyl-D-ribofuranosyl bromide 2,3-cyclic carbonate, prepared from methyl 5-*O*-benzoyl-β-D-ribofuranoside 2,3-cyclic carbonate (3.23 g, 11.0 mmol), and 9-propenylhypoxanthine (10, 1.76 g, 10.0 mmol) in DMA (100 ml) was left at room temperature for 4 days and then evaporated to dryness *in vacuo*. Trituration of the residue with Et_2O gave a buff-colored solid. A solution of this solid in MeOH (500 ml) was stirred and chilled in an ice bath while 4% aqueous $KMnO_4$ (100 ml) was slowly added. The resulting brown precipitate was removed by filtration and washed with MeOH. The combined filtrate and washings were evaporated to dryness *in vacuo*, the residue was triturated with boiling $CHCl_3$ (300 ml), and the insoluble material was removed by filtration. The $CHCl_3$ filtrate was dried over $MgSO_4$ and evaporated to dryness. The colorless glass (1.1 g) obtained was purified by column chromatography (4 cm × 25 cm) eluting first with $CHCl_3$ (1650 ml) and then with 95:5 $CHCl_3$–MeOH (600 ml) to give a glass weighing 100 mg. This material was dissolved in MeOH (26 ml) containing NaOMe (54 mg, 1.0 mmol), and the solution was refluxed for 30 min, neutralized with glacial AcOH, and evaporated to dryness *in vacuo*. An aqueous solution of the residue was extracted with $CHCl_3$, which on evaporation to dryness gave a white solid.

The $CHCl_3$-insoluble material was extracted with MeOH, and the inorganic solid was removed by filtration. Evaporation of the filtrate gave a white glass (2.01 g). Cleavage of the cyclic carbonate was effected with MeOH (78 ml) containing NaOMe (162 mg, 3.0 mmol). A white solid was isolated as described above.

The combined solids from the two methoxide treatments were purified by column chromatography (2.5 cm × 40 cm); $CHCl_3$–MeOH (3:1) was the eluate. The product was obtained as a white solid (1.05 g), which was further purified by chromatography on two Avicel plates. The product was obtained as a white solid upon eluting the combined α and β bands with H_2O: yield 950 mg. This material was found by uv spectrophotometry to be 65% 5c, thus giving a yield of 23%. The nmr spectrum of this solid showed that it was a 2:1 mixture of α- and β-5c.

7-β-D-Ribofuranosylhypoxanthine (β-5c).—A solution of 7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-benzylhypoxanthine[3] (β-4a, 1.34 g, 2.00 mmol) in EtOH (200 ml) was hydrogenolyzed with 50 psi of H_2 in the presence of 5% Pd–C (400 mg) at 80° and for 18 hr. The catalyst was removed by filtration and washed with EtOH. The filtrate and washings were combined and evaporated to dryness *in vacuo*. A white glass weighing 1.22 g was obtained. Examination of this material by tlc showed that it was a mixture of 7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-hypoxanthine (β-5a) and 3-benzyl-2,3-dihydro-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)hypoxanthine.[3] Separation of the two products was effected by column chromatography using $CHCl_3$–MeOH (97:3) as the eluent. The ring-reduced compound was obtained first in a total yield of 662 mg (50%). The desired product (β-5a) was then obtained in a total yield of 393 mg (34%).

A solution of the blocked nucleoside β-5a in MeOH (21.3 ml) containing NaOMe (72.4 mg, 1.34 mmol) was refluxed for 0.5 hr, neutralized with AcOH, and evaporated to dryness *in vacuo*.

(23) M. Prystas and F. Sorm, *Collect. Czech. Chem. Commun.*, **31**, 1053 (1966).

(24) A comprehensive review of the Hilbert–Johnston reaction including its stereochemistry has recently appeared: J. Pliml and M. Prystas, *Advan. Heterocycl. Chem.*, **8**, 115 (1967).

(25) M. Prystas and F. Sorm, *Collect. Czech. Chem. Commun.*, **31**, 1035 (1966).

(26) American Viscose Division of FMC Corp., Newark, Del.

The residue was dissolved in H_2O (20 ml). The solution was washed with $CHCl_3$ (two 20-ml portions) and evaporated to 4 ml, and the precipitate that formed was collected by filtration: yield 74 mg (14% over-all yield).

The analytical sample of β-**5c** was obtained by recrystallization from MeOH. It was dried at 78°: mp 216–218°; $[\alpha]^{25}D$ +30.0 ± 1.3 (*c* 0.44, H_2O); δ (ppm) 3.68 (m, C_5'-H_2), 4.00 and 4.38 (m, C_2'-H, C_3'-H, and C_4'-H), 6.23 (d, $J_{1'2'}$ = 4.3 Hz, C_1'-H), 8.03 and 8.60 (C_2-H and C_8-H).

Anal. Calcd for $C_{10}H_{12}N_4O_5$: C, 44.79; H, 4.51; N, 20.90. Found: C, 44.75; H, 4.56; N, 20.65.

7-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)purine-6(1*H*)-thione (β-**6a**).—To a solution of 7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)hypoxanthine (β-**5a**, 1.46 g, 2.52 mmol) in pyridine (40 ml) was added P_2S_5 (2.47 g, 11.1 mmol). The resulting suspension was stirred and refluxed for 10 min to give a clear solution. Addition of 2 drops of H_2O created the desired orange turbidity, and reflux was continued for 4 hr. The orange, turbid mixture was chilled, and the liquid portion was decanted. The liquid was evaporated to a thin syrup. Both the orange solid and the thin syrup were added portionwise to 1 l. of boiling H_2O. Boiling was continued for 0.5 hr. The mixture was cooled, and the solid was collected by filtration. A $CHCl_3$ solution of the solid was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The yellow glass (1.35 g) obtained was purified by column chromatography (3.2 cm × 22 cm); EtOAc was the eluent. The product (β-**6a**) crystallized from C_6H_6–EtOAc: yield 612 mg (41%) [366 mg (25%) of β-**5a** was recovered].

An analytical sample of β-**6a** was obtained by recrystallization from C_6H_6–EtOAc. The sample was dried at 100°: λ_{max}, nm (ε × 10^{-3}), 0.1 *N* HCl 243 (34.9), 345 (17.4); pH 7 235 (39.2), 342 (15.0); 0.1 *N* NaOH 226 (34.9), 319 (15.0).

Anal. Calcd for $C_{31}H_{24}N_4O_7S$: C, 62.41; H, 4.05; N, 9.39. Found: C, 62.35; H, 4.06; N, 9.33.

7-β-D-Ribofuranosylpurine-6(1*H*)-thione (β-**6c**).—A solution of 7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)purine-6(1*H*)-thione (β-**6a**, 495 mg, 0.85 mmol) in dry MeOH (52 ml) containing NaOMe (108 mg, 2.0 mmol) was refluxed for 45 min, chilled in an ice bath, and treated with Amberlite IR-120 (H) ion-exchange resin to remove Na^+ ions. The resin was filtered off and washed with H_2O. The combined filtrate and washings were evaporated to dryness *in vacuo*. An aqueous solution of the residue was washed with $CHCl_3$. Concentration of the aqueous solution to 10 ml gave 14 mg of crystalline purine-6(1H)-thione that was collected by filtration. The gel that formed in the filtrate was collected by filtration. The solid weighed 91 mg and was found by tlc to be β-**6c** contaminated with purine-6(1*H*)-thione. The product was purified by preparative tlc; $CHCl_3$–MeOH (3:1) was the developing solvent. The product band was eluted with boiling MeOH. Evaporation of the MeOH gave a white solid, which was dried at 100°: yield 45 mg (19%); λ_{max}, nm (ε × 10^{-3}), 0.1 *N* HCl 221 (8.80), 331 (15.7); pH 7 221 (8.80), 328 (15.5); 0.1 *N* NaOH 230 (10.6), 318 (15.3).

Anal. Calcd for $C_{10}H_{12}N_4O_4S$: C, 42.25; H, 4.25; N, 19.71. Found: C, 42.20; H, 4.15; N, 19.78.

3-Benzhydryl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)hypoxanthinium Bromide (β-**7b**).—A solution of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide, prepared from 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose (4.77 g, 15.0 mmol), and 3-benzhydrylhypoxanthine (**3**, 3.02 g, 10.0 mmol) in DMA (105 ml) was kept at room temperature for 5 days and then evaporated to dryness *in vacuo*. Trituration of the residue with two 200-ml portions of Et_2O followed by two 200-ml portions of $CHCl_3$ produced a white powder: yield 2.51 g (39%).

The analytical sample was obtained by filtering a solution of the solid (100 mg) in 200 ml of 50% EtOH–$CHCl_3$ and then evaporation of the filtrate without heat. The white residue was triturated with $CHCl_3$ and collected by filtration before it was dried at room temperature: yield 88 mg; δ (ppm) 1.97, 2.03, and 2.13 (CH_3 of acetyl), 4.07 and 4.37 (m, C_5'-H_2, C_4'-H, and H_2O), 5.35 (C_4'-H), 5.77 (C_3'-H), 6.17 (d, $J_{1'2'}$-*ca.* 2 Hz, C_1'H), 7.44, 7.61 (Ph_2CH), 8.55 (C_2-H), 9.00 (C_8-H).

Anal. Calcd for $C_{29}H_{29}BrN_4O_8 \cdot 1.5H_2O$: C, 52.10; H, 4.82; N, 8.39. Found: C, 52.24; H, 4.61; N, 8.47.

The Mercuri Salt of 9-Propenylhypoxanthine (**9**).—To a solution of $HgCl_2$ (2.72 g, 10.0 mmol) in EtOH (200 ml) was added 9-propenylhypoxanthine (**10**, 3.52 g, 20.0 mmol). The resulting suspension was stirred while 1 *N* NaOH (20 ml) was slowly added. The resulting yellow color was quickly dispelled by heating the reaction mixture to the boiling point, and the white suspension was diluted with 400 ml of H_2O and chilled. The white solid was collected by filtration, washed with H_2O until free of Cl^- ions, and dried for 2.5 hr at 100° (0.07 mm) over P_2O_5: yield 5.14 g (90%).

The analytical sample was obtained by dissolving some of the compound in hot EtOH, filtering the solution, and evaporating it to dryness. The residue was dried at 100°.

Anal. Calcd for $C_{16}H_{14}HgN_8O_2 \cdot 1H_2O$: C, 33.77; H, 2.83; N, 19.69. Found: C, 33.90; H, 2.67; N, 19.13.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)hypoxanthine (**12**).—To 50 ml of Me_2CO was added 2,2-dimethoxypropane (0.17 ml) followed by 70% $HClO_4$ (0.22 ml). The resulting solution was stirred at room temperature for 5 min before adding 1-β-D-ribofuranosylhypoxanthine (β-**13c**, 128 mg, 0.48 mmol). The solid dissolved in 15 min, and stirring was continued for 20 min longer. The solution was neutralized with pyridine (0.25 ml) and evaporated to dryness *in vacuo*. To the residue suspended in H_2O (30 ml) was added concentrated NH_4OH (three 25-portions). The resulting solution was extracted with CH_2Cl_2 (two 30-ml portions) and then evaporated to 20 ml, whereupon a precipitate formed. The precipitate was collected by filtration: yield 99 mg (67%).

The analytical sample of **12** was obtained by recrystallization from H_2O. It was dried at 100°: mp 271–273°; λ_{max}, nm (ε × 10^{-3}), 0.1 *N* HCl 248 (9.44); pH 7 251 (8.90); 0.1 *N* NaOH 261 (9.60); δ (ppm) 1.30 and 1.52 (CH_3), 3.66 (d, C_5'-H), 4.19 (m, C_4'-H), 4.98 (m, C_2'-H and C_3'-H), 6.22 (d, $J_{1'2'}$ = 2.2 Hz, C_1'-H), 8.17 (C_8-H), 8.47 (C_2-H).

Anal. Calcd for $C_{13}H_{16}N_4O_5$: C, 50.65; H, 5.23; N, 18.17. Found: C, 50.59; H, 5.35; N, 18.37.

1-β-D-Ribofuranosylhypoxanthine (β-**13c**).[3] **A.**—A solution of 3-benzhydryl-1-β-D-(2,3,5-tri-*O*-acetyl)ribofuranosylhypoxanthinium bromide (β-**7b**, 1.62 g, 2.43 mmol) in 1 l. of EtOH was refluxed for 30 min and evaporated to dryness. A solution of the residue in $CHCl_3$ was dried over $MgSO_4$ and evaporated to dryness. A solution of this residue in dry MeOH (54 ml) containing NaOMe (222 mg, 4.12 mmol) was refluxed for 30 min, then stirred with Amberlite IR-120 (H) ion-exchange resin, and evaporated to dryness *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ solution was dried over $MgSO_4$ and evaporated to dryness. A gelatinous like residue was obtained that weighed 400 mg (38%). Spectral data indicate that this material is 9-benzhydryl-1-β-D-ribofuranosylhypoxanthine (β-**14c**). The analytical sample was obtained by precipitation from $CHCl_3$–petroleum ether. It was dried at 78°: δ (ppm) 3.67 (C_5'-H_2), 4.00 (m, C_4'-H, C_3'-H, and C_2'-H), 5 (broad m, OH), 6.15 (d, $J_{1'2'}$ = *ca* 4 Hz, C_1'-H), 7.08, 7.35 (Ph_2CH), 7.96 (C_8-H), and 8.68 (C_2-H).

Anal. Calcd for $C_{23}H_{22}N_4O_5$: C, 63.59; H, 5.10; N, 12.90 Found: C, 63.64; H, 4.91; N, 12.75.

The H_2O solution was evaporated to dryness giving a white glass that was chromatographically homogeneous. It crystallized from a small amount of H_2O on seeding: yield 200 mg of β-**13c**; δ (ppm) 3.68 (m, C_5'-H_2), 4.00 (m, C_2'-H, C_3'-H, and C_4'-H), 5.50 (broad m, OH and NH), 6.13 (d, $J_{1'2'}$ = 4.2 Hz, C_1'-H), 8.09 (C_8-H), 8.55 (C_2-H). This material is identical with that prepared from **2**.[3]

Evaporation of the aqueous filtrate to dryness produced a glass weighing 288 mg. This material was found by uv spectrophotometry to be 45% β-**13c**. The total yield of β-**13c** was 51%.

B.—To a cold solution of 9-propenyl-1-β-D-ribofuranosylhypoxanthine (β-**15c**, 368 mg, 1.20 mmol) in 0.5 *N* methanolic NaOH (20 ml) and H_2O (2 ml) was added dropwise 4% $KMnO_4$ solution (12 ml). The resulting brown precipitate was filtered off and washed with H_2O. The filtrate and washings were combined and stirred with Amberlite IR-120 (H) ion-exchange resin until pH 5 was attained. The resin was filtered off and washed with H_2O. The filtrate and washings were combined and evaporated to dryness *in vacuo*. A solution of the residue in MeOH was evaporated to dryness giving 197 mg of a cream-colored glass. This material was purified by preparative tlc on two Brinkmann silica gel F-254 plates; $CHCl_3$–MeOH (3:1) was the developing solvent. The product band was eluted with boiling MeOH. Evaporation of the MeOH solution gave the product (β-**13c**) as a white solid: yield 45 mg. This material was identical with that prepared as described in A above.

9-Propenyl-1β-D-ribofuranosylhypoxanthine (β-**15c**).—To an azeotropically dried, refluxing suspension of the mercury salt of 9-propenylhypoxanthine (**9**, 2.04 g, 3.60 mmol) and Celite (2 g) in 250 ml of xylene was added 50 ml of a dry xylene solution of 2,3,5-

TABLE I

ULTRAVIOLET SPECTRAL DATA

Compd	0.1 N HCl λmax (ε × 10⁻³)	0.1 N HCl λmin (ε × 10³)	pH 7 buffer λmax (ε × 10⁻³)	pH 7 buffer λmin (ε × 10⁻³)	0.1 N NaOH λmax (ε × 10⁻³)	0.1 N NaOH λmin (ε × 10⁻³)
1,3-Dibenzylhypoxanthinium bromide[a]	254 (10.2) 280[b]	236 (7.1)	245[b] 290–300 (0.55)		Unstable	
3-Benzhydryl-1-(tri-*O*-acetyl-β-D-ribofuranosyl)hypoxanthine bromide (7b)	253 (9.78) 280[b] (3.52)	238 (7.98)	255[b] (7.17) 290–310 (3.13)		Unstable	
3,7-Dibenzylhypoxanthine[c]	255.5 (10.1)	237 (7.06)	266 (11.8)	238.5 (5.8)	266 (11.7)	238 (5.5)
1-Benzylhypoxanthine[c]	249 (9.58)	228 (5.60)	251 (9.15)	230 (4.8)	261 (9.75)	239 (4.67)
1-Methylhypoxanthine[d]	249 (9.40)	219 (2.22)	250 (9.00)	224 (2.70)	2.60 (9.60)	236 (3.36)
1-β-D-Ribofurahosylhypoxanthine (13c)	249 (8.95)	223 (3.76)	251 (8.55)	228 (3.91)	261 (8.53)	238 (3.32)
1,9-Dibenzylhypoxanthine[c]	253 (10.6)	232 (6.2)	253 (10.4)	232.5 (5.5)	252 (10.4)	232.5 (5.7)
9-Benzhydryl-1-β-D-ribofuranosylhypoxanthine (β-14c)	253 (12.2)	234 (7.93)	253 (12.2)	234 (7.38)	253 (11.5)	237 (8.93)
1-Methyl-9-propenylhypoxanthine[d]	220 (18.4) 253[b]		225 (24.2) 254[b] 270[b]		225 (25.0) 254[b] 270[b]	
9-Propenyl-1-β-D-ribofuranosylhypoxanthine (15c)	223 (21.4) 253[b]		226 (26.3) 270[b]		226 (25.8) 270[b]	
7-α-D-Ribofuranosylhypoxanthine (α-5c)	252 (9.23)	226 (3.95)	257 (8.40)	229 (3.70)	263 (8.83)	230 (4.00)
7-β-D-Ribofuranosylhypoxanthine (β-5c)	252 (9.10)	226 (4.00)	256 (8.48)	229 (4.07)	263 (9.23)	229 (4.16)

[a] Data from ref 7. [b] Shoulder. [c] Data from ref 2. [d] Data from ref 9.

tri-*O*-benzoyl-D-ribofuranosyl bromide, prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (3.78 g, 7.5 mmol). The mixture was refluxed with stirring for 1 hr and then filtered. The filter cake was washed with boiling $CHCl_3$ (four 25-ml portions). The xylene filtrate was evaporated to dryness *in vacuo;* the residue was dissolved in $CHCl_3$ (100 ml); and this solution was combined with the $CHCl_3$ washings. The solution was washed with 30% KI (two 200-ml portions), then with H_2O (two 200-ml portions), dried over $MgSO_4$, and evaporated to dryness *in vacuo*. A solution of the crude blocked nucleoside was dissolved in MeOH (157.5 ml) containing NaOMe (405 mg, 7.5 mmol), refluxed for 30 min, neutralized with AcOH, and evaporated to dryness. A solution of the residue in 100 ml of H_2O was washed with $CHCl_3$ (50 ml), treated with charcoal, filtered, and then concentrated to 40 ml, whereupon a white solid crystallized, yield 418 mg (18%).

The analytical sample was obtained from a previous run by recrystallization from H_2O. It was dried at 78°: mp 168–170°; δ (ppm) 1.84 (m, CH_3), 3.32 (H_2O), 3.72 (C_5'-H), *ca.* 4.1 (m, C_2'-H, C_3'-H, and C_4'-H), 5.32 (broad m, OH), 6.16 (d, $J_{1'2'}$ = 3 Hz, C_1'-H), 8.37 (C_8-H), 8.75 (C_2-H). The AB portion of the ABX_3 absorption of the propenyl protons is observed as a complex multiplet between 6.1 and 7.4 ppm.

Anal. Calcd for $C_{18}H_{16}N_4O_5 \cdot 0.1H_2O$: C, 50.39; H, 5.23; N, 18.08. Found: C, 50.26; H, 5.46; N, 18.07.

Registry No.—α-5c, 19895-30-8; β-5c, 10280-01-0; β-6a, 20187-88-6; β-6c, 20187-89-7; β-7b, 20290-59-9; 12, 20187-90-0; β-13c, 20187-91-1; β-14c, 20187-92-2; β-15c, 20187-93-3.

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Deuterium Incorporation during the Conversion of 1-Amino-1-deoxy-D-fructose Derivatives to 5-(Hydroxymethyl)-2-furaldehyde[1]

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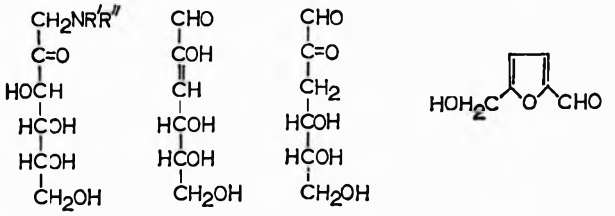
The formation of Amadori products (1-amino-1-deoxy-2-ketoses) and their subsequent decomposition to melanoidin polymers, furan derivatives, and colored substances is of considerable importance, forming the basis for the syndrome frequently referred to as the nonenzymatic browning reaction.[2] In acidic solution, Amadori products are known[3,4] to undergo decomposition with the production of 2-furaldehyde derivatives as the major monomeric reaction product. It has been suggested[4,5] that the mechanism of this decomposition involves a 1,2 enolization of the Amadori product (I), followed by a dehydration to give the enolic form (II) of a 3-deoxyglycosulose (III), or a Schiff base thereof. In subsequent steps it has been suggested[4] that II or III undergoes further dehydration to the 2-furaldehyde derivative (IV).

In this work, 1-amino-1-deoxy-D-fructose derivatives derived from *p*-toluidine, dibenzylamine, and morpholine were prepared[6] and their decompositon in acidic solution was studied. In both acetic acid and hydrochloric acid, the major monomeric reaction product was 5-(hydroxymethyl)-2-furaldehyde (IV). Yields of IV, determined spectrophotometrically,[7] were variable (see Experimental Section) and the use of acetic acid as a catalyst favored the formation of IV in the over-all reaction. This is in general agreement with the data reported by Gottschalk,[3] for a series of Amadori products composed of weakly basic amines.

In order to investigate the mechanism of the dehydration reaction, the Amadori products were converted

(1) Journal Paper No. 5584, Missouri Agricultural Experiment Station.
(2) T. U. Reynolds, *Advan. Food Res.*, **12**, 1 (1963).
(3) A. Gottschalk, *Biochem. J.*, **52**, 455 (1952).
(4) E. F. L. J. Anet, *Advan. Carbohyd. Chem.*, **19**, 181 (1964), and references therein.
(5) H. Kato, *Bull. Agr. Chem. Soc. Jap.*, **24**, 1 (1960).
(6) J. E. Hodge and B. E. Fisher in "Methods in Carbohydrate Chemistry," Vol. II, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press, New York, N. Y., 1963, p 99.
(7) J. F. Harris and coworkers, *Forest Prod. J.*, **X**, 125 (1960).

to IV in deuterium oxide solution using both acetic and hydrochloric acid as catalysts. Estimates of the amount of deuterium incorporated into IV during the conversion were made by proton signal diminution measurements of nmr spectra. A 60-MHz nmr spectra of a pure, crystalline sample of IV showed the aldehyde proton as a singlet at δ 9.53, the ring proton at position 3 as a doublet centered at δ 7.59 (J = 3 cps), the ring proton position 4 as a doublet centered at δ 6.78 (J = 3 cps), and the carbon-bound hydroxymethyl protons as a singlet at δ 4.69.



I II III IV

A comparison of the signal intensities at δ 4.69, 6.78, 7.59, and 9.53 indicated that only the latter two signals showed any variation in intensity during the various experiments and was taken to indicate that significant incorporation occurred only at position 3 and at the aldehydic carbon atom. Measurements (Table I) were made by a comparison of signal intensity at δ 4.69 with that from the proton in question and were determined to be accurate to ± 0.1 atom of deuterium per molecular position.

TABLE I

DEUTERIUM INCORPORATION INTO 5-(HYDROXYMETHYL-2-FURALDEHYDE DERIVED FROM 1-AMINO-1-DEOXY-D-FRUCTOSE DERIVATIVES IN DEUTERIUM OXIDE

Amine substituent	Acid[b]	Incorporation (%)[c] at aldehyde carbon	Incorporation (%)[c] at position 3
p-Toluidine	Acetic	23	77
p-Toluidine	HCl	0	0
Dibenzylamine	Acetic	75	75
Dibenzylamine	HCl	44	0
Morpholine[a]	Acetic	87	87

[a] The low yield (less than 4%) of 2-furaldehyde from this compound precluded a measurement in HCl. [b] In all cases, 2 *N* acetic or 1 *N* HCl was used as solvent at a reaction temperature of 100°. [c] These conversions were made in 90% deuterium oxide and the figures are not corrected for water initially contained by the solvent, nor for protons introduced from the acid catalysts or the carbohydrate hydroxyl groups.

Deuterium incorporation at the aldehyde carbon atom of IV is consistent with a reversible enolization of the Amadori product as a first step in the reaction, and differences in the extent of incorporation may be attributed to combinations of amine basicity, acid strength, and the reactivity of the enolic form. While incorporation at position 3 of IV might be due to either reversible 2,3 enolization of I or to reversible equilibration of II and III during the reaction, the finding that, under certain conditions, no detectable incorporation occurs clearly indicates that 3-deoxy-D-glucosulose (III) is not a necessary intermediate in the reaction.

3-Deoxyglucosuloses and their enolic derivatives have been suggested as intermediates in reactions such as the formation of metasaccharinic acids[8] from hexoses in alkaline solution and in the acidic dehydration of hexoses to 5-(hydroxymethyl)-2-furaldehyde,[9] as well as in the reaction considered above. It is interesting to note that recent isotope exchange experiments indicate that III likewise does not appear to be formed during the conversion of D-glucose or D-fructose to IV[10] under a variety of conditions, but the formation of metasaccharinic acid from D-glucose is consistent with III as an intermediate.[11]

The participation of III in the over-all dehydration reaction was further examined by the preparation of III[12] followed by its conversion to IV in deuterium oxide solution at the conditions used for the decomposition of the Amadori products. In both experiments, the resulting IV contained no carbon-bound deuterium.

Experimental Section

Materials and Methods.—Nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer at 60 MHz using deuterium oxide as solvent and sodium 3-(trimethylsilyl)propane sulfonate as the internal standard. Standard 5-(hydroxymethyl)-2-furaldehyde (IV) was a commercial sample once recrystallized from ether–hexane. Concentrations of IV in solution were determined by measurement at 283 mμ using a Beckman DB-G spectrometer on which IV had λ_{max} 283 mμ and ϵ 17,400. Total absorption at this wavelength was assumed to be due to IV, and calculations were made on the basis of an absorption of 1.0 = 9.1 mg/l. Dehydration products were qualitatively identified by thin layer chromatography using silica gel GF as the support and chloroform–acetic acid (9:1) as irrigant. Purity of Amadori products was determined by paper chromatography using butanol–pyridine–water (6:4:3) as irrigant. Aniline hydrogen phthalate[13] spray reagent was used for both thin layer and paper chromatographic visualizations.

Preparation of the Amadori Products.—These compounds were prepared by the procedures described by Hodge and Fisher.[6] The morpholino derivative had mp 143–44°, the *p*-toluidino derivative mp 151–52°, and the dibenzylamino derivative mp 165°. All three compounds ran as single spots on paper chromatograms.

Reactions of the Amadori Products in Acidic Solution.—A 3.0-g sample of 1-deoxy-1-toluidino-D-fructose was dissolved in 80 ml of water, and, after the addition of 10 ml of acetic acid, the solution was heated at 100°. At the end of 60 min, when spectral measurements indicated that a maximum yield (33%) had been reached, the solution was cooled to 25°, passed through a column containing Dowex 50 (hydrogen form), and evaporated to dryness at reduced pressure at 40°. The resulting brown solid, when examined by thin layer chromatography, showed the presence of IV as the major reaction product along with traces of an unknown component having an R_f approximately twice that of IV. A uv spectrum of this material in aqueous solution was superimposable with that of a known spectrum of IV, and a nmr spectrum of the material showed signals for all of the protons contained by IV. In this and all subsequent experiments, an approximate 30% loss in IV was observed during isolation. Parallel experiments using solutions of standard IV indicated that this was largely due to irreversible adsorption of IV on the ion-exchange resin. No attempt was made to quantitatively elute the product.

For decompositions in 1 *N* HCl, 3 g of Amadori product was dissolved in 80 ml of acid and heated at 100°. After 2 hr, when the yield of VII from 1-deoxy-1-toludino-D-fructose reached a maximum value of 15%, the solution was cooled and cation exchanged. The effluent was carefully neutralized with 10 *N* NaOH and evaporated to dryness. IV was identified as the major reaction product as above.

(8) J. C. Speck, Jr., *Advan. Carbohyd. Chem.*, **13**, 63 (1958).

(9) E. F. L. J. Anet, *Australian J. Chem.*, **18**, 240 (1965).

(10) M. S. Feather and J. F. Harris, *Tetrahedron Lett.*, 5807 (1968).

(11) M. S. Feather and J. F. Harris, Abstracts of Papers, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969.

(12) H. Kato, *Agr. Biol. Chem.*, **26**, 187 (1962).

(13) S. M. Partridge, *Nature*, **164**, 443 (1949).

The same procedures were followed for the remaining compounds, in which case the morpholino derivative gave a maximum yield of 3.6% in HCl after 6 hr and 15% in acetic acid after 6 hr, while the dibenzylamino derivative gave 30% yield in 6 hr in acetic acid and 21% in HCl after 2 hr.

Preparation and Acidic Degradation of 3-Deoxyglucosulose (III).—This material was prepared from *n*-butyl-D-glucosylamine as described by Kato.[9] A paper chromatographic examination of the syrupy product using *n*-butanol–acetic acid–water (4:1:1) as irrigant showed that it contained largely the glucosulose along with some contaminating glucose. When this preparation was heated at 100° for 1 hr in either 2 *N* acetic acid or 1 *N* HCl and the solutions worked up as described for the Amadori products, all the glucosulose was converted to IV, while parallel experiments showed that the yield of IV from D-glucose was less than 1%.

Conversions to VII in Deuterium Oxide.—The Amadori products and III were converted to IV in 90% deuterium oxide solution, either 2 *N* in acetic acid or 1 *N* in HCl, using the same procedures as described above. Following evaporation, the preparations were evaporated to dryness several times from 99% deuterium oxide and the spectra run in the usual way.

Registry No.—IV, 67-47-0.

Studies in the Ganglioside Series. II. Further Application of *N*-Dichloroacetylhexosaminyl Bromides to the Synthesis of Aminosaccharides[1,2]

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The synethesis of galactosaminyl-(1→6)-galactose by two different routes is reported. It involves condensation of bromide III with diketal IV, or with 1,2,3,4-tetraacetylgalactose. The protecting dichloroacetyl group, in addition to its removal by mild alkaline hydrolysis, can be directly converted into the acetyl group by catalytic hydrogenation.

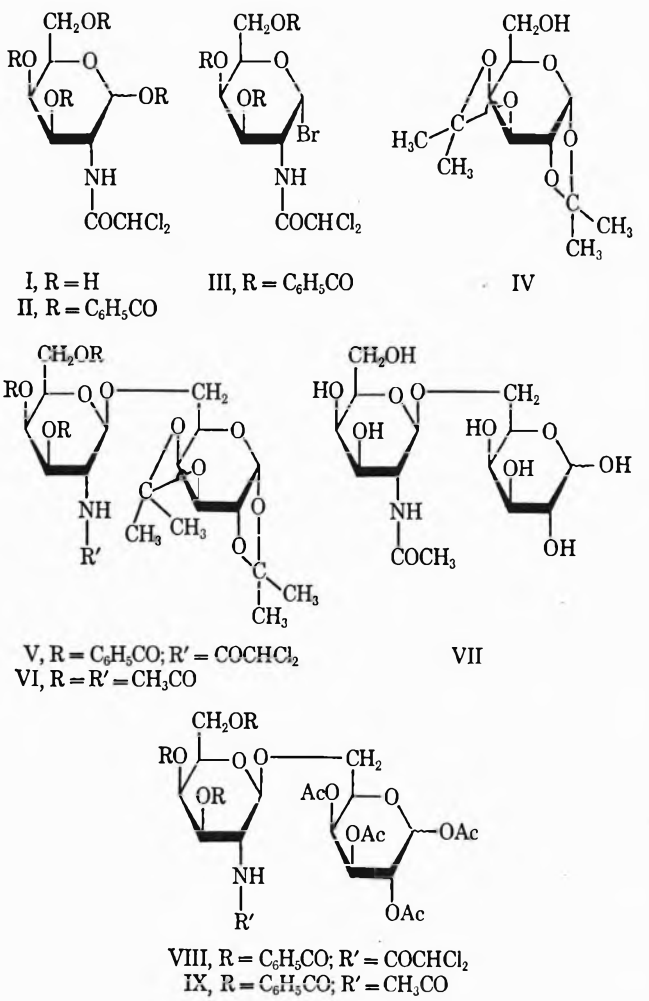
In paper I of this series[3] we described the synthesis of *N*-acetylglucosaminyl-(1→4)-galactose. *N*-Dichloroacetamido-2-deoxy-3,4,6-tri-*O*-benzoylglucopyranosyl bromide used in the Koenigs–Knorr reaction was found to be a reactive and highly stable compound which gave rise to the disaccharide in satisfactory yield. The dichloroacetyl group could be removed by 0.4 *N* aqueous methanolic barium hydroxide at room temperature.

As a preliminary attempt to employ this new type of bromide in the synthesis of galactosaminyl oligosaccharides we have now carried out the synthesis of 6-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-D-galactopyranose (VII) (Chart I). Oligosaccharides containing the hexosamine (1→6) hexose linkage have been found in human blood group substances.[4,5]

It is noteworthy that, although glucosamine and galactosamine differ only by the steric arrangement at C-4, the latter hexosamine displayed peculiar physical and chemical properties, and we encountered difficulties in the preparation of the key substances. Compound II was obtained in a lower yield as a result of incomplete benzoylation, while the bromide III, although it was chromatographically pure, could not be induced to crystallize. The bromide reacted smoothly with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (IV) in the presence of mercuric cyanide to give V in 90% yield. Lloyd and Roberts[6] have condensed the same diketal with 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide and obtained the substituted β-disaccharide in yields of 15–29%, depending on the solvent and the catalyst applied. After debenzoylation and removal of the dichloroacetyl group with barium hydroxide the diketal V was converted into the acteyl derivative VI.

The 1→6 linkage in oligasaccharides is reported to be the least susceptible to acid hydrolysis, in contrast to

CHART I



(1) This work was supported by the National Institutes of Health, Grant No. 425115.

(2) Part of the Ph.D. Thesis of A. J. Acher, The Weizmann Institute of Science.

(3) D. Shapiro, A. J. Acher, and E. S. Rachaman, *J. Org. Chem.*, **32**, 3767 (1967).

(4) W. P. Aston, A. S. R. Donald, and W. T. J. Morgan, *Biochem. Biophys. Res. Commun.*, **30**, 1 (1968).

(5) K. O. Lloyd and E. A. Kabat, *Carbohyd. Res.*, **4**, 165 (1967).

(6) P. F. Lloyd and G. P. Roberts, *J. Chem. Soc.*, 6910 (1965).

acetolysis.[7] However, in the present case it was observed that removal of the ketal groups by means of dilute sulfuric acid was accompanied by a rupture of the glycosidic bond to a considerable extent, thus leading to comparatively low yield of VII.

Alternatively, the bromide III was coupled with 1,2,3,4-tetra-*O*-acetylgalactose. The reaction proceeded satisfactorily and gave the disaccharide VIII in high yield. Kuhn and Kirschenlohr[8] condensed the same aglucon with the acetobromo derivative of glucosamine and obtained 6-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-D-galactose in a 16% yield.

Attempts to remove the dichloroacetyl group from VIII by hydrolysis with barium hydroxide entailed complete rupture of the glycosidic linkage. The sensitivity of the hexosaminyl-(1→6)-hexose bond to alkaline media has been reported in the literature.[4] It was eventually found that the N-dichloroacetyl group could be directly converted into the N-acetyl group by catalytic hydrogenation, giving IX in good yield. This result facilitates the synthesis of alkali sensitive hexosaminyloligosaccharides and thus enhances the usefulness of the dichloroacetyl group in the protection of the amine function.

Experimental Section[9]

2-Deoxy-2-dichloroacetamido-D-galactopyranose (I).—A stirred mixture of dried galactosamine hydrochloride (Mann Research Laboratories, 5 g), dried sodium dichloroacetate (10.4 g), and dichloroacetic anhydride (Eastman, 25 ml) was gradually warmed within 2 hr to 70°. This temperature was maintained for 6 hr. The dark syrup was allowed to cool and poured into ice–water (0.5 l.). After decantation, the remaining semisolid was dissolved in chloroform (300 ml) and the solution was washed with five 50-ml portions of water. The dried chloroform solution was shaken with charcoal (2 g) and the filtrate was evaporated *in vacuo* to constant weight. The residue, dried over phosphorus pentoxide, was dissolved in absolute methanol (150 ml), and the solution was treated with 1 *N* barium methoxide (3 ml) for 4 hr at −10°. The precipitated amide I was filtered and washed with cold absolute methanol. Crystallization from methanol (10 ml) and ethyl acetate (150 ml) at 2–5° yielded 5.5 g (81.6%) of mp 194–195°; $[\alpha]^{20}D$ +63.6° (c 1, water) after mutarotation from +75.3° (1 hr). The infrared spectrum showed bands at 3.0 (OH), 5.8, 6.45 (amide), 11.45 (galactopyranosyl ring) and 12.3 μ (CCl); tlc (benzene–methanol, 7:3), R (N-acetylgalactosamine) 1.6.

Anal. Calcd for $C_8H_{13}Cl_2NO_6$: C, 33.12; H, 4.52; Cl, 24.44. Found: C, 33.34; H, 4.50; Cl, 24.23.

2-Deoxy-2-dichloroacetamido-1,3,4,6-tetra-*O*-benzoyl-D-galactopyranose (II).—A warm solution of I (5 g) in pyridine (180 ml) was cooled with stirring to −10°, freshly distilled benzoyl chloride (16 ml) was added, and the mixture was allowed to stand at ambient temperature for 20 hr. The reaction product was poured into ice–water (500 ml) and the heavy oil, separated by decantation, was dissolved in methylene chloride (300 ml). The solution was shaken twice with cold 1.5 *N* hydrochloric acid, washed with water until neutral, dried over sodium sulfate, and evaporated *in vacuo* to constant weight. The residue was taken up with methylene chloride and purified by a column of silica gel (250 g, 0.05–0.2 mm, 70–325 mesh, ASTM Merck). The product II, eluted with methylene chloride–ether (998:2), was dissolved in ethyl acetate (3 ml) and, after the addition of isopropyl ether (200 ml) to the warm solution, allowed to crystallize at 2–5° overnight: yield 5 g (41%); mp 146–147°; $[\alpha]^{20}D$ +109.2° (c 1, chloroform); tlc (benzene–ether 9:1); R_f 0.45.

Anal. Calcd for $C_{36}H_{29}Cl_2NO_{10}$: C, 61.19; H, 4.14; Cl, 10.04. Found: C, 61.03; H, 4.00; Cl, 10.03.

2-Deoxy-2-dichloroacetamido-3,4,6-tri-*O*-benzoyl-α-D-galactopyranosyl Bromide (III).—To a stirred solution of the benzoate II (3.54 g, 5 mmol) in acetic anhydride (7 ml) cooled to −15° was added a cold 45% solution of hydrogen bromide in acetic acid (12.5 ml). After 15 min the temperature was allowed to rise, and the mixture was stirred at 18–21° for 7 hr. The yellow solution was then concentrated *in vacuo* (1 mm). For complete removal of the anhydride, the oily product was coevaporated with eight portions each of 8–10 ml of toluene at 25–30°. The white foamy residue showed on tlc (benzene–ether, 9:1) a single spot, R_{II} 1.1 (with no trace of II). This substance was directly used for the glycosidation reaction.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2-deoxy-2-dichloroacetamido-3,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-α-D-galactopyranose (V).—In the reaction flask containing the freshly prepared bromide III (5 mmol) were placed a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (IV)[10] (5.2 g, 20 mmol, $[\alpha]^{20}D$ −59.3°) in dry dichloroethane (50 ml) and mercuric cyanide (0.75 g, 29.5 mmol). The mixture, protected from moisture and light, was stirred at 35–40° for 7 days. The cooled reaction product was shaken thoroughly with ice–water and chloroform (200 ml). The organic layer was washed four times with water, dried, and evaporated *in vacuo* to constant weight. The residue was dissolved in methylene chloride and passed through a silica gel column (350 g, Davison, grade 950, 60–200 mesh). The product V was eluted with methylene chloride–ether (88:12), crystallized from ether and recrystallized from isopropyl alcohol. The yield of the pure glycoside amounted to 3.8 g (90.5%): mp 125°; $[\alpha]^{21}D$ −4.2° (c 1.2, chloroform); tlc (benzene–methanol, 9:1), R_{IV} 1.8. The ir spectrum showed bands at 5.8, 6.45 (amide), 11.2 (β-glycoside) and a weak absorption at 11.7 μ (α-glycoside). The nmr spectrum showed signals at τ 2–2.8 (15 aromatic protons), 4.15 (dichloroacetyl proton) and 8.69, 8.58, 8.47 (12 diisopropylidene protons).

Anal. Calcd for $C_{41}H_{43}Cl_2NO_{14}$: C, 58.30; H, 5.13; Cl, 8.40. Found: C, 58.06; H, 5.00; Cl, 8.65.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranose (VI).—A solution of V (3.2 g) in absolute methanol (20 ml), to which 1 *N* barium methoxide (0.5 ml) had been added at −15°, was allowed to stand in the refrigerator at 2° for 6 hr. For hydrolysis of dichloroacetyl group more 1 *N* barium methoxide (7.5 ml) and water (2 ml) were added, and the solution was allowed to stand at room temperature. After 24 hr, tlc (benzene–methanol, 2:1) indicated the completion of the reaction (R_I 0.7). The solution was neutralized with 2 *N* sulfuric acid and centrifuged and the supernatant was evaporated *in vacuo* to dryness. The amino sugar was further dried over phosphorus pentoxide for 48 hr, dissolved in pyridine (20 ml) and treated with acetic anhydride (15 ml) at room temperature overnight. After warming at 50° for 2 hr, the solution was concentrated *in vacuo* and coevaporated several times with toluene. The residue (2.4 g) was taken up with methylene chloride and passed through a silica gel column (150 g). Elution with methylene chloride–ethyl acetate (2:8) and crystallization from isopropyl alcohol gave 2.0 g (89.2%) of mp 142–144°; $[\alpha]^{20}D$ −62.5° (c 1, chloroform); tlc (ethyl acetate) R_V 0.4. The ir spectrum showed bands at 6.05, 6.5 (acetamide), 11.2 (β-glycoside), 11.45 μ (galactopyranosyl ring). The nmr spectrum showed signals corresponding to a ratio of 12 acetyl to 12 isopropylidene protons.

Anal. Calcd for $C_{26}H_{39}NO_{14}$: C, 52.96; H, 6.67; N, 2.38. Found: C, 52.69; H, 6.76; N, 2.25.

6-*O*-(2-Acetamido-2-deoxy-β-D-galactopyranosyl)-D-galactopyranose (VII).—The diketal VI (0.590 g) was refluxed with 0.1 *N* sulfuric acid (15 ml) for 75 min. The cooled solution was neutralized with barium carbonate, the precipitate was separated by centrifugation and the filtered supernatant was evaporated. The dried residue was acetylated in the usual manner, and the resulting crude product was chromatographed on a column of silica gel G (50 g). Three main fractions were collected. Methylene chloride–ether (8:2) eluted 160 mg of pentaacetylgalactose. The same solvents in a ratio of 2:8 eluted 150 mg of pentaacetylgalactosamine, which was followed by 280 mg (42%) of the peracetyl derivative of VII. The latter fraction still contained traces of pentaacetylgalactosamine and could not be induced to

(7) R. D. Guthrie and J. F. McCarthy, *Advan. Carbohyd. Chem.*, **22**, 21 (1967).

(8) R. Kuhn and W. Kirschenlohr, *Chem. Ber.*, **87**, 384 (1954).

(9) Details concerning the specification of chemicals and the type of apparatus for physical measurements used in this investigation are given in paper I of this series.

(10) A. L. Raymond and E. F. Schroeder, *J. Amer. Chem. Soc.*, **70**, 2785 (1948).

crystallize. The compound (200 mg) was dissolved in absolute methanol (10 ml) and was deacetylated with 1 *N* barium methoxide (0.1 ml) as described above. The solution was neutralized by stirring with Dowex 50W-X[8], H^+ form, and the residue resulting from the evaporation of the filtrate was crystallized from methanol–ether and recrystallized from water–methanol–ether (1:5:20): yield 80 mg of VII; mp 204–205°; $[\alpha]^{18}D$ +38.5° (c 0.9, water). The ir spectrum showed bands at 3.0 (OH), 6.1, and 6.45 (amide), 11.2 (β-glycoside), and 11.45 μ (galactopyranose ring); tlc (benzene–methanol, 2:3), *R* (lactose) 0.5 and *R* (galactose) 0.31.

Anal. Calcd for $C_{14}H_{25}NO_{11}$: C, 43.86; H, 6.57; N, 3.64. Found: C, 43.62; H, 6.75; N, 3.58.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-trityl-D-galactopyranose[8,11] was prepared by treating 6-*O*-trityl-D-galactopyranose[11] (10 g) with acetic anhydride (100 ml) in pyridine (300 ml) at room temperature for 48 hr. The reaction mixture was evaporated *in vacuo* and coevaporated several times with toluene. The product was eluted from a silica gel column with benzene–ethyl acetate, 150:30, and crystallized from isopropyl alcohol (10 ml) and hexane (100 ml): yield 10 g; mp 94–96°; $[\alpha]^{22}D$ −19.5° (c 1, chloroform); tlc (benzene–methanol, 8:2) R_f 0.85 and *R* (pentaacetylgalactose) 1.1, The nmr spectrum showed the expected ratio between aromatic and acetyl protons (15:12).

Anal. Calcd for $C_{33}H_{34}O_{10}$: C, 67.10; H, 5.80. Found: C, 67.09; H, 5.73.

1,2,3,4-Tetra-*O*-acetyl-D-galactopyranose[8] was now prepared in chromatographically pure form. After detritylation of the preceding compound with hydrogen bromide,[12] the residue resulting from the evaporation of the acetic acid *in vacuo* was chromatographed on a column of silica gel. Methylene chloride–ether (85:15) eluted an oil which showed a single spot on tlc, *R* (trityl derivative) 0.66. The nmr spectrum showed signals of four acetyl groups.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2-deoxy-2-dichloroacetamido-3,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-D-galactopyranose (VIII).—The reaction of 3 mmol of III with 4 mmol of 1,2,3,4-tetraacetylgalactose and 1.8 mmol of mercuric cyanide was carried out as described for V. The residue (3.1 g) resulting from the evaporation of the chloroform was dissolved in methylene chloride and passed through a silica gel column (160 g). The product was eluted with methylene chloride–ether (94:6). It was crystallized from ether and recrystallized from alcohol: yield 2.1 g (75.5%); mp 156–157°; $[\alpha]^{23}D$ +4.0° (c 1.1, chloroform); tlc (benzene–methanol, 9:1), R_V 0.89. The nmr spectrum showed signals of 15 aromatic, 1 dichloroacetyl, and 12 acetyl protons.

Anal. Calcd for $C_{43}H_{43}Cl_2NO_{18}$: C, 55.37; H, 4.65; Cl, 7.60. Found: C, 55.23; H, 4.62; Cl, 7.38.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-D-galactopyranose (IX).—A solution of VIII (0.400 g) in warm alcohol (150 ml) was hydrogenated with 10% palladium on charcoal at 55 psi during 48 hr. The residue resulting from the evaporation of the filtrate was purified by chromatography on silica gel (30 g), using methylene chloride–ether (85:15) as eluent: yield 0.275 g (75%); tlc, R_{VIII} 0.85. The nmr spectrum showed signals of 15 aromatic and 15 acetyl protons (one more acetyl group than in VIII, but no signal for a dichloroacetyl proton). On deacylation, the resulting product was identical in every respect with VII.

Registry No.—I, 20072-85-9; II, 20072-86-0; V, 20072-87-1; VI, 20072-88-2; VII, 20072-89-3; 1,2,3,4-tetra-*O*-acetyl-6-*O*-trityl-D-galactopyranose, 20072-90-6; VIII, 20072-91-7.

(11) M. Onuki, *Bull. Inst. Phys. Chem. Res.* (Tokyo), **12**, 614 (1933); *Chem. Abstr.*, **28**, 113 (1934).

(12) B. Helferich, L. Moog, and A. Junger, *Chem. Ber.*, **58**, 872 (1925).

2-Oxazolidinone Derivatives of D-Glucose and Glycolaldehyde[1]

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A 4-hydroxy-3-phenyl-5-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)-2-oxazolidinone structure (**3**) is established for the compound previously registered as 2-carbanilino-D-glucose. Hydrolysis of *N*-(2-*O*-phenylcarbamoyl-β-D-glucopyranosyl)piperidine first forms 2-*O*-phenylcarbamoyl-D-glucopyranose which rapidly converts into **3** in alkaline solution. The mechanism proposed for this cyclization requires attack of the amido nitrogen on the adjacent carbonyl group. Cyclization of glycolaldehyde carbanilate to 4-hydroxy-3-phenyl-2-oxazolidinone in high yield at pH 4 requires a free carbonyl group. Treatment of **3** with methanolic hydrogen chloride produces an α-D-glucofurano-2-oxazolidinone derivative, 5-(D-*glycero*-1,2-dihydroxyethyl)tetrahydro-6-hydroxy-3-phenylfuro[2,3-*d*]oxazol-2-(3*H*)-one, isolated as a triacetate. The structure is assigned by nmr analysis.

In 1952, Hodge and Rist[3] reported the synthesis of a compound provisionally identified as 2-*O*-phenylcarbamoyl-D-glucose. It was isolated from *N*-(2-*O*-phenylcarbamoyl-β-D-glucopyranosyl)piperidine (**1b**) after hydrolysis with hydrochloric acid and neutralization with silver carbonate. The product gave the empirical formula of a hexose monocarbanilate and was not characterized beyond noting an atypical minimal mutarotation and low reducing power toward hot Fehling solution.

Investigations published since 1952 have demonstrated that the phenylcarbamoyl ester is a poor blocking group. Although these esters are easily prepared in crystalline form and are stable to hydrolysis,[4,5] they undergo acyl migrations in basic solutions[6] and readily cyclize[7-9] by displacements of sensitive neighboring groups. Because the urethan radical is an ambident nucleophile, two cyclization paths are available. Although a basic environment promotes formation of a 2-oxazolidinone by preferential nitrogen participation, an acidic medium favors formation of an unstable anil by carbonyl oxygen participation. Such selective displacements have been exploited by Baker, *et al.*, and others[10] to introduce nitrogen, oxygen, or

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(2) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

(3) J. E. Hodge and C. E. Rist, *J. Amer. Chem. Soc.*, **74**, 1498 (1952).

(4) W. M. Hearon in "Methods in Carbohydrate Chemistry," Vol. 2, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press, New York, N. Y., 1963, pp 239–241.

(5) H. Bredereck, A. Wagner, G. Faber, W. Huber, G. Immel, and H. Kreiselmeier, *Chem. Ber.*, **91**, 2819 (1958).

(6) H. O. Bouveng, *Acta Chem. Scand.*, **15**, 87, 96 (1961).

(7) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967).

(8) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957).

(9) F. L. Scott and D. F. Fenton, *Tetrahedron Lett.*, 1681 (1964).

(10) B. R. Baker, K. Hewson, L. Goodman, and A. Benitez, *J. Amer. Chem. Soc.*, **80**, 6577 (1958); B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1057 (1964), and references cited therein.

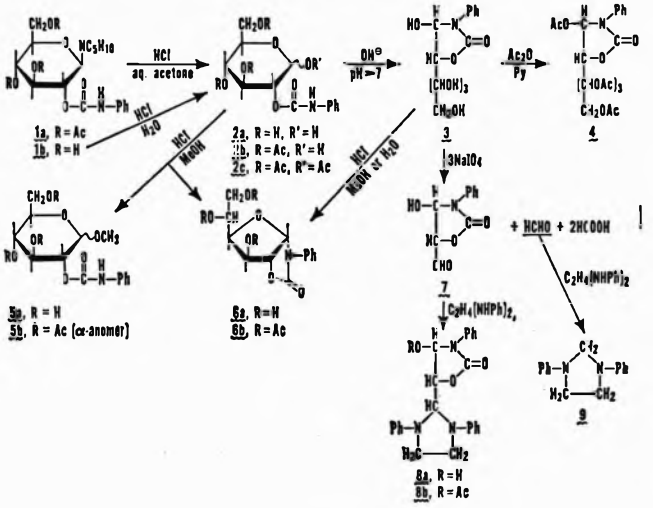
sulfur into selected nucleosides *via* cyclic intermediates (including 2-oxazolidinones) generated from neighboring urethano, ureido, or thiourethano substituents. Carbohydrate 2-oxazolidinones have also been prepared by indirect routes, often involving eliminations from carbobenzoxy derivatives of amino sugars.[11-17]

The literature cited above and the reported N cyclization of an acyloin during carbanilation[18] suggested that the compound of Hodge and Rist[3] may have undergone such a cyclization. The low reducing power, limited mutarotation, and absence of an amide II band in the ir spectrum of the compound supported this view. These unusual properties were sufficient to warrant further investigation.

Results and Discussion

The aqueous hydrolysis of **1b** (derived by deacetylation of **1a**) was monitored chromatographically (tlc and glpc) for 48 hr. Hydrolysis was complete within 24 hr and three products were identified (Scheme I).

SCHEME I



The major product in the acidic hydrolysate was the anticipated 2-*O*-phenylcarbamoyl-D-glucopyranose (**2a**). Smaller amounts of the oxazolidinone open-chain form (**3**) were present with still smaller amounts of the bicyclic oxazolidinone-D-glucofuranose derivative (**6a**). Increases in both temperature of hydrolysis and concentrations of acid caused a marked increase in he proportion of **6a** relative to **2a** and **3** (Table I).

The concentration of the reducing pyranose 2-carbanilate (**2a**) diminished slowly during the final 24 hr with a corresponding increase of **3**. At any given time the composition could be fixed by neutralizing the hydrolysis mixture with a weakly basic ion-exchange resin. The product mixtures were stable for 6 months or longer in the freezer, but they converted slowly into the oxazolidinone form (**3**) within several days at room temperature. If, however, the isolated product mixtures were made alkaline, a rapid increase in the rate of cyclization was noted. An 85% conversion into **3** was noted after 15 min at pH 11. This pH is quickly reached during neutralization of the hydrolysate with Ag_2CO_3; thereafter **3** was isolated.[3]

TABLE I

HYDROLYSIS OF **1b** AND VARIATION IN PRODUCT COMPOSITION[a]

Compd	Hydrolyst	Temp, °C	Time, hr	Base	Composn, % 2a[b]	3	6a	5a[b]
1b	0.1 *N* HCl	25	24	IR-45	83	10	8	
			48	IR-45	72	21	6	
			48	Ag_2CO_3	8	86	6	
1b	IR-120 (H^+) in aqueous acetone	25	20		67	32		
2a	H_2O	25	0.25	$NaHCO_3$	75	25		
			0.25	Na_2CO_3	15	80	5	
2a	0.5 *N* HCl	100	3	C_5H_5N	48	4	48	
2a	2% MeOH–HCl	25	48	IR-45			41	59
3	0.5 *N* HCl	100	3	IR-45		<5	>95	
3	2% MeOH–HCl	25	24	IR-45		<5	>95	

[a] Glpc of pertrimethylsilyl ethers at 200° with 3% JXR on Gas Chrom Q. [b] Sum of the α-D and β-D forms.

The identity of syrupy **2a** was confirmed by characterization of a crystalline fraction isolated after acetylation in pyridine. The physical properties and nmr spectrum were identical with those previously determined for a reference sample of 2-*O*-phenylcarbamoyl-1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**2c**).

The hexose monocarbanilate reported by Hodge and Rist[3] proved to be 4-hydroxy-3-phenyl-5-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)-2-oxazolidinone[19,20] (**3**). Structural assignments for **3** and its pentaacetate (**4**) were suggested by analyses of their nmr spectra. Application of double-resonance techniques established the spectral contributions of each alkyl chain proton. Chemical shifts and first-order coupling constants representing those portions of the spectra amenable to analysis are listed in Tables II and III.

TABLE II

CHEMICAL SHIFT DATA[a] FOR 2-OXAZOLIDINONE COMPOUNDS

Proton[b]	3[c]	4[d]	8a[c]	8b[d]	14a[c]	14b[d]
H-2′			3.99	3.93		
H-4	4.37	3.51	4.44	3.48	4.29	3.34
H-5	5.60	5.32	5.41	5.14	5.58	5.42
H-5′					5.95	5.76
H-6	6.20	4.42				
H-7	6.49[e]	4.51				
H-8		4.83				
H-9		5.76				
H-9′		5.91				
OH-4	3 17		3.35		3.18	
OH-6	4 97					
OH-7	5.48[e]					
OH-8						
OH-9						

[a] On τ scale. [b] Based on the systematic name. [c] In methyl sulfoxide-d_6. [d] In chloroform-*d*. [e] Complex multiplet.

(11) K. Heyns, R. Harrison, and H. Paulsen, *Chem. Ber.*, **100**, 271 (1967).
(12) K. Brendel, P. H. Gross, and H. K. Zimmerman, Jr., *Ann. Chem.*, **691**, 192 (1966).
(13) S. R. Kulkarni and H. K. Zimmerman, Jr., *ibid.*, **684**, 223 (1965).
(14) P. H. Gross, K. Brendel, and H. K. Zimmerman, *Angew. Chem. Intern. Ed. Engl.*, **3**, 379 (1964).
(15) P. H. Gross, K. Brendel, and H. K. Zimmerman, Jr., *Ann. Chem.*, **680**, 159 (1964).
(16) P. R. Steyermark, U. S. Patent 3,120,510 (Feb 4, 1964); *Chem. Abstr.*, **60**, 9349 (1964).
(17) B. R. Baker and J. P. Joseph, *J. Amer. Chem. Soc.*, **77**, 15 (1955).
(18) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **27**, 2927 (1962).

(19) An alternative name is (*R*)-1-*C*-(*N*-carboxyanilino)-D-glucitol γ-lactone.
(20) We are grateful to Dr. K. L. Loening, Director of Nomenclature, Chemical Abstracts Service, who suggested the systematic names of **3** and **6a**.

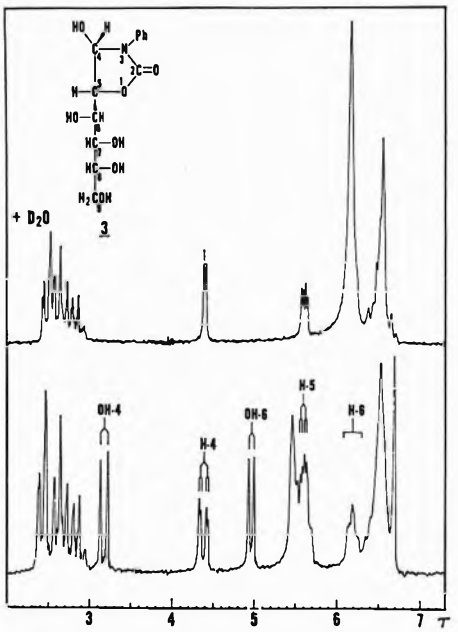


Figure 1.—The low-field portion of the 100-MHz spectrum of **3** in methyl sulfoxide-d_6 (bottom), and with added D_2O (top).

TABLE III

COUPLING CONSTANT DATA FOR 2-OXAZOLIDINONE COMPOUNDS

Coupling constant,[a] J	3[b]	4[c]	8a[b]	8b[c]	14a[b]	14b[c]
2′,5			1.8	1.3		
4,5	2	1	1.5	1.5	2	1.5
4,5′					6	5.5
5,5′					9.5	10.5
5,6	4.5	<1.5				
8,9		~3				
8,9′		~4				
9,9′		~12				
4,OH	9		8.5		8	
6,OH	6					

[a] In hertz. Numerical designations based on the systematic name. [b] In methyl sulfoxide-d_6. [c] In chloroform-*d*.

The nmr spectrum of **3** in methyl sulfoxide-d_6 is reproduced in Figure 1, before and after addition of D_2O. The integration curve (not included) indicated five hydroxyl groups. The two labeled groups and three others colocated with H-5 were verified by exchange with D_2O. The upper trace shows the simplified spectrum after exchange.

The presence of five acetyl groups in **4** was confirmed by acetyl analysis and by inspection of the integration curve in the methyl proton region of the nmr spectrum. Deshielding of all methine protons, but that of C-5 (C-2 of glucose chain), was observed owing to the presence of acetoxy substituents at these sites.

These spectra deny a 2-*O*-phenylcarbamoyl-D-glucose structure in pyranose, furanose, or acyclic *aldehydo* form. The ring forms would have yielded tetraacetates and the acyclic form a tetra- or hexaacetate. The absence of an amido proton in **3** or **4** was indicated by the lack of amide II bands in the ir spectra and the absence of NH resonances in the nmr spectra. N cyclization of the phenylcarbamoyl group with the adjacent reducing group of the isolated intermediate, 2-*O*-phenylcarbamoyl-D-glucopyranose (**2a**), formed a new hydroxyl group. This accounts for the fifth hydroxyl group observed. The deshielding of H-4 in the 2-oxazolidinone ring results from the combined effects of the vicinal OH-4 (or C-4 acetoxy) and N–Ph groups.

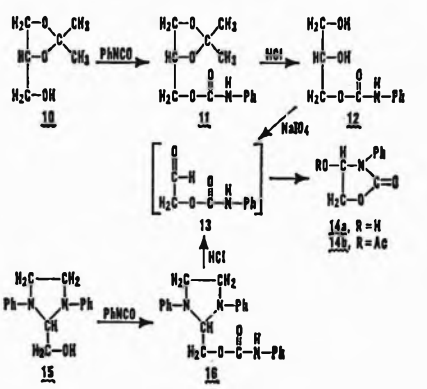
The small coupling constants for the vicinal ring protons (**3**, $J_{4,5}$ = 2 Hz; **4**, $J_{4,5}$ = 1 Hz) are consistent with a *trans* relationship on a five-membered 2-oxazolidinone ring; the configuration at C-4 is therefore *R*. These small values allow confidence in this assignment, although such decisions are questionable when the coupling constant exceeds 2 Hz.[21]

Each mole of **3** consumed 3 mol of $NaIO_4$, yielding 2 mol of formate and 1 mol each of formaldehyde and 5-*aldehydo*-4-hydroxy-3-phenyl-2-oxazolidinone (**7**). Both aldehydes were converted into stable 1,3-diphenyl-2-imidazolidinyl derivatives[22] and isolated. The formaldehyde derivative, 1,3-diphenyl-2-imidazolidine (**9**), was readily identified by comparison with the literature. The other, 4-hydroxy-5-(1′,3′-diphenyl-2′-imidazolidinyl)-3-phenyl-2-oxazolidinone (**8a**), and its derived monoacetate (**8b**) were examined by double-resonance nmr. All chain protons were identified and their coupling constants determined (Tables II and III). The ir spectra displayed the anticipated amide I, ester carbonyl, and phenyl (C=C skeletal and CH out of plane) absorptions. The absence of an amide II band confirmed the survival of the 3-phenyl-2-oxazolidinone ring structure.

The proposed mechanism for the conversion of **2a** into **3** requires that **2a** be in an acyclic form before an irreversible nucleophilic attack by the amido nitrogen. Two diastereoisomeric forms of **3** can be produced having H-4 and H-5 in a *cis* or *trans* relationship. The isolation of the *trans* form in high yield reflects the unfavorable steric effects in the *cis* form caused by eclipsing of the OH-4 and the tetrahydroxybutyl groups.

The carbonyl requirement was tested by preparing a model compound containing the requisite *O*-phenylcarbamoyl group adjacent to an aldehyde group. The model selected, *O*-phenylcarbamoylglycolaldehyde (**13**), is so reactive that it required generation *in situ* (Scheme II). Compound **13** was prepared by the action of aqueous $NaIO_4$ on 1-*O*-phenylcarbamoylglycerol (**12**). Concomitant cyclization was essentially complete in the weakly acidic solution, and racemic 4-hydroxy-3-phenyl-2-oxazolidinone (**14a**) was isolated in an overall yield greater than 80%.

SCHEME II



(21) E. Walton, F. W. Holly, G. E. Boxer, and R. F. Nutt, *J. Org. Chem.*, **31**, 1163 (1964), and references cited therein.

(22) H. W. Wanzlick and W. Löchel, *Chem. Ber.*, **86**, 1463 (1953).

Alternatively, glycolaldehyde was converted into 1,3-diphenyl-2-hydroxymethylimidazolidine (**15**), carbanilated, and hydrolyzed. Yields of **14a** were reduced, presumably because of decomposition reactions during hydrolysis.

The nmr spectra of **14a** and its monoacetate (**14b**) displayed the anticipated ABX patterns with the X proton (H-4 of **14a**) coupled to the hydroxyl proton (Table II). The BX coupling agrees with those values previously obtained for the *trans* vicinal ring protons (H-4, H-5), and the magnitude of AX agrees with the value reported for the comparable *cis* protons of **6b**.

The failure to isolate **13** at pH 4 stands in sharp contrast to the previously noted stability of **2a** at pH ≤ 7. Aqueous solutions of reducing carbohydrates generally contain small concentrations of *aldehydo* or *keto* forms. Glucose derivatives are predominately in a hemiacetal ring form at pH <7, although structural factors or high pH can produce more of the *aldehydo* form. Polarographic investigations have demonstrated that the carbonyl content increases markedly at alkaline pH values.[23,24] It is reasonable, therefore, to postulate that an elevated carbonyl content accounts for the sharp increase in the rate of N cyclization observed when solutions of **2a** are raised to pH >7.

Factors other than low free aldehyde content may retard the N cyclization of **2a** at pH ≤ 7, *e.g.*, steric effects, reduced nitrogen nucleophilicity, and formation of an intermediate acyloxonium species similar to that postulated for the anhydrous acid polymerization of 2,3,6-tri-*O*-phenylcarbamoyl-D-glucose.[25,26] These possibilities were not investigated. However, the spontaneous cyclization of **13** in a weakly acidic solution (pH 4) stands against lowered nitrogen nucleophilicity. Furthermore, the acyloxonium intermediate would form an unstable anil in aqueous solution with subsequent hydrolysis to produce aniline and a carbonate derivative. If anil formation represented a major reaction, large losses of **2a** would have occurred with an adverse effect on the over-all yields of **3**. No such losses were detected.

The role of **3** as a precursor in the formation of an oxazolidinone glucofuranose (**6a**) derivative was established by heating a pure sample in 0.5 *N* HCl while monitoring with tlc. During 3 hr, conversion into **6a** was essentially complete; thereafter, small amounts of degradation products formed. Use of 2% HCl in MeOH completely converted **6a** within 48 hr at 25° with less degradation (Scheme I). Purification by silica gel column chromatography yielded syrupy 5-(D-*glycero*-1,2-dihydroxyethyl)tetrahydro-3-phenylfuro-[2,3-*d*]oxazol-2-(3*H*)-one (**6a**) and from it a crystalline triacetate (**6b**). To designate its carbohydrate origin, **6a** also is named 4,5-(1′-amino-1′-deoxy-α-D-glucofuranosyl)-3-phenyl-2-oxazolidinone.

The structure of crystalline **6b** was deduced by nmr analysis (Figure 2). The chemical shifts and coupling constants are almost exactly duplicated in the spectrum of 3,4,6-tri-*O*-acetyl-1,2-*O*-isopropylidine-α-D-glucofuranose (**17**)[27,28] and the recently published spectra of analogous oxazolidinthiones[29,30] and imidazolidinones.[31] The nmr spectrum of **6a** is reproduced in Figure 2, and the data are compared with those for **17** in Table IV. A numbering system based on the six atoms of the glucose chain is used hereafter for the comparisons. Site numbers derived from the systematic name are given in parentheses either to achieve clarity or to allow other comparisons to be made.

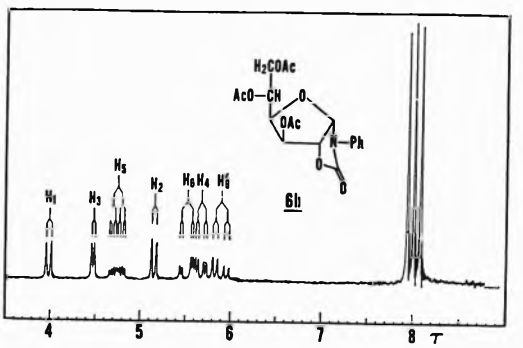


Figure 2.—The 100-MHz spectra of oxazolidinone glucofuranose triacetate (**6b**) in chloroform-*d*. For clarity, numbering is based on glucose.

TABLE IV

COMPARISON OF NMR DATA FOR **6b**[a] AND **17**[b]

Proton	Chemical shifts, τ		—Coupling constants,[c] Hz—		
	6b	**17**	*J*	**6b**	**17**
H-1	3.96	4.06	1,2	5.5	3.5
H-2	5.13	5.49	1,3	0.5	*d*
H-3	4.45	4.64	2,3	<0.5	<0.5
H-4	5.65	5.58	3,4	2.8	3.0
H-5	4.72	4.77	4,5	9.1	9.0
H-6[e]	5.50	5.39	5,6	2.4	2.0
H-6′[e]	5.86	5.84	5,6′	5.2	6.3
			6,6′	12.3	12.3

[a] Measured in chloroform-*d*. [b] Data of Abraham, *et al.*,[27] in chloroform at 60 MHz. [c] By direct measurement of peak spacings. [d] Not reported. [e] The proton on C-6 giving the higher field signal is designated H-6′.

The nearly identical $J_{2,3}$ (<0.5 Hz) and $J_{3,4}$ (2.8 Hz, 3.0 Hz) suggest similar symmetrical twist conformations for **6b** and **17**. In **6b** a smaller dihedral angle is predicted between H-1 and H-2 (H-4 and H-5 of the 2-oxazolidinone ring) on the basis of a larger coupling constant (5.5 Hz). This greater eclipsing would be caused by less flexibility in the 2-oxazolidinone ring than in the isopropylidene ketal ring of **17**.

After formation of the furanose ring of **6a** from **3**, the only configurational change indicated was at C-1 (C-4); H-1 was brought into the *cis* relationship with H-2 by ring fusion. The possibility that **3** could have undergone an unsuspected epimerization to a *manno* configuration during the original cyclization was banished by observing the minimal $J_{2,3}$ (<0.5 Hz) value of **6b**, indicating a *trans* relationship of H-2 and H-3. This relationship is characteristic of the *gluco*

(23) W. G. Overend, A. R. Peacocke, and J. B. Smith, *J. Chem. Soc.*, 3487 (1961).

(24) S. M. Cantor and Q. P. Peniston, *J. Amer. Chem. Soc.*, **62**, 2113 (1940).

(25) I. J. Goldstein and T. L. Hullar, *Advan. Carbohyd. Chem.*, **21**, 440 (1966).

(26) E. Husemann and G. J. M. Müller, *Makromol. Chem.*, **91**, 212 (1966).

(27) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, *Chem. Ind.* (London), 213 (1962); *J. Chem. Soc.*, 3699 (1962).

(28) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964).

(29) J. C. Jochims, A. Seeliger, and G. Taigel, *Chem. Ber.*, **100**, 845 (1967).

(30) J. Yoshimura and H. Hashimoto, *Bull. Chem. Soc. Jap.*, **41**, 261 (1968).

(31) H. Fritz, C. J. Morel, and O. Wacker, *Helv. Chim. Acta*, **51**, 569 (1968).

configuration. Epimerization at the other chain carbon atoms would be improbable.

Methanolysis of **2a** yields a mixture of compounds (Scheme I, Table I). The major component was **6a** isolated as **6b**. The other components were the methyl 2-*O*-phenylcarbamoyl-α,β-D-glucopyranosides (**5a**). A crystalline fraction isolated after acetylation of **5a** was identified as methyl 3,4,6-tri-*O*-acetyl-2-*O*-phenylcarbamoyl-α-D-glucopyranoside (**5b**) by comparison with an authentic sample.

An anomaly was observed in the ir spectra of derivatives containing the 2-oxazolidinone ring. Although the amide I carbonyl absorption usually falls in the 1740–1780-cm^{-1} range,[7] it is often observed at wavenumbers above 1760 cm^{-1}. However, this band was found between 1710 and 1735 cm^{-1} for the 4-hydroxy-3-phenyl forms (**3**, **8a**, **14a**). Substitution of the OH-4 caused a shift to higher frequencies. Participation as the furanose ring oxygen in **6a** raised the absorption band to 1750 cm^{-1}; acetylation caused an even greater shift to 1775–1780 cm^{-1} (**4**, **8b**). An alternative assignment of the higher frequency band as ester carbonyl is less probable, since carbohydrate acetates and carbanilates not containing 2-oxazolidinone rings have carbonyl absorptions at the usual 1740–1745 cm^{-1}.

Experimental Section

Nmr spectra were measured at 100 MHz on a Varian HA-100 spectrometer with tetramethylsilane (τ 10.0) as the internal standard. Chemical shifts and coupling constants are first-order values, measured directly from spectral spacings. Hydroxyl group resonances of compounds dissolved in methyl sulfoxide-d_6 were identified by exchange with added D_2O. Ir spectra were recorded with a Perkin-Elmer Model 621 spectrophotometer by the potassium bromide disk technique.

All samples for glpc were dissolved in pyridine and converted into their trimethylsilyl ethers approximately 18 hr before injection into an F & M research chromatograph, Model 700. The column was 4-ft, 1/8-in.-o.d. stainless steel tubing, packed with 3% JXR on Gas Chrom Q (trademark of the Applied Science Laboratories) (100–120 mesh). Operation was isothermal at 200° with helium as the carrier gas and flame ionization detection (Table V).

TABLE V

RELATIVE RETENTION VALUES OF 2-*O*-PHENYLCARBAMOYL-D-GLUCOSE AND DERIVATIVES[a]

Sample[b]	Anomer	Retention value[c]
2a	α-D	0.47
	β-D	0.61
3		0.53
5a	α-D	0.50
	β-D	0.55
6a		0.42
Maltose	β	1.00

[a] t/t_{std} at 200°, as pertrimethylsilyl ethers. [b] The order of appearance of the anomers is presumed to follow that observed for known compounds. [c] With 3% JXR on Gas Chrom Q.

Silica gel G (E. Merck, Darmstadt, Germany) was used for tlc without heat activation of the plates. Solvents were proportioned on a v/v basis. Reducing compounds were detected as red spots after spraying the chromatoplates with a saturated chloroform solution of 2,3,5-triphenyl-2*H*-tetrazolium chloride followed by 2.5 *N* alcoholic potassium hydroxide. Mild heat was applied when necessary. For column chromatography Baker Analyzed silica gel (J. T. Baker Chemical Co., Phillipsburg, N. J.) was used without pretreatment.

Melting points were determined in capillary tubes and are corrected. Solutions were evaporated below 40° under diminished pressure. Pyridine was removed from organic phases by repeated washes with 5% aqueous cupric sulfate.

***N*-(3,4,6-Tri-*O*-acetyl-2-*O*-phenylcarbamoyl-β-D-glucopyranosyl)piperidine (1a).**—The method of Hodge and Rist[3] was used to prepare **1a** (30 g) from β D-glucose pentaacetate (100 g). The pure compound was crystallized from methanol: mp 165–166° (lit. 164°);[3] nmr (pyridine-d_5) τ 2.11 (d, two Ph protons), 2.78 (m, three Ph protons), 4.31 (m, H-3), 4.52 (m, H-2), 4.64 (m, $J_{4,5}$ = ~10 Hz, H-4), 5.49 (pair of doublets, $J_{5,6}$ = 5 Hz, H-6), 5.68 (m, $J_{6,6'}$ = 2.8 Hz, $J_{6,6'}$ = 12.5 Hz, H-6'), 5.72 (d, $J_{1,2}$ = 8.5 Hz, H-1), 6.16 (m, H-5), 6.82 (m, 2 α protons, piperidine), 7.38 (m, 2 α′ protons, piperidine), 7.98–8.02 (m, three CH_3), 8.62 (m, 6 β, γ protons, piperidine).

***N*-(2-*O*-Phenylcarbamoyl-β-D-glucopyranosyl)piperidine (1b).**—An 18-g portion of **1a** was converted into **1b** by deacetylation in methanolic ammonia. One recrystallization from methanol gave 12.6 g of pure **1b**, mp 152–154° (lit. mp 153°).[3]

4-Hydroxy-3-phenyl-5-(D-*arabino*-1,2,3,6-tetrahydroxybutyl)-2-oxazolidinone (3).—A 9.5-g sample of **1b** was dissolved in 380 ml of 0.1 *N* HCl and held at room temperature. Tlc monitoring (5:1 ethyl acetate–methanol) indicated complete hydrolysis within 24 hr and no further changes during another 24 hr. The clear solution was neutralized by stirring 15 min with silver carbonate (10 g of Malinckrodt AR) then filtered. Residual silver salts were removed by treating the filtrate with 5 ml of pyridine and sweeping with hydrogen sulfide. The clear solution was reduced to one-half the original volume after filtration and extracted with three 100-ml portions of diethyl ether. After further evaporation to a thin syrup, **3** was again extracted with diethyl ether and dissolved in 99.5% ethanol. A final evaporation produced crude solids, which upon being twice recrystallized from 4:1 ethyl acetate–ethanol yielded 6.1 g (78%) of **3**: mp 166–167.5°; $[\alpha]^{20}D$ +42 → 46° (*c* 0.5, 50% aqueous CH_3OH); ir (KBr) 1710 (amide I C=O), 1600, 1500, 760, 690 cm^{-1} (Ph); for nmr data see Figure 1 and Tables II and III.

4-Acetoxy-3-phenyl-5-(D-*arabino*-1,2,3,6-tetraacetoxybutyl)-2-oxazolidinone (4).—A 1-g sample of **3** was dissolved in 50 ml of cold pyridine and mixed with 5 ml of acetic anhydride. After 12 hr at 0° and 36 hr at room temperature, the product was isolated from ethyl acetate. Two crystallizations from 95% ethanol produced **4**: mp 105–106°; $[\alpha]^{20}D$ +47° (*c* 0.55, $CHCl_3$); ir (KBr) 1780 (amide I C=O), 1745 (ester C=O), 1595, 1500, 685 cm^{-1} (Ph); for nmr data see Tables II and III.

Anal. Calcd for $C_{22}H_{27}NO_{12}$: C, 54.22; H, 5.34; N, 2.75; acetyl, 42.2. Found: C, 54.08; H, 5.37; N, 2.74; acetyl, 42.6.[32]

Reaction of 3 with $NaIO_4$. A. Reaction Stoichiometry.—Two samples of **3** (0.1805 and 0.0645 g) was dissolved in 25-ml portions of deionized water. Each solution was mixed with 25 ml of 0.091 *M* $NaIO_4$ and held in the dark at 25°. Aliquots (10 ml) were titrated at 5, 60, 120, and 240 min against 0.105 *M* $Na_2S_2O_3$. Reaction was complete within 5 min with no further periodate uptake for 4 hr. The periodate consumed was 2.98 and 2.80 mol/mol of **3**. Formic acid was determined titrimetrically after 6 and 22 hr, averaging 1.95 mol/mol of **3**. The presence of formaldehyde was indicated by chromotropic acid and verified by isolation in a derivative form (**9**) described below.

B. 5-*aldehydo*-4-Hydroxy-3-phenyl-2-oxazolidinone (7).—A solution containing 1 g of **3** and 2.5 g of $NaIO_4$ in 250 ml of water was allowed to react in the dark for 2 hr at 25°. The solution was concentrated to dryness with 99.5% ethanol so as to remove any residual water. The final solids were extracted serially with 100-ml portions of hot ethyl acetate, acetone, and ethanol. The bulk of the products was recovered from the ethyl acetate extract. A tlc examination (ethyl acetate) of the combined product mixture confirmed that **3** had reacted completely.

The entire product mixture was dissolved in 50 ml of methanol containing 2.6 g of *N*,*N*′-diphenyl-1,2-diaminoethane[22] and 1.4 ml of 50% aqueous acetic acid. The flask containing the solution was stoppered, immersed in a 60° water bath for 1 hr, and then stored 2 days at −5°. After the solids were collected, an examination by tlc (12:1 chloroform–acetone) revealed formic acid and two other components. One of the other components was the formaldehyde derivative, 1,3-diphenyl-2-imidazolidine (**9**). Crystallization from warm methanol yielded 0.23 g of **9**. Comparison with an authentic sample proved the identity: mp 125–

(32) M. L. Wolfrom and A. Thompson in "Methods of Carbohydrate Chemistry," Vol. 1, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press, New York, N. Y., 1962, p 448.

127°, mixture melting point undepressed, identical R_f on tlc plates. The major component (7) was isolated as follows.

Isolation of 7 as 4-Hydroxy-5-(1′,3′-diphenyl-2′-imidazolidinyl)-3-phenyl-2-oxazolidinone (8a).—The original liquors and mixed solids were combined, evaporated, and fractionated on a silica gel column packed and irrigated with 12:1 chloroform–acetone. The fraction containing **8a** (1.4 g, 72%) also had traces of the original reagent. However, three recrystallizations from methanol gave the pure product: mp 175–177°; $[\alpha]^{20}D$ +57.4° (c 1.06, pyridine); ir (KBr) 3440 (OH), 1735 (amide I C=O), 1595, 1500, 690 cm^{-1} (Ph); for nmr data see Tables II and III.

Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; N, 10.47. Found: C, 71.94; H, 5.97; N, 10.38.

Acetylation of 8a.—A 650-mg sample of **8a** was dissolved in 10 ml of cold pyridine and mixed with 1 ml of acetic anhydride. After 24 hr at room temperature, the product was isolated and recrystallized twice from 99.5% ethanol, mp 142.5–143.5°.

This derivative, 4-acetoxy-5-(1′,3′-diphenyl-2′-imidazolidinyl)-3-phenyl-2-oxazolidinone (**8b**), was unstable in a chloroform solution and decomposed within several weeks. In the solid state it remained unchanged for 6 months; for nmr data see Tables II and III.

Anal. Calcd for $C_{26}H_{25}N_3O_4$: C, 70.41; H, 5.68; N, 9.47. Found: C, 70.57; H, 5.92; N, 9.45.

Hydrolysis of 1b under Varying Conditions. A. Time.—A 2.5-g sample of **1b** was dissolved in 100 ml of 0.1 *N* HCl and held at 25°. Aliquots (25 ml) were removed after 24 and 48 hr, neutralized with Amberlite IR-45 resin (Malinckrodt), and evaporated to a thin syrup. A portion of each sample was converted into the pertrimethylsilyl ether form and analyzed by glpc (Table I). Three compounds (four peaks) were detected and later identified as **2a** (α and β forms), **3**, and **6a**. The decrease in the concentration of **2a** with an equivalent rise in that of **3** is in agreement with Scheme I.

B. Neutralization with Ag_2CO_3.—The balance of the hydrolysis solution (A) was neutralized with silver carbonate and treated as described earlier. The solution was concentrated, analyzed (Table I), and afforded pure **3** (0.6 g) by crystallization.

C. Use of Ion-Exchange Resin.—Duplicate 3-g samples of Amberlite IR-120 (H^+) resin were added to two previously prepared solutions containing 1 g of **1b** in 100 ml of 50% aqueous acetone. The first was stirred 20 hr at 25°, filtered, and concentrated. Glpc (Table I) showed **2a** and **3** in approximately a 2:1 ratio with trace amounts of **6a**. The duplicate mixture was stirred at reflux for 30 min to produce **2a**, **3**, and **6a** in approximately equal amounts (tlc estimation).

2-*O*-Phenylcarbamoyl-α,β-D-glucopyranose (2a).—A 5-g sample of **1b** was dissolved in 200 ml of 0.1 *N* HCl and allowed to stand 36 hr at 25°. The solution was neutralized with Amberlite IR-45 resin, the filtrate extracted twice with 100-ml portions of diethyl ether, and the extract evaporated to a thin syrup. All efforts to crystallize this syrup failed. Tlc examinations confirmed that **2a** was the major component and that 6-month storage in the freezer produced no change.

Conversion of 2a into 3 by $NaHCO_3$ and Na_2CO_3.—Duplicate 75-mg portions of crude **2a** were dissolved in 5 ml of water containing 50 mg of $NaHCO_3$ (pH 8.1) or Na_2CO_3 (pH 11.4) and held 15 min at 25°. Excess acetic acid was added to each, and both samples were evaporated to dryness. The results of glpc analysis are summarized in Table I demonstrating the high pH required for the conversion in to **3**.

Acetylation of 2a.—A 1-g sample of **2a** was dissolved in 100 ml of cold pyridine containing 5 ml of acetic anhydride. After 48 hr, the product was isolated and crystallized from 95% ethanol. After an additional recrystallization, the ir and nmr spectra were identical, and the mp 197–199° was undepressed on admixture with authentic 1,3,4,6-tetra-*O*-acetyl-2-*O*-phenylcarbamoyl-α-D-glucopyranose (**2c**).

1,3,4,6-Tetra-*O*-acetyl-2-*O*-phenylcarbamoyl-α-D-glucopyranose (2c).—A 4-g sample of **1a** was dissolved in 50 ml of acetone and 10 ml of 1 *N* HCl. Hydrolysis was complete after the mixture was left overnight at 25° as judged by tlc examination (7:1 chloroform–acetone). The major component, 3,4,6-tri-*O*-acetyl-2-*O*-phenylcarbamoyl-α,β-D-glucopyranose (**2b**), weighed 1.5 g after purification on a silica gel column (1:1 ethyl acetate–benzene). The syrupy **2b** was acetylated in cold pyridine containing acetic anhydride and crystallized from 95% ethanol: mp 199–200.5°; $[\alpha]^{20}D$ +109° (c 0.5, $CHCl_3$); ir (KBr) 1750 (C=O ester and amide I), 1540 (amide II), 1595, 1495, 760, 695 cm^{-1} (Ph); nmr (chloroform-*d*) τ 2.78 (m, five Ph protons), 3.58 (d, $J_{1,2}$ = 3.7 Hz, H-1), 4.50 (m, $J_{3,4}$ = 9.5 Hz, H-3), 4.81 $J_{4,5}$ = ~9 Hz, H-4), 4.95 (m, $J_{2,3}$ = 10 Hz, H-2), 5.80 (m, H-6, H-6′), 5.97 (m, H-5), 7.87–8.03 (four CH_3).

Anal. Calcd for $C_{21}H_{25}NO_{11}$: C, 53.96; H, 5.39; N, 3.00; acetyl, 36.8. Found: C, 54.16; H, 5.56; N, 2.95; acetyl, 37.2.

2,3-*O*-Isopropylideneglycerol (10).—A mixture containing 18.5 g of glycerol, 60 ml of dry acetone, 11 g of anhydrous cupric sulfate, and 0.1 ml of concentrated H_2SO_4 was placed in a 250-ml round-bottomed flask and vigorously shaken 24 hr. The supernatant liquid was mixed with an equal volume of benzene, decanted, and dried over anhydrous potassium carbonate. The solution was mixed with 2 ml of pyridine and evaporated to a clear syrup (20 g, 73%) of satisfactory purity.

2,3-*O*-Isopropylidene-1-*O*-phenylcarbamoylglycerol (11).—A solution containing 20 g of **10** in 100 ml of pyridine was cooled to 0° and treated with 16 ml of phenyl isocyanate. After the solution stood 18 hr at 25°, 5 ml of water was added and the product isolated from ethyl acetate. Tlc (4:1 benzene–ethyl acetate) showed only traces of substances other than **11**. Evaporation yielded a tan syrup that spontaneously crystallized. Charcoal decolorization and crystallization from hexane gave the final product (31 g, 82%), mp 59–61° (lit.[33] mp 56–57°). Spots on the tlc plates were visualized either by exposure to iodine vapor or by spraying with water.

1-*O*-Phenylcarbamoylglycerol (12).—A 15-g sample of **11** was dissolved in 100 ml of acetone, 25 ml of water, and 1 ml of concentrated HCl, and then the solution refluxed 1 hr. Tlc (3:1 benzene–ethyl acetate) showed complete hydrolysis. After excess sodium acetate was added, the mixture was evaporated to a small volume and then dissolved in 200 ml of water. All colored material was removed by extraction with two 100-ml portions of diethyl ether. The aqueous layer was reconcentrated, taken up in 100 ml of acetone, and filtered. Evaporation afforded 11.5 g of syrupy product essentially free of impurities, assumed to be **12**.

4-Hydroxy-3-phenyl-2-oxazolidinone (14a).—A 4-g portion of **12** was dissolved in 400 ml of water containing 4 drops of glacial acetic acid and 5.3 g of $NaIO_4$. After 4 hr in the dark at 25°, the solution was evaporated to dryness and extracted with 250 ml of hot acetone. The acetone solution was cooled, filtered, evaporated to dryness, and extracted with three 50-ml portions of diethyl ether. The residual **14a** was washed with hexane and dried; it weighed 2.75 g (80%). The ether extract weighed 0.8 g of which **14a** was the major component admixed with formaldehyde and colored materials. Recrystallization from water gave pure **14a**: mp 116–117.5°; ir (KBr) 3420 (OH), 1715 (amide I C=O), 1595, 1495, 755, 690 cm^{-1} (Ph); for nmr data see Tables II and III.

Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.49; H, 5.01; N, 7.79.

4-Acetoxy-3-phenyl-2-oxazolidinone (14b).—A 2-g sample of **14a** was dissolved in a mixture containing 20 ml of pyridine, 10 ml of ethyl acetate, and 3 ml of acetic anhydride; the solution was left overnight at room temperature. Pure **14b** was crystallized from methanol–water: mp 69–71°; for nmr data see Tables II and III.

This compound, unstable at room temperature, eliminates acetic acid within several hours. Decomposition in chloroform-*d* was complete within 2 weeks. The solution then showed a two-proton multiplet at τ 3.10 and the CH_3 singlet of acetic acid at τ 7.95. The ABX system originally observed for **14b** could not be detected.

1,3-Diphenyl-2-hydroxymethylimidazolidine (15).—Dimeric glycolaldehyde (2.0 g) was dissolved in 200 ml of methanol containing 10.4 g of *N*,*N*′-diphenyl-1,2-diaminoethane and 3.0 ml of 50% aqueous acetic acid. The solution was heated in a closed flask for 2 hr at 60°, and then evaporated to solids under reduced pressure. This mixture was dissolved in methanol and stored 2 days at −5°. The precipitate, after being collected and washed twice with cold methanol, yielded 7.4 g (82%) of **15**. Tlc (10:1 chloroform–acetone) showed the product to be essentially homogeneous. Recrystallization gave pure **15**: mp 107–110°.

Carbanilation of 15.—A 5.5-g sample of **15** was dissolved in a solution containing 50 ml of benzene, 10 ml of pyridine, and 2

(33) V. A. Welch and P. W. Kent, *J. Chem. Soc.*, 2266 (1962); prepared in three steps from **10**.

ml of phenyl isocyanate. The product, isolated after 18 hr at room temperature, was 6.4 g of the monocarbanilate (16). Tlc (ethyl acetate–benzene 1:9 or methanol–benzene 1:9) showed complete reaction. After two recrystallizations from 99.5% ethanol, 16 had mp 122–124°.

Anal. Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 73.94; H, 6.19; N, 11.28.

Hydrolysis of 16.—A 1-g sample of 16 was dissolved in 25 ml of 1,2-dimethoxyethane and treated with 5 ml of 6 *N* HCl. A heavy precipitate formed in the flask, which was stoppered and shaken 1 hr. The mixture was diluted with an equal volume of acetone and filtered; the solids were rinsed with additional acetone. The filtrate was neutralized with $NaHCO_3$, refiltered, and evaporated to dryness. Extraction with 100 ml of hot acetone and filtration removed the residual salts. The filtrate was reconcentrated, diluted with 100 ml of water, and decolorized with charcoal. Filtration and concentration to 20 ml produced **14a** (0.150 g, 31%), mp 116–117°.

5-(D-*glycero*-1,2-Dihydroxyethyl)tetrahydro-6-hydroxy-3-phenylfuro[2,3-*d*]oxazol-2-(3*H*)-one (6a).—Crystalline **3** (5.0 g) was dissolved in 200 ml of methanol, treated with 3 ml of acetyl chloride, and stored 24 hr in the dark at 25°. The colorless solution was neutralized with Amberlite IR-45 resin, filtered, and concentrated. Tlc examination (5:1 ethyl acetate–methanol) showed complete conversion into **6a**. Quantitation by glpc gave the results shown in Table I. Attempts to crystallize **6a** from a variety of solvents were unsuccessful.

Aqueous Production of 6a.—A 0.5-g sample of **3** was dissolved in 50 ml of 0.5 *N* HCl and heated 3 hr at 100°. The sample was analyzed by glpc after isolation (Table I) and found to duplicate the methanolysis results.

6-Acetoxy-5-(D-*glycero*-1,2-diacetoxyethyl)tetrahydro-3-phenylfuro[2,3-*d*]oxazol-2-(3*H*)-one (6b).—A pyridine solution (50 ml) containing **6a** (2 g) and acetic anhydride (5 ml) was held at 0° for 48 hr and the product was isolated from ethyl acetate. After two recrystallizations from 95% ethanol, **6b** gave mp 130.5–131.5°; $[\alpha]^{20}D$ +44.9° (*c* 0.55, $CHCl_3$); ir (KBr) 1770 (amide I C=O), 1735 (ester C=O), 1600, 1500, 755, 690 cm^{-1} (Ph); for nmr data see Figure 2 and Table IV.

Anal. Calcd for $C_{19}H_{21}NO_9$: C, 56.02; H, 5.20; N, 3.44. Found: C, 56.31; H, 5.40; N, 3.42.

Methyl 2-*O*-Phenylcarbamoyl-D-glucopyranoside (5a).—A 1-g sample of **2a** was dissolved in 50 ml of 2% methanolic HCl and held 48 hr at 25°. Tlc (20:3 ethyl acetate–methanol) showed two compounds, **6a** and **5a**. Results of glpc quantitation are listed in Table I. No change in product composition was observed after diluting to 100 ml with fresh methanol and refluxing 2 hr. The solution was neutralized with Amberlite IR-45 resin, concentrated, and acetylated in pyridine.

The acetylated products were separated on a silica gel column irrigated with 4.5:10 acetone–hexane, and crystallized from 95% ethanol: **6b**, mp 130–131.5°; **5b**, mp 167.5–169°, mixture melting point with the authentic α-glucoside (**5b**) undepressed. All physical properties matched those of authentic **5b** (see below).

Methyl 3,4,6-Tri-*O*-acetyl-α-D-glucopyranoside (19).—A solution containing 6 g of 3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl chloride (18)[34] in 200 ml of methanol and 20 ml of pyridine was allowed to stand 20 hr at 25°. Tlc monitoring (3:2 ethyl acetate–benzene) showed the reaction to be essentially complete within 2–3 hr and to have no apparent change thereafter. Glpc was used to identify and quantitate the reaction components after deacetylation and conversion to the trimethylsilyl ethers. The calculated yield of **19** was 84% and that of the β anomer, 6.5%; these percentages closely approximate earlier estimates based on optical rotations.[35,36] The reaction solution was evaporated to a thin syrup, dissolved in 500 ml of ethyl acetate, and freed of pyridine.

Methyl 3,4,6-Tri-*O*-acetyl-2-*O*-phenylcarbamoyl-α-D-glucopyranoside (5b).—The crude **19** was dissolved in 100 ml of benzene and treated with 5 ml of phenyl isocyanate. Water (5 ml) was added after the solution had been stored 24 hr at 25° and then it was evaporated to dryness. The solids were extracted with 100 ml of cold diethyl ether and filtered; the residual solids were crystallized from methanol. Yield was 5 g (62%): mp 167.5–169°; $[\alpha]^{20}D$ +112.6° (c 0.76, $CHCl_3$); nmr (acetone) τ 2.72 (three multiplets, Ph), 4.50 (unsymmetrical t, $J_{3,4}$ = 9.5 Hz, H-3), 4.91 (m, H-4), 4.94 (d, $J_{1,2}$ = 3.5 Hz, H-1), 5.09 (pair of doublets, $J_{2,3}$ = 10 Hz, H-2), 5.69 (m, $J_{5,6}$ = 5 Hz, $J_{5,6'}$ = 2.4 Hz, H-6), 5.90 (m, $J_{6,6'}$ = 12 Hz, H-6′), 6.02 (m, H-5), 6.59 (OCH_3).

Anal. Calcd for $C_{20}H_{25}NO_{10}$: C, 54.67; H, 5.72; N, 3.19; OCH_3, 7.06; acetyl, 29.4. Found: C, 54.76; H, 5.68; N, 3.22; OCH_3 7.80; acetyl, 29.1.

Registry No.—**1a**, 20147-90-4; **2c**, 20-126-09-4; **3**, 20-126-18-5; **4**, 20-126-19-6; **5b**, 20-126-10-7; **6b**, 20-126-17-4; **8a**, 20-126-11-8; **8b**, 20-126-12-9; **14a**, 20-126-13-0; **14b**, 20-126-14-1; **15**, 20-126-15-2; **16**, 20-126-16-3.

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(34) R. U. Lemieux and J. Howard in "Methods of Carbohydrate Chemistry," Vol. 2, R. L. Whistler and L. M. Wolfrom, Ed., Academic Press, New York, N. Y., 1963, p 401.

(35) W. J. Hickenbottom, *J. Chem. Soc.*, 1676 (1929).

(36) F. H. Newth and G. O. Phillips, *ibid.*, 2904 (1953).

Synthesis of Methyl *dl*-Jasmonate

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Reaction of pyrrolidine enamine (**2**) of methyl 2-oxocyclopentane-1-acetate (**1**) with 3-bromo-2-pentanone (**5**) in dioxane afforded methyl (±)-2-oxo-3-(1′-ethyl-2′-oxopropyl)cyclopentane-1-acetate (**3**) along with a small quantity of methyl (±)-2-oxo-3-(2′-oxopentyl)cyclopentane-1-acetate (**4**). When, however, toluene was used as the solvent instead of dioxane, the major product was **4** and the minor one was **3**. Intramolecular aldol condensation of **3** gave (±)-2-ethyl-6-methoxycarbonylmethylbicyclo[3.3.0]oct-1-en-3-one (**7**). Epoxydation of **7** followed by treatment with *p*-toluenesulfonylhydrazine gave methyl (±)-dehydrojasmonate (**10**). Restricted hydrogenation of **10** gave methyl *dl*-jasmonate (**11**).

Jasmone,[1] methyl jasmonate,[2] and jasmine ketolactone[3] constitute indispensable ingredients as the perfume of jasmine flower, known as the Queen of Aroma. These compounds structurally resemble each other and are considered to be produced biogenetically through a related route.[4,5]

Syntheses of jasmone have been reported by many authors[6] and have been the subject of more recent publications.[7,8] Methyl *dl*-jasmonate was synthesized by Demole and Stoll[4] starting from methyl *dl*-3-oxocyclopentane-1-acetate, but their route involved isomer separation *via* the semicarbazones.

An investigation was carried out to synthesize methyl *dl*-jasmonate by another route, starting from the readily available methyl 2-oxocyclopentane-1-acetate (**1**),[9,10] in order to avoid the difficult separation problem.

The pyrrolidine enamine of **1** was prepared according to Stork, *et al.*[11] The structure of the enamines of 2-substituted cyclanones has been examined by various authors,[12] including Stork, *et al.*[11] According to them the pyrrolidine enamine of 2-alkylcyclohexanone exists predominantly as the isomer with the less substituted double bond rather than that with the more substituted one. The nmr spectrum of the present enamine showed a vinyl proton at τ 5.86 with *ca.* one-third the integration of the ester methyl group, and the mass spectrum demonstrated *m/e* 209 (M), 208 (M − 1) with a base peak 136 ($M-CH_2COOCH_3$).[13] The gas chromatogram of the enamine showed a single peak. These observations indicated that the predominant product of the enamine from **1** was methyl 2-pyrrolidinyl-2-cyclopentene-1-acetate (**2**) possibly containing a small (~5%) amount of the corresponding 1-cyclopentene derivative (**2′**).

In accord with the reported reaction[11,14] of an alicyclic pyrrolidine enamine with a primary α-halo ketone to produce a 1,4-dicarbonyl compound, the reaction of **2** with 3-bromopentan-2-one[15] (**5**) in dioxane, followed by hydrolysis, afforded keto esters which were separated into major (87%) and minor (13%) products. On gas chromatography the major component showed two peaks not clearly separated which indicated an existence of a mixture of stereoisomers. The mass spectrum of the component showed peaks *m/e* 240 and 197 corresponding to the molecular ion and the fragment ion of $M-COCH_3$, respectively. In the nmr spectrum absorption of a methyl ketone methyl group were shown at τ 7.78 and 7.88. Thus the major component was considered to be a *trans–cis* isomer mixture of methyl (±)-2-oxo-3-(1′-ethyl-2′-oxopropyl)cyclopentane-1-acetate (**3**) with presumably *trans* isomer predominating.[16]

The minor component, which showed a similar infrared spectrum to that of the major one, exhibited a mass spectrum with different fragmentation patterns. The absence of *m/e* 197 indicated that the compound was not a methyl ketone. In the nmr spectrum, there was no absorption corresponding to the methyl group of a methyl ketone. When the reaction of **2** with 1-bromopentan-2-one[15] (**6**) was carried out in dioxane or in toluene, there was obtained methyl (±)-2-oxo-3-(2′-oxopentyl)-cyclopentane-1-acetate (**4**) as a major product (95%) with a minor component (5%) which seemed to be methyl (±)-2-oxo-1-(2′-oxopentyl)cyclopentane-1-acetate (**4′**). The compound **4** coincided with the above-mentioned minor component in ir, mass spectra and vpc. The ratio of 95:5 seemed to indicate the ratio of the pyrrolidine enamine of **2** and the double-bond isomer **2′**, respectively. The absence of the isomer methyl (±)-2-oxo-1-(1′-ethyl-2-oxopropyl)cyclopentane-1-acetate (**3′**) in the reaction of **2** with **5** might be due to the steric hindrance between the secondary halide and the enamine **2′**.

When the reaction of **2** with **5** was carried out in toluene instead of dioxane, keto esters **3** and **4** were obtained in a ratio of 16:81 with a small amount (3%) of a compound presumed to be methyl (±)-2-oxo-1-(2′-oxopentyl)cyclopentane-1-acetate (**4′**) (Scheme I). The reac-

(1) (a) L. Ruzicka and M. Pfeiffer, *Helv. Chim. Acta*, **16**, 1208 (1933); (b) W. Treff and H. Werner, *Ber.*, **66**, 1521 (1933).

(2) E. Demole, E. Lederer, and D. Mercier, *Helv. Chim. Acta*, **45**, 675 (1962).

(3) E. Demole, B. Willhalm, and M. Stoll, *ibid.*, **47**, 1152 (1964).

(4) E. Demole and M. Stoll, *ibid.*, **45**, 692 (1962).

(5) E. Sundt, B. Willhalm, and M. Stoll, *ibid.*, **47**, 408 (1964).

(6) (a) W. Treff and H. Werner, *Ber.*, **68**, 640 (1935); (b) H. Hunsdiecker, *ibid.*, **75**, 460 (1942); (c) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 869 (1952); (d) S. H. Harper and J. D. Smith, *ibid.*, 1512 (1955).

(7) (a) K. Sisido, S. Torii, and M. Kawanisi, *J. Org. Chem.*, **29**, 2290 (1964); (b) K. Sisido, Y. Kawasima, and T. Isida, *Perfum Essent. Oil Rec.*, **57**, 364 (1966).

(8) (a) G. Stork and R. Borch, *J. Amer. Chem. Soc.*, **86**, 935 (1964); (b) G. Büchi and H. Wüest, *J. Org. Chem.*, **31**, 977 (1966).

(9) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 940 (1934).

(10) S. Hauptmann and K. Hirschberg, *J. Prakt. Chem.*, **34**, 272 (1966).

(11) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(12) (a) W. D. Gurowitz and M. A. Joseph, *Tetrahedron Lett.*, 4433 (1965); (b) S. K. Malhorta and F. Johnson, *ibid.*, 4027 (1965); (c) S. Karady, M. Lenfent, and R. E. Wolff, *Bull. Soc. Chim. Fr.*, 2472 (1965); (d) R. Jacquier, C. Petrus, and F. Petrus, *ibid.*, 2845 (1966).

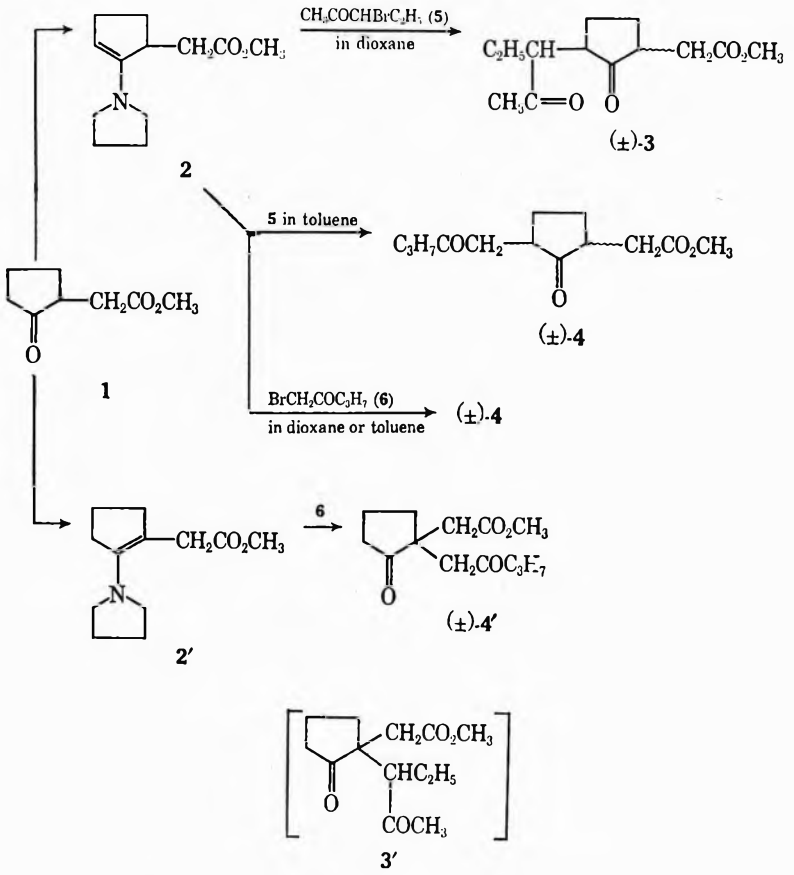
(13) H. J. Jakobsen, S. O. Lawesson, J. T. B. Marshall, G. Schroll, and D. H. Williams, *J. Chem. Soc., B*, 940 (1966).

(14) (a) J. Szmuszkovicz in *Advan. Org. Chem.*, **4**, 1 (1963); (b) H. E. Baumgarten, P. I. Creger, and C. E. Villars, *J. Amer. Chem. Soc.*, **80**, 6609 (1958).

(15) J. R. Catch, D. H. Hey, E. R. H. Jones, and W. Wilson, *J. Chem. Soc.*, 276 (1948).

(16) K. Sisido, S. Kurozumi, K. Utimoto, and T. Isida, *J. Org. Chem.*, **31**, 2795 (1966).

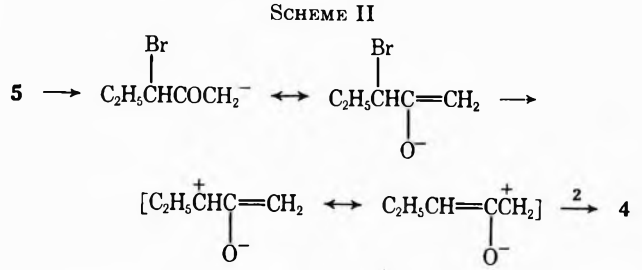
SCHEME I



tion of ethyl 2-oxo-3-ethoxycarbonylcyclopentane-1-acetate with **5** in toluene using potassium followed by saponification, decarboxylation, and esterification gave **3** and **4** in the same ratio of 15:85.

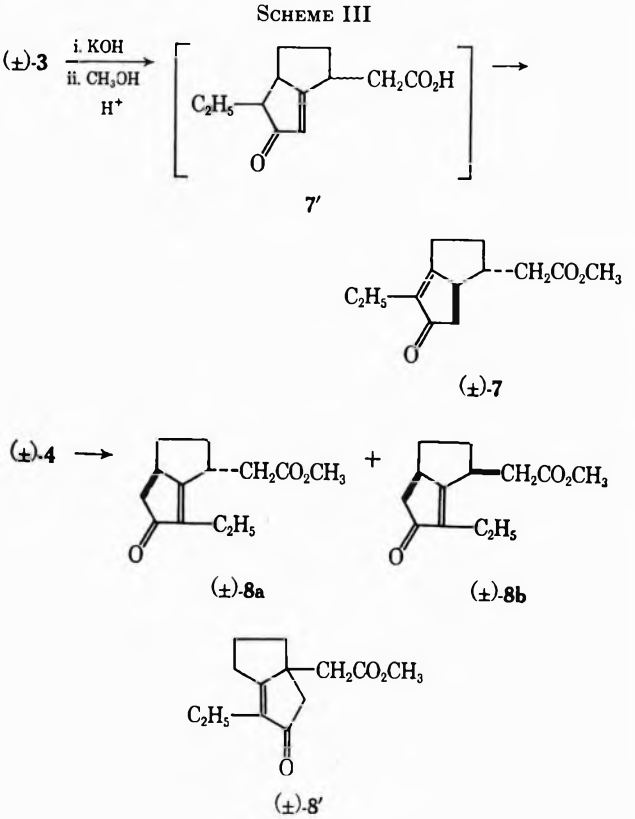
As to the production of **4**, the possibility that the formation of **6** from **5** involved bromine transfer[17] *via* carbanions[18,19] was considered. However, the halo ketone recovered from the reaction contained no 1-bromopentan-2-one (**6**). An alternative and more convincing possibility could involve the formation of the zwitterion[20] suggested as the intermediate in some Favorskii rearrangements (Scheme II). This may be followed by an attack of **2** to afford **4**.

SCHEME II



Intramolecular aldol condensation of **3** (contaminated with 13% **4**) with aqueous potassium hydroxide followed by esterification afforded two products (in a ratio of 7:93), both of which appeared, from their ir and uv spectra, to be esters containing an α,β-disubstituted cyclopentenone moieties (Scheme III). The mass spectra of these compounds showed, however, different

SCHEME III



(17) N. L. Wendler, R. P. Graber, and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

(18) W. D. McPhee and E. Klingsberg, *J. Amer. Chem. Soc.*, **66**, 1132 (1944).

(19) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *ibid.*, **89**, 6704 (1967).

(20) (a) A. S. Kende, *Org. Reactions*, **11**, 261 (1960); (b) J. G. Aston and J. D. Newkirk, *J. Amer. Chem. Soc.*, **73**, 3900 (1951); **73**, 3902 (1951); (c) N. J. Turro and W. B. Hammond, *ibid.*, **87**, 3258 (1965); (d) F. G. Bordwell and R. G. Seamehorn, *ibid.*, **90**, 6751 (1968).

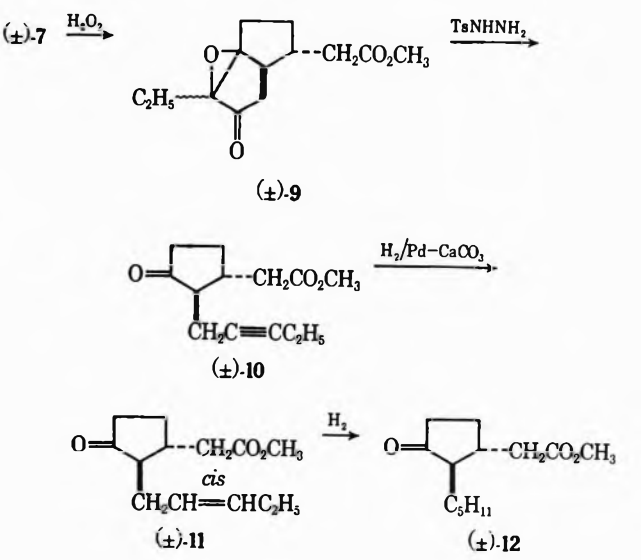
fragmentation patterns. In view of the absence of an olefinic proton in the nmr spectra of both compounds, the major one was considered to be (±)-2-ethyl-6-methoxycarbonylmethylbicyclo[3.3.0]oct-1-en-3-one (**7**) derived from **3**, while the minor one, (±)-2-ethyl-8-methoxycarbonylmethylbicyclo[3.3.0]oct-1-en-3-one (**8**) derived from **4**. The compound **7** was presumed to be derived *via* 2-ethyl-6-carboxymethylbicyclo[3.3.0]oct-4-en-3-one (**7'**) by a double-bond migration to the more substituted enone under the conditions of an alkaline aldol condensation. Treatment of **4** (contaminated with 5% **4'**) with potassium hydroxide afforded **8** (96%) with a small amount (4%) of the compound which was considered to be (±)-2-ethyl-5-methoxycarbonylmethylbicyclo[3.3.0]oct-1-en-3-one (**8'**) derived from **4'**. More precise gas chromatography of **8** showed two peaks (86:14), the mass spectra of which showed the same fragmentation patterns except for differences in relative peak intensities. Thus the two components were stereoisomers, the major one of which was considered to be *trans* isomer **8a** and the minor one *cis* isomer **8b**.[16] The stereochemistry of **7** is assumed to be *trans* since in the process of the double-bond migration the configuration of the bicyclic compound would become the thermodynamically more stable one.

Upon epoxydation of the compound **7** (contaminated with 7% **8**) with hydrogen peroxide in aqueous alkaline solution,[21] the epoxide **9** was obtained in 61% yield as a mixture of two stereoisomers contaminated with unchanged **8**. The ir spectrum of the product showed a very weak absorption corresponding to the conjugated carbonyl group of **8**. Owing presumably to a steric factor, **8** was not readily epoxydized. The separation of **8** and **9** was not feasible by gas chromatography. The crude epoxide **9** was converted into the *p*-toluenesulfonylhydrazone derivative with an equivalent amount of *p*-toluenesulfonylhydrazine,[22] and the product was chromatographed on silica gel. There was obtained in 51% yield methyl (±)-2-(2'-pentynyl)-3-oxocyclopentane-1-acetate (methyl dehydrojasmonate)[4] (**10**) whose analyses and mass spectrum were consistent with the postulated structure.

Hydrogenation of **10** over Lindlar catalyst[23] gave methyl (±)-jasmonate (**11**) whose ir spectrum coincided with that of Demole and Stoll (Scheme IV).[4] The mass spectrum showed a molecular ion peak (*m/e* 224). In the nmr spectrum of the product, the two olefinic protons showed an AB coupling pattern with a *cis* coupling constant of 6 Hz.

When **10** was hydrogenated over palladium–charcoal, methyl (±)-dihydrojasmonate (**12**) was obtained whose mass and ir spectra coincided with those of an authentic sample.[24] The stereochemistry of the substituents on the cyclopentanone ring would be predominantly *trans* for the reason mentioned in the case of compound **7** as well as those described by Varech, *et al.*[25]

SCHEME IV



Experimental Section

Gas chromatography was carried out on Shimadzu GC-2C, with 3 m × 3 mm steel columns packed with 30% PEG-6000 and 30% HVSG on Chromosorb W (80–100 mesh). Infrared spectra were recorded as liquid films on Shimadzu IR-27. Ultraviolet spectra were obtained in ethanol on Hitachi EPS-2 spectrometer. Nmr spectra were measured at 60 MHz with Varian Associates A-60 and Japan Electron Optics C-60-H in 5% solution. Mass spectra were obtained on Hitachi RMS-4 spectrometer. Microanalyses were carried out by Mrs. Huzimoto of this laboratory using Yanagimoto automatic analyzer CHN Corder MT-1. Temperatures are uncorrected.

Pyrrolidine Enamine (2) of Methyl 2-Oxocyclopentane-1-acetate (1).—According to the procedure of Stork, *et al.*,[11] from 16 g (0.10 mol) of methyl 2-oxycyclopentane-1-acetate (**1**)[9,10] and 9.2 g (0.13 mol) of pyrrolidine, 18 g (86%) of pyrrolidine enamine (**2**) was obtained: bp 110–115° (1 mm); ir (liquid film) 3030 (HC=), 1745 (ester C=O), 1625 cm^{-1} (NC=C); nmr ($CDCl_3$) τ 8.40–7.60 (15), 6.34 (s, 3, CO_2CH_3), 5.86 (equivocal t, 1, HC=); mass spectrum (70 eV) *m/e* (relative intensity) 209 (M^+, 91), 208 (37), 194 (7), 178 (20), 150 (70), 136 (100), 135 (99), 122 (27), 108 (17), 94 (12), 79 (20), 70 (47). Gas chromatography (PEG-20M) showed a single peak. Owing to the lability of the substance, an analysis was not performed.

Methyl (±)-2-Oxo-3-(1'-ethyl-2'-oxopropyl)cyclopentane-1-acetate (3).—To a crude pyrrolidine enamine **2**, prepared from 70 g (0.45 mol) of **1**, in 200 ml of dioxane, was added 78 g (0.47 mol) of 3-bromopentan-2-one (**5**)[15] in 50 ml of dioxane. After refluxing for 4 hr, 180 ml of water and 20 ml of concentrated hydrochloric acid were added and refluxing was continued for 30 min. The reaction mixture was poured into saturated sodium chloride solution and extracted with ether. The ether extract, when distilled, gave 26 g (31%) of keto esters, bp 140–150° (2 mm), and 13 g (18%) of the starting material **1**. Gas chromatography (HVSG) of the product showed two main peaks corresponding to **3** and **4** in a ratio of 87:13 with an uncharacterized small peak. The keto ester **3** was purified by preparative gas chromatography: ir (liquid film) 1745, 1740 (ester C=O, cyclic C=O) and 1715 cm^{-1} (C=O); nmr ($CDCl_3$) τ 9.10 9.01 (two triplets, 3, J = 7 Hz, CH_3CH_2–), 8.83–7.90 (m, 5), 7.88, 7.78 (two singlets, 3, CH_3CO–), 7.66–6.80 (6), 6.31 (s, 3, CO_2CH_3).

As expected from the nmr spectrum, **3** showed two close peaks on gas chromatography (HVSG and PEG-20M). The separation of these peaks was unsuccessful: mass spectrum (70 eV) *m/e* 240 (M^+). *Anal.* Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.85; H, 8.20.

Methyl (±)-2-Oxo-3-(2'-oxopentyl)cyclopentane-1-acetate (4).—To the crude enamine **2** prepared from 16 g (0.10 mol) of **1** dissolved in 50 ml of toluene was added 17 g (0.10 mol) of **5** in 20 ml of toluene. The reaction was carried out under reflux for 8 hr. After the addition of 26 ml of water and additional re-

(21) R. L. Wasson and H. O. House, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 552.

(22) (a) J. Schreiber, D. Felix, A. Eschenmoser, M. Winter, F. Gautschi, K. H. Schulte-Elte, E. Sundt, G. Ohloff, J. Kalvoda, H. Kaufmann, P. Wieland, and G. Anner, *Helv. Chim. Acta*, **50**, 2101 (1967); (b) P. Wieland, H. Kaufmann, and A. Eschenmoser, *ibid.*, **50**, 2108 (1967); (c) A. Eschenmoser, D. Felix, and G. Ohloff, *ibid.*, **50**, 708 (1967); (d) M. Tanabe, D. F. Crowe, R. L. Dehn, and G. Detre, *Tetrahedron Lett.*, 3739 (1967); (e) M. Tanabe, D. F. Crowe, and R. L. Dehn, *ibid.*, 3943 (1967).

(23) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(24) E. Demole, E. Lederer, and D. Mercier, *ibid.*, **45**, 685 (1962).

(25) D. Varech C. Ouannes, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1662 (1965).

fluxing for 2 hr the mixture was treated as above. There was obtained 8.0 g (34%) of keto esters (**3** and **4** in a ratio of 16:81), bp 155–160° (2–3 mm), and 4.7 g (30%) of starting material **1**. Gas chromatography (HVSG) of the product showed two main peaks (**3** and **4**) with a small peak (3%) which was considered to be methyl (±)-2-oxo-1-(2′-oxopentyl)cyclopentane-1-acetate (**4′**) (see below). The major component **4** was separated by preparative gas chromatography: ir (liquid film) 1745, 1740 (ester C=O, cyclic C=O), and 1715 (C=O) cm^{-1}; nmr ($CDCl_3$) τ 9.06 (t, 3, J = 7 Hz, CH_3CH_2), 8.40 (heptet, 2, J = 7 Hz, $CH_3CH_2CH_2$–), 8.10–7.10 (12), 6.30 (s, 3, CO_2CH_3); mass spectrum (70 eV) m/e (relative intensity) 240 (M^+, 4), 222 (7), 208 (33), 181 (13), 169 (23), 164 (17), 152 (31), 149 (28), 137 (77), 123 (28), 109 (16), 105 (7), 81 (20), 71 (100), 55 (24), 43 (95); *Anal.* Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.26; H, 8.11.

Reaction of Ethyl 2-Oxo-3-ethoxycarbonylcyclopentane-1-acetate.—When 16 g (66 mmol) of ethyl 2-oxo-3-ethoxycarbonylcyclopentane-1-acetate[26] was added to 2.5 g (65 mg-atoms) of potassium dispersed in 70 ml of toluene and treated with 16 g (97 mmol) of **5** for 20 hr under reflux, there was obtained 12 g (57%) of keto esters, bp 150–190° (2 mm). On gas chromatography the product showed two peaks in a ratio of 4:6 whose mass spectra demonstrated the similar fragmentation patterns (M^+, m/e 326).

These components were considered to be a pair of stereoisomers of ethyl 2-oxo-3-ethoxycarbonyl-3-(2′-oxopentyl)cyclopentane-1-acetate contaminated with ethyl 2-oxo-3-ethoxycarbonyl-3-(1′-ethyl-2′-oxopropyl)cyclopentane-1-acetate.

Hydrolysis of 11 g (34 mmol) of the keto ester with hydrochloric acid followed by reesterification with methanol in methylene chloride gave 2.1 g (26%) of a mixture of **3** and **4** in a ratio of 15:85, bp 160–163° (4 mm).

Methyl (±)-2-Oxo-3-(2′-oxopentyl)cyclopentane-1-acetate (4).—A mixture of the crude enamine **2** prepared from 16 g (0.10 mol) of **1** and 17 g (0.10 mol) of **6**[15] was stirred and refluxed in 180 ml of toluene for 6 hr and treated as described above. There was obtained, beside 4.5 g (28%) of the starting material **1**, 10 g (42%) of **4**, bp 140–145° (1 mm). Gas chromatography of the product demonstrated two peaks in a ratio of 5:95. The minor component was considered to be methyl 2-oxo-1-(2′-oxopentyl)cyclopentane-1-acetate (**4′**).

When the reaction was carried out in dioxane instead of toluene, the same result was obtained.

(±)-2-Ethyl-6-methoxycarbonylmethylbicyclo[3.3.0]oct-1-en-3-one (7).—A mixture of 5.0 g (21 mmol) of **3** contaminated with 13% of **4**, 2.5 g (45 mmol) of potassium hydroxide, and 75 ml of water was refluxed for 15 hr. After extraction with ether, the aqueous layer was acidified with dilute hydrochloric acid and extracted with ether. The latter ethereal solution, on removal of the solvent, afforded 4.0 g of (±)-2-ethyl-6-carboxymethylbicyclo[3.3.0]oct-1-en-3-one, which, on esterification with 6.0 g of methanol and 5 drops of concentrated sulfuric acid in 30 ml of methylene chloride, gave 2.6 g (56%) of (±) **7**, bp 130–135° (1 mm). The product was shown to be contaminated with 7% of **8** by gas chromatography. Purification of **7** was performed by preparative gas chromatography: uv max (95% ethanol) 238 mμ (ε 10,060); ir (liquid film) 1745 (ester C=O), 1705 (conjugated C=O), 1660 cm^{-1} (conjugated C=C); nmr ($CDCl_3$) τ 8.97 (t, 3, J = 7 Hz, CH_3CH_2–), 8.50–7.10 (12), 6.32 (s, 3, $COOCH_3$); mass spectrum (70 eV) m/e (relative intensity) 222 (M^+, 24), 194 (4), 191 (8), 163 (7), 149 (100), 133 (12), 120 (20), 105 (30), 91 (20), 79 (24), 55 (10), 41 (19). *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.44; H, 8.20.

2,4-Dinitrophenylhydrazone of 7 had mp 139–142°. *Anal.* Calcd for $C_{19}H_{22}O_6N_4$: C, 56.71; H, 5.51; N, 13.92. Found: C, 56.46; H, 5.47; N, 13.66.

(±)-2-Ethyl-8-methoxycarbonylmethylbicyclo[3.3.0]oct-1-en-3-one (8).—A mixture of 6.1 g (25 mmol) of **4** contaminated with 17% **3** (but no detectable amount of **4′**), 3.1 g (55 mmol) of potassium hydroxide, and 70 ml of water was treated as above and there was obtained 2.8 g (50%) of a product. Gas chromatography of the product showed three components corresponding to 74% **8**, 24% **7**, and 2% **8′**. The major compound **8** was purified by preparative gas chromatography (HVSG): uv max (95% ethanol) 238 mμ (ε 7060); ir (liquid film) 1745 (ester C=O), 1705 (conjugated C=O), 1660 cm^{-1} (conjugated C=C); the fingerprint region of **8** was different from that of **7**; nmr ($CDCl_3$) τ 8.96 (t, 3, J = 7 Hz, CH_3CH_2–), 8.50–6.70 (12), 6.28 (s, 3, $COOCH_3$). *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.38; H, 8.15.

2,4-Dinitrophenylhydrazone of 8 had mp 180.5–181°. *Anal.* Calcd for $C_{19}H_{22}O_6N_4$: C, 56.71; H, 5.51; N, 13.92. Found: C, 56.65; H, 5.46; N, 13.66.

Gas chromatographic analyses (PEG-20M) of **8** showed two peaks in a ratio of 86:14, the major one of which was considered to be *trans* isomer **8a** and the minor one, *cis* isomer **8b**.

The mass spectrum [70 eV, m/e (relative intensity)] of **8a** showed 222 (M^+, 46), 194 (32), 178 (4), 163 (23), 149 (32), 135 (20), 134 (19), 133 (16), 120 (100), 105 (60), 91 (44), 79 (41), 65 (12), 55 (16), 41 (29); **8b**, 222 (M^+, 84), 194 (32), 178 (4), 163 (87), 149 (89), 135 (21), 134 (20), 133 (28), 120 (100), 105 (76), 91 (78), 79 (75), 65 (20), 55 (33), 41 (44).

Similar treatment of **4** (contaminated with 5% **4′**) gave a product consisting 79% **8a**, 17% **8b**, and 4% **8′**.

(±)-1,2-Epoxy-2-ethyl-6-methoxycarbonylmethylbicyclo[3.3.0]-octan-3-one (9).—To a solution of 8.2 g (37 mmol) of **7** (contaminated with 7% **8**) in 40 ml of methanol, 11.5 ml of 30% aqueous hydrogen peroxide solution, and 6.6 ml (20 mmol) of 3 N sodium hydroxide solution were added at 15–25°. After standing overnight the reaction mixture was poured into saturated sodium chloride solution and extracted with ether and the solvent was removed. There was obtained 5.4 g (61%) of **9**, bp 135–145° (1 mm), whose ir showed the presence of a very small amount of unchanged **8**. Gas chromatography (HVSG) of the product showed two main peaks (stereoisomers) with three small, uncharacterized peaks. The separation of **9** and **8** on gas chromatography was unsuccessful: mass spectrum (70 eV) m/e 238 (M^+). *Anal.* Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.95; H, 7.64.

Methyl (±)-Dehydrojasmonate (10).—A mixture of 2.0 g (8.4 mmol) of crude **9** and 1.6 g (8.4 mmol) of *p*-toluenesulfonylhydrazine in 80 ml of ethanol was warmed at 40–50° for 1.5 hr. Removal of the solvent gave crude tosylhydrazone which was chromatographed over 15 g of silica gel (Mallinckrodt, 100 mesh) using benzene and ethyl acetate (3:1). When the elute was concentrated and distilled, there was obtained 0.95 g (51%) of methyl (±)-dehydrojasmonate (**10**): bp 140–150° (2 mm) [lit.[4] bp 88° (0.001 mm)]; ir (neat) showed similar absorptions of that of methyl jasmonate[4] except slight differences in the fingerprint region; ir (liquid film) 1745, 1465, 1435, 1370, 1340, 1320, 1290, 1265, 1230, 1195, 1165, 1090, 1070, 1015, 995 cm^{-1}; mass spectrum (70 eV) m/e (relative intensity) 222 (M^+, 2), 207 (3), 193 (33), 191 (5), 163 (2), 149 (10), 133 (13), 122 (100), 107 (38), 91 (18), 79 (18), 67 (7), 55 (15), 41 (15). Analyses gave correct values.

Methyl (±)-Jasmonate (11).—Restricted hydrogenation of 0.21 g (0.96 mmol) of **10** over 0.50 g of Lindlar catalyst[23] in 5 ml of methanol gave 0.13 g (60%) of **11**: bp 130–140° (2 mm) [lit.[4] bp 81–84° (0.001 mm)]; ir spectrum was consistent with that of an authentic sample;[4] nmr ($CDCl_3$) τ 9.04 (t, 3, J = 7 Hz, CH_3CH_2–), 8.80–7.10 (12), 6.30 (s, 3, $COOCH_3$), 4.72 (d, 1, J = 6 Hz, HC=), 4.53 (d, 1, J = 6 Hz, HC=); mass spectrum (70 eV) m/e (relative intensity) 224 (M^+, 28), 206 (4), 193 (9), 177 (3), 167 (4), 165 (4), 156 (25), 151 (50), 133 (16), 121 (11), 109 (25), 95 (31), 83 (100), 67 (27), 55 (33), 41 (58). Analyses afforded correct values.

Methyl (±)-Dihydrojasmonate (12).—Hydrogenation of 40 mg (0.18 mmol) of **10** over 0.25 g of 5% palladium–charcoal in 5 ml of methanol gave 35 mg (87%) of methyl (±)-dihydrojasmonate (**12**): ir of the product coincided with that of an authentic sample;[24] mass spectrum (70 eV) m/e (relative intensity) 226 (M^+, 4), 195 (4), 169 (3), 156 (36), 153 (24), 137 (3), 124 (14), 109 (4), 95 (7), 83 (100), 74 (7), 67 (8), 55 (20), 41 (20).

Registry No.—**2**, 20073-04-5; **3**, 20073-05-6; **4**, 20073-06-7; **7**, 20073-07-8; **7** 2,4-dinitrophenylhydrazone, 20126-08-3; **8a**, 20073-08-9; **8a**, 2,4-dinitrophenylhydrazone, 20073-09-0; **8b**, 20073-10-3; **8b**, 2,4-dinitrophenylhydrazone, 20073-11-4; **9**, 20073-12-5; **11**, 20073-13-6.

(26) J. P. Schaefer, *Org. Reactions*, **15**, 1 (1967).

The Synthesis of Caseadine Methyl Ether

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Received February 3, 1969

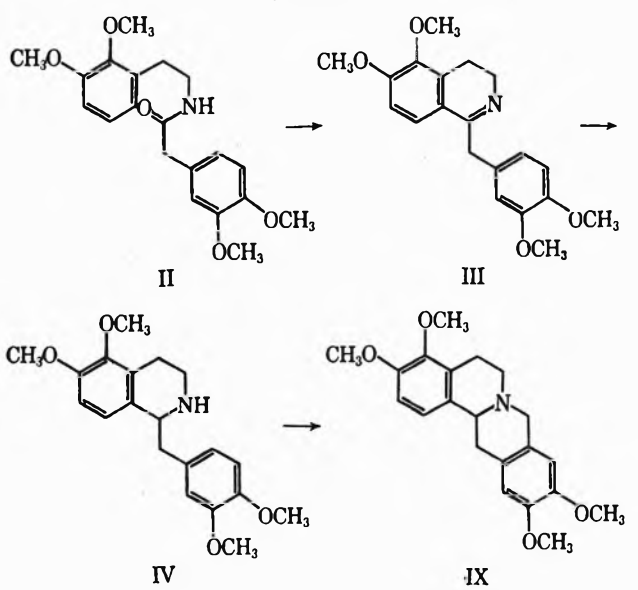
Syntheses are described for the isomeric racemic bases 3,4,10,11-tetramethoxy-5,6,7,8,13,13a-hexahydrodibenzo[*a*,*g*]quinolizine (IX) and 1,2,10,11-tetramethoxy-5,6,7,8,13,13a-hexahydrodibenzo[*a*,*g*]quinolizine (X). The latter was shown to be the racemic form of the methyl ether of the novel tetrahydroprotoberberine base, (−)-caseadine, thus giving synthetic support to the caseadine structure Ia assigned by Chen, MacLean, and Manske on spectroscopic and biogenetic grounds.

The isolation of two minor phenolic alkaloids, originally designated F-33 and F-35, was reported from *Corydalis caseana A.* Gray in 1938.[1] A recent elegant study of these trace alkaloids, now named caseamine and caseadine, respectively, indicated that they are tetrahydroprotoberberines having the same novel substitution pattern. Spectroscopic considerations narrowed the structure of the more abundant monophenolic base caseadine to Ia or Ib. Of these two possibilities, structure Ia was regarded as the more likely on the basis of biogenetic analogy with other known alkaloids of the benzylisoquinoline family.[2] Since caseadine has been converted into a crystalline methyl ether, we undertook the synthesis of both of the possible methyl ether structures IX and X.

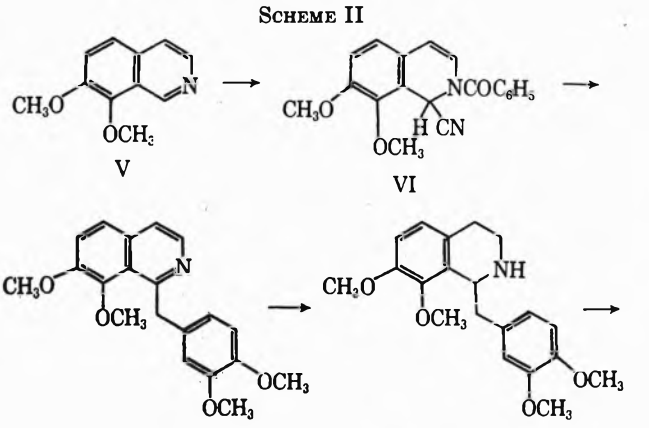
The starting material for the synthesis of the 3,4,10,-11-tetramethoxytetrahydroprotoberberine IX was the known dihydroisoquinoline III,[3] which we obtained by a much improved procedure (79% yield) involving polyphosphate ester cyclization of amide II (Scheme I). Sodium borohydride reduction of III afforded, in 61% yield, the crystalline 1-veratryl-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IV), characterized as its hydrochloride. Condensation of the latter salt with formaldehyde according to the general procedure of Corrodi and Hardegger[4] gave a good yield of the desired tetrahydroprotoberberine IX, mp 158.5–160°. Infrared examination showed this base to be definitely different from caseadine methyl ether.

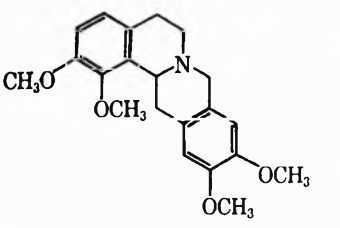
The isomeric 1,2,10,11-tetramethoxytetrahydroprotoberberine X was synthesized starting from 7,8-dimethoxyisoquinoline (V) (Scheme II).[5] Reaction of isoquinoline V with benzoyl chloride and potassium cyanide gave, in 43% yield, the corresponding Reissert compound VI, mp 158°. Using the general procedure of Kershaw and Uff,[6] reaction of VI with veratryl

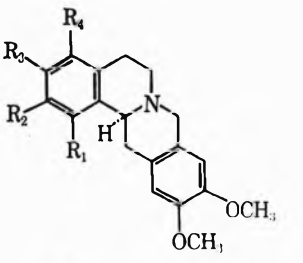
SCHEME I



SCHEME II







Ia, $R_1 = OH$; $R_2 = OCH_3$; $R_3 = R_4 = H$

Ib, $R_1 = R_2 = H$; $R_3 = OCH_3$; $R_4 = OH$

(1) R. H. F. Manske and M. R. Miller, *Can. J. Res., B*, **16**, 153 (1938).

(2) C.-Y. Chen, D. B. MacLean, and R. H. F. Manske, *Tetrahedron Lett.*, 349 (1968).

(3) A. Lindenmann, *Helv. Chim. Acta*, **32**, 69 (1949). The PCl_5 cyclization of II to the amorphous III in unspecified yield is reported in this paper; this product was not subjected to further transformations.

(4) H. Corrodi and E. Hardegger, *ibid.*, **39**, 889 (1956).

(5) W. J. Gensler, K. T. Shamsundar, and S. Marburg, *J. Org. Chem.*, **33**, 2864 (1968).

(6) J. R. Kershaw and B. C. Uff, *Chem. Commun.*, 331 (1966). In this communication concerning a new benzylisoquinoline synthesis, 1-anisyl-7,8-dimethoxyisoquinoline is mentioned as one of the compounds prepared. Implicitly, Reissert compound VI was the intermediate used in this case, although it was not specifically described in any way. We, therefore, report our synthesis of VI.

chloride and sodium hydride, followed by aqueous alkaline hydrolysis, gave, in 83% yield, 1-veratryl-7,8-dimethoxyisoquinoline (VII), mp 79–81°. Catalytic reduction of VII yielded the amorphous 1-veratryl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII), characterized as its crystalline N-acetyl derivative. Acid-catalyzed condensation of VIII with formaldehyde gave the desired tetrahydroprotoberberine X, mp 165°, the infrared spectrum of which in chloroform solution was identical with that of the methyl ether of natural (−)-caseadine. This result, considered with the earlier reported spectroscopic evidence, confirms the structure Ia for caseadine itself, as proposed by Chen, MacLean, and Manske.[2]

The facile resolution of several 1,2,3,4-tetrahydroisoquinolines by (2*R*:3*R*)-2′-nitrotartranilic acid was reported recently.[7] Although we were unable to effect a resolution of racemic caseadine methyl ester (X) using this acid, we found it to be an advantageous acid catalyst for the formaldehyde cyclization of VIII, since the salt of the acid with the resulting caseadine methyl ether crystallized directly in a state of purity from the reaction mixture.

Experimental Section[8]

Polyphosphate Ester.[9]—Phosphorus pentoxide (150 g) was added to a solution of 300 ml of anhydrous ether and 150 ml of alcohol-free chloroform. The reaction mixture was refluxed under dry nitrogen for 4 days and the resulting clear solution was decanted from a small amount of residue. The solution was concentrated to a colorless syrup in a rotary evaporator; residual traces of solvent were removed by heating the syrup for 36 hr at 40° *in vacuo*.

1-Veratryl-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IV).—Amide II[3] (3.36 g, 9.35 mmol) was mixed with 24 g of polyphosphate ester and the mixture was heated on a hot plate at 80° for 12 hr. The reaction mixture was poured into 200 ml of water and the resulting clear solution was stirred at room temperature for 0.5 hr and was then extracted twice with 50-ml portions of ether. The aqueous layer was made basic with ammonium hydroxide and was extracted with four 100-ml portions of 1:1 benzene–ether. The organic extract was dried over magnesium sulfate and was evaporated to an oil *in vacuo*. The dihydroisoquinoline (III, yield 2.52 g, *ca.* 79%) could not be crystallized, but was used directly in the next step of the synthesis.

A solution of 0.445 g (1.30 mmol) of the dihydroisoquinoline (III)[3] in 10 ml of methanol was treated with 200 mg of sodium borohydride, added in small portions during 15 min. The reaction mixture was allowed to stand for 0.5 hr at room temperature and was then diluted with water to the cloud point. On standing overnight it deposited white needles of the tetrahydroisoquinoline (IV), 0.273 g (61%), mp 70–73°.

The product was analyzed in the form of its hydrochloride, which was recrystallized from ethanol. Thus, a solution of 3.00 g of IV in ethanol was treated with hydrogen chloride gas to give 2.58 g (78%) of the hydrochloride of IV: mp 237–238°; $\lambda_{max}^{H_2O}$ 230 mμ (log ε 4.22), 278 (3.62).

Anal. Calcd for $C_{20}H_{26}ClNO_4$: C, 63.26; H, 6.90; Cl, 9.33; N, 3.69. Found: C, 63.30; H, 7.01; Cl, 9.40; N, 3.55.

3,4,10,11-Tetramethoxy-5,6,7,8,13,13a-hexahydrodibenzo[*a*,*g*]quinolizine (IX).—Aqueous formaldehyde solution (0.8 ml, 37%) was added dropwise during 0.25 hr with occasional stirring to a solution of 0.380 g (1.00 mmol) of the tetrahydroisoquinoline (IV) hydrochloride in 4.5 ml of water while the latter was heated on a steam bath. The reaction mixture was diluted with 1.0 ml of 6 *N* hydrochloric acid and was cooled in an ice bath to give 0.332 g (85%) of IX hydrochloride as white crystals, mp 232–234° dec, obtained in two crops. The analytical sample, mp 232–234° dec, was recrystallized from 0.05 *N* hydrochloric acid: $\lambda_{max}^{H_2O}$ 225 mμ sh (log ε 4.23), 282 (3.72).

Anal. Calcd for $C_{21}H_{26}ClNO_4$: C, 64.36; H, 6.69; Cl, 9.05; N, 3.57. Found: C, 64.08; H, 6.77; Cl, 9.05; N, 3.61.

Treatment of the hydrochloride salt of IX with base gave the free amine, mp 158.5–160°, which resembles caseadine methyl ether (X) in its R_f (0.87 on Merck tlc plates, silica gel F-254, developed with 1:10 absolute ethanol–chloroform), but which differed unmistakably from X in its nmr spectrum and its infrared spectrum.

1-Cyano-2-benzoyl-7,8-dimethoxy-1,2-dihydroisoquinoline (VI).[6]—A solution of 10 g (0.0052 mol) of the isoquinoline V[5] in 100 ml of methylene chloride was treated at 0° with excess benzoyl chloride (10 ml) in the presence of potassium cyanide (10 g, 0.154 mol) in 25 ml of water. The mixture was stirred for 1 additional hr at room temperature. The organic layer was washed several times with water and was dried. The solvent was removed and the residue was crystallized from alcohol to give VI, 8.56 g (43%), mp 158°.

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.24; H, 5.17; N, 8.74.

1-Veratryl-7,8-dimethoxyisoquinoline (VII).—Sodium hydride (1.452 g) was added to a stirred mixture of 3.326 g (0.004 mol) of VI and 2.948 g (0.015 mol) of veratryl chloride[10] in 100 ml of dimethylformamide at 0° under nitrogen. The mixture was stirred for 3 hr more at ambient temperature, and then diluted with water and extracted with methylene chloride. The residue from the organic extract was refluxed with a mixture of 200 ml of 10% aqueous alkali and 100 ml of ethanol for 3 hr. The ethanol was removed in a rotary evaporator and the residue was extracted with ether. Reextraction of the ether extract with 2 *N* hydrochloric acid, followed by basification of the acid extract, furnished crude VII, mp 69–76° (2.936 g, 83%), which on recrystallization from dry ether gave the pure product: mp 79–81° (1.7 g); λ_{max}^{EtOH} 215 mμ (ε 3.71), 245 (3.68), 295 (2.85), 370 (2.71).

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.54; H, 6.46; N, 4.30.

The picrate of VII, mp 150–154°, was prepared and was recrystallized from ethanol.

Anal. Calcd for $C_{26}H_{24}N_4O_{11}$: C, 54.93; H, 4.25; N, 9.86. Found: C, 55.03; H, 4.45; N, 9.98.

1-Veratryl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII).—A solution of 0.600 g of VII in 60 ml of ethanol containing 2 drops of 6 *N* hydrochloric acid was shaken with hydrogen at 30 psi in the presence of 0.10 g of platinum oxide. After 7 hr, the catalyst was filtered off and the solvent was removed *in vacuo*. The residue was basified and worked up in the usual manner to give 0.6 g of VIII as a gum which resisted crystallization. However, 0.099 g of an N-acetyl derivative, mp 91°, was obtained from 0.100 g of the crude product (VIII).

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.44; H, 7.05; N, 3.71.

1,2,10,11-Tetramethoxy-5,6,7,8,13,13a-hexahydrodibenzo[*a*,*g*]quinolizine (X).—The crude hydrochloride of VIII, obtained by reduction of 1.00 g of VII (see above), was dissolved in 10 ml of water on a steam bath and treated with 2 ml of 37% formaldehyde solution, added during 15 min. Heating was continued for 1 hr. The mixture was basified and extracted with methylene chloride as usual. The sticky solid (0.7 g) obtained by evaporation of the solvent was recrystallized from dry ether to give 0.2 g of X: mp 165°; λ_{max}^{EtOH} 215 mμ (log ε = 5.00), 235 (4.20), 288 (3.79).

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.86; H, 7.12; N, 4.07.

In another run, a solution of 0.9 g of VIII in 10 ml of ethanol was treated with a solution of 0.5 g of (2*R*:3*R*)-2′-nitrotartranilic acid[7] in ethanol. The crude salt obtained by evaporation of the solvent was extracted with boiling water. The aqueous extract was treated with a few drops of formalin and heated on the steam

(7) T. A. Montzka, T. L. Pindell, and J. D. Matiskella, *J. Org. Chem.*, **33**, 3993 (1968).

(8) Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Melting points are uncorrected.

(9) The procedure described here is based in part on the best features of three previous procedures: (a) Y. Kanaoka, O. Yonemitsu, K. Tanizawa, and Y. Ban, *Chem. Pharm. Bull. Jap.*, **12**, 773 (1964); (b) W. Pollmann and G. Schramm, *Biochem. Biophys. Acta*, **80**, 1 (1964); (c) G. Schramm, H. Grotsch, and W. Pollmann, *Angew. Chem. Intern. Ed. Engl.*, **1**, 1 (1962).

(10) K. Kindler and B. Gehlhaar, *Archiv. Pharm.*, **274**, 377 (1936).

bath for 2 hr. The yellow nitrotartranilate of X, 0.8 g, mp 165°, separated on cooling and was recrystallized from ethanol.

Anal. Calcd for $C_{31}H_{35}N_3O_{11}$: C, 59.52; H, 5.6; N, 6.72. Found: C, 59.07; H, 5.68; N, 6.47.

Treatment of the nitrotartranilate salt with base liberated the amine (X), identical in R_f, infrared spectrum ($CHCl_3$), and nmr spectrum ($CDCl_3$) with caseadine methyl ether prepared from natural (−)-caseadine.[2]

Registry No.—IV 20122-04-7; IV hydrochloride, 20122-05-8; VI, 20122-06-9; VII, 20122-48-9; VII picrate, 20122-49-0; VIII (N-acetyl derivative), 20122-07-0; IX, 20122-08-1; IX hydrochloride, 20122-09-2; X, 20122-10-5; X nitrotartranilate, 20122-11-6.

Acknowledgment.—We are grateful to Dr. D. B. MacLean and Dr. R. H. F. Manske for a small comparison sample of caseadine methyl ether, and for direct infrared and nmr comparisons of the synthetic and naturally derived bases. We also thank the Smith Kline and French Co., Philadelphia, for financial support of this investigation.

Some Approaches to the Total Synthesis of Lycorine

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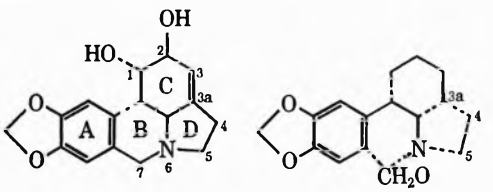
Received November 1, 1968

The problem of the synthesis of the lycorine family of *Amaryllidaceae* alkaloids is analyzed and two separate kinds of synthetic routes are examined experimentally. The first route, based on a Diels–Alder formation of ring C, leads to a product containing the lycorine skeleton with a nonaromatic ring C reasonably functionalized to complete the synthesis. The second approach, involving several variations on a roughly biosynthetic analogy, was frustrated on each occasion by reactions, usually internal conjugate additions, which took an undesirable course.

Lycorine (**1**) is the principal member of a family of *Amaryllidaceae* alkaloids[2] which have not been synthesized to date and which present an interesting synthetic challenge. In the present work we present an analysis of the synthetic problem and experimental work directed to several of the routes developed from this analysis, over a number of years.

The problem chiefly centers around ring C, which bears all four asymmetric centers and is in the same oxidation state as an aromatic ring, to which it readily reverts by double dehydration, destroying all asymmetric centers. The glycol is *trans* diaxial, hence in an unstable configuration on the rigid, *trans* decalin ring system. This situation argues for *trans* hydroxylation of a $\Delta^{1,2}$ double bond, while a $\Delta^{3,3a}$ double bond, presumably more susceptible to oxidation, must be retained in lycorine.



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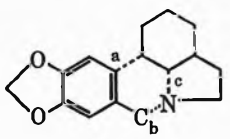
2



3

Starting material for the synthesis will presumably be piperonal (3,4-methylenedioxybenzaldehyde), which is readily available. Hence a second C–C bond must be formed to the aromatic ring. The piperonal aldehyde carbon can either be used as the carbon at the B/C-ring junction or as the aromatic link to the nitrogen atom. Two dissections of the skeleton into reasonable "synthons"[3] are shown in **2** and **3**, using piperonal in these two possible ways. The first dissection, **2**, is built on a Diels–Alder creation of ring C so as to assure *trans*-ring-fusion stereochemistry; the requisite diene can be four or six carbons and ring B would finally be cyclized using formaldehyde. The second dissection, **3**, is that which is utilized in biosynthesis of the *Amaryllidaceae* alkaloids,[4] oxidative coupling of phenols creating bond "a", followed by conjugate addition of nitrogen for bond "c"; this conjugate addition destroys the aromaticity of ring C which arises biosynthetically from tyrosine. We considered the Pschorr cyclization on a diazonium site to substitute for the biosynthetic oxidative coupling in linking rings A and C (bond "a").

The Diels–Adler Approach.[5]—The dienophile implicit in dissection **2** is 3,4-methylenedioxy-ω-nitrostyrene, bearing the correct skeleton and *trans* geometry and easily prepared from piperonal and nitromethane.[6] Unfortunately, this is a weakly activated dienophile, so that, while it reacted acceptably with butadiene to form **4a**, only polymers (and unchanged nitrostyrene) resulted from dienes with more than four carbons, like hexatriene or vinylacrylic acid. With vinylfuran, the nitrostyrene was consumed, but the reaction yielded a host of products (with saturated $-NO_2$ in the ir spectra) inseparable by chromatography. The expected product, **5**, should yield a bromo ketone

(1) Abstracted in part from the doctoral dissertation of D. R. D., UCLA, 1961.

(2) (a) W. C. Wildman, "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, p 289; (b) H. G. Boit, "Ergebnisse der Alkaloid Chemie bis 1960, "Akademie–Verlag, Berlin, 1961.

(3) E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

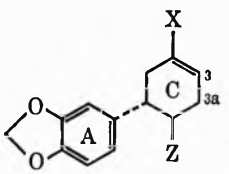
(4) (a) D. H. R. Barton and T. Cohen, "Festschrift A. Stoll," Birkhauser, Basle, 1957, p 117; (b) A. R. Battersby, *Quart. Rev.*, **15**, 278 (1961); (c) D. A. Archer, S. W. Breuer, R. Binks, A. R. Battersby, and W. C. Wildman, *Chem. Comm.*, 168 (1963).

(5) A similar Diels–Alder construction was later used to synthesize the lycoranes by R. K. Hill, J. A. Joule, and L. J. Loeffler, *J. Amer. Chem. Soc.*, **84**, 4951 (1962).

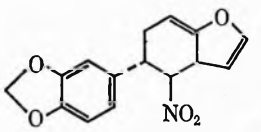
(6) L. Bouveault and A. Wahl, *Compt. Rend.*, **135**, 42 (1902). We used a modification of the procedure of D. E. Worrall, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941.

on bromination/hydrolysis, but, while bromine was consumed, no spectral indication of ketone resulted. The six-carbon diene **6** was also used under a variety of thermolysis conditions, none of which short of charring led to consumption of the nitrostyrene.

If a four-carbon diene is used, the final two carbons (4 and 5 in 2) may conveniently be attached as an amide and cyclized to ring C later. As this later cyclization requires activating groups in ring C, we examined alternate dienes to provide other functionality there. Both 2-ethoxy-[7] and 2,3-diethoxybutadienes[8] were examined, but neither provided significant rate or yield enhancement in the cycloaddition, and both adducts were contaminated with ketonic hydrolysis products despite strenuous efforts to maintain anhydrous conditions. The pure adduct **4c**[9] from the former diene was cleanly converted to a bromo ketone on bromination, but bromination of the total cycloaddition product yielded an unacceptable mixture. Hence the choice was made to develop the simple butadiene adduct **4a** on grounds of economical logistics, since the substituted dienes themselves cost two synthetic steps to prepare. The adduct **4a** is formed in 72% yield in 48 hr at 125° and requires two successive oxidations from the ring C olefin to afford a ketone at C-3 for activating cyclization of a two-carbon amide to C-3a.



4a, X = H; Z = NO_2
b, X = H; Z = NH_2
c, X = OEt; Z = NO_2



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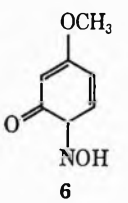
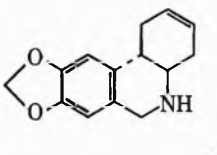
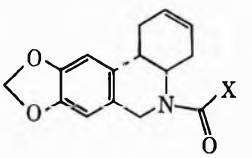


6

Chemical reduction with zinc and hydrochloric acid smoothly transformed the nitro **4a** into amino **4b** function without affecting the double bond, and this primary amine was converted in high yield to the secondary amine **7** by Helfer's procedure[10] with formaldehyde and hydrochloric acid. Before proceeding, however, it was necessary to confirm structure **7**, first with respect to retention of the *trans* ring junction, and second as to the orientation of formaldehyde condensation onto the aromatic ring. It was accepted that the diene addition produced the *trans* isomer, **4a**, and that catalytic reduction of **4a** in neutral solvent produced the dihydro derivative of **4b** without change in any configuration. We found that, when **4b** produced by zinc reduction was hydrogenated, the same dihydro derivative resulted. On the other hand, lithium aluminum hydride reduction of **4a** yielded a roughly 1:1 mixture of amino-olefins (**4b** and the epimerized *cis* isomer) which were separated as crystalline hydrochlorides and identified.[11] **4b** gave the same dihydro derivative as before when subjected to catalytic reduction, while the other gave an isomeric saturated amine. Thus, we concluded that zinc reduction in fact yields the *trans* isomer **4b**. Proof of the orientation of the formaldehyde cyclization as indicated in **4** was obtained by permanganate oxidation of **7** to 3,4-methylenedioxyphthalic (hydrastic) acid, identical with an authentic sample similarly prepared from lycorine.



7



8a, X = $CHCl_2$
b, X = $COOC_2H_5$
c, X = $CH(OCH_3)_2$

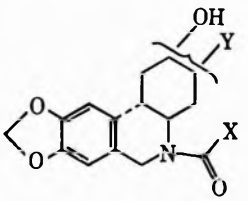
Two series of amides, **8a** and **8b**, were prepared from amine **7** with the appropriate acid chlorides and examined in detail, based on a plan of cyclization to the enol of a C-3 ketone; **8c** proved unstable to acidic conditions for olefin oxidation. To create the C-3 ketone requires unsymmetrical oxidative functionalization of the double bond, which has no strong asymmetry to influence directionality of attack. However, conversion of olefin to acyloin (α-hydroxy ketone) will allow tautomeric equilibration of the two isomers, and this equilibrium mixture can provide activation for cyclization and so be driven completely to the correct product.

Several routes can convert olefin to acyloin. The first oxidation step can create two possible bromohydrins or epoxides but only one *trans*-diol. The epoxide(s) from **8a**, *via* perbenzoic acid, yielded only diol **9b** on attempted oxidation to acyloins **11c** with dimethyl sulfoxide–boron trifluoride.[12] *trans*-Diol **10b** was created with performic acid. It was hoped that Oppenauer oxidation conditions using *t*-butoxide and benzophenone (or fluorenone) would convert this diol to acyloins **12c**, equilibrate these, and further catalyze Dieckmann cyclization to **14a**, but no enolic products were detected, nor indeed any oxidation of diol at all.

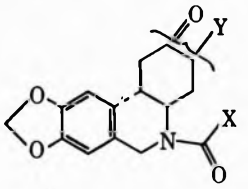
Bromohydrins **9a** and **10a** were formed in very high yield with N-bromosuccinimide in wet dimethyl sulfoxide.[13] The approximately 1:1 mixture **9a** was separable by crystallization, while **10a** was not. In each case, the mixture was smoothly oxidized to a noncrystalline bromo ketone mixture, **11a** or **11b**, respectively. Each bromo ketone mixture yielded an acetoxy ketone mixture (**11b** and **12b**, respectively) with potassium acetate in dimethylformamide; mass spectra later supported these formulations. A variety of hydrolysis and methanolysis experiments to convert **11b** to **11c**, even under stringent oxygen-free conditions, yielded only an acid product, tentatively formulated as **13** from ir spectrum, analysis, and neutralization equivalent.[14] This curious and unexpected oxidation

(7) H. L. Holmes and K. M. Mann, *J. Amer. Chem. Soc.*, **69**, 2000 (1947).
(8) J. R. Johnson, W. H. Jobling, and G. W. Bodamer, *ibid.*, **63**, 131 (1941).
(9) The structure of the adduct is based on analogy to the case reported by W. C. Wildman, R. B. Wildman, W. T. Norton, and J. B. Fine, *ibid.*, **75**, 1912 (1953).
(10) L. Helfer, *Helv. Chim. Acta*, **7**, 945 (1924).
(11) Similar differences in configuration on aliphatic nitro reduction are reported by N. Kornblum and L. Fishbein, *J. Amer. Chem. Soc.*, **77**, 6266 (1955).
(12) T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1961).
(13) Subsequently investigated further: D. R. Dalton, J. B. Hendrickson, and D. Jones, *Chem. Commun.*, 591 (1966).
(14) Later attempts to characterize this product by nmr and mass spectra were foiled by its insolubility and lack of volatility, although a mass spectrum of the precursor **11b** was consistent with that formulation.

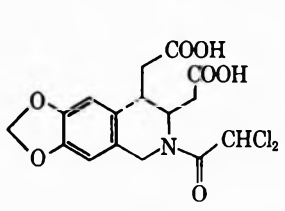
terminated the **8a** → **11c** route but showed in passing no cyclization under the basic conditions used in hydrolysis of **11b**.



9 (X = $CHCl_2$) **10** (X = $COOC_2H_5$)
a, Y = Br **a**, Y = Br
b, Y = OH **b**, Y = OH



11 (X = $CHCl_2$) **12** (X = $COOC_2H_5$)
a, Y = Br **a**, Y = Br
b, Y = OAc **b**, Y = OAc
c, Y = OH **c**, Y = OH



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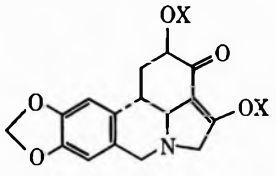
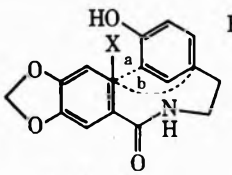


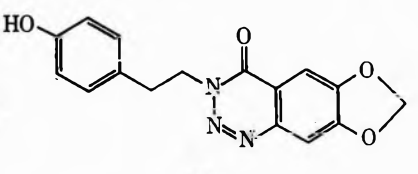
14a, X = H
b, X = Ac

In the oxalamide series **8b** → **12b** a small amount of crystalline keto acetate **12b** was obtained on extensive chromatography. Treatment of this product with methoxide in methanol yielded an enolic product, **14a**,[15] which could be acetylated to a crystalline diacetate **14b**. However, similar methoxide treatment of the noncrystalline mixture **12b** yielded no crystalline products. Accordingly, we turned our attention to other synthetic avenues.

The Biosynthetic Model Approach.—The direct analog of the biosynthetic coupling is a Pschorr coupling of two aromatic rings as in **15**, either through a nine-membered ring ("a") to the lycorine skeleton or a seven-membered ring ("b") to the crinine system, the other major *Amaryllidaceas* skeleton.[2] Conjugate addition of the nitrogen to the intermediate ring C diene would complete either reaction, just as in the natural biosynthesis. Models imply little steric strain in such cyclizations, but the statistical improbability of attaining the correct transition geometry is a grave disadvantage. However, the reaction has the advantage of being easy to try.



15a, X = NO_2
b, X = NH_2
c, X = $N_2^+BF_4^-$



16

(15) This structure of **14a** is written for convenience in only one of the two tautomeric forms possible for the 1,3-diketone system.

The *p*-hydroxyphenethyl amide of 6-nitropiperonylic acid (**15a**) was readily prepared by allowing 6-nitropiperonylic acid chloride to react with *p*-hydroxyphenethylamine.[16] Hydrogenation then afforded the amine, **15b**, which was diazotized in fluoroboric acid to the crystalline diazonium fluoroborate, **15c**, which melts at 140° and bubbles at about 170°. On heating in water, this is converted to the benztriazinone, **16**, which does not bubble on heating to 300°. Pyrolysis of the diazonium salt causes extensive decomposition at atmospheric pressure under nitrogen and slow sublimation of benztriazinone *in vacuo*. This stable product is also unchanged on heating in nitrobenzene, polyphosphoric acid, or alkali, and unaffected by photolysis.[17] Although it is in principle in equilibrium with the diazonium salt in strong acid, the benztriazinone was unaffected by anhydrous fluoroboric acid[18] or refluxing boron trifluoride in diglyme.

Thus it was apparent that, without the amide nitrogen fully substituted, we could not proceed beyond its internal attack on the diazonium grouping to form a triazinone.

The foregoing experiments were aimed not only at coupling the aromatic rings but also at destroying the aromaticity of ring C. In the subsequent experiments, we undertook to do this operation first and separately. One procedure for breaking into the aromaticity of a phenol in a way which provides useful product functionality for our purpose is the Wessely lead tetraacetate oxidation of phenols, which affords a quaternary site bearing acetoxy on a dienone.[19] Oxidation of the *o*-hydroxyphenethyl amide of 6-nitropiperonylic acid (analogous to the *para* derivative **15a**) with lead tetraacetate gave a poor yield of a neutral substance which, after chromatography, exhibited only one spot on a thin-layer plate and an ultraviolet absorption maximum of 300 mμ, like the model product from *o*-cresol, but could not be induced to crystallize. The evidence points to its formulation as **17**. It was clear, however, that the amide nitrogen had not spontaneously cyclized as desired by conjugate addition, and several different attempts to effect this by treatment with acid led only to alkali-soluble substances with no evidence either of ketone by ir or of the initial uv absorption remaining at 300 mμ. In these cases acid-catalyzed dienone–phenol rearrangement presumably intervened as the fastest reaction. Conversely, treatment with sodium hydride in tetrahydrofuran to generate the amide anion caused no change whatever in the dienone absorption at 300 mμ.

In a variation on this approach, we sought to provide

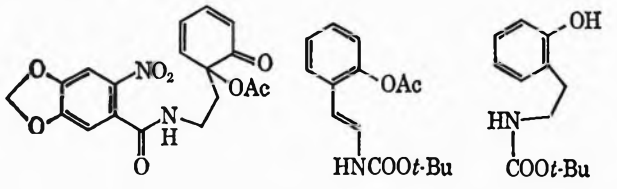
(16) The phenethylamines used in this work were synthesized from the appropriately methoxylated benzaldehyde, *via* nitromethane condensation to the β-nitrostyrene and reduction with lithium aluminum hydride to the methoxyphenethylamine; the methyl ethers were cleaved with hydriodic acid.

(17) Photolysis of benztriazines has been reported; *e.g.*, E. M. Burgess and L. McCullagh, *J. Amer. Chem. Soc.*, **88**, 1580 (1966).

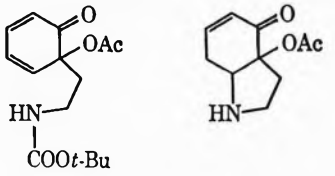
(18) A convenient source of a strong anhydrous acid containing poor nucleophiles is the solution made from commercial aqueous fluoroboric acid (50%) and trifluoroacetic anhydride. This solution, at about 1 *M* concentration in HBF_4, protonates anthraquinone completely and nitro- and 2,4-dinitrobenzene detectably by visual color change.

(19) Reviewed by J. D. Loudon in "Progress in Organic Chemistry," Vol. 5, Butterworths and Co. Ltd., London, 1961, p 51.

the nitrogen for the internal conjugate addition in the more nucleophilic form of a free amine rather than the deactivated amide which did not cyclize in **17**. However, the amine must be protected during the lead tetraacetate oxidation and subsequently released under very mild conditions after the dienone is prepared. For this purpose, we selected the *t*-butyloxycarbonyl group and synthesized compound **19** by the expedient of carrying out a Curtius rearrangement on *o*-acetoxycinnamoyl azide in boiling *t*-butanol to yield the *t*-butylurethan, **18**,[20,21] which was then hydrogenated and subjected to mild methanolysis of the phenolic *o*-acetyl, yielding **19**.



17 **18** **19**

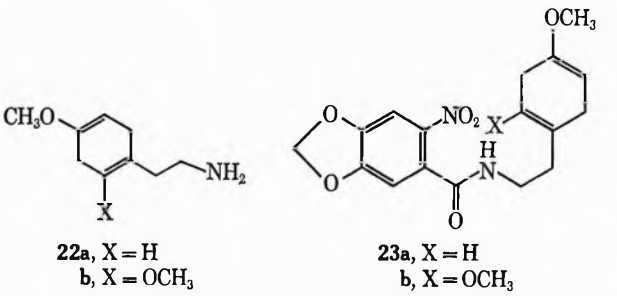


20 **21**

When the phenol **19** was subjected to lead tetraacetate treatment, the dienone **20** was obtained pure only after extensive chromatography and in very low yield; this dienone again exhibited a 301-mμ ultraviolet absorption maximum, indicating that the urethan nitrogen had not cyclized. When the urethan was dissolved in trifluoroacetic acid, it bubbled immediately and retained its dienone chromophore at 301 mμ for over an hour, but, when the solution was made basic after 3 min and worked up, only traces of nonacidic material were found. Thus it appeared that the free amine did not cyclize to **21** rapidly enough to prevent base-catalyzed rearrangement of the dienone, or that its cyclization, being reversible, did not inhibit the irreversible rearrangement.[22]

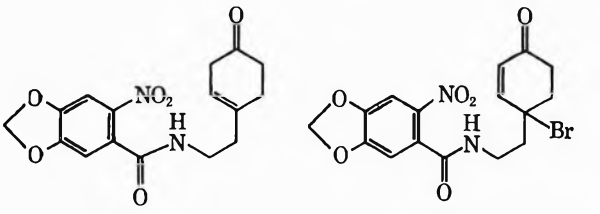
Following dissection (**3**) the expected compound **21** was to have been acylated with an appropriate piperonylic acid derivative with a view to cyclization of a ring C enol to a diazonium grouping on the piperonylic ring A. In an alternative also involving destruction of ring C aromaticity, we undertook initial Birch reduction of the phenethylamine components[16] with *p*-methoxy- or *o*,*p*-dimethoxy groups, so that on hydrolysis the nitrogen would have a basis for cyclization. With each of these phenethylamines, Birch reduction led to **22** and acylation afforded **23**.

Hydrolysis of neither free amine **22** produced characterizable secondary amino bicyclic ketones, but hydrolysis of **23a** produced a crystalline saturated ketone, characterized as **24** by analysis and spectral evidence (ir 5.8 μ, one vinyl proton at τ 4.5 in the nmr) as well as by rapid bromination to **25** which exhibited λ_{max} 227 mμ (after substraction of the 6-nitropiperonylamide chromophore) and two vinyl protons in the nmr. The salient feature here is that the amide nitrogen did not cyclize in a Michael addition, either by acid equilibration of the double bond in **24**[23] or directly in **25**.



22a, X = H
b, X = OCH_3

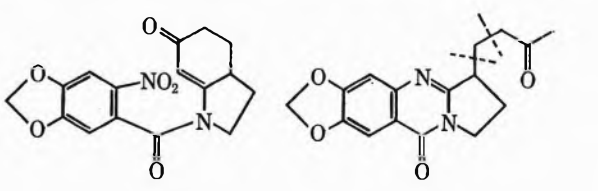
23a, X = H
b, X = OCH_3



24 **25**

The cyclization of the amide nitrogen was assured in the oxidized derivative **23b**, which on hydrolysis afforded the crystalline amide **26** of a bicyclic amino ketone, characterized by λ_{max} 289 mμ, strong ir bands at 5.94, 6.05, 6.20, 6.55, and 7.50 μ, and a single vinylic hydrogen singlet at τ 3.85. Ordinary procedures for nitro group reduction led also to destruction of the 289-mμ chromophore, but hydrogen transfer using α-phellandrene with palladium on charcoal[24] produced a crystalline product with the correct analysis and mass for the product of nitro reduction to amine in **26**.

We had anticipated that the amino group formed might add in a conjugate addition to the unsaturated ketone, but assumed that the subsequent diazotization would reverse this process; however, diazotization had no effect on this new product. The ultraviolet spectrum of this reduction product (λ_{max} 238 mμ, 320 mμ) was very reminiscent of that of the several benztriazinones (λ_{max} 242 mμ, 320 mμ), and the nmr showed no vinylic or exchangeable hydrogens, but a total of twelve protons above τ 6, three of them in a sharp singlet at τ 7.8. Since the ir showed a saturated ketone (5.84 μ) and bands at 6.02, 6.13, and 6.28 μ, we recognized the molecule as the stable 4-quinazolone derivative **27**, consistent with a formation *via* conjugate addition of the



26 **27**

(20) *t*-Butylurethans are not only conveniently prepared by the Curtius rearrangement, usually carried out directly in refluxing *t*-butanol, but serve to improve enormously the classical use of the Curtius procedure for conversion of acids to amines, since the traditional hydrolysis of isocyanates and urethans is usually plagued by intractable urea formation, while treatment of *t*-butylurethans in trifluoroacetic acid at room temperature affords the amine salt instantly and quantitatively.

(21) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 98 (1957).

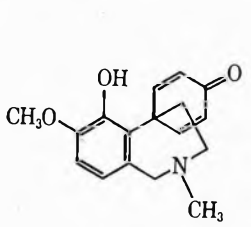
(22) A comparable base-catalyzed dienone rearrangement may be found in S. Goodwin and B. Witkop, *ibid.*, **79**, 179 (1957).

(23) For a study of α,β- $\rightleftarrows$ β,γ-cyclohexenone equilibria, see K. G. Lewis and G. J. Williams, *Tetrahedron Lett.*, 4573 (1965).

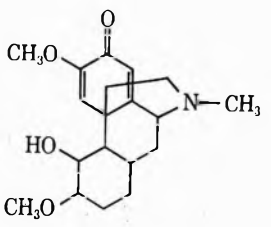
(24) R. Pallaud and H. Anh-Hoa, *Comp. Rend.*, **250**, 2730 (1960); **252**, 2896 (1961).

aromatic amino group followed by an irreversible retro-aldol reaction. In the mass spectrum, besides the parent peak (M = 300), compound **27** showed major peaks at 243 (M − 57) and 229 (M − 71) corresponding to fragmentations at the dotted lines in **27** by McLafferty rearrangements.

This results clearly puts an end to this synthetic approach to lycorine; in fact, all of the latter approaches may be said to have been frustrated by internal conjugate additions, both those which did not go as anticipated and those which went irreversibly when not desired. Previous experience in polycyclic alkaloid syntheses also implies that internal conjugate additions of heteroatoms are not always equilibrium favored, even when forming five- and six-membered rings. The steric and conformational factors which control these equilibria appear to be too complex to assess in these molecules, for the phenolic hydroxyl in **28** cyclized spontaneously[25] whereas in **29** it did not.[26]



28



29

Experimental Section[27]

Diels–Alder Reactions with β-Nitro-3,4-methylenedioxystyrene.[6]—These were carried out in sealed Pyrex Carius tubes, with small amounts of hydroquinone added for polymerization inhibition; the dienes in most cases were kept over molecular sieve and distilled from this directly into the flame-dried Carius tube. Dried solvent was added as necessary, and the tube was flushed with nitrogen, sealed, and heated in a Wood's metal bath. The following experimental conditions were examined.

These reactions were worked up by adding chloroform to the opened tube and examining the ir for the presence of the 7.45 μ band of the starting nitrostyrene and of the 6.45 μ band shown by adducts. If some of the latter was present, the mixture was chromatographed on alumina and fractions examined by ir. In the first two cases above, the nitrostyrene was always recovered in over 90% yield; much insoluble matter remained in most cases. In the third case, both starting materials were isolated in high yields. With 2-vinylfuran, disappearance of the 7.45 μ band occurred only in the nonsolvent cases. In such cases extensive column chromatography of the dark reaction residue afforded no crystalline products and thin-layer chromatography was not at that time in use. Both unreacted starting materials were recovered in low yield.

TABLE I

Diene (g, mmol)	Dienophile, g, mmol	Time, hr	Temp, °C	Solvent
Vinylacrylic acid	3.18,	20	25–30	Toluene
(14.7, 150)	16	20	25–30	None
		8	100–105	Toluene
		8	100–105	None
		48	200–210	Toluene
1,3,5-Hexatriene	2.51,	48	32	Ether
(2.4, 29)	13	5	90–100	Toluene
		12	190–200	Toluene
		48	180–190	Xylene
		96	180–190	Xylene
2-Nitroso-5-methoxy-	1.0,	9	220–230	Toluene
phenol (1.0, 6.5)	5.0	48	220–230	Toluene
		48	220–230	None
2-Vinylfuran	5.0,	20	100–105	Toluene
(5.0, 53)	25	20	200–210	Toluene
		10	100–105	None
		20	100–105	None
		9	140–145	None
		6	155–160	None

Bromination of the vinylfuran products in carbon tetrachloride led to bromine uptake, and addition of water afterwards gave an acidic reaction. The solution was then shaken with aqueous thiosulfate and the organic layer evaporated to a red gum and chromatographed. This procedure again produced neither a crystalline residue nor an ir absorption from 5.5–6.1 μ.

1-Ethoxy-4-nitro-5-(3,4-methylenedioxyphenyl)cyclohexene (4c).—To 5.0 g (25 mmol) of β-nitro-3,4-methylenedioxystyrene, powdered and dried *in vacuo* at 80°, was added 2-ethoxy-1,3-butadiene[7] (5.0 g, 51 mmol) by direct distillation from a molecular sieve into a dry Carius tube. Several crystals of hydroquinone were added, and the tube was flushed with dry nitrogen, sealed, and heated for 24 hr at 120°. On opening the tube, rinsing out the chloroform, evaporation, and chromatography on alumina in benzene, there was obtained the adduct **4c**: 2.3 g (31%); mp 105–106°; ir 6.00, 6.45 μ.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.82; H, 5.89; N, 5.02.

A second material from the chromatography was the nitro ketone corresponding to **4c**: 3.10 g (46%); mp 197–198°; ir 5.82, 6.44 μ. 100 mg of **4c** was refluxed for 10 hr in 5 ml of 95% ethanol containing 1 drop of 5% sulfuric acid. The solution was cooled, water was added, and an ether extraction was performed. The extract on washing, drying, and evaporation yielded an oil which crystallized from methanol: 82 mg (91%), mp and mmp 197–198° with the ketone above.

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.07; H, 5.17; N, 5.27.

Bromination of the enol ether **4c** in chloroform afforded the expected bromo ketone, crystallized from methanol: mp 121–130°; ir 5.82, 6.04 μ.

Anal. Calcd for $C_{13}H_{12}NO_5Br$: C, 45.62; H, 3.78; N, 4.07. Found: C, 45.51; H, 3.77; N, 3.88.

***trans*-4-Nitro-5-(3,4-methylenedioxyphenyl)cyclohexene (4a).**—3.5 g of β-nitro-3,4-methylenedioxystyrene and a few crystals of hydroquinone were added to 8.0 g of liquefied butadiene and 15 ml of toluene in a cooled steel-clad pyrex bomb. The bomb was sealed and heated for 3 days at 120–125°, then cooled in Dry Ice and opened. The contents were dissolved in a minimum of ether and passed through 40 g of alumina with about a liter of ether. Evaporation yielded 2.98 g (72%) of adduct **4a**, mp 99.8–100.2°.

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.92; H, 5.21; N, 5.87.

***trans*-4-Amino-5-(3,4-methylenedioxyphenyl)cyclohexane (4b).**—The nitro olefin **4a** (10 g, 40.5 mmol) was placed in a 1-l. three-neck flask with stirrer, condenser, addition funnel, and heating mantle. To the nitro olefin was added purified zinc dust (50 g, 0.766 g-atom), water (50 ml), and *t*-butyl alcohol (3 ml). Heating and stirring was begun, and, when the water started to reflux, 1:1 aqueous hydrochloric acid (150 ml) was added slowly over about 2 hr, then refluxed for 4 hr and filtered through glass wool. The solution was cooled, made strongly basic with 20% sodium hydroxide, and continuously extracted with ether.

(25) D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 806 (1962).

(26) D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas *ibid.*, 2423 (1965).

(27) Melting points were determined with a Fisher–Johns block and are corrected. Infrared spectra were recorded in chloroform or methylene chloride solution unless indicated by (KBr) for solid state spectra, and were taken on a Perkin-Elmer Model 137 Infracord. All methylenedioxy compounds showed a diagnostic infrared peak at 9.6 μ, which is not separately recorded in the experiments. Ultraviolet spectra were observed in 95% ethanol solution on a Cary 14 recording spectrophotometer or a Perkin-Elmer Model 202 recording spectrophotometer and are recorded as λ_{max} in mμ (log ε). Proton magnetic resonance spectra were obtained with a Varian A-60A instrument purchased with funds from the National Science Foundation; they were recorded in $CDCl_3$ unless otherwise noted. Microanalyses were performed by Miss Heather King at UCLA, where the early work was performed, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., for later work. The described experimental work was begun in 1958 at UCLA by D. R. Dalton, and part of the present study is incorporated in his doctoral thesis in 1961 at that institution. Nmr and mass spectra were not available to use for those early studies and are therefore absent from the experimental descriptions except in a few key cases for which samples were run recently for confirmation.

The ether extract (about 300 ml) was dried, 5 ml of anhydrous methyl alcohol followed by anhydrous hydrogen chloride, added, and the solution left to crystallize in the refrigerator. The crystals of amine hydrochloride (9.9 g, 97%) were filtered and recrystallized from methyl alcohol: mp 208–209°.

Anal. Calcd for $C_{13}H_{16}NO_2Cl$: C, 61.53; H, 6.35; Cl, 13.98. Found: C, 61.52; H, 6.51; Cl, 13.89.

trans-2-(3,4-Methylenedioxyphenyl)cyclohexylamine. A.—The amine **4b** was generated as an oil by making an aqueous solution of the above hydrochloride basic and extracting with methylene chloride. To 447 mg (2.06 mmol) in 10 ml of 95% ethanol was added 25 mg of platinum oxide and hydrogenation at atmospheric pressure was carried to an uptake of one equivalent of hydrogen. On filtration, evaporation to small volume, and treatment with 1:1 hydrochloric acid, 354 mg (79%) of crystalline hydrochloride was obtained, mp 260–261°.

Anal. Calcd for $C_{13}H_{13}NO_2Cl$: C, 61.10; H, 7.10; Cl, 13.88. Found: C, 61.19; H, 7.32; Cl, 13.61.

B.—The nitro olefin **4a** (322 mg, 1.47 mmol) in 40 ml of 95% ethyl alcohol was hydrogenated at 40-lb pressure with W-5 Raney nickel. After filtration of the solution through a mat of Celite, it was evaporated to a colorless oil which yielded a tan solid (89%) on treatment with 1:1 aqueous hydrochloric acid (4 ml). This solid, mp 247–255°, recrystallized from chloroform–ethanol to mp 260–261°, mmp with the hydrochloride from A above, 260–261°.

cis-4-Amino-5-(3,4-methylenedioxyphenyl)cyclohexane.—To lithium aluminum hydride (9 g, 0.237 mol), suspended in anhydrous ether (300 ml) in a 1-l. three-neck flask with condenser, stirrer, and addition funnel, was added 4-nitro-5-(3,4-methylenedioxyphenyl)cyclohexene (10 g, 0.40 mol) in anhydrous ether (200 ml). The nitro olefin was added slowly with stirring, maintaining a slow reflux throughout the addition. After 1 hr for the addition, the solution was refluxed with stirring for an additional 3.5 hr, then cooled, and the excess hydride decomposed by careful addition of 5% aqueous potassium hydroxide. On sudden precipitation of solids, the addition of base was halted and the ether decanted. The precipitate was washed with ether and the solution and washings were combined, washed with water, and dried. After filtration, the ether was evaporated to a small volume (about 50 ml), methyl alcohol (5 ml) added, and the solution cooled in an ice bath while anhydrous hydrogen chloride was passed in.

On cooling overnight in the refrigerator, 4.2 g (41%) of a white crystalline solid, mp 231–233°, were deposited.

Anal. Calcd for $C_{13}H_{16}NO_2Cl$: C, 61.53; H, 6.36; Cl, 13.98. Found: C, 61.48; H, 6.22; Cl, 13.98.

After filtration, the mother liquors were evaporated and the residue taken up in hot 4:1 chloroform–methanol. On cooling, 4.05 g (40%) of colorless crystals were collected, mp and mmp with the *trans*-amino olefin **4b** above, 208–210°. Hydrogenation yielded the same dihydro compound as above, mp and mmp 260–261°.

cis-2-(3,4-Methylenedioxyphenyl)cyclohexylamine.—Hydrogenation of the *cis*-amino olefin as described above yielded a dihydro compound as the hydrochloride (91%), mp 227–228°.

Anal. Calcd for $C_{13}H_{13}NO_2Cl$: C, 61.10; H, 7.10; Cl, 13.88. Found: C, 60.92; H, 6.85; Cl, 13.59.

sec-Amino Olefin 7.—The *trans*-4-amino-5-(3,4-methylenedioxyphenyl)cyclohexene (**4b**) hydrochloride (5.22 g, 2.06 mmol) was converted to the free amine with aqueous hydroxide. This was extracted into ether, dried, and evaporated to an oil. The oil was treated, dropwise, with stirring and steam bath warming, with 10 g of 20% formaldehyde solution, then stirred and heated for 1 hr. To the gum and solution, hot benzene was added and the benzene extracts were dried and evaporated to a colorless oil, which was treated with warm 1:1 hydrochloric acid to yield a white crystalline solid, 5.0 g (91%), mp 270.5–271°.

Anal. Calcd for $C_{14}H_{16}NO_2Cl$: C, 63.77; H, 6.07; N, 5.27. Found: C, 63.28; H, 6.03; N, 5.30.

1.0 g was dissolved in water and heated during dropwise addition of 4 g of potassium permanganate (in 100 ml of water) for 1 hr, treated with sulfur dioxide, and the clear acidic solution concentrated, washed with ethyl acetate, then continuously extracted with ether to yield 137 g of a gum, sublimation of which afforded 27 mg of white crystals, mp 174–175°, mmp 173–175° with a sample of hydrastic acid comparably produced from permanganate oxidation of natural lycorine.

N-Dichloroacetyl Amino Olefin (8a).—The amine hydrochloride (839 mg, 3.15 mmol) was converted to free amine **7** as above; its ether solution (80 ml) was treated with 5 ml of triethylamine and a solution of 1.0 g (6.85 mmol) of dichloroacetyl chloride in ether (20 ml); the ether solution was added dropwise over a period of 15 min; and the solution was allowed to stir at room temperature overnight. This was poured into ice (100 g) and sulfuric acid (1 *N*, 20 ml) extracted with methylene chloride; the extracts were combined and washed with aqueous potassium hydroxide (5%) until the wash was clear, then with 1 *N* sulfuric acid and water. The methylene chloride was dried, filtered, and evaporated to yield 957.2 mg (89%) of offwhite crystals. Recrystallization from 1:1 methyl alcohol–chloroform gave 946 mg of white needles, mp 223–224°, ir 6.02 μ.

Anal. Calcd for $C_{16}H_{15}NO_3Cl_2$: C, 56.49; H, 4.44; Cl, 20.85. Found: C, 56.29; H, 4.75; Cl, 20.50.

The dibromide was prepared by bromination of the olefin in chloroform solution: mp 193.5–194.0°.

Anal. Calcd for $C_{16}H_{15}NO_3Cl_2Br_2$: C, 38.43; H, 3.02; N, 2.80. Found: C, 38.61; H, 3.26; N, 2.80.

Epoxidation of the Dichloroacetamide 8a.—The amido olefin **8a** (914 mg, 2.68 mmol) was dissolved in chloroform (50 ml) and perbenzoic acid (6.5 ml of 0.44 *M* or 2.86 mmol) in chloroform was added. The mixture was allowed to stand overnight. Saturated sodium bicarbonate solution (20 ml) was added, stirred for half an hour, and the chloroform washed with water, dried, filtered, and passed through a plug of alumina (neutral). The eluent yielded a white crystalline epoxide (836 mg), mp 251–252°.

Anal. Calcd for $C_{16}H_{15}NO_4Cl_2$: C, 53.95; H, 4.25; N, 3.93. Found: C, 54.06; H, 4.31; N, 3.78.

Attempted Oxidation of the Epoxide to the Acyloin (11c).—The epoxide (732 mg, 2.05 mmol) was dissolved in anhydrous dimethyl sulfoxide (60 ml), the solution treated with anhydrous boron trifluoride etherate (0.2 ml), and the mixture warmed on the steam bath with a drying tube. After 5 hr, an additional 0.2 ml of boron trifluoride was added, and after 10 hr an additional 0.2 ml. After 22 hr the dark mixture was removed, poured into ice–water (1 l.), and the aqueous solution extracted with ether. The ether extract was washed with 5% aqueous potassium hydroxide, 1:1 aqueous hydrochloric acid, and water, dried, filtered, and evaporated to 397 mg of light yellow oil, which crystallized on standing in chloroform, depositing 74 mg of crystals, mp 216–218°; like the total oil, these showed no ir absorption at 5.8–6.0 μ but did have bands around 3 μ, suggestive of the diol **9b**.

Bromohydrins 9a.—The amido olefin **8a** (993 mg, 2.91 mmol) was dissolved in 5:1 diglyme–water (100 ml), heated in a water bath (80–90°), and stirred while 8 drops of perchloric acid was added. The solution was then treated, over a 45-min period, with N-bromosuccinimide (1.0 g, 5.62 mmol). The color of the solution following the addition of a portion of the N-bromosuccinimide was allowed to fade before the next portion was added. After the addition was complete, the solution still retained a slight yellow color and was allowed to remain at 80–90° for an additional 30 min. Afterward, a few crystals of sodium bisulfite were added to destroy the excess N-bromosuccinimide.

The colorless solution was partitioned between ether and water and the ether dried and evaporated to an oil; treatment with several drops of methyl alcohol resulted in the deposition of 1.18 g (93%) of crystalline material, mp 170–177°.

Several recrystallizations from benzene gave one isomer, mp 223–224°, in 44% yield.

Anal. Calcd for $C_{16}H_{16}NO_4BrCl_2$: C, 43.96; H, 3.69; N, 3.20. Found: C, 44.05; H, 3.94; N, 3.42.

Combination and evaporation of the mother liquors yielded 490 mg (41%) of the other isomer, mp 211–212°.

Anal. Calcd for $C_{16}H_{16}NO_4BrCl_2$: C, 43.96; H, 3.69; N, 3.20. Found: C, 43.61; H, 3.51; N, 3.47.

An admixture of these isomers possessed a melting point of 174–183°.

Bromo Ketones (11a).—The crystalline bromohydrin mixture (5.04 g, 11.5 mmol) was dissolved in acetone (250 ml) with warming, the solution was cooled to −5°, and 2.86 ml (7.67 mmol) of chromic anhydride solution (made from 26.7 g of anhydride in 23 ml concentrated sulfuric acid and diluted to 100 ml with water) was added dropwise over 1.25 hr below 0°. The solution was allowed to warm to room temperature over a period of 1.5 hr and poured into 1 l. of cold water; the resulting suspension was filtered and the precipitate dissolved in warm chloroform, which was dried and evaporated to yield 5.07 g of slightly yellow oil, which crystallized on treatment with methanol.

Recrystallization from 1:1 methanol–chloroform yielded 2.6 g, mp 219–220°, ir 5.80, 6.06 μ.

Anal. Calcd for $C_{16}H_{14}NO_4BrCl_2$: C, 44.17; H, 3.24; N, 3.22. Found: C, 43.94; H, 3.39; N, 3.36.

Evaporation of the mother liquors yielded 2.4 g of material with ir identical with that of the crystalline sample and presumed to consist of a mixture of the two bromo ketones, **11a**.

Treatment of the Bromo Ketone 11a with Alkali.—The crystalline bromo ketone (254 mg, 0.582 mmol) was suspended in a cup above a solution of 2.0 mmol of potassium hydroxide in absolute ethanol (20 ml). After the system had been flushed with helium, the cup was inverted and the bromo ketone allowed to fall into the solution. An immediate yellow color and a white precipitate developed. After stirring at room temperature overnight, the solution was treated with water (25 ml) and 1 *N* sulfuric acid until it was acidic to litmus, and then continuously extracted with ether. The ether extract was washed once with water, dried, filtered, and evaporated to yield 103 mg of the crystalline acid, mp 221–223°, recrystallized from chloroform to 97 mg: mp 225–226°; ir (KBr) 3–3.5, 5.80, 5.91, 6.10 μ.

Anal. Calcd for $C_{16}H_{15}NO_7Cl_2$: C, 47.53; H, 3.74; Cl, 17.54. Found: C, 46.48, 49.00; H, 3.90, 4.13; Cl, 16.76. Neutralization equivalent: 197.2, 198.2.

When only one equivalent of base was used under comparable conditions, only starting material was isolated in 91% yield.

Keto Acetate 11b.—The bromo ketone **11a** (52.5 mg, 0.12 mmol) was dissolved with stirring in dimethylformamide (5 ml), and potassium acetate (48.2 mg, 0.492 mmol) was added. The solution was stoppered and allowed to stir at room temperature overnight, then diluted with water (50 ml) and extracted with ether; the ether extracts were washed once with water, dried, filtered, and evaporated; and the residue was treated with several drops of methanol. The crystals which formed weighed 30.2 mg (61%), mp 250–252°. Recrystallization from chloroform yielded white microcubes: mp 256–257°; ir 5.64, 5.70, 6.02 μ; mass spectrum, see keto acetate **12b** below.

Anal. Calcd for $C_{18}H_{17}NO_6Cl_2$: C, 52.19; H, 4.14; Cl, 17.12. Found: C, 52.47; H, 4.51; Cl, 16.99.

Treatment of 68 mg of this material with excess alkali, as with bromo ketone, afforded 51 mg of the same acid **13**, mp 222–223°.

N-Ethoxalyl Amino Olefin 8b.—20 g (7.5 mmol) of the amine hydrochloride was converted as before to the free amine **7** in 100 ml of chloroform, and 10 g of ethoxalyl chloride (7.5 mmol) in 50 ml of chloroform was added and stirred for 15 min. 100 ml of 5% aqueous potassium hydroxide was then stirred with this slurry for 20 min and the phases were separated. The chloroform was washed with 2 *N* hydrochloric acid and water, dried, and evaporated to an oil which was crystallized from a small amount of methanol to 16.4 g (70%) of colorless crystals which melted in two polymorphic modifications in different preparations, 130° and 160–161°, both giving the higher melting point when seeded with 160° material and both showing the same ir spectrum in solution: 5.74, 6.07 μ.

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.38; H, 5.65; N, 4.45.

Hydroxylation of Olefin 8b.—To 861 mg (2.62 mmol) of olefin **8b** in 5 ml of trifluoroacetic acid and 0.5 ml of water was added 13 drops (350 mg, 1.2 equiv) of 30% hydrogen peroxide at 0°. The temperature was raised to 40°, and in 45 min 5 more drops of peroxide was added. After 2 hr, excess peroxide was destroyed with aqueous sodium bisulfite and the solution was made alkaline and continuously extracted with chloroform. The 500 mg residue was dissolved in 25 ml of 1 *N* hydrochloric acid in ethanol and refluxed for 4 hr to remove trifluoroacetate esters. The hydrochloric acid–ethanol was then evaporated and the residue was chromatographed on silica in chloroform–acetone mixtures. 300 mg of oil was obtained from the 1:1 solvent eluents. The oil crystallized from chloroform to yield 229 mg (33%) of **10b**: mp 159–160°, recrystallized to 161–162°; ir 3.0, 5.75, 6.12 μ; uv λ_{max} 290 mμ (log ε 3.72).

Anal. Calcd for $C_{18}H_{21}NO_7$: C, 59.50; H, 5.82; N, 3.85. Found: C, 59.78; H, 5.91; N, 3.70.

Oppenauer Oxidations of the Diol 10b.—35 mg of diol **10b** and 23 mg of benzophenone were dissolved in 2 ml of dimethyl sulfoxide (previously dried with molecular sieve) under dry nitrogen, and 18 mg of sublimed potassium *t*-butoxide was added, causing a clear orange color. After several hours, the color had deepened somewhat and water was added to the mixture, which was extracted (with difficulty owing to emulsions) with chloroform. Drying of the extracts afforded 13 mg of an oil, which was shown by ir comparison to be largely benzophenone. Acidification of the aqueous layer and extraction with chloroform led to 22 mg of a yellow oil with a negative ferric chloride test and an ir and uv spectrum virtually identical with the starting ester diol, and with a sample of the presumed oxamic acid separately obtained from it, as an impure powder, by saponification.

The use of fluorenone under the same conditions overnight led to nearly quantitative recovery of fluorenone (96%) and a base-soluble residue similarly showing the spectral characteristics only of the oxamic acid diol. Overnight refluxing of toluene, fluorenone, and the diol led only to intractable gums and some recovered fluorenone. The Oppenauer oxidation using aluminum *t*-butoxide in refluxing toluene with quinone or fluorenone likewise returned those ketones largely unchanged along with a residue, a nonmelting and largely insoluble solid which left a residue on combustion. The nonmelting solid contained the ir absorptions only of the ethoxamide carbonyls.

Bromohydrins 10a.—To 3.36 g (10.2 mmol) of olefin **8b** in 100 ml of dimethyl sulfoxide was added 12 drops of perchloric acid. 1.89 g (10.6 mmol) of N-bromsuccinimide was added over 45 min, and the solution was stirred overnight and poured into water. The precipitate was filtered, dissolved in chloroform, washed with 5% potassium hydroxide and water, dried, and evaporated to 3.82 g of a gum with an ir (2.80, 5.75, 6.09 μ) consistent with the expected product, **10a**. The gum would not crystallize and was used directly.

Bromo Ketones 12a.—2.88 g of crude bromohydrin **10a** was treated as above for **9a** with 2 ml (5.3 mmol) of chromic anhydride solution. The resultant 2.50 g of oil exhibited ir bands at 5.78 and 6.08 μ, similar to the previous bromo ketones, but could not be induced to crystallize despite several attempts at chromatographic purification.

Keto Acetate 12b.—1.65 g of the crude bromo ketones **12a** was dissolved in 30 ml of dimethylformamide, and 1.46 g of dry potassium acetate was added. Allowed to stand overnight, the solution turned very dark and was poured into water and extracted with ether, which was dried and evaporated to a weight-constant residue. This was dissolved in chloroform and washed with 5% potassium hydroxide, 1:1 hydrochloric acid, and water, dried, and evaporated to 0.70 g of a gum which was chromatographed on alumina. The first chloroform fractions contained a major band which partially crystallized, yielding 0.40 g, mp 145–155°, recrystallized from methanol to mp 204–205°, ir (no OH band) 5.76, 6.04, 8.1 μ.

Anal. Calcd for $C_{20}H_{21}NO_8$: C, 59.55; H, 5.25; N, 3.47. Found: C, 58.69; 58.74; H, 5.36, 5.53.

Mass spectra of the two keto acetates, **11b** and **12b**, have subsequently been measured and confirm the assignments. Both show correct parent peaks, a major peak at *m/e* 187 ($C_{11}H_9NO_2$), and a methylenedioxy–isoquinoline fragment with an added methyl as well as a hydroxypenanthridine from ring C aromatization and loss of amide at *m/e* 242 ($C_{14}H_{12}NO_3$); both show peaks at P − 60 for loss of acetic acid and peaks for loss of the acyl unit from nitrogen. Below *m/e* 242 the spectra are very similar. The dichloroacetamide exhibits three parent peaks (*m/e* 413, 415, 417) in the expected intensities for two chlorines, and also peaks arising from loss of one or both of these chlorines.

Dieckmann Cyclization of 12b to 14a.—47 mg of crystalline keto acetate **12b** was dissolved in 5 ml of methanol containing 122 mg of sodium methoxide and stirred for 19 hr to a clear yellow solution. This was brought to about pH 3 with five drops of concentrated hydrochloric acid and evaporated almost to dryness, then partitioned between water and chloroform. The chloroform yielded 23 mg of yellow foam with a green ferric chloride color (in pyridine): uv λ_{max} 291 mμ (log ε 3.6); ir 5.65, 5.80, 6.05 μ.

The product was acetylated in 2 ml each of pyridine and acetic anhydride overnight at room temperature. After evaporation and chromatography on alumina, the main fraction (22 mg) afforded crystals from benzene (10 mg): mp 139–140°; ir 5.62, 5.72, 5.82, 6.08 μ.

N-(6-Nitro-3,4-methylenedioxybenzoyl)tyramide (15a).—2.11 g (10.0 mmol) of 6-nitropiperonylic acid[28] and 2.2 g of phosphorus pentachloride were covered with 10 ml of carbon tetrachloride, refluxed for 20 min, and the carbon tetrachloride evaporated off. 20 ml more carbon tetrachloride was added and boiled off, and the residue was dissolved in ether (50 ml) and washed with water.

(28) J. B. Ekely and M. S. Klemme, *J. Amer. Chem. Soc.*, **50**, 2711 (1928).

A solution of 1.74 g (10.0 mmol) of tyramine hydrochloride in 20 ml of water and 20 ml of triethylamine was mixed in and shaken for 10 min. The precipitated solid was separated by centrifugation, dissolved in 1 *N* sodium hydroxide, and washed with ether. After acidification and filtration, the collected solid was crystallized from methanol, yielding a first crop of 0.59 g, mp 218–220°, and a second crop of 0.42 g, mp 210–215° (total yield 33%), with ir (KBr) 3.1, 6.08, 6.45, 6.55 μ; uv λ_{max} 225 (log ϵ 4.47), 250 (4.68), 340 (3.70) mμ.

Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.17; H, 4.27; N, 8.48. Found: C, 57.96; H, 4.31; N, 8.27.

Diazonium Fluoroborate 15c.—1.00 g of nitro amide **15a** and 42 mg of platinum oxide were hydrogenated in 75 ml of absolute ethanol at atmospheric pressure; hydrogenation became very slow after an uptake of 232 ml (theoretical uptake is 243 ml for nitro reduction). The catalyst was filtered and the solvent was evaporated to a gum (1.0 g) which showed ir bands at 2.88, 2.98, and 6.04 μ, but none at 6.5 μ. The gum was treated with 1.20 ml of 50% fluoroboric acid and 25 ml of water and warmed to effect solution. It was then cooled to −5°, and a solution of 2.70 g of sodium nitrite was added. A precipitate formed immediately, and more came out on addition of 15 ml of fluoroboric acid. The yellow crystalline solid was washed with fluoroboric acid, methanol, and ether and dried over P_2O_5: mp 140–145°, bubbled at 160–170°; ir (KBr) 3.0, 4.44, 6.01 μ and a large BF_4^- absorption at 9.0–9.7 μ.

Decompositions of Diazonium Salt 15c.[29]—7 mg of the diazonium salt **15c** was added to a solution of 100 mg of potassium hydroxide in 15 ml of water and heated on the steam bath for 8 hr. The salt dissolved only slowly, and was replaced by a new crystalline solid which, after cooling, was extracted with methylene chloride and obtained, after drying and solvent evaporation, as colorless crystals, mp 206–208° (6 mg), no bubbling below 300°.

20.7 mg of salt **15c** heated at 250° under nitrogen gave only intractable tars; 10 mg heated at 220° at 20-μ pressure for 1 hr exhibited some bubbling and sublimation of a major fraction, mp 210–211°, the remaining material being negligible or charred.

13.3 mg of salt **15c** was dissolved in 5 ml of nitrobenzene and heated at reflux for 1 hr, then poured into 130 ml of water and 100 ml boiled off to remove the nitrobenzene. Extraction with methylene chloride, drying, and evaporation afforded 7.8 mg of orange solid, mp 201–205°.

20.0 mg of salt **15c** was added to freshly prepared polyphosphoric acid (1 ml) and heated for 1 hr at 185°, then poured into water when cool and extracted with methylene chloride, which yielded no organic product; continuous extraction of the aqueous phase with ether afforded 3 mg of black tar, which was discarded.

The solids obtained in each case were shown to be the benztriazinone **16**, which was recrystallized from methanol to mp 210–211° and ir 2.80, 6.00, 6.80 (s) μ; uv showed 243 (log ϵ 4.24), 248 (4.27), 254 (4.26), 260 (4.16). 318 (3.47) mμ.

Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.78; H, 4.31; N, 13.35.

Reactions of the Benztriazinone 16.[30]—Anhydrous fluoroboric acid was made by adding 1.0 g of 50% aqueous fluoroboric acid to 5.9 g of redistilled trifluoroacetic anhydride at 0° with stirring; the phases become homogeneous in 10 min. The resulting solution is 7.1% or 0.81 *M* in fluoroboric acid. 35.2 mg of benztriazinone **16** in 2 ml of this acid was slowly heated to reflux. In the cold, the solution was clear yellow with most of the salt undissolved, and became orange-brown and all dissolved at reflux temperature. The solution was refluxed for 27 hr, cooled, poured into ice and ether, and extracted with ether. The ether extracts were washed with bicarbonate solution and water, dried, and evaporated to a partly crystalline residue, identified as substantially pure starting material from ir and tlc comparisons.

103 mg (0.33 mmol) of benztriazonone **16** was dissolved in 8 ml of diglyme (distilled from hydride), and 57 mg (0.4 mmol) of distilled boron trifluoride etherate was added. The solution was refluxed for 3 hr and allowed to stand overnight. The solution and black gummy deposits were washed out with benzene and 1 *N* NaOH and partitioned. The benzene layer on filtration and evaporation yielded 4 mg of a gum exhibiting the ir and uv spectra of starting material, while acidification and extraction of the alkali yielded a similar crude product.

77 mg of benztriazinone **16** was dissolved in 6 ml of dioxane, saturated with argon gas, and photolyzed for 16 hr in Pyrex with an Osram lamp. Work-up by partitioning between benzene and alkali as above afforded less than 2 mg from the benzene layer, essentially only benztriazinone, and the remainder, alkali soluble, proving to be the same.

***N*-(6-Nitropiperonyl)-*o*-hydroxyphenethylamide.**—The procedure for the tyramide analog **15a** above was utilized with 1.91 (14 mmol) of *o*-hydroxyphenethylamine[16] to create 1.98 g (43%) of pale crystals, crystallized from methanol: mp 159–162°; ir 2.90, 6.00, 6.55 μ; λ_{max} 225 (log ϵ 4.41), 268 (3.69), 342 (3.66) mμ.

Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.17; H, 4.27; N, 8.48. Found: C, 57.88; H, 4.02; N, 8.16.

Lead Tetraacetate Oxidation to 17.—330 mg (1.0 mmol) of N-(6-nitropiperonyl)-*o*-hydroxyphenethylamide and 800 mg of lead tetraacetate were heated on the steam bath in 15 ml of acetic acid for 10 min. Work-up of an aliquot showed starting material on tlc. Another 800 mg of lead tetraacetate was added and heating continued for 10 min. The cooled solution was poured onto excess sodium carbonate decahydrate covered with 50 ml of methylene chloride, 100 ml water was added, and the lead dioxide was filtered out with Celite. The layers were separated, and the organic layer was washed, dried, and evaporated to a small volume and passed onto a silica column. Elution with chloroform yielded no substance, and the fractions taken with 15% acetone in chloroform were monitored with uv spectra. A major fraction of 211 mg of yellow foam showed a uv maximum at 300 mμ (ϵ 5500), one major and one close minor spot on tlc, and ir bands at 2.90, 5.74, 6.00, and 6.55 μ.

The crude dienone was treated with (a) concentrated sulfuric acid in acetic acid (5% solution) for 10 min at reflux; (b) 1 equiv of *p*-toluenesulfonic acid in methylene chloride for 2 hr at room temperature; (c) excess sodium hydride in dry tetrahydrofuran for 2 hr at room temperature. In all cases, tlc and ir showed the isolated material to be essentially all starting material.

***N*-(*o*-Acetoxy-β-styryl)-*t*-butylurethan (18).**—*o*-Acetoxycinnamic acid was made from salicylaldehyde and converted to its acid chloride, mp 53° (lit. mp 54°), following the precedure of Houben and Pfankuch.[31] 23.44 g of the acid chloride was converted to the azide by dissolving in 100 ml of acetone, chilling to 0°, and adding, over 10 min with stirring, an iced solution of 10 g of sodium azide in 40 ml of water. Stirring was continued at 0° for 1 hr (when an aliquot removed for ir showed essentially complete conversion) and another hour at room temperature; 200 ml of ether was added and the phases were separated. The ether layer was washed with water, dried, and evaporated to the crystalline azide, mp 36–39°; ir 4.68, 5.69, 5.94 μ.

The total azide was dissolved in *t*-butyl alcohol (250 ml) and benzene (50 ml), refluxed for 4 hr, evaporated, and dissolved in CH_2Cl_2. This solution was washed with 1 *N* hydrochloric acid, aqueous sodium bicarbonate, and brine, and evaporated to 50 ml. Benzene was twice added and evaporated down to 100 ml. Addition of 40 ml of hexane and cooling yielded 10.90 g of colorless crystals, mp 137°; the mother liquors yielded a further 1.50 g, mp 127–132°, recrystallized from benzene to mp 138–139° and ir 2.90, 5.71, 5.78, 6.01, 6.65 μ.

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 56.35; H, 7.10; N, 5.16.

Hydrolysis of 18 to *N*-(*o*-Hydroxy-β-styryl)-*t*-butylurethan.—347 mg of urethan **18** was suspended in 3 ml of methanol and 300 mg of potassium hydroxide, and 2 ml of water was added with stirring. After 5 min, the solution was filtered, acidified dropwise with 1 *N* hydrochloric acid to about pH 5, and extracted with chloroform; the extract was washed with bicarbonate solution, dried, and evaporated to 246 mg of slightly yellow oil, yielding 188 mg of white crystals, mp 100–102°, recrystallized from benzene–petroleum ether to ir 2.80 (w), 2.90, 3.00, 5.87, 6.04, 6.65 μ; uv λ_{max} 273 (log ϵ 4.27), 282 (4.19), 305 (4.04), 313 (4.05) mμ.

Hydrogenation to 19.—3.15 g of *N*-(*o*-hydroxy-β-styryl)-*t*-butylurethan was hydrogenated at atmospheric pressure over 33 mg of platinum oxide in 25 ml of 95% ethanol; the catalyst clumped together and hydrogen uptake stopped at 147 ml (theory, 300 ml) in 40 hr. A further 85 mg of catalyst was added, affording a further 254-ml uptake (114% of theoretical)

(29) It should be pointed out that reactions on these compounds in strong acid are often characterized by the opening of the methylenedioxy ring, which is acid labile as an acetal of formaldehyde. A classical color test for the presence of a methylenedioxy ring is its dark discoloration in sulfuric acid.

(30) F. E. King, J. A. Barltrop, and R. J. Wally, *J. Chem. Soc.*, 277 (1954).

(31) J. Houben and E. Pfankuch, *Chem. Ber.*, **59**, 1598 (1926).

in 5 hr more. Filtration and evaporation left 3.15 g of a nearly colorless oil. Preparative tlc produced crystals which seeded the oil and allowed its recrystallization from benzene–hexane to 1.53 g of **19**, mp 74–77°; the mother liquors were nearly indistinguishable on tlc or ir comparison. Analyses were variable; the compound decomposes slowly over several weeks at room temperature or on heating to 100°; ir showed 2.90, 3.05, 5.85 (sh), 5.93, 6.65 μ.

Oxidation of Phenol 19 to the Dienone 20.—To 243 mg of the phenol **19** in 2 ml of acetic acid was added 623 mg of solid lead tetraacetate (recrystallized from acetic acid and washed dry with ether); the solution was stirred in a 20° bath and went very dark. After one minute, the mixture was poured into a slurry of 6.4 g of sodium carbonate decahydrate and 25 ml of methylene chloride. The solution was stirred for 5 min and the organic layer was separated. The residual salts were washed white with more methylene chloride, and the combined organic phases washed with aqueous sodium bicarbonate, dried, and evaporated to 266 mg of dark residue, showing five spots on tlc. This was placed on three preparative tlc plates in ethyl acetate–chloroform (1:3) and four bands taken, all of roughly equal yield, and examined on analytical plates and by uv spectra. The promising fraction (λ_{max} 300 mμ) was rechromatographed and one fraction from the second plate crystallized from cold ether to 14 mg of crystals: mp 87–90°; ir 2.90, 5.75, 5.87, 5.98, 6.65 μ; uv λ_{max} 301 (log ε 3.43). In a repeat experiment, the same fraction (identical by tlc and spectra) could not be crystallized.

Decomposition of the Dienone 20.—34 mg of dienone **20**, as a colorless oil from chromatography spectrally identical with the crystalline sample, was dissolved in 1 ml of trifluoroacetic acid and bubbled vigorously. After 1 min, aqueous sodium bicarbonate was added and the mixture extracted with methylene chloride. On drying and evaporation, the extract yielded only 3 mg of an oil which darkened on standing, showed indiscriminate tailing from 215 to 400 mμ in the uv, one major carbonyl band at 5.75 μ, and a very minor band at 5.95 μ. In another experiment, 10 ml of methylene chloride and 1.5 ml of triethylamine were added after 5 min to the trifluoroacetic acid solution of 39 mg of dienone.

The solution was evaporated, taken up in benzene, and extracted with water. On evaporation of benzene, only 2 mg remained, with an ir spectrum resembling starting material's. In each case, continuous extraction of the aqueous layers, after basification with alkali, yielded negligible material.

When 1 mg of crystalline dienone **20** was dissolved in 1 drop of trifluoroacetic acid, left for five minutes, and diluted with acetonitrile, the uv showed the band at 301 mμ unchanged, and little change was seen after 22 hr. If, after dilution with acetonitrile, 2 drops of triethylamine is added, the band at 301 mμ disappeared, but only a long tailing absorption without maxima replaced it.

1-Methoxy-4-(β-aminoethyl)-cyclohexadiene-1,4 (22a).—2.0 g of *p*-methoxyphenethylamine[32] were dissolved in 10 ml of methanol, and about 150 ml of liquid ammonia was distilled into the solution, cooling it to −70°. 1.6 g of sodium metal was added with stirring over 3 min, and the blue color disappeared in about 5 min. The ammonia was evaporated, ether and water were added, and the mixture was extracted with ether, which was dried and evaporated to 1.7 g of an oil. It exhibited ir bands at 5.90 and 6.02 μ, completely lacked several strong absorptions due to starting material, and exhibited only end absorption in the uv above 215 mμ and nmr at 4.56 (~s, 1 H), 5.39 (s, 1 H), 6.50 (s, 3 H), 7.3 (m, 6 H), 7.9 (m, 4 H). Distillation at 60° (15 μ) yielded 1.0 g of an oil which did not materially differ in its spectra.

Hydrolysis of this enol ether **22a** in 2 *N* sulfuric acid at room temperature for 1 hr yielded variable amounts of ether-extractible material after basification. These oils could not be distilled without decomposition, and no crystalline hydrochloride or picrate could be prepared. Extended manipulation afforded increasing amounts of an insoluble yellow amorphous solid, and only small amounts were recoverable from silica chromatography.

6-Nitropiperonylamide (23).—A solution of 6-nitropiperonyl chloride in ether [from 5 g (24 mmol) of nitro acid and 5 g of phosphorus pentachloride as above for **15a**] was added to a solution of 3.9 g (25 mmol) of the amino enol ether, **22a**, in ether containing 10 ml of triethylamine, and stirred for 12 hr. The solution was washed with hydrochloric acid, sodium hydroxide, and water, dried, and evaporated to 4.9 g of an oil from which 2.9 g (35%) crystallized from benzene: mp 158–159°; ir 2.90, 5.98, 6.55, 7.50 μ.

Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.10. Found: C, 58.61; H, 5.12; N, 7.92.

Hydrolysis of 23a to 24.—100 mg of the nitro amide, **23a**, was dissolved, with warming, in 20 ml of 95% ethanol with 1 drop of concentrated hydrochloric acid and stirred at room temperature for 2 hr. Most of the ethanol was removed *in vacuo*, and water and methylene chloride were added. The mixture was washed with more methylene chloride.

The combined organic layers were dried and were then evaporated to 75 mg of a gum from which 48 mg of crystals were obtained from benzene: mp 134–137°; ir 2.90, 5.85, 6.00, 6.52 μ; uv λ_{max} 242 (log ε 4.0), 343 (3.6); nmr 2.60 (s, 1 H), 3.30 (s, 1 H), 3.85 (s, 2 H), 4.45 (m, 1 H), 6.6 (m, 2 H), 7.2–8.4 (m, 8 H), none exchangeable with D_2O.

Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.82; H, 4.85; N, 8.44. Found: C, 57.89; H, 5.01; N, 8.57.

Bromination of 24 to 25.—To 60 mg (0.18 mmol) of ketone **24** in methylene chloride was added 29 mg (0.18 mmol) of bromine in methylene chloride. The solution was left until virtually colorless, washed with water and sodium thiosulfate solution, dried, and evaporated to 64 mg of **25**, mp 151–153°, giving a precipitate with alcoholic silver nitrate: ir 2.90, 6.00, 6.55 μ; uv λ_{max} 228 (log ε 3.8), 243 (3.7), 285 (3.3), 342 (3.3), and subtraction of **24** from **25** showed a peak at 227 mμ; nmr 2.52 (s, 1 H), 2.90 (s, 1 H), 3.09 (s, 1 H), 3.25 (~ s, 1 H), 6–8 (m, 8 H).

Anal. Calcd for $C_{16}H_{15}BrN_2O_6$: C, 46.73; H, 3.68; N, 6.82. Found: C, 46.81; H, 3.59; N, 6.71.

1,5-Dimethoxy-4-(β-aminoethyl)cyclohexadiene-1,4 (22b).—2,4-Dimethoxyphenethylamine[33] was reduced as described for its analog **22a** except that ethanol was required as the alcohol and was added in portions over 1.5 hr until the sodium color disappeared. The crude reduction product, as a colorless oil containing no starting amine (by tlc and nmr), was used without further purification.

6-Nitropiperonylamide (23b).—This amide was prepared by a completely analogous procedure to that for the amide **23a**, using the crude product from reduction of 1.0 g (5.5 mmol) of 2,4-dimethoxyphenethylamine and obtaining, after crystallization from petroleum ether, 650 mg (31%) of needles: mp 154–156°; ir 2.90, 5.88 (w), 6.00, 6.55, 6.62 μ.

Anal. Calcd for $C_{18}H_{20}N_2O_7$: C, 57.45; H, 5.36; N, 7.45. Found: C, 57.56; H, 5.32; N, 7.11.

Hydrolysis of (22b). Formation of 26.—In no case could crystalline material, as free amine or its salts, be isolated from hydrolyses of the bis enol ether **22b** under conditions similar to those tried for **22a**. The following procedure produced a derivative. 260 mg of enol ether **22a** was refluxed for 0.5 hr in 95% ethanol containing 0.25 ml of concentrated hydrochloric acid and evaporated to a residue which was partitioned between methylene chloride and aqueous sodium hydroxide. The organic phase was washed with water, evaporated to 90 mg of an oil, and dissolved in ether. 6-Nitropiperonylic acid (220 mg) was converted to its acid chloride in ether as described above and added to the crude amine and about 100 mg of triethylamine. After stirring overnight, the ether was washed with water, dried, and evaporated to yield a gum (170 mg) which yielded crystals on removing the major spot from a preparative tlc plate (silica, 1% methanol in chloroform). The crystals were recrystallized from ethanol: mp 215–220°; ir 5.94, 6.05, 6.20, 6.55, 7.50 μ; uv λ_{max} 246 (log ε 4.1), 289 (4.3), 340 (sh, 3.8); nmr 2.36 (s, 1 H), 3.20 (s, 1 H), 3.78 (s, 2 H), 3.85 (s, 1 H), 6.0–8.5 (m, 9 H).

Anal. Calcd for $C_{16}H_{14}N_2O_8$: C, 58.17; H, 4.27; N, 8.48. Found: C, 57.96; H, 4.31; N, 8.32.

Hydrolysis of the Enol Ether Amide 23b.—300 mg (0.8 mmol) of the bis enol ether **23b** was dissolved in 50 ml of 95% ethanol, 0.3 ml of concentrated hydrochloric acid was added, and the system was refluxed for 2 hr, boiled down to 10 ml, and cooled. The deposited crystals were filtered (220 mg) and recrystallized from ethanol to yield 120 mg (46%) of the same product as above, **26**, by comparison of spectra and melting point (mp 217–219°, mmp 215–220°).

Reduction of 26.—160 mg (0.5 mmol) of nitro amide **26** and 160 mg of palladium–charcoal were added to α-phellandrene (20

(32) L. H. Klemm, R. Mann, and C. D. Lind, *J. Org. Chem.*, **23**, 346 (1958).

(33) The procedure of R. I. T. Crombie and J. Harley-Mason, *J. Chem. Soc.*, 2525 (1952), was used, affording the 2,4-dimethoxy-β-nitrostyrene, mp 102–103°, followed by 2,4-dimethoxy-β-phenethylamine, hydrochloride mp 158–160°.

ml) and heated with stirring on an oil bath. At about 130°, a vigorous evolution of gas occurred and the temperature rose to 150°. When this activity subsided, the suspension was cooled, filtered, and washed with 5 *N* hydrochloric acid. The aqueous layer was made basic and extracted with methylene chloride, and the organic phase was dried and evaporated to yield 110 mg (75%) of crystals, recrystallized from benzene to mp 134–135°; ir 5.84, 6.01, 6.14 μ; uv λ_{max} 238 (log ϵ 4.2), 320 (3.7); nmr 2.49 (s, 1 H), 3.03 (s, 1 H), 3.92 (s, 2 H), 4.0 (m, 2 H), 7.82 (s, 3 H), 6.5–8.3 (7 H), no protons exchanged with D_2O; mass spectrum major peaks *m/e* 300 (p), 243, 229.

Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.57; H, 5.25; N, 9.66.

Diazotization in aqueous nitrous acid or with isoamyl nitrite in trifluoroacetic acid led only to unchanged starting material, identified by spectra and tlc.

Registry No.—**1**, 476-28-8; **4a**, 20286-59-3; **4b** HCl, 20302-79-8; **4c**, 20286-60-6; **4c** (nitro ketone), 20286-61-7; **4c** (bromo ketone), 20286-62-8; *trans*-2-(3,4-methylenedioxyphenyl)cyclohexylamine HCl, 20302-80-1; *cis*-4-amino-5-(3,4-methylenedioxyphenyl)cyclohexene HCl, 20286-63-9; *cis*-2-(3,4-methylenedioxyphenyl)cyclohexylamine HCl, 20286-64-0; **7**, 20286-65-1; **8a**, 20286-66-2; **8a** (dibromide), 20286-67-3; **8a** (epoxide), 20286-68-4; **8b**, 20286-69-5; **9a**, 20286-70-8; **9a**, 20286-71-9; **10b**, 20286-72-0; **11a**, 20286-73-1; **11a**, 20286-74-2; **11b**, 20286-75-3; **11b**, 20286-76-4; **12b**, 20286-77-5; **12b**, 20286-78-6; **15a**, 20286-79-7; **15c**, 20287-27-8; **16**, 20286-80-0; N-(6-nitropiperonyl)-*o*-hydroxyphenethylamide, 20286-81-1; **18**, 20286-82-2; N-(*o*-hydroxy-β-styryl)-*t*-butylurethan, 20286-83-3; **19**, 20286-84-4; **20**, 20286-85-5; **23a**, 20286-86-6; **23b**, 20286-87-7; **24**, 20286-88-8; **25**, 20286-89-9; **26**, 20286-90-2; **27**, 20286-91-3.

Acknowledgment—We should like to express our deepest gratitude to the National Institutes of Health for continued and patient support of these and other studies in the synthesis of *Amaryllidaceae* alkaloids over many years.

Syntheses and Optical Rotatory Dispersion Studies of (*S*)-5-(2′-Pentyl)barbituric Acid Derivatives[1]

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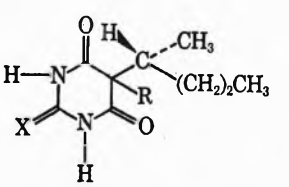
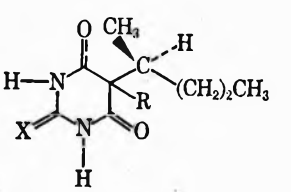
The syntheses of several (*S*)-5-(2′-pentyl)barbituric acid derivatives are reported and their optical properties have been investigated. Although the ultraviolet spectra of (*S*)-(−)-5-ethyl-5-(2′-pentyl)barbituric acid (IIa) shows only one maximum under the conditions studied, optical rotatory dispersion measurements have shown two Cotton effects. Some pH dependent optical rotatory dispersion studies indicate that the lower wavelength Cotton effect is the result of a π–π^* transition and the higher wavelength Cotton effect is of type n–π^*. The π–π^* Cotton effect is positive and the n–π^* Cotton effect is negative. The ultraviolet spectrum of the monosubstituted barbituric acid, (*S*)-(+)-5-(2′-pentyl)barbituric acid (IIc), in acid solution showed one maximum and the optical rotatory dispersion curve in the same solvent showed a negative π–π^* low wavelength and a positive n–π^* high wavelength Cotton effect. These results show that the biologically active IIa has optical rotatory dispersion properties greatly different from those of the biologically inactive IIe. These results are discussed in relation to the differences in the structure of these two compounds.

In a recent paper the preparation of some (*R*)-5-(2′-pentyl)barbituric acid derivatives (I) was reported.[2] In order to compare the optical properties, the pharmacological effects, and the metabolic fate, it was necessary to obtain the enantiomeric (*S*)-5-(2′-pentyl)barbituric acid derivatives (II) in high optical purity. The (*R*)-isomers I could be readily prepared in a high state of optical purity from commercially available (*R*)-(+)-pulegone.[2] However, the unavailability of the corresponding (*S*) isomer or other similar (*S*) derivative convertible to the (*S*)-barbituric acid derivatives II, made it necessary to seek a different synthesis of these enantiomers. Although there are two reports of the preparation of (*S*)-(−)-5-ethyl-5-(2′-pentyl)barbituric acid (IIa) in the literature, in both cases the optical purity was very low. A method reported by Kleiderer and Shonle[3] involved a displacement reaction at the asymmetric carbon atom and proved to be unsuitable for the preparation of the (*S*) isomers II in high optical purity.[4]



I



II

a, R = C_2H_5, X = O
b, R = C_2H_5, X = S
c, R = H, X = O
d, R = CH_2=$CHCH_2$—, X = O
e, R = CH_2=$CHCH_2$—, X = S

In 1966 Knabe and Philipson[5] reported the separation of racemic 5-ethyl-5-(2′-pentyl)barbituric acid (pentobarbital) into its optical antipodes *via* fractional crystallization of its diastereomeric N-methylquininium salt from a methanol and ether mixture followed by regeneration of the acid. The (*S*) isomer IIa thus obtained had $[\alpha]^{20}D$ −3.5° and was, therefore, only 28% optically pure when compared to $[\alpha]^{20}D$ 13.12° obtained for Ia.[2] Since the (*S*) isomer was reported to be the more crystalline of the two salts and easier to separate, further recrystallization of this salt should lead to optically pure IIa. Indeed, we found that IIa having $[\alpha]^{24}D$ −13.38°

(1) This research was carried out under Contract PH43-65-1057 of the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Md.

(2) C. E. Cook and C. R. Tallent, *J. Heterocycl. Chem.*, **6**, 203 (1969).

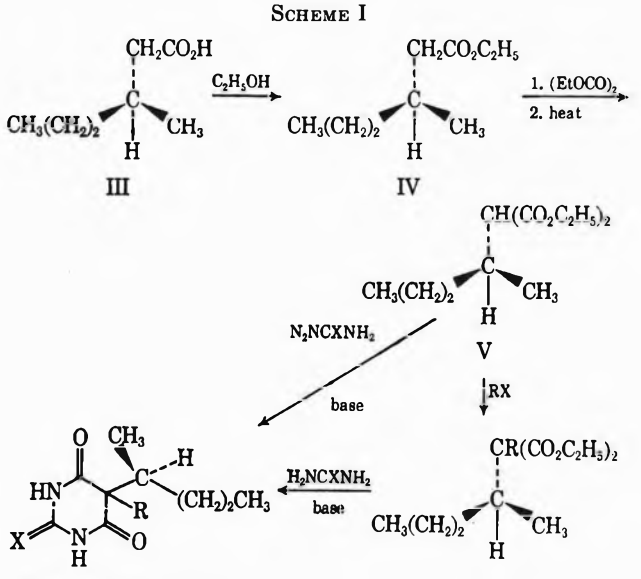
(3) E. C. Kleiderer and H. A. Shonle, *J. Amer. Chem. Soc.*, **56**, 1772 (1934).

(4) The optical purity of IIa obtained by Kleiderer and Shonle (ref 3) was 36%.

(5) J. Knabe and K. Philipson, *Arch. Pharm.* (Weinheim), **299**, 232 (1966).

could be obtained by this method. However, it was necessary to recrystallize the N-methylquininium salt twelve times from a methanol and ethyl acetate mixture in order to obtain 3% of the optically pure IIa. The low yield obtained, as well as the necessity of carrying out a separate resolution for each (*S*) isomer II desired, made this procedure unattractive for the preparation of reasonable amounts of a series of pure (*S*)-5-(2′-pentyl)-barbituric acid derivatives (II). In 1931, while engaged in a study of the Walden inversion, Levene and Marker[6] reported the preparation of (*S*)-(−)-3-methylhexanoic acid (III), bp 113° (17 mm), $[\alpha]^{27}D$ −2.52°. The fact that the magnitude of the reported rotation is of comparable value and opposite sign to the (*R*)-(+)-3-methylhexanoic acid prepared by Cook and Tallent[2] from (*R*)-(+)-pulegone prompted us to reinvestigate this preparation. We found that six recrystallizations of the cinchonidine salt of racemic 3-methylhexanoic acid followed by regeneration of the acid afforded III having $[\alpha]^{24}D$ −2.63°. When this acid was subjected to the reaction scheme shown in Scheme I, the optically pure 5-(2′-pentyl)barbituric acid derivatives (II) were obtained. A comparison of the $[\alpha]D$ and melting points of the (*R*)- and (*S*)-5(2′-pentyl)barbituric acid derivatives is given in Table I. Since the absolute configuration of the starting (*S*)-(−)-3-methylhexanoic acid (III) has been established,[7] the absolute configuration of the (*S*)-5-(2′-pentyl)barbituric acid derivatives (II) is known and is as represented in Scheme I. The

Scheme I



IIa, R = C_2H_5; X = O
b, R = C_2H_5; X = S
c, R = H; X = O
d, R = CH_2=$CHCH_2$; X = O
e, R = CH_2=$CHCH_2$; X = S

identity of each compound was shown by elemental analysis, infrared, and mass spectra. As expected, the infrared and mass spectra of each derivative II were identical with those of the corresponding (*R*) isomer I,

(6) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **91**, 77 (1931).

(7) I. A. Holliday and N. Polgar [*J. Chem. Soc.*, 2934 (1957)] has correlated III with methyl hydrogen β-methyl glutarate, which was related to methylsuccinic acid by S. Stallberg-Slenhagen, *Arkiv Kimi, Min., Gral.*, 25A, No. 10 (1948).

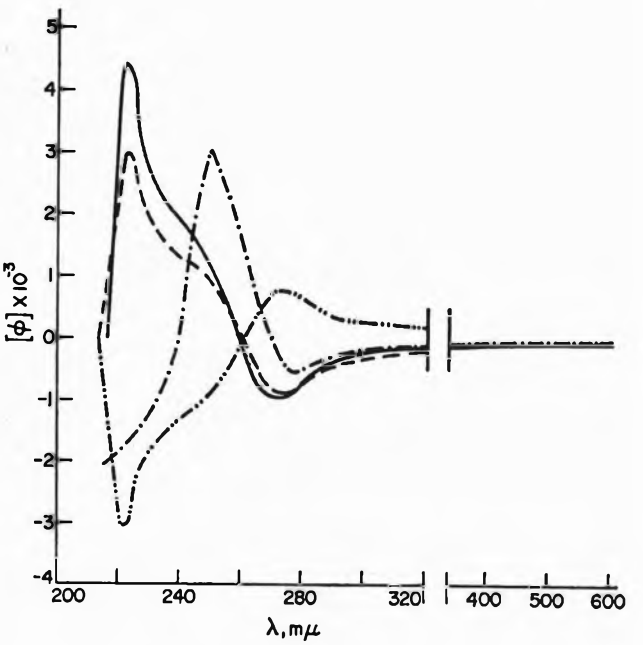


Figure 1.—Optical rotatory dispersion of (*S*)-(−)-5-ethyl-5-(2′-pentyl)barbituric acid (IIa) in methanol (- - - -), in 50% v/v methanol–0.1 *N* hydrochloric acid (——), in 50% v/v methanol–0.1 *N* sodium hydroxide (-·-·-), and (*R*)-(+)-5-ethyl-5-(2′-pentyl)barbituric acid (Ia) in methanol (-··-··-).

and the optical rotations were of essentially equal magnitude and of opposite sign[2] (Table I).

We have investigated the optical rotatory dispersion (ORD) of this series of optically active compounds.[8] The ORD curves of these compounds were of particular interest because of their potential application in determining the structure of metabolites which are isolated in only very small quantities. In addition, the information from the ORD studies may be of value in assigning electronic transitions to the barbituric acids. Finally, a comparison of the ORD of the active hypnotic and sedative, (*S*)-(−)-5-ethyl-5-(2′-pentyl)barbituric acid (IIa), and the biologically inactive (*S*)-(+)-5-(2′-pentyl)-barbituric acid (IIc) might reveal differences in their structure which would be helpful in explaining their biological differences.

The ORD curve of IIa in methanol (Table II, Figure 1) shows a negative Cotton effect with the trough at 274 mμ. The peak occurs at 240 mμ as a shoulder on a second positive Cotton effect, the peak of which is at 223 mμ. The trough of this second Cotton effect could not be measured. As expected, the curve of IIa was the mirror image of its enantiomer Ia (Figure 1). The shape of the ORD curve of IIa in acid solution was essentially the same as that in methanol; however, the extrema of the long wavelength Cotton effect was shifted to lower wavelengths and the amplitudes of both Cotton effects were increased. In contrast the ORD curve of IIa in alkaline solution showed a bathochromic shift and showed only one peak and one trough at 250 mμ and 278 mμ, respectively. It could be argued that the two Cotton effects observed in the ORD curve of IIa in

(8) Optical rotatory dispersion were measured at the University of North Carolina at Chapel Hill as a courtesy of Dr. J. Hermans and with the help of Mr. D. J. Puett, and at Duke University as a courtesy of Dr. C. Tanford and with the help of Mr. Bob Roxby. Measurements were made with a Cary 60 spectropolarimeter at 28°. Concentration varied from c 0.02 to c 0.2. Values of molecular rotation have an accuracy of approximately 10%, except at very low wavelengths where the error is somewhat larger.

TABLE I

COMPARISON OF OPTICAL ROTATION AND MELTING POINT OF (*R*)- AND (*S*)-5-(2′-PENTYL)BARBITURIC ACID DERIVATIVES

Compound[a]	Optical rotation[b] $[\alpha]^{24}D$ (*S*) isomer	Optical rotation[b] $[\alpha]^{24}D$ (*R*) isomer[d]	Mp, °C[c] (*S*) isomer	Mp, °C[c] (*R*) isomer[d]
5-Ethyl-5-(2′-pentyl)barbituric acid (pentobarbital)	−13.19	13.12	121.5–122	122–122.5
5-Ethyl-5-(2′-pentyl)-2-thiobarbituric acid (thiopental)	−10.85	10.66	148–149	151–151.5
5-(2′-pentyl)barbituric acid	5.88	−4.8	182–182.5	182.5–183
5-Allyl-5-(2′-pentyl)barbituric acid (secobarbital)	−8.55	9.23	102.5–103.5	103–106
5-Allyl-5-(2′-pentyl)-2-thiobarbituric acid (thiamylal)	−6.53	6.68	116–116.5	117–118

[a] The name given in parentheses is the generic name of the *dl*-mixture. [b] Optical rotations were measured on a Rudolph Model 80 polarimeter at *c* 2.0 to 3.0. [c] Melting points were obtained by capillary method on sublimed samples, except for thiamylal which was purified by recrystallization from an ethyl acetate and hexane mixture. [d] Taken from ref. 2.

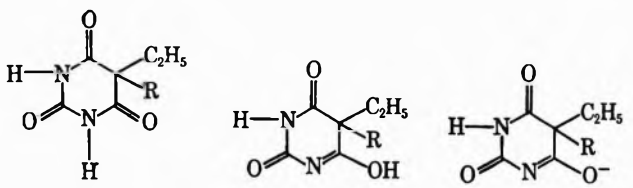
TABLE II

OPTICAL ROTATORY DISPERSION AND ULTRAVIOLET ABSORPTION DATA OF 5-(2′-PENTYL)BARBITURIC ACID DERIVATIVES

Compound	Condition	ORD λ, mμ[a]	ORD $[\phi]^b$	uv absorption λ_{max}	uv absorption $\epsilon \times 10^{-3}$
I	CH_3OH	320	180		
		274 P	786		
		260	0		
		240 T[c]	−1300		
		222 T	−3050		
		213.5	0		
IIa	CH_3OH	320	−200	210	9.5
		274 T	−880		
		260	0		
		240 P[c]	1300		
		223 P	3025		
		213.5	0		
IIa	pH 1.4[d]	600	−37	212	7.4
		272 T	−980		
		259	0		
		240 P[c]	1900		
		222 P	4400		
		216.5	0		
IIa	pH 12.1[e]	600	−37	240	10.0
		278 T	−540		
		269	0		
		250 P	3000		
		240	0		
		215	−2050		
IIc	CH_3OH	320	140	208[f]	8.5
		275 P	1170	268	12.1
		261.5	0		
		248 T[c]	−1150		
		223 T	0		
		15	−1200		
IIc	pH 1.4[d]	320	150	209[f]	9.1
		272.5 P	1160		
		260	0		
		245 T[c]	−1150		
		222 T	−2700		

[a] P = peak, T = trough. [b] The optical rotations are given as molar rotation, $[\phi]^{28}\lambda = [\alpha]^{28}D \times$ mol wt/100. [c] This extremum occurs as a shoulder on a lower wavelength extremum. [d] 50% v/v methanol–0.1 *N* hydrochloric acid. [e] 50% v/v methanol–0.1 *N* sodium hydroxide. [f] Shoulder on end absorption.

methanol and in acid solution result from a single electronic transition of a keto (IIaA) and enol (IIaB) form, which are converted in alkaline solution to one species, the anion (IIaC), which then shows only one Cotton effect. However, the ultraviolet spectrum of IIa in methanol or acid solution which shows only one maximum in both cases is inconsistent with this interpretation. In addition, this interpretation would indicate a $\lambda_0^{pH\ 12.1}$ 269 mμ[9] (Table II, Figure 1) for the ORD of IIa whereas the uv shows only one maximum at 240 mμ at pH 12.1. The increase in amplitude of the higher wavelength Cotton effect in going from methanol to acid solution as well as the extreme unsymmetrical character of the ORD curve of IIa in alkaline solution are also inconsistent with this interpretation. Alternatively, the two Cotton effects could result from different electronic transitions. The uv spectrum of IIa in methanol shows an absorption at 210 mμ. The position as well as the



IIaA IIaB IIaC

R = —$CH(CH_3)C_3H_7$

high intensity of this absorption suggest that it is a type $\pi-\pi^*$ transition.[10] As a result of the presence of several nonbonding, lone-pair electrons on heteroatoms (O and N), the uv spectrum of IIa would also be expected to show $n-\pi^*$ transition(s) at longer wavelengths. Although such a transition is not perceptible in the uv spectra of IIa, it would seem reasonable to attribute the long wavelength tail of the $\pi-\pi^*$ transition to a $n-\pi^*$ transition.[11] The midpoint, λ_0 213.5 mμ,[9] of the shorter wavelength Cotton effect in methanol as well as the bathochromic shift in alkaline solution, λ_0 240 mμ, agrees well with the ultraviolet maximum of IIa, $\lambda_{max}^{CH_3OH}$ 212 mμ and $\lambda_{max}^{pH\ 12.1}$ 240 mμ. Apparently this high-amplitude low wavelength Cotton effect and the strong ultraviolet absorption band are the result of the same $\pi-\pi^*$ electronic transition.[10] The second Cotton effect at λ_0 260 mμ in methanol of lower amplitude is probably due to the presence of a low intensity transition at higher wavelength even though the uv spectrum does not show a maximum in this region.[11] Because of its low intensity, its occurrence at higher wavelength than the $\pi-\pi^*$ transition, and its shift to lower wavelength in

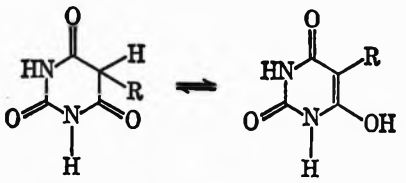
(9) λ_0 refers to the wavelength at which the rotation is zero.

(10) D. W. Turner has attributed an absorption band at 185–198 mμ in a number of cyclic imides to a $\pi-\pi^*$ transition. See D. W. Turner in "Determination of Organic Structures by Physical Methods," Vol. 2, F. C. Nachod and W. D. Philips, ed., Academic Press, New York, N. Y., 1962, Chapter 5.

(11) The ultraviolet spectrum of IIa does not show a second maximum. However, the spectrum has Σ 50–200 in methanol at 300–250 mμ and shows a very small inflection between 230 and 245 mμ.

going from alkaline to acid medium, the second transition is most likely a n–π^* type.[12,13] This interpretation of the ORD curves of IIa would be consistent with its uv spectra and the change in amplitude of the longer wavelength Cotton effect with change in pH. In addition, the extreme unsymmetrical character of the ORD curve in alkaline solution would be explained if the peak of both Cotton effects occurs at 250 mμ as this interpretation suggests.

In contrast to IIa, the uv spectrum of the monosubstituted barbituric acid, (*S*)-(+)-5-(2′-pentyl)barbituric acid (IIc), in methanol showed two intense absorption bands at 208 and 268 mμ (Figure 2). An analysis of the uv spectra of IIc as a function of pH as well as reference to the spectral data of other monosubstituted barbituric acids indicate that IIc exists as an equilibrium mixture of IIcA and IIcB[14] in methanol solution and in the form of IIcA at pH 1.4.[15,16]



IIcA IIcB

R = $CH(CH_3)C_3H_7$

The enol form IIcB could be considered as a 6-hydroxyuracil derivative and might be expected to show electronic transition similar to those assigned to uracil and other pyrimidines.[17] As a result one might expect the ORD curve of IIcB to be different from that of IIcA.[18] Since the ORD curves of IIc (Figure 2, Table II) in both methanol and acid solution are almost identical,[19] the curve in methanol must be due mainly to form IIcA, or the ORD properties of IIcA and IIcB, or essentially the same. The latter explanation seems less likely since the optically active 2′-pentyl side chain would be connected to the heterocyclic chromophore *via* a sp^3 bond in IIcA and a sp^2 bond in IIcB.[20] The ORD curve of IIc in acid solution shows a positive high wavelength Cotton effect with the first extremum at λ 272.5 mμ and a negative low wavelength Cotton effect with the first extremum at λ 222 mμ. Therefore, in contrast

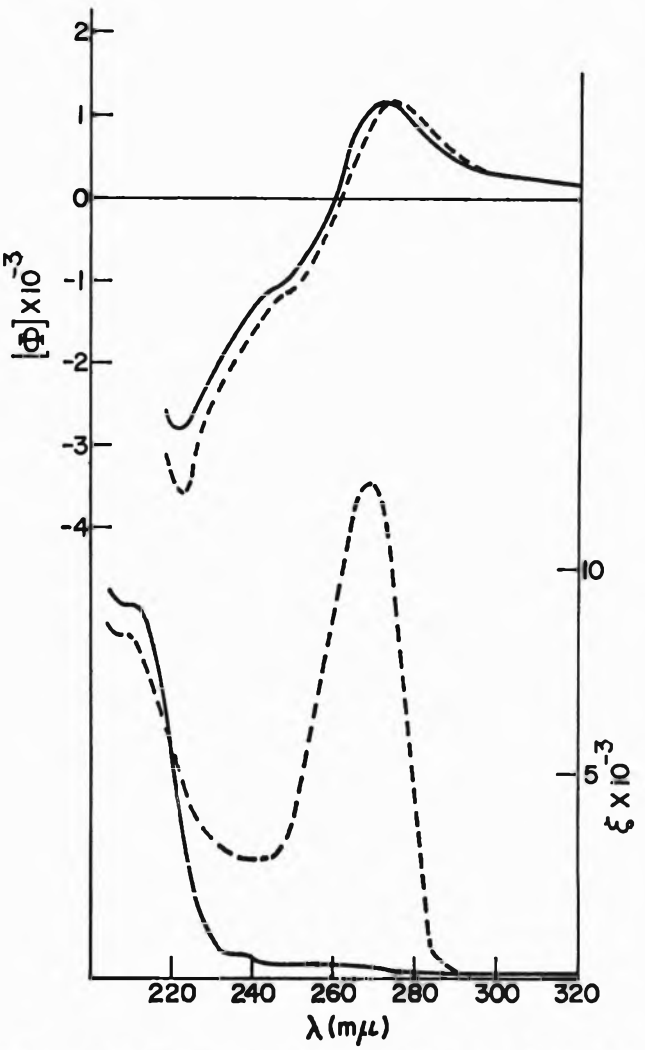


Figure 2.—Optical rotatory dispersion and absorption spectra of (*S*)-(+)-5-(2′-pentyl)barbituric acid (IIc) in methanol (- - - - -), and in 50% v–v methanol/0.1 *N* hydrochloric acid (——).

to IIa, the π–π^* Cotton effect is negative and the n–π^* Cotton effect is positive.

Since the curves of IIa and IIc in acid solution presumably result from the triketonic form IIaA and IIcA, respectively, this strikingly different rotatory behavior would indicate that the two compounds have different steric relationships between the absorption chromophore and the optically active side chain. Although the 2′-pentyl side chain would have free rotation about the 5 position of the barbituric acid ring, these differences indicate that the optically active side chain may have different preferred conformations in the two compounds. Molecular models of IIa and IIc indicate that IIa is considerably more sterically crowded than IIc and that free rotation would be considerably more difficult. This steric crowding is also evident in the uv spectrum of IIa, which shows a shift to longer wavelength relative to the spectrum of IIc, indicating increased noncoplanarity of the barbituric acid ring of IIa.[21] It is also possible that IIa and IIc have different optically active transitions or different solution characteristics. However, because of the very close similarity

(12) Since lone-pair transitions are strongly affected by changes in pH, the blue shift observed in going from the monoanion of IIa, to the neutral molecule, to the weakly protonated form, is consistent with an n–π^* transition. In a study of the ORD, CD, and uv properties of pyrimidine and purines, D. W. Miles, R. K. Robins, and H. Eyring [*Proc. Nat. Acad. Sci. U. S.*, **57**, 1138 (1967)] showed that n–π^* transitions undergo blue shifts when the pH was lowered.

(13) This long wavelength Cotton effect could be due to one or more optically active transitions.

(14) Two identical structures can be drawn for form IIcB.

(15) W. J. Doran, in "Medicinal Chemistry," Vol. IV, F. F. Blicke and R. H. Cox, Ed., John Wiley & Sons, Inc., New York, N. Y., 1959, p 1.

(16) J. J. Fox and D. Shugar, *Bull. Soc. Chem. Belges.*, **61**, 44 (1952) and references cited.

(17) L. B. Clark and I. Finoco, Jr., *J. Amer. Chem. Soc.*, **87**, 11 (1965).

(18) D. W. Miles, R. K. Robins, and H. Eyring, *J. Chem. Phys.*, **57**, 1138 (1967), have correlated the ORD and CD curves of uridine and thymidine with the electronic transition of these bases and have shown that they are derived from those of benzene.

(19) This blue shift of the first extremum in going from methanol to acid solution would be expected of a n–π^* transition. The difference in rotation of the low wavelength π–π^* transition is due partly to uncertainties in measurements in this region.

(20) An examination of CPK molecular models of IIcA and IIcB shows that different heterocyclic chromophore–optically active side-chain steric relationships exist in the two forms. An ORD and CD study at various pH's may be helpful in solving this problem.

(21) D. W. Turner (ref 10) attributed a shift in the uv to longer wavelength shown by glutarimide relative to succinimide to noncoplanarity of the imide group.

in structure, this explanation seems less likely. The extreme difference of the optical rotatory properties of IIa and IIc suggest that additional ORD as well as circular dichroism (CD) and possibly magnetic circular dichroism (MCD)[22] studies of barbituric acid derivatives might be useful in explaining the biological properties of these compounds. In addition, the CD and MCD studies of II would provide additional evidence for the electronic transitions suggested in the present communication.

Experimental Section[23]

Resolution of *dl*-5-Ethyl-5(2'-pentyl)barbituric Acid (Pentobarbital).—*dl*-Pentobarbital (168 g, 0.74 mol) was converted to its N-methylquininium salt according to the method of Knabe and Philipson.[5] Twelve recrystallizations of this salt from a methanol and ethyl acetate mixture followed by regeneration of the acid from the separated N-methylquininium salt of (−)-pentobarbital gave 2.8 g (3%) of IIa purified by sublimation, mp 121–121.5°, $[\alpha]^{24}D$ −13.38° (*c* 2.38, absolute ethanol); lit.[5] mp 128°, $[\alpha]^{20}D$ −3.5° (*c* 1.83, absolute ethanol).

(*S*)-(−)-3-Methylhexanoic Acid (III).—The acid III was obtained by six recrystallizations of the cinchonidine salt from an aqueous ethanol solution according to the procedure of Levene and Marker.[6] From 415 g of *dl*-3-methylhexanoic acid, 90 g of III was obtained: bp 109–110° (13 mm), $n^{25}D$ 1.4205, $[\alpha]^{24}D$ −2.63° (neat); lit.[6] bp 113° (17 mm), $n^{25}D$ 1.4214, $[\alpha]^{27}D$ −2.52° (neat).

Ethyl (*S*)-(−)-3-Methylhexanoate (IV).—This ester was prepared according to the procedure of Levene and Marker:[6] bp 60° (7.0 mm), $[\alpha]^{23}D$ −0.40 (neat); lit.[6] bp 60° (10 mm), $[\alpha]^{27}D$ −0.42°.

(*S*)-(−)-Diethyl 2-Pentylmalonate (V).—This ester was prepared by the same procedure that Cook and Tallent[2] used to prepare the (*R*)-(+) isomer, with the exception that benzene was used in place of ether as the reaction solvent. Starting with 12 g (76.9 mmol) of ester IV, 10.2 g (57%) of V was obtained: bp 105° (2 mm), $n^{25}D$ 1.4260, $[\alpha]^{24}D$ −0.59° (neat); lit.[24] bp 103–104° (4 mm), $n^{20}D$ 1.4273 for the *dl* ester (V).

(*S*)-(−)-Diethyl Ethyl-2-pentylmalonate (VI, R = C_2H_5).—Using the procedure that Cook and Tallent[2] used to prepare the (*R*)-(+) isomer malonic ester V (4.8, g, 0.21 mol) gave 4.2 g (76%) of VI (R = C_2H_5): bp 115° (2 mm), $n^{25}D$ 1.4348, $[\alpha]^{23}D$ −14.84° (neat); lit.[3] bp 123–124° (10 mm), $n^{25}D$ 1.4330, $[\alpha]^{25}D$ −11.02° (neat).

(*S*)-(−)-Diethyl Allyl-2-pentylmalonate (VI, R = CH_2=$CHCH_2$—).—Using a procedure similar to that used to prepare VI (R = C_2H_5), malonic ester (V) (15 g, 65 mmol) and 3-bromopropene (23.7 g, 20 mmol) yielded 13.7 g (78%) of VI (R = CH_2=$CHCH_2$—): bp 129–130° (1.0 mm), $n^{25}D$ 1.4437, $[\alpha]^{23}D$ −16.36°; lit.[25] bp 137–140° (15 mm) for *dl* ester VI (R = CH_2=$CHCH_2$—).

(*S*)-(−)-5-Ethyl-5-(2'-pentyl)barbituric Acid (IIa).—Treatment of VI (R = C_2H_5) (3.0 g, 11.8 mmol) with urea according to the procedure that Cook and Tallent[2] used to prepare Ia gave 2.1 g (77%) of IIa.

Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.35; H, 8.10; N, 12.46.

(*S*)-(−)-5-Ethyl-5-(2'-pentyl)-2-thiobarbituric Acid (IIb).—The title compound prepared from malonic ester VI (R = C_2H_5) and thiourea[2] followed by work-up and sublimation had mp 148–149°.

Anal. Calcd for $C_{11}H_{18}N_2O_2S$: C, 54.40; H, 7.42; N, 11.54; S, 13.20. Found: C, 54.48; H, 7.57; N, 11.62; S, 13.05.

(*S*)-(+)-5-(2'-Pentyl)barbituric Acid (IIc).—Condensation of malonic ester V (0.90 g, 3.9 mmol) and urea with sodium ethoxide in ethanol[2] followed by purification and sublimation gave 0.71 g (50%) of IIc.

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.65; H, 7.23; N, 14.05.

(*S*)-(−)-5-Allyl-5-(2'-pentyl)barbituric Acid (IId).—Treatment of VI (R = CH_2=CH—CH_2) (10 g, 37.1 mmol) with urea by a procedure similar to that used to prepare IIa gave 5.7 g (65%) of IId.

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.48; H, 7.61; N, 11.76. Found: C, 60.34; H, 7.65; N, 11.83.

(*S*)-(−)-5-Allyl-5-(2'-pentyl)-2-thiobarbituric Acid (IIe).—Treatment of VI (R = CH_2=$CHCH_2$—) (2.0 g, 7.4 mmol) with thiourea by a procedure similar to that used to prepare IIb gave 0.52 g (31%) of IIe.

Anal. Calcd for $C_{12}H_{18}N_2O_2S$: C, 56.66; H, 7.13; N, 11.02; S, 12.61. Found: C, 56.62; H, 7.21; N, 10.97; S, 12.38.

Registry No.—IIa, 5767-32-8; IIb, 20224-43-5; IIc, 20224-44-6; IId, 20224-45-7; IIe, 20224-46-8.

Acknowledgment.—We take pleasure in thanking Dr. M. E. Wall, Director of this laboratory, for his kind encouragement and support of this work.

(22) See W. Voelter, R. Records, E. Bunnenburg, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 6143 (1968), for the use of MCD in an investigation of some pyrimidines.

(23) Melting points were determined using the Thomas–Hoover capillary melting point apparatus, and ultraviolet and visible spectra were measured on a Cary Model 14 spectrophotometer. Infrared spectra were measured with a Perkin-Elmer 221 spectrophotometer; samples were prepared in the form of pressed KBr disks. Mass spectra were determined on an AEI MS-902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

(24) H. A. Shonle, A. K. Kiltch, and E. E. Swanson, *J. Amer. Chem. Soc.*, **52**, 2440 (1930).

(25) K. Abe, T. Ishiraka, and Y. Tsukamoto, *J. Pharm. Soc. Jap.*, **75**, 891 (1955).

Synthesis of P,P,P′,P′-Tetraalkylated 1,4-Diphosphoniacyclohexadiene-2,5 Salts

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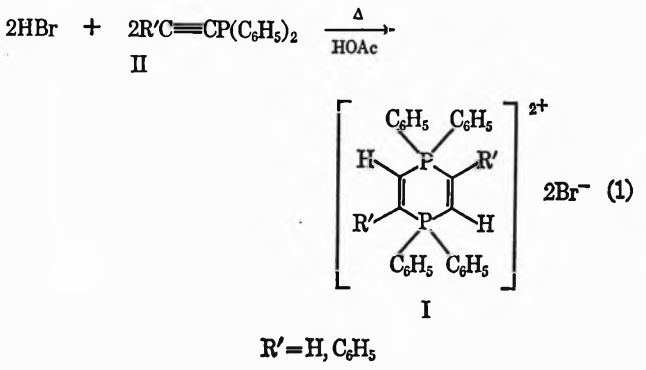
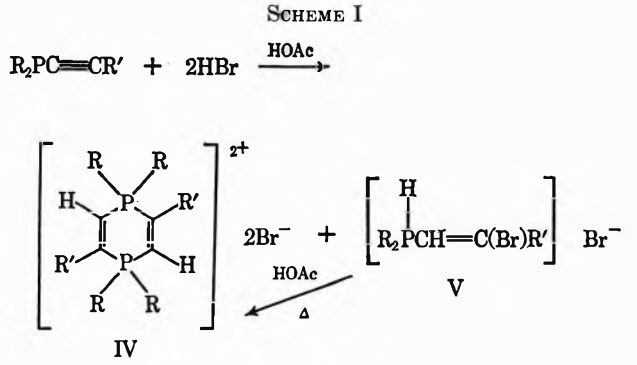
The preparation of the new class of phosphorus alkylated 1,4-diphosphoniacyclohexadiene-2,5 salts and β-halovinylphosphines from dialkyl-1-alkynylphosphines is described. Implications toward possible reaction sequences are discussed.

The preparation of 1,1,4,4-tetraphenyl-1,4-diphosphoniacyclohexadiene-2,5 dibromides (I) by the reaction of diphenyl-1-alkynylphosphines (II) with hydrogen bromide in hot glacial acetic acid was reported from this laboratory in 1967 (eq 1).[3,4]



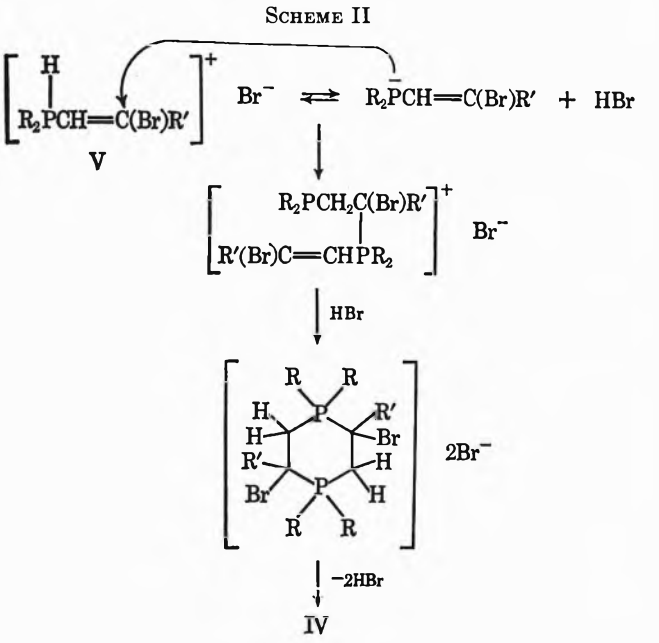
This synthesis was limited to the P-phenylated "diphosphoniapyrazine" salts (I) owing to the difficulty in obtaining dialkyl-1-alkynylphosphines (III).[5] This difficulty has now been overcome.[6] Treatment of the dialkyl-1-alkynylphosphines (III) with hydrogen bromide in boiling glacial acetic acid did not lead to the tetraalkylated salts (IV) in most cases, and in the one case in which the salt was obtained, the yield was less than 10%. At room temperature or lower, however, the same reagents do give rise to IV and β-bromovinylphosphine hydrobromides (V) (Scheme I). The major product under these conditions is usually V. Conversion of V into IV occurs readily in boiling glacial acetic acid (Scheme I).

SCHEME I



A series of acid-catalyzed Michael additions of phosphines to β-bromovinylphosphine hydrobromides and phosphonium salts followed by elimination of hydrogen bromide may explain the formation of IV from V (Scheme II).

SCHEME II



Although treatment of the isolated V with hot glacial acetic acid leads to IV, formation of IV can occur without the intermediacy of β-bromovinylphosphines by a series of acid-catalyzed Michael additions to alkynylphosphines (Scheme III).

This is shown by the fact that the dichlorides of IV are formed in higher yields than are the corresponding dibromides by the use of hydrogen chloride gas instead of hydrogen bromide. Further support for this explanation is found in the fact that usually no chlorovinylphosphines or their hydrochlorides are isolated under these conditions. These data are summarized in Table I.

It seems that there is competition between the halide ion and phosphine in the acid-catalyzed addition step to the alkynylphosphine. The bromide ion competes effectively with the phosphines and leads to some bromovinylphosphine. The chloride ion, on the other hand, is not so effective in the competitive nucleophilic addition. Relative acidity of the acid is apparently not so important as the nucleophilicity of its conjugate

(1) NDEA Predoctoral Fellow, 1965–1969.

(2) NASA Predoctoral Fellow, 1966–1969; NDEA Predoctoral Fellow, 1967–1969; NSF Predoctoral Fellow 1969–1970.

(3) A. M. Aguiar, K. C. Hansen, and G. S. Reddy, *J. Amer. Chem. Soc.*, **89**, 3067 (1967).

(4) A. M. Aguiar and K. C. Hansen, *ibid*, **89**, 4235 (1967).

(5) W. E. Davidsohn and M. C. Henry, *Chem. Rev.*, **67**, 73 (1967).

(6) A. M. Aguiar, J. R. S. Irelan, C. J. Morrow, J. P. John, and G. W. Prejean, *J. Org. Chem.*, **34**, 2684 (1969).

TABLE I

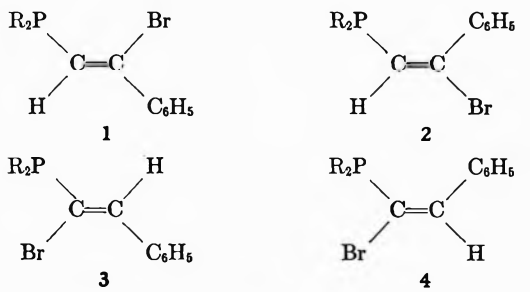
				IV			V	
R	R′	X⁻	Temp, °C	Yield, %	Mp (dec), °C	Picrate mp (dec), °C	Yield, %	Mp (dec), °C
CH_3	C_2H_5	Br	25	0	···	···	50	149–151
CH_3	C_2H_5	Br	125	35[a]	370–372	246–248	0	···
CH_3	C_2H_5	Cl	25	32	365–370	246–248[c]	0	···
CH_3	C_6H_5	Br	125	0	···	···	0	···
CH_3	C_6H_5	Br	25	51[b]	327–328[b]	273[c]	38	146.5–147.5
CH_3	C_6H_5	Cl	25	45	314–316	273[c]	0	···
C_2H_5	CH_3	Cl	25	20	305–307	245–247	0	···
C_2H_5	CH_3	Br	125	7.6[b]	318–320	245–247	76	···
C_2H_5	C_6H_5	Br	125	10	279–281	265–266[c]	40	150–152
C_2H_5	C_6H_5	Br	125	20[d]	279–281	265–266	0	···
C_2H_5	C_6H_5	Cl	25	30	285–287	265–266[c]	0	···
$(CH_3)_2CH$	$(CH_2)_2CH_3$	Cl	25	30	280–283	200–202	0	···
$(CH_3)_2CH$	H	Cl	25	38	285–287	200–202	0	···
$(CH_3)_2CH$	C_6H_5	Cl	25	7.2	270–273	263–265	0	···
$C_6H_5CH_2$	CH_3	Cl	25	45[b]	260–262	242–244	77	···

[a] Retreatment of isolated V with HX in glacial acetic acid. [b] Obtained by boiling V in glacial acetic acid. [c] Mixture melting point undepressed. [d] Added $R_2PC{\equiv}CR'$ to refluxing solution of HBr in HAc.

base. As predicted by this mechanistic explanation, hydrogen iodide seems to give only the β-iodovinylphosphine hydriodides, while trifluoroacetic acid leads to ring formation with little difficulty.

The conclusion that V is a bromovinylphosphine hydrobromide is based upon elemental analysis (where R = C_2H_5, R′ = C_6H_5), the presence of a P–H band of high intensity at 2260 cm^{-1}, immediate formation of a precipitate upon treatment with aqueous silver nitrate, and failure to form a picrate when treated with sodium picrate. Conversion of V to VI by pyridine further supports this conclusion. No 2260 cm^{-1} band was found for VI.

There are four stereochemical possibilities for the structure of VI (**1**, **2**, **3**, and **4**).



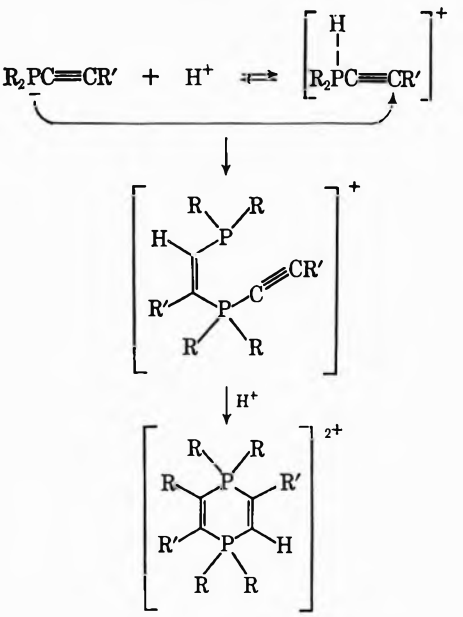
That the intermediate VI is not an α-bromovinylphosphine (**3** and **4**) is supported by the results obtained when diphenyl-1-butynylphosphine was treated with dry HBr in benzene (eq 2).

$$(C_6H_5)_2PC{\equiv}CC_2H_5 + HBr \xrightarrow{C_6H_6} (C_6H_5)_2PCH{=}C(Br)C_2H_5 \quad (2)$$

In this reaction, HBr added once across the triple bond to yield a β-bromovinylphosphine, evidenced by the lack of a coupling constant between the vinyl proton and the methylene of the ethyl group as well as the simplicity of the vinyl proton signal (see Experimental Section for spectrum).

The stereochemistry of VI is suspected to be either a mixture of **1** and **2** or only **1** rather than **2**, for there is reason to expect equilibration and **1** would be expected to be more stable, but this awaits further work.

SCHEME III



Experimental Section

All reactions, from the introduction of acetic acid until the removal of solvent, were performed under nitrogen. The hydrogen chloride and hydrogen bromide were used directly from the bottle (Matheson Chemical Co.). The acetic acid was deaerated by bubbling in nitrogen for 10–20 min. Picrates were formed by metathetical reaction between a methanolic solution of the phosphonium salt and a methanolic solution of sodium picrate.

P,P,P′,P′-Tetraalkyl-1,4-diphosphoniacyclohexadiene-2,5 Salts. General Procedure.—To 50 ml of deaerated acetic acid was added a 10-ml acetic acid solution of 2–5 g of dialkyl-1-alkynylphosphine, and then dry hydrohalic acid was bubbled in at room temperature or with the flask immersed in an ice bath. Slow addition of HX was carried out for 30–60 min and the mixture was allowed to stand under nitrogen at room temperature for 3–5 days or the solution was refluxed for 2–4 hr. The acetic acid was then removed in each case by heating with a hot (60–80°) water bath and stirring (magnetic) under aspirator pressure. The last traces of acetic acid were removed *in vacuo* at 60–80° (1.0–0.1 mm) for 1–3 hr. The resulting gum was triturated with ether, and acetone was added. If the salt precipitated, it was filtered out. If no solid formed, the acetone solution was cooled to −20° until precipitation occurred. The resulting diphosphonium salt was normally recrystallized from methanol–ethyl acetate. If the intermediate V was isolated (as indicated by

spectra), it was dissolved in 50 ml of acetic acid, refluxed for 4–6 hr, and worked up on the same manner as before.

Frequently, the salts were hygroscopic or associated with small amounts of solvents, rendering purification difficult. The picrate salts, which could be obtained pure, were thus formed, and microanalyses were performed on these.

Characteristics of the salts are as follows.

IV, R = CH_3, R′ = CH_2CH_3, X = Br.—The ir spectrum (KBr) showed bands at 1705, 1600 (C=C), 1465, and 1410 cm^{-1}. The nmr spectrum in trifluoroacetic acid (TFA) presented a pseudotriplet[3,4] at δ 7.62 ($J \approx 26$ cps) for the vinyl protons (2 H), a multiplet at δ 2.6–3.15 for the allyl protons (4 H), two sharp peaks at δ 2.32 and 2.56 above a broad center peak at δ 2.45 representing the methyl groups on phosphorus (12 H), and a triplet at δ 1.47 (J = 7 cps) for the terminal methyl groups (6 H).

IV, R = CH_3, R′ = CH_2CH_3, X = Cl.—The nmr spectrum (TFA) of the dichloride is like that of the dibromide but displaying the vinyl pseudotriplet at δ 7.59 (slightly upfield).

IV, R = CH_3, R′ = CH_2CH_3, X = Picrate.

Anal. Calcd for $C_{24}H_{27}N_6O_{14}P_2$: C, 42.00; H, 4.08; N, 12.24; P, 9.03. Found: C, 41.88; H, 4.12; N, 12.16; P, 9.13.

IV, R = CH_3, R′ = C_6H_5, X = Br.—The ir spectrum (KBr) showed significant bands at 1560 (C=C), 1495, 1447, and 1302 cm^{-1}. The nmr spectrum (TFA) exhibited a broadened aromatic singlet at δ 7.70 above the vinyl pseudotriplet at δ 7.89 (J = 26 cps, 12 H together) and the methyl groups on phosphorus as two sharp peaks at δ 2.49 and 2.74 above a broad center peak at δ 2.60 (12 H).

IV, R = CH_3, R′ = C_6H_5, X = Cl.—The ir spectrum (KBr) displayed significant bands at 1630, 1550 (C=C), 1480, 1435, 1403, and 1285 cm^{-1}. The nmr spectrum (TFA) showed the same spectrum as the dibromide but displayed the aromatic protons as a multiplet at δ 7.41–8.32 above the vinyl pseudotriplet at δ 7.82 (J = 26 cps). The methyl groups on phosphorus show the same pattern at the same shift as the dibromide.

IV, R = CH_3, R′ = C_6H_5, X = Picrate.

Anal. Calcd for $C_{32}H_{28}N_6O_{14}P_2$: C, 49.11; H, 3.61; N, 10.74. Found: C, 48.41; H, 3.80; N, 10.33.

IV, R = CH_2CH_3, R′ = CH_3, X = Br.—The nmr spectrum (TFA) displayed the vinyl pseudotriplet at δ 7.90 (J = 25 cps, 2 H), the methylenes on phosphorus and the allyl methyl groups as a complex multiplet at δ 2.5–3.2 (14 H), and the methyls of the ethyl groups as two triplets at δ 1.60 and 1.23 (J = 7.5 cps each) above a broad region at δ 1.05–1.80 (12 H).

IV, R = CH_2CH_3, R′ = CH_3, X = Cl.—The ir spectrum (KBr) showed bands at 1470 (C=C), 1410, 1310, 1250, and 1110 cm^{-1}. The nmr spectrum (TFA) showed the same spectrum as the dibromide but displayed the vinyl pseudotriplet at δ 7.69 (J = 25 cps).

IV, R = CH_2CH_3, R′ = CH_3, X = Picrate.

Anal. Calcd for $C_{26}H_{32}N_6O_{14}P_2$: C, 43.71; H, 4.51; N, 11.76; P, 8.67. Found: C, 43.78; H, 4.39; N, 12.09; P, 8.39.

IV, R = CH_2CH_3, R′ = C_6H_5, X = Br.—The ir spectrum (KBr) showed bands at 1595 (C=C) 1481, 1445, 1400, 1285, and 1262 cm^{-1}. The nmr spectrum (TFA) exhibited a broad aromatic multiplet at δ 7.5–7.95 above the upfield half of the vinyl pseudotriplet at δ 8.12 (J = 25 cps, 12 H together), a broad multiplet at δ 2.3–3.5 for the methylenes next to phosphorus (8 H), and a broad multiplet at δ 1.1–1.9 which contains two triplets at δ 1.35 and 1.71 (J = 7.5 cps each, 12 H).

IV, R = CH_2CH_3, R′ = C_6H_5, X = Cl.—The ir spectrum (KBr) displayed bands at 1610 (C=C), 1500, 1450, 1392, 1295, and 1281 cm^{-1}. The nmr spectrum (TFA) showed the same spectrum as the dibromide, except that the vinyl pseudotriplet appeared upfield at δ 7.70 (J = 25 cps).

Anal. Calcd for $C_{24}H_{32}Cl_2P_2$: C, 63.58; H, 7.11; Cl, 15.64; P, 13.66. Found: C, 63.35; H, 7.11; Cl, 15.69; P, 13.12.

IV, R = CH_2CH_3, R′ = C_6H_5, X = Picrate.

Anal. Calcd for $C_{36}H_{36}N_6O_{14}P_2$: C, 51.56; H, 4.33; N, 10.02; P, 7.39. Found: C, 51.64; H, 3.63; N, 10.24; P, 7.62.

IV, R = $(CH_3)_2CH$, R′ = $(CH_2)_2CH_3$, X = Cl.—The nmr spectrum (TFA) exhibited the vinyl pseudotriplet at δ 7.61 (J = 25 cps, 2 H), the central hydrogens in the isopropyl groups with the allyl methylenes as two broad multiplets δ 2.6–3.8 (8 H), and the remainder of the hydrogens in a multipeak region at δ 1.0–2.3 (34 H).

IV, R = $(CH_3)_2CH$, R′ = $(CH_2)_2CH_3$, X = Picrate.

Anal. Calcd for $C_{34}H_{48}N_6O_{14}P_2$: C, 49.40; H, 5.85; N, 10.17; P, 7.49. Found: C, 49.07; H, 5.76; N, 10.17; P, 7.64.

IV, R = $(CH_3)_2CH$, R′ = H, X = Cl.—The ir spectrum (KBr) showed bands at 1453 (C=C), 1260, 1253, and 1042 cm^{-1}. The nmr spectrum (TFA) displayed the vinyl pseudotriplet at δ 8.13 (J = 26 cps, 4 H), the central hydrogens in the isopropyl groups as a broad multiplet at δ 2.83–3.50 (4 H), and the methyl groups as four sharp peaks at δ 1.20, 1.31, 1.53, and 1.65 above a broad multiplet at δ 1.10–1.75 (12 H).

IV, R = $(CH_3)_2CH$, R′ = H, X, = Picrate.

Anal. Calcd for $C_{28}H_{36}N_6O_{14}P_2$: C, 45.29; H, 4.89; N, 11.32; P, 8.34. Found: C, 45.28; H, 4.93; N, 12.19; P, 8.21.

IV, R = $(CH_3)_2CH$, R′ = C_6H_5, X = Cl.—The ir spectrum (KBr) displayed bands at 1610 (C=C), 1450, 1395, 1295, and 1280 cm^{-1}. The nmr spectrum (TFA) exhibited the vinyl pseudotriplet at δ 7.89 (J = 24 cps) beneath an aromatic multiplet at δ 7.5–8.0 (6 H together), the central hydrogen in the isopropyl groups as a multiplet at δ 3.2–3.9 (4 H), and the methyl groups as a group of eight broadened peaks at δ 1.17–1.97 (12 H).

IV, R = $(CH_3)_2CH$, R′ = C_6H_5, X = Picrate.

Anal. Calcd for $C_{40}H_{44}N_6O_{14}P_2$: C, 53.70; H, 4.96; N, 9.39; P, 6.94. Found: C, 53.76; H, 4.82; N, 9.32; P, 7.06.

IV, R = $C_6H_5CH_2$, R′ = CH_3, X = Cl.—The ir spectrum (KBr) showed bands at 1620, 1590, 1490 (C=C), 1450, and 1270 cm^{-1}. The nmr spectrum (TFA) showed two close aromatic multiplets at δ 6.95–7.65 covering all but the downfield peak at δ 7.87 of the vinyl pseudotriplet (22 H together), a broad multiplet at δ 3.6–4.1 for the benzyl hydrogens (8 H), and a multiplet at δ 2.45–2.70 for the allyl methyls showing two rounded peaks at δ 2.54 and 2.72 (6 H).

IV, R = $C_6H_5CH_2$, R′ = CH_3, X = Picrate.

Anal. Calcd for $C_{46}H_{40}N_6O_{14}P_2$: C, 57.30; H, 4.15; N, 8.73; P, 6.44. Found: C, 57.13; H, 4.15; N, 8.56; P, 6.34.

V, R = CH_3, R′ = CH_2CH_3, X = Br.—The ir spectrum ($CHCl_3$) displayed bands at 2435 (P-H), 1600 (C=C), and 1355 cm^{-1}. The nmr spectrum (TFA) exhibited a crude vinyl doublet at δ 6.52 (J = 16 cps, 1 H), a crude quartet for the allyl methylene at δ 2.90 (J = 7 cps, 2 H), a sharp doublet for the phosphorus methyls at δ 2.09 (J = 13.5 cps, 6 H), and a triplet for the terminal methyl group at δ 1.30 (J = 7 cps, 3 H).

V, R = CH_3, R′ = C_6H_5, X = Br.—The ir spectrum ($CHCl_3$) displayed bands at 2450 (P-H), 1587 (C=C), 1570, 1447, and 1294 cm^{-1}. The nmr spectrum (TFA) showed an aromatic multiplet at δ 7.40–7.95 (5 H), the vinyl proton as two doublets at δ 7.13 and 6.83 (J = 6 cps, 17.5 cps apart, 1 H), and the phosphorus methyls as two doublets at δ 2.35 and 2.25 (J = 15 cps, 5 cps apart, 6 H).

Anal. Calcd for $C_{10}H_{13}Br_2P$: C, 37.07; H, 4.07; Br, 49.31; P, 9.55. Found: C, 37.50; H, 4.07; Br, 48.04; P, 9.91.

V, R = CH_2CH_3, R′ = CH_3, X = Br.—The ir spectrum ($CHCl_3$) showed bands at 2430 (P-H), 1615 (C=C), 1450, and 1370 cm^{-1}. The nmr spectrum (TFA) displayed the vinyl proton as a crude doublet at δ 6.52 (J = 13.5 cps, 1 H), the methylenes next to phosphorus as a multiplet at δ 2.35–3.00 (4 H), the allyl methyl group as a broadened singlet at δ 1.70 (3 H), and the methyls on the ethyl groups as a triplet at δ 1.32 (J = 7.5 cps, 6 H).

V, R = CH_2CH_3, R′ = C_6H_5, X = Br.—The ir spectrum (KBr) exhibited bands at 2260 (P-H), 1592, 1572, 1490 (C=C), 1448, and 1406 cm^{-1}. The nmr spectrum (TFA) showed an aromatic multiplet at δ 7.35–7.95 (5 H), the vinyl proton as a doublet at δ 7.08 (J = 7.5 cps, 1 H), the methylenes next to phosphorus as a multiplet at δ 2.3–3.1 (4 H), and the methyl groups as two triplets at δ 1.70 and 1.34 (J = 7 cps each, 6 H).

Anal. Calcd for $C_{12}H_{17}Br_2P$: C, 40.94; H, 4.87; Br, 45.40; P, 8.80. Found: C, 40.86; H, 4.92; Br, 45.12; P, 9.13.

V, R = $C_6H_5CH_2$, R′ = CH_3, X = Cl.—The nmr spectrum exhibited an aromatic singlet at δ 3.43 (10 H), the vinyl proton as two crude doublets at δ 5.89 and 6.15 (J = 7 cps each, 16 cps apart, 1 H), the benzyl protons as two crude doublets at δ 3.80 and 4.05 (J = 5 cps each, 15 cps apart, 4 H), and the methyl protons as a close doublet at δ 2.42 ($J \approx 0.5$ cps, 3 H).

VI, R = C_2H_5, R′ = C_6H_5, X = Br.—To a dry 50-ml tetrahydrofuran suspension of 3.0 g of diethyl-1-(2-bromo-2-phenylethenyl)phosphine hydrobromide was added 1.0 ml of pyridine. The mixture was stirred under nitrogen at 30–40° for 5 hr. The mixture was filtered and the filtrate stripped, leaving a gummy yellow material. The residue was recrystallized from ether–acetonitrile–methanol: yield, 1.2 g of light yellow powder (52%); mp *ca.* 27°. The ir spectrum ($CHCl_3$) showed bands at 1670, 1585, 1572, 1487, and 1448 cm^{-1} and no PH band at 2260 cm^{-1}. The nmr spectrum ($CDCl_3$) displayed an aromatic mul-

tiplet at δ 7.2–7.8 (5 H), a broad vinyl singlet at δ 6.88 (1 H), and two merged multiplets for the ethyl groups at δ 1.6–2.3 and 0.8–1.6 (10 H).

Diphenyl-1-butynylphosphine.—Approximately 20 ml of 1-butyne (Matheson) was condensed through an 8-mm glass U-tube in a Dry Ice bath into a 3-neck flask in a Dry Ice bath and under a nitrogen atmosphere. To the condensate was added 100 ml of dry tetrahydrofuran followed by 125 ml of 1.6 *M* *n*-butyllithium in hexane (Foote) over a 30-min period. The mixture was stirred for 20 min and warmed to ice bath temperature. An 80-ml dry tetrahydrofuran solution of 44.00 g of diphenylphosphinous chloride (Aldrich) was added during a 30-min period with stirring. The mixture was stirred at room temperature for 20 min and the solvent stripped. Ether (500 ml) was added to the residue, the mixture was filtered, and the ether was stripped from the filtrate. The resultant dark liquid was distilled through a 10-cm Vigeraux column at 0.45 mm, collecting one fraction (small amount of forerun discarded), bp 133–136°, to give 41.80 g of colorless liquid (87.9%). The ir spectrum ($CHCl_3$) showed significant absorptions at 2186 (C≡C, strong), 1478, 1437 (phenyl-P), and 1312 cm^{-1}. The nmr spectrum ($CDCl_3$) exhibited an aromatic multiplet at δ 7.1–7.7 (10 H), the allyl protons as a quartet (J = 7.5 cps) at δ 2.37 showing fine splitting ($J \approx 1.5$ cps, 2 H), and the terminal methyl group at δ 1.15 as a triplet (J = 7.5 cps, 3 H).

Diphenyl-1-(2-bromobutenyl)phosphine.—Into a solution of 1.15 g of diphenyl-1-butynylphosphine dissolved in 50 ml of benzene, hydrogen bromide was bubbled with stirring for 10 min and the solvent stripped to leave 1.54 g of red-yellow oil (quant). The ir spectrum ($CHCl_3$) showed bands at 1590 (C=C), 1485, and 1440 cm^{-1}. The nmr spectrum ($CDCl_3$) showed an aromatic multiplet at δ 7.20–7.60 with a sharp peak at δ 7.34 (10 H), a vinyl triplet at δ 6.53 (J = 1 cps, 1 H), the allyl methylene as a quartet at δ 2.67 (J = 7 cps) with fine splitting ($J \approx 1$ cps, 2 H), and the terminal methyl groups as a triplet at δ 1.20 (J = 7 cps, 3 H).

The bromophosphine was dissolved in 10 ml of acetone, and 3% hydrogen peroxide (aqueous) was added with stirring until the mixture was barely translucent. Acetone was added (a few drops) until the mixture was clear, and the solvent was allowed to evaporate to dryness in air. Water was added and the mixture filtered to leave 1.64 g of white solid (99% from the alkynylphosphine). Recrystallization from ethanol–water provided the analytical sample, mp 118–120°. The ir spectrum ($CHCl_3$) displayed the phosphoryl group at 1180 cm^{-1}. The nmr spectrum exhibited an aromatic multiplet at δ 7.00–7.55 (10 H), a vinyl doublet at δ 6.44 (J = 15.5 cps) with each peak split to a fine triplet (J = 1 cps, 1 H), the allyl methylene as a quartet at δ 2.60 (J = 7 cps) showing a small coupling constant ($J \approx 1$ cps, 2 H), and the terminal methyl as a triplet at δ 1.14 (J = 7 cps, 3 H).

Anal. Calcd for $C_{16}H_{16}BrOP$: C, 57.33; H, 4.81; Br, 23.84; P, 9.24. Found: C, 57.20; H, 4.76; Br, 23.92; P, 9.42.

Registry No.—IVa, 20439-89-8; IVb, 20439-90-1; IVa, b (picrate), 20439-91-2; IVc, 20439-92-3; IVd, 20439-93-4; IVc/d (picrate), 20439-94-5; IVe, 20439-95-6; IVf, 20439-96-7; IVe, f (picrate), 20439-97-8; IVg, 20439-98-9; IVh, 20439-99-0; IVg, h (picrate), 20440-00-0; IVi, 20440-01-1; IVi (picrate), 20440-02-2; IVj, 20440-03-3; IVj (picrate), 20440-04-4; IVk, 20440-05-5; IVk (picrate), 20440-06-6; IVl, 20440-07-7; IVl (picrate), 20440-08-8; Va, 20440-09-9; Vc, 20440-10-2; Vf, 20440-11-3; Vg, 20446-21-3; Vl, 20446-22-4; VIg, 20446-23-5; diphenyl-1-butynylphosphine, 20446-24-6; diphenyl-1-(2-bromobutenyl)phosphine, 20446-25-7; phosphoryl derivative of diphenyl-1-(2-bromobutenyl)phosphine, 20446-20-2.

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A Convenient, Synthetic Pathway to Dialkyl-1-alkynylphosphines

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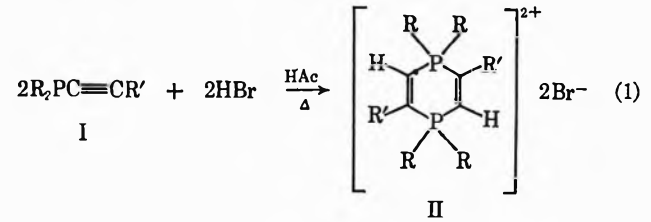
A new, convenient preparation of dialkyl-1-alkynylphosphines employing the readily available diethyl phosphorochloridite is described.

Interest in the preparation of dialkyl-1-alkynylphosphines (I, R = alkyl) was aroused by the discovery in this laboratory that the P-phenylated analogs are precursors to the P,P′-tetraphenylated 1,4-diphosphoniacyclohexadiene-2,5 salts (II) (eq 1).[3,4]



$$2R_2PC{\equiv}CR' + 2HBr \xrightarrow[\Delta]{HAc} \text{II}\ 2Br^- \quad (1)$$

I

R = C_6H_5
R′ = H, C_6H_5

A recent review on alkynylphosphines reveals the shortage of useful synthetic approaches to the dialkyl-1-alkynylphosphines.[5] Reaction of an alkynyllithium with the proper dialkylphosphinous halide (III) constitutes the most direct method of preparation of these compounds (eq 2).[6] This method depends upon the availability of the dialkylphosphinous chlorides.

$$\underset{\text{III}}{R_2PCl} + LiC{\equiv}CR' \longrightarrow \underset{\text{I}}{R_2PC{\equiv}CR'} + LiCl \quad (2)$$

Dialkylation of phosphorus trichloride is not readily achieved by alkyl Grignards unless the alkyl group is sterically demanding.[7] An example of the latter is the preparation of diisopropylphosphinous chloride from the reaction of isopropyl magnesium bromide with phosphorus trichloride (eq 3).[8]

$$2(CH_3)_2CHMgBr + PCl_3 \longrightarrow [(CH_3)_2CH]_2PCl + MgBr_2 + MgCl_2 \quad (3)$$

(1) NASA Predoctoral Fellow, 1966–1969; NDEA Predoctoral Fellow, 1967–1968; NSF Predoctoral Fellow, 1969–1970.

(2) NDEA Predoctoral Fellow, 1965–1969.

(3) A. M. Aguiar, K. C. Hansen, and G. S. Reddy, *J. Amer. Chem. Soc.*, **89**, 3067 (1967).

(4) A. M. Aguiar and K. C. Hansen, *ibid.*, **89**, 4235 (1967).

(5) W. E. Davidsohn and M. C. Henry, *Chem. Rev.*, **67**, 73 (1967).

(6) W. Voskuil and J. F. Arens, *Rec. Trav. Chim. Pays Bas*, **81**, 993 (1962).

(7) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley & Sons, Inc., New York, N. Y., 1950, p 16.

(8) W. Voskuil and J. F. Arens, *Rec. Trav. Chim. Pays Bas*, **82**, 302 (1963).

In our early attempts at obtaining dimethyl and diethylphosphinous chlorides, we employed many of the known methods of preparation of these compounds and found them to be badly lacking.[9,10] Two of these routes are summarized below (Schemes I and II).

SCHEME I

$$PCl_3 + 2HNR_2' \longrightarrow Cl_2PNR_2' + [R_2'NH_2]Cl$$

$$R_2'NPCl_2 + 2RMgX \longrightarrow R_2PNR_2' + MgX_2 + MgCl_2$$

$$R_2PNR_2' + 2HCl \longrightarrow \underset{\text{III}}{R_2PCl} + [R_2'NH_2]Cl$$

SCHEME II

$$RMgX + PSCl_3 \longrightarrow [R_2P(S)]_2 + ?$$

(excess)

$$[R_2P(S)]_2 + C_6H_5PCl_2 \longrightarrow \underset{\text{III}}{2R_2PCl} + ?$$

Not only are these compounds obtained in low yields by the methods shown above, but they are also pyrophoric and, consequently, difficult to handle.

We wish to report here a new, versatile, convenient approach to the P-dimethyl-, diethyl-, and dibenzylalkynylphosphines.

Reaction of the commercially available diethyl phosphorochloridite (IV) with an alkynyllithium can be easily controlled to yield the diethyl alkynyl-1-phosphonite (V) (eq 4). Reaction of the unisolated phosphonite V with 2 mol of methyl, ethyl, or benzyl magnesium halide yields the corresponding P-dialkyl-1-alkynylphosphine with little difficulty (eq 5).

$$\underset{\text{IV}}{(CH_3CH_2O)_2PCl} + LiC{\equiv}CR' \longrightarrow \underset{\text{V}}{(CH_3CH_2O)_2PC{\equiv}CR'} + LiCl \quad (4)$$

$$\underset{\text{V}}{(CH_3CH_2O)_2PC{\equiv}CR'} + 2RMgX \longrightarrow \underset{\text{I}}{R_2PC{\equiv}CR'} + (CH_3CH_2O)_2Mg + MgX_2 \quad (5)$$

R′ = H, CH_3, C_2H_5, C_6H_5

R = CH_3, CH_3CH_2, $CH_2C_6H_5$

Some of the phosphines produced in this manner are listed in Table I along with their boiling points and yields.

It is relatively simple to prepare the starting diethyl phosphorochloridite by the known disproportionation reaction of phosphorus trichloride and triethyl phosphite (eq 6).[11]

$$PCl_3 + (CH_3CH_2O)_3P \rightleftharpoons \underset{\text{VI}}{(CH_3CH_2O)PCl_2} + \underset{\text{IV}}{(CH_3CH_2O)_2PCl} \quad (6)$$

Either the diethyl phosphorochloridite (IV) or ethyl phosphorodichloridite (VI) can be obtained in very pure form by employing adequate distillation procedures.

The success of this method for preparing dialkyl-1-alkynylphosphines is easily explained by the reasonable assumption that the chloride ion is much more easily displaced than the ethoxide ion. It is also probable that the great difference in rates of displacement of these two groups may involve the nature of the cation or the hydrocarbon moiety of the organometallic reagent.

(9) K. Issleib and W. Seidd, *Chem. Ber.*, **92**, 2681 (1959).
(10) G. W. Parshall, *J. Inorg. Nucl. Chem.*, **12**, 372 (1960).
(11) H. G. Cook and G. More, *J. Chem. Soc.*, 2921 (1949).

Diethyl ethynylphosphonite was prepared from the monomagnesium bromide salt of acetylene, indicating that the metal is not critical.

In this connection, it is interesting to note that the reaction of 1 mol of alkynyllithium with phosphorus trichloride, followed by addition of 2 mol of alkyl Grignard, does lead to a higher yield of the dialkyl-1-alkynylphosphine than if the Grignard is added first (eq 7 and 8).

$$PCl_3 + LiC{\equiv}CR' \longrightarrow Cl_2PC{\equiv}CR' + LiCl \quad (7)$$

$$R'C{\equiv}CPCl_2 + 2RMgX \longrightarrow R_2PC{\equiv}CR' + MgX_2 + MgCl_2 \quad (8)$$

The P-methyl, ethyl, and benzyl derivatives, however, can be obtained by this path only with some degree of hazard and in low yields. Trisalkynylphosphines are probably obtained as by-products, for, in one instance, detonation occurred upon attempted distillation of the crude mixture.

The dialkyl-1-alkynylphosphines prepared in this work were very air-sensitive, and they were converted to the corresponding 1,4-diphosphoniacyclohexadiene-2,5 salts immediately after preparation and characterization by nuclear magnetic resonance and infrared spectroscopy. Formation of these salts is discussed in another paper.

Experimental Section

All of the reactions were run under nitrogen, from the introduction of diethyl phosphorochloridite until after the addition of water. Lithium phenylacetylide was prepared by slowly adding 0.10 mol of *n*-butyllithium in hexane (63 ml of 1.6 *M* solution, Foote Chemical Co.) to a tetrahydrofuran solution of phenylacetylene immersed in an ice bath. Butynyllithium was prepared by condensing *ca.* 15 ml of 1-butyne in a Dry Ice bath, diluting with tetrahydrofuran, and slowly adding 0.10 mol of *n*-butyllithium. Propynyllithium was prepared in the same manner as butynyllithium, or the commercially available material (Foote) was used. This material existed primarily as a suspension when added to tetrahydrofuran. Tetrahydrofuran was dried over calcium hydride for 3–4 days and distilled from calcium hydride. The Grignard reagents were prepared in the usual manner in dry ether. Boiling points are uncorrected.

Preparation of Dialkyl-1-alkynylphosphines. General Procedure.—Diethyl phosphorochloridite (15.6 g, 0.10 mol) dissolved in 50–150 ml of tetrahydrofuran was immersed in a Dry Ice bath. A 50–100-ml suspension of 0.10 mol of the alkynyllithium compound in tetrahydrofuran was added with stirring over a 30–50-min period. The mixture was allowed to warm to room temperature, stirred for 30 min, and cooled in an ice bath. A quantity of 0.2 mol of the corresponding Grignard reagent in 100–150 ml of ether was added with stirring over a 30–90-min period. The mixture was stirred for 2–4 hr at room temperature and cooled in an ice bath, and 100 ml of saturated ammonium chloride solution was slowly added. Water (300 ml) was added, followed by 200 ml of ether. The phases were separated, and the ether was washed twice with water, dried ($MgSO_4$ or Na_2SO_4), and evaporated. The residue was distilled (short head or 10-cm Vigreux) at reduced pressure to yield the phosphine as a colorless liquid.

Spectra are as follows.

Dimethyl-1-butynylphosphine.—The ir spectrum ($CHCl_3$) showed bands at 4.58 (C≡C), 7.00, 7.60, 10.55, and 10.98 μ. The nmr spectrum ($CDCl_3$) displayed a crude quartet at δ 2.32 (J = 7.5 cps, 2 H), and a doublet at δ 1.27 for the methyl groups on phosphorus (J = 3.5 cps) above the terminal methyl triplet at δ 1.17 (J = 7.5 cps, 9 H together).

Dimethyl(phenylethynyl)phosphine.—The ir spectrum ($CHCl_3$) showed absorptions at 4.65 (C≡C), 6.26, 6.72, 7.00, 10.57, and 11.05 μ. The nmr spectrum ($CDCl_3$) exhibited a complex aromatic multiplet at δ 7.10–7.55 (5 H) and a methyl doublet at δ 1.33 (J = 4 cps, 6 H).

TABLE I

Compd	Registry no.	Bp, °C (mm)	Yield, % (after distillation)
$(CH_3)_2PC{\equiv}CC_2H_5$	20505-07-1	76–80 (90)	20[b]
$(CH_3)_2PC{\equiv}CC_6H_5$	30505-08-2	62–65 (0.6)	57
$(C_2H_5)_2PC{\equiv}CCH_3$[a]	6224-89-1	84–85 (50)	50
$(C_2H_5)_2PC{\equiv}CC_6H_5$[a]	7528-15-6	105–107 (0.7)	47
$(C_6H_5CH_2)_2PC{\equiv}CCH_3$	20505-11-7	168–171 (0.6)	16[c]
$(C_2H_5O)_2PC{\equiv}CH$	20505-16-2	75–80 (20)	30[d]

[a] C. Charrier, M. P. Simonnin, W. Chookiewicz, and P. Cadlot, *Compt. Rend.*, 258, 1537 (1964). [b] Adequate precautions were not taken to account for the low volatility of the product, and the yield was probably higher. [c] This product oxidizes fairly rapidly, and exposure of the reaction mixture to air during work-up probably reduced the yield considerably. [d] Polymerization of this product occurs when heated, decreasing the yield.

Diethyl-1-propynylphosphine.—The ir spectrum ($CHCl_3$) showed absorptions at 4.57 (C≡C), 6.77, 8.10 (broad), and 9.71 μ. The nmr spectrum ($CDCl_3$) displayed the allyl methyl as a close doublet at δ 1.96 (J = 1 cps) above the edge of a complex multiplet representing the ethyl groups on phosphorus at δ 0.80–2.10.

Diethyl(phenylethynyl)phosphine.—The ir spectrum (film) displayed bands at 4.62 (C≡C), 6.26, 6.71, 6.88, and 11.97 μ. The nmr spectrum ($CDCl_3$) exhibited a complex aromatic region at δ 7.15–7.60 (5 H) and a complex aliphatic region at δ 0.85–2.00 (10 H) for the ethyl groups on phosphorus.

Dibenzyl-1-propynylphosphine.—The ir spectrum ($CHCl_3$) showed absorptions at 4.61 (C≡C), 6.29, 6.72, 6.90, and 7.09 μ. The nmr spectrum ($CDCl_3$) displayed an aromatic singlet at δ 7.30 (10 H), a doublet at δ 2.90 (J = 2 cps) for the benzyl protons (4 H), and a doublet at δ 1.80 (J = 1 cps) for the allyl methyl (3 H).

Diethyl Ethynylphosphonite.—The ir spectrum (film) showed bands at 3.08 (≡CH), 4.91 (C≡C), 7.22, 9.72 (broad, P—O), and 10.80 μ (broad, P—O). The nmr spectrum ($CDCl_3$) exhibited a multiplet at δ 3.6–4.3 for the methylenes in the ethyl groups (4 H), a doublet at δ 3.09 (J = 2 cps) for the acetylenic proton (1 H), and a crude triplet at δ 1.29 (J = 7 cps) for the methyl groups (6 H).

Diisopropyl-1-alkynylphosphines.—Diisopropylphosphinous chloride was prepared from two equivalents of isopropyl Grignard reagent and one equivalent of phosphorus trichloride as described by W. Voskuil.[8] The diisopropyl-1-alkynylphosphines were prepared by adding diisopropylphosphinous chloride to a dry tetrahydrofuran solution (or suspension) of the prepared alkynyllithium (or Grignard) compound in a Dry Ice bath, and was worked up in the same manner as before. Boiling points and spectra of phosphines prepared are as follows.

Diisopropylethynylphosphine had bp 43–45° (11 mm), 31% yield. The ir spectrum (film) displayed absorptions at 3.04 (≡CH), 4.88 (C≡C), 6.83, 7.20, and 7.30 μ. The nmr spectrum ($CDCl_3$) exhibited a doublet at δ 2.86 (J = 9.5 cps, 1 H) for the acetylenic proton, a broad multiplet at δ 1.54–2.38 (2 H) for the methynyl protons next to phosphorus, and a nine-line pattern at δ 0.90–1.54 (12 H) which seems to include three triplets (J = 7 cps) at δ 1.02, 1.19, and 1.24 (9.5 cps apart).

Diisopropyl-1-pentynylphosphine had bp 68–69° (1.25 mm), 26.1% yield. The ir spectrum ($CHCl_3$) showed bands at 4.60 (C≡C), 6.85, 7.21, and 7.30 μ. The nmr spectrum ($CDCl_3$) displayed two *merged* multiplets, one as a basic triplet at δ 2.32 (J = 6–7 cps), and the other as a complex pattern at δ 0.8–2.2 with the more intense peaks in the upfield half.

Diisopropyl-1-octynylphosphine had bp 89–93° (0.4 mm), 48.3% yield. The ir spectrum ($CHCl_3$) showed absorptions at 4.58 (C≡C), 6.82, 7.21, and 7.30 μ. The nmr spectrum ($CDCl_3$) displayed two *merged* multiplets, one at δ 2.1–2.5 appearing as a crude triplet at δ 2.30 ($J \approx 6$ cps), and the other as a complex pattern at δ 0.6–2.1 with the more intense peaks in the region δ 0.6–1.6.

Diisopropyl(phenylethynyl)phosphine had bp 116–120° (0.75 mm), 36% yield. The ir spectrum (film) displayed bands at 4.60 (C≡C), 6.24, 6.70, 6.82, 7.20, and 7.30 μ. The nmr spectrum ($CDCl_3$) exhibited an aromatic multiplet at δ 7.1–7.6 (5 H), a broad multiplet at δ 1.53–2.25 (2 H) for the methynyl protons next to phosphorus, and an eight-line pattern at δ 0.93–1.48 (12 H) for the methyl protons, which appears to be four doublets at δ 1.33, 1.28, 1.14, and 1.01, each having a coupling constant of 6–6.5 cps and each having a more intense downfield peak.

Registry No.—Diisopropylethynylphosphine, 20505-12-8; diisopropyl-1-pentynyl phosphine 20505-13-9; diisopropyl-1-octynylphosphine, 20505-14-0; diisopropyl(phenylethynyl)phosphine, 20505-15-1.

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The Reactions of Diphenylphosphine with α-Substituted Ketones. A New Dehalogenation and Demesylation Procedure[1]

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Diphenylphosphine converts acyclic α-halo ketones and α-mesyloxyketones into the dehalogenated or demesylated ketone, respectively. Reaction with cyclohexanone, α-chlorocyclohexanone, or α-mesyloxycyclohexanone gives the corresponding carbonyl adduct, an α-hydroxydiphenylphosphine, which is isolated as the phosphine oxide. The debromination reaction exhibits a moderate and negative Hammett ρ value. The reaction of diphenylphosphine with α-bromoacetophenone or with 2,4,6-trimethyl-α-bromoacetophenone, a hindered carbonyl case, proceeds at about the same rate. These facts, as well as other data which are given, suggest that the dehalogenation reactions proceed *via* nucleophilic displacement on halogen by phosphorus with transfer of an incipient proton to carbonyl oxygen. Other mechanistic pathways and the scope of the reactions of carbonyl compounds with diphenylphosphine are discussed.

We[3,4] and others[5,6] have shown that α-bromo ketones are debrominated with triphenylphosphine in the presence of hydroxylic solvents such as alcohols, water, or acetic acid. This behavior is in contrast to the reactions of triphenylphosphine with α-chloro ketones[7] or with α-mesyloxy ketones[8] which usually give ketophosphonium salts in either nonhydroxylic or hydroxylic solvents. Several α-chloro ketones give enol phosphonium salts with triphenylphosphine in aprotic solvents.[8] These systems yield the dehalogenated ketone if the reaction is performed in the presence of an alcohol since enol phosphonium salts are readily solvolyzed by alcohols or water.[8,9]

We have sought organophosphorus reagents which would generally cause the removal of groups adjacent to a carbonyl. Such reagents might prove to be useful in organic synthesis and they should aid us in our continuing study of the modes and sites of reaction of nucleophiles with α-halo ketones and with other activated carbonyl compounds.

We now report our results on the reactions of diphenylphosphine with α-halo ketones, α-mesyloxy ketones, and other carbonyl species.

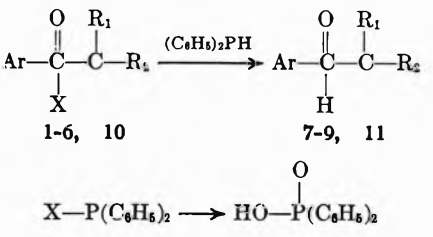
Results and Discussion

The Reactions of Diphenylphosphine with α-Halo Ketones.—Diphenylphosphine (DPP) reacts with a number of acyclic α-chloro or α-bromo ketones to give the dehalogenated ketone and halodiphenylphosphine, in good yield (Table I, Scheme I). In most of the reactions, the halodiphenylphosphine was allowed to hydrolyze and oxidize to diphenylphosphinic acid by exposure to the atmosphere.[10]

In contrast to the dehalogenation of acyclic ketones, DPP adds to the carbonyl group of 2-chlorocyclohexanone (**12**) to give 1-hydroxy-1-diphenylphosphinoxy-2-chlorocyclohexane (**15**) (Scheme II). A mixture of *cis* and *trans* isomers for **15** is indicated by the presence of two hydroxyl peaks (30:70) in the nmr spectrum. The stereochemistry of the isomers has not been determined. A similar adduct, **17**, is obtained with cyclohexanone (**14**). Primary and secondary phosphines have been previously shown to react with a variety of carbonyl compounds to give carbonyl adducts.[11a] It is not surprising that addition to cyclohexanone carbonyl, a most reactive carbonyl in addition reactions,[12] occurs more rapidly than do other processes such as dehalogenation.

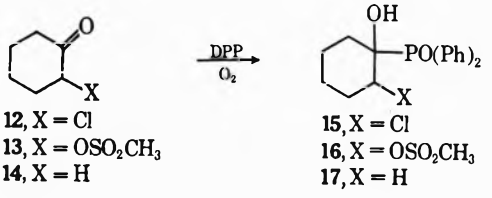
The reactions of 2-bromocyclohexanone and 2-chlorocyclopentanone with DPP give ill-defined products involving little if any dehalogenation. The debromination of diethyl bromomalonate with DPP, as with bromoacetophenone (**1**), proceeds rapidly at room temperature. Benzyl bromide reacts with DPP to give an unidentified product but no toluene. Competition experiments show that the bromoacetophenone **1**/bro-

SCHEME I



Halo ketone	X = Br	X = Cl	Ketone
Ar = C_6H_5, $R_1 = R_2 = H$	1	4	7
Ar = C_6H_5, $R_1 = CH_3$, $R_2 = H$	2	5	8
Ar = C_6H_5, $R_1 = R_2 = CH_3$	3	6	9
Ar = 2,4,6-tri-$CH_3C_6H_2$, $R_1 = R_2 = H$	10		11

SCHEME II



12, X = Cl
13, X = OSO_2CH_3
14, X = H

15, X = Cl
16, X = OSO_2CH_3
17, X = H

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(3) (a) I. J. Borowitz and L. I. Grossman, *Tetrahedron Lett.*, 471 (1962); (b) I. J. Borowitz and R. Virkhaus, *J. Amer. Chem. Soc.*, **85**, 2183 (1963).

(4) I. J. Borowitz, K. C. Kirby, Jr., and R. Virkhaus, *J. Org. Chem.*, **31**, 4031 (1966).

(5) H. Hoffman and H. J. Diehr, *Tetrahedron Lett.*, 583 (1962).

(6) S. Trippett, *J. Chem. Soc.*, 2337 (1962).

(7) K. C. Kirby, Jr., unpublished results. See also ref 4.

(8) P. Rusek, Ph.D. Thesis, Yeshiva University, New York, N. Y., 1968.

(9) R. D. Partos and A. J. Speziale, *J. Amer. Chem. Soc.*, **87**, 5068 (1965).

(10) "Methoden Der Organischen Chemie," Houben-Weyl, K. Sasse, Ed., G. Thieme Verlag, Stuttgart, 1963, Vol. 12/1, p 69.

(11) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965: (a) p 201; (b) p 33.

(12) H. C. Brown and K. Ichikawa, *Tetrahedron Lett.*, No. 1, 221 (1957).

TABLE I

THE REACTIONS OF DIPHENYLPHOSPHINE WITH α-HALOCARBONYL COMPOUNDS

α-Halocarbonyl compound	Reaction conditions	Time	Product	Yield, %
α-Bromoacetophenone[a]	C_6H_6, reflux	2 hr	Acetophenone	100[b]
α-Bromoacetophenone[a]	CCl_4[d]	10 min	Acetophenone	100[c]
α-Bromopropiophenone	CCl_4[d]	10 min	Propiophenone	100[c]
α-Chloropropiophenone	C_6H_6, reflux	7 days	Propiophenone	62[e]
α-Bromoisobutyrophenone	CCl_4[d]	16 hr	Isobutyrophenone	100[c]
α-Chloroisobutyrophenone	neat, 95–100°	6 days	Isobutyrophenone	72[c]
Diethyl bromomalonate	CCl_4[d]	20 min	Diethyl malonate	100[c]
p-Methoxy-α-bromoacetophenone	CCl_4[d]	20 min	*p*-Methoxyacetophenone	100[c]
p-Bromo-α-bromoacetophenone	CCl_4[d]	20 min	*p*-Bromoacetophenone	100[c]
2,4,6-Trimethyl-α-bromoacetophenone	CCl_4[d]	20 min	2,4,6-Trimethylacetophenone	100[c]

[a] Similar result in CCl_4 with collidine (0.2 equiv) present. [b] Isolated yield, by vpc analysis. [c] Not isolated from reaction in nmr tube. [d] At room temperature. [e] Isolated yield.

TABLE II

COMPETITION DEBROMINATIONS OF α-BROMO KETONES WITH DIPHENYLPHOSPHINE

$$R_1{-}C_6H_4{-}\overset{O}{\overset{\|}{C}}{-}CH_2Br\ (A) + R_2{-}C_6H_4{-}\overset{O}{\overset{\|}{C}}{-}CH_2Br\ (B) \xrightarrow[E]{Ph_2PH} R_1C_6H_4{-}\overset{O}{\overset{\|}{C}}{-}CH_3\ (C) + R_2C_6H_4{-}\overset{O}{\overset{\|}{C}}{-}CH_3\ (D)$$

Initial moles A = B = E	R_1	R_2	Final nmr area: Ratio	Final nmr area: B/A	Final nmr area: Ratio	Final nmr area: C/D	Average ratio	$k_2A/k_2(B)$
0.0054	*p*-CH_3O	*p*-Br	2.23[a]	2.11[b]	2.21[a]	2.35[b]	2.22	3.14
0.0072	*p*-CH_3O	H	...		1.59[a]	1.57[b]	1.50	1.79
0.0122	*p*-CH_3O	H	1.12[a,c]		1.35[a]	1.49[b]	1.50	1.79
0.0102	H	*p*-Br	...		1.14[a]		1.20	0.69
0.0150	H	*p*-Br	...		1.26[a]		1.20	0.69

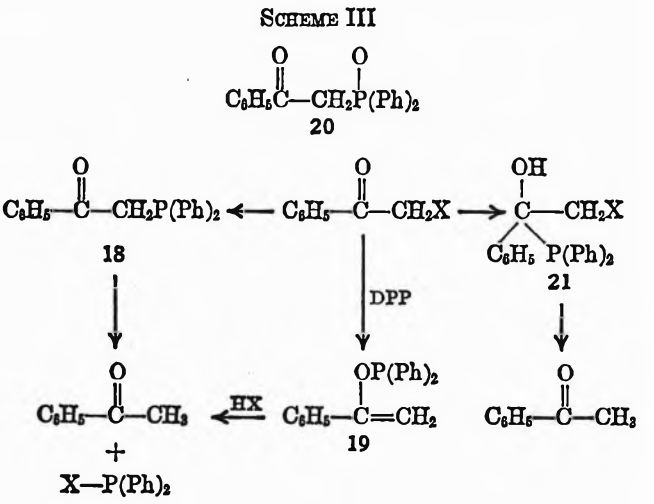
[a] Area calculated by triangulation of nmr peaks. [b] Area calculated by planimeter measurement of nmr peaks. [c] Value not used in relative rate calculation. Calculated ρ from three-point graph (CH_3O/H, H, H/Br) = −0.74. Calculated ρ from above ratios = −0.76.

mopropiophenone **2** reaction rate ratio with DPP is *ca.* 15 while the bromopropiophenone **2**/bromoisobutyrophenone **3** rate ratio is *ca.* 7.0. The α-bromoacetophenone **1**/trimethyl-α-bromo-acetophenone **10** reaction ratio is 5.3. The bromoacetophenone/chloroacetophenone rate ratio is greater than 162:1. This is based on the observed ratio of 1/4 of 162 with triphenylphosphine,[13] and the fact that triphenylphosphine reacts more rapidly than does DPP with **1** while DPP is faster than triphenylphosphine in reaction with **4** (see Experimental Section).

Comparison of the relative reactivities of **1** with its *p*-methoxy and *p*-bromo derivatives, by competition experiments, indicates that the debromination of bromoacetophenones with DPP (Table II) exhibits a moderate and negative Hammett ρ value (*ca.* −0.74). The debromination of **1** with DPP is not affected by the initial presence of collidine, *i.e.*, the dehalogenation is presumably not acid catalyzed. This result is in contrast to the debromination of **1** or **2** with triphenylphosphine and ethanol. Our kinetic studies show that these dehalogenation reactions are acid catalyzed. They are furthermore greatly inhibited by the initial presence of triethylamine which removes free acid.[14]

There are several pathways, *a priori*, for the DPP dehalogenation reactions. Thus one might have postulated initial reaction of an α-halo ketone with DPP to give the corresponding ketophosphine, such as **18**, or the enol phosphine, such as **19**, *via* one of several pathways (Scheme III).

SCHEME III



The dephosphorylation of **18** or **19** would then have to be postulated to occur, perhaps with the aid of hydrogen halide. The dehalogenations occur in the absence of acid (note no effect by collidine). Furthermore, **18** is a known species which is stable to methanesulfonic acid[8] and is stable enough in neutral pH solution to be air oxidized to **20**.[15] This data and the observed similar reaction rates of **1** and **10**, which has a hindered

(13) I. J. Borowitz and H. Parnes, *J. Org. Chem.*, **32**, 3560 (1967).

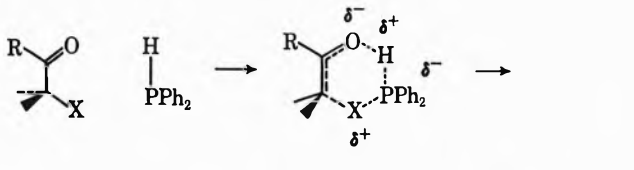
(14) The effect of triethylamine in curbing the debromination of α-bromoacetophenones by triphenylphosphine–alcohol, and thereby allowing ketophosphonium salt formation to occur, has been noted by K. Fukui, R. Sudo, M. Masaki, and M. Ohta, *ibid.*, **33**, 3504 (1968). These authors have ascribed their observations to a catalysis of ketophosphonium salt formation by the amine. We have shown kinetically that there is no such catalysis and we believe that the true function of the triethylamine is to prevent the acid-catalyzed debromination reaction.

(15) G. Burchman Borowitz and M. Saunders, *Tetrahedron Lett.*, 8 (1959).

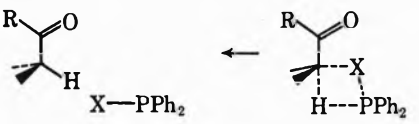
carbonyl, eliminate rate-determining SN2 processes from consideration.[16] The intermediacy of hydroxyphosphines, such as **21**, can also be dismissed on the basis of the similar reactivities of **1** and **10** and the fact that no reasonable pathway exists for the further conversion of species such as **21** into the dehalogenated ketone. Finally, the observed negative ρ value is not explained by any of these pathways.

We believe that our data is best explained by mechanism A (Scheme IV), a six-centered transition state featuring attack on "soft" halogen by "soft" phosphorus and a transfer of an incipient "hard" proton to "hard" oxygen.[17]

SCHEME IV



mechanism A



mechanism B

This pathway accounts for the negative ρ value since there is a stabilization of positive charge on oxygen in the postulated transition state, and it accounts for the relatively small rate ratios for the primary, secondary, and tertiary α-bromo ketones, **1:2:3**. These ratios are quite smaller than those found in normal solvolysis at carbon.[18] Nucleophilic displacement at carbon, a "hard" center, should be more subject to steric factors than displacement at bromine, a polarizable or "soft" center. The great reactivity of an α-bromo ketone when compared with an α-chloro ketone (more stabilization for displacement of "positive" bromine than chlorine) and the relatively high reactivity of **10** (the hindered carbonyl is not involved in halogen attack) are also well explained by mechanism A.

A four-centered pathway (mechanism B) does not explain the apparent need for a carbonyl in the dehalogenation reactions. It is also anticipated that steric requirements for this pathway would be greater than for mechanism A. Therefore mechanism B is considered to be a less likely possibility.

The Reaction of Diphenylphosphine with α-Mesyloxy Ketones.—We have synthesized a number of α-mesyloxy ketones by the reaction of α-bromo ketones with silver mesylate (Table III). We have also converted several α-hydroxy ketones, such as 2-hydroxycyclohexanone or benzoin, into the mesyloxy ketone with methanesulfonyl chloride and triethylamine. Mesylate formation under these conditions has been shown to involve the intermediacy of sulfene.[19] It has been more satisfactory than the formation of the corresponding α-tosyloxy ketone,[20] in our hands.

As indicated in Table IV, several acyclic α-mesyloxy ketones are demesylated by DPP. These reactions proceed more slowly than do the corresponding dehalogenation reactions. Ostensibly we might convert α-hydroxy ketones (acyloins) into the parent ketone *via* the intermediacy of mesyloxy ketones. 2-Mesyloxycyclohexanone (**13**) (Scheme II), however, gives the carbonyl adduct **16** and no cyclohexanone. In contrast to the infrared spectra of **15** and **17**, which show free and bonded OH absorption, the spectrum of **16** reveals only hydrogen-bonded OH absorption. This may be due to interaction of the hydroxyl group with the adjacent mesyloxy group, and it suggests a predominance of that isomer of **16** wherein the groups are *cis* oriented. Unfortunately, the limited solubility of **16** and its apparent decomposition in solution precluded nmr studies. 2-Mesyloxycyclodecanone gives no reaction with DPP while 2-mesyloxycyclododecanone is converted into cyclododecanone in 12% yield. Attempts to make these alicyclic demesylations more synthetically feasible are in progress.

In contrast to the above results, α-hydroxyacetophenone, benzoin, α-acetoxydeoxybenzoin, and α-phenylphenacyltriphenylphosphonium mesylate[8] do not react with DPP. Neither carbonyl addition nor removal of the group adjacent to the carbonyl is observed. Interestingly, a mesyloxy group adjacent to a ketone can be removed but not a similarly situated acetoxy group. The paucity of our data on the demesylations makes speculation as to the mechanistic pathway involved rather risky. A pathway similar to mechanism A above, involving attack by DPP at alkyl oxygen, may be involved.[21]

In summary, diphenylphosphine shows promise as a reagent for the selective removal of certain groups adjacent to a carbonyl. Addition to carbonyl is observed as an alternative process only in cyclohexyl cases.[22]

Experimental Section[23]

All of the solvents used were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions were usually conducted under an atmosphere of nitrogen to prevent air oxidation of DPP. Organic solutions were dried over magnesium sulfate.

α-Bromoacetophenone and α-chloroacetophenone (J. T. Baker) were recrystallized from absolute diethyl ether to mp 49–50° and 53–54°, respectively. Cyclohexanone (J. T. Baker) was distilled prior to use, bp 154–156°. α-Bromopropiophenone, α-bromoisobutyrophenone, diethyl α-bromomalonate, and benzyl bromide (Aldrich) were used without further purification. α-Chlorocyclohexanone and α-chlorocyclopentanone (Aldrich) were redistilled before use. *p*-Nitro-α-bromoacetophenone, *p*-methoxy-α-bromoacetophenone, *p*-bromo-α-bromoacetophenone, and

(16) The 2,4,6-trimethyl-α-bromoacetophenone system reacts quite slowly in SN2 displacements. See R. G. Pearson, S. H. Langer, F. W. Williams, and W. J. McGuire, *J. Amer. Chem. Soc.*, **74**, 5130 (1952).

(17) (a) R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967); (b) B. Saville, *Angew. Chem. Intern. Ed. Engl.*, **6**, 928 (1967).

(18) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill, Inc., New York, N. Y., 1962, pp 11–20.

(19) (a) J. F. King and A. Durst, *J. Amer. Chem. Soc.*, **86**, 287 (1964); (b) W. E. Truce, R. W. Campbell, and J. R. Norell, *ibid.*, **86**, 288 (1964).

(20) P. S. Wharton, S. Dunny, and L. Soto Krebs, *J. Org. Chem.*, **29**, 958 (1964).

(21) Diphenylphosphinic acid is also isolated in these reactions, perhaps *via* the intermediacy of mesyloxydiphenylphosphine. Further research on these reactions is in progress.

(22) Our carbonyl adducts are clearly not phosphinites; *i.e.*, we do not obtain addition of diphenylphosphine to carbonyl oxygen. The latter pathway has been found in the reactions of diphenyl- or dicyclohexylphosphine with hexafluoroacetone: R. F. Stockel, *Chem. Commun.*, 1594 (1968).

(23) The instrumental and other techniques used have been recorded previously.[4]

TABLE III

THE SYNTHESIS AND PROPERTIES OF α-MESYLOXY KETONES

Mesyloxy ketone, method	Registry no.	Starting compound, time	Yield, %	Properties of mesyloxy ketones: Mp, °C	Ir (CH_2Cl_2), μ	Nmr ($CDCl_3$), τ
α-Mesyloxyacetophenone[a]	20187-61-5	α-Bromoacetophenone, 24 hr	88	78.0–79.5	5.91 (C=O), 7.41, 8.50 (OSO_2CH_3)	6.78 (s, 3, OSO_2CH_3), 4.50 (s, 2, CH_2C=O), 2.00–2.80 (m, 5, phenyl H)
α-Mesyloxyacetophenone[b]		α-Hydroxyacetophenone	65	77–78		
α-Mesyloxypropiophenone[a]	20187-62-6	α-Bromopropiophenone, 30 days	77	67.0–68.0	5.90, 7.41, 8.50	8.40 (d, 3, C—CH_3), 6.90 (s, 3, OSO_2CH_3), 3.95 (quart, 1, CH), 1.9–2.6 (m, 5, phenyl H)
α-Mesyloxyisobutyrophenone[a]	17231-17-3	α-Bromoisobutyrophenone, 30 days	68	90.0–91.0	5.92, 7.5, 8.5	8.13 (s, 6, C—CH_3), 7.17 (s, 3, OSO_2CH_3), 2.0–2.6 (m, 5, phenyl H)
α-Mesyloxycyclohexanone[a]	20187-64-8	α-Bromocyclohexanone, 7 days	88	60–61.5	5.78 (C=O), 7.40, 8.40	7.3–8.6 (m, 8, alicyclic H), 6.83 (s, 3, OSO_2CH_3), 4.80 (m, 1, methine H)
α-Mesyloxycyclohexanone[b]		Adipoin	91	60–61.0	Similar	
α-Mesyloxycyclododecanone[a]	3667-85-4	α-Bromocyclododecanone, 4 months	59	109–111	5.80 (C=O), 7.45, 8.50	7.15–9.1 (m, 18, alicyclic H), 7.4 (t, 2, CH_2C=O), 6.85 (s, 3, OSO_2CH_3), 4.90 (t, 1, methine H)
2,4,6-Trimethyl-α-mesyloxyacetophenone[a]	20187-66-0	2,4,6-Trimethyl-α-bromoacetophenone, 30 days	51	99–101	5.80 (C=O), 7.39, 8.40	7.8 (s, 6, *o*-CH_3), 7.75 (s, 3, *p*-CH_3), 6.81 (s, 3, OSO_2CH_3), 4.95 (s, 2, CH_2C=O), 3.1 (s, 2, *m*-phenyl H)
α-Mesyloxydesoxybenzoin[b]	19255-01-7	Benzoin	69	120–121	5.89 (C=O), 7.40, 8.50	6.95 (s, 3, OSO_2CH_3), 3.15 (s, 1, methine H), 2.0–2.9 (m, 10, phenyl H)
α-Mesyloxycyclodecanone[b]	20187-68-2	α-Hydroxycyclodecanone	*ca.* 82 (crude)[c]	Oil		6.90 (s, OSO_2CH_3), 7.5–8.6 (m, alicyclic H)[d]

[a] From the reaction with silver mesylate in acetonitrile. [b] From the reaction with methanesulfonyl chloride and triethylamine. [c] Crude compounds shows presence of small amount of starting material as well as product (tlc, nmr). [d] Integrated areas only approximately correct.

TABLE IV

THE REACTIONS OF DIPHENYLPHOSPHINE WITH α-MESYLOXY KETONES AND WITH OTHER KETONES

Ketone	Reactions conditions	Time, days	Products	Yield, %
α-Mesyloxyacetophenone	C_6H_6, reflux	4	Acetophenone	43
			Diphenylphosphinic Acid	100
α-Mesyloxyisobutyrophenone	C_6H_6, reflux	14	Isobutyrophenone	51
α-Mesyloxybenzylphenyl ketone	C_6H_6, reflux	6	Deoxybenzoin	70
α-Mesyloxycyclodecanone	Glyme, reflux	30	No reaction	
α-Mesyloxycyclododecanone	C_6H_6, reflux	35	Cyclododecanone	12
α-Hydroxyacetophenone	C_6H_6, reflux	4	No reaction	(recovery 100%)
Benzoin	C_6H_6, reflux	4	No reaction	(recovery 100%)
α-Acetoxybenzylphenyl ketone	C_6H_6, reflux	5	No reaction	(recovery 86%)
α-Phenylphenacyl triphenylphosphonium mesylate	C_6H_6, reflux	10	No reaction	(recovery 83%)

α-bromocyclohexanone were prepared as previously reported[13] or purchased commercially. 2,4,6-Trimethyl-α-bromoacetophenone was prepared by the bromination of 2,4,6-trimethylacetophenone in 51% yield, mp 53–54.5° (lit.[16] mp 54°).

α,α-Dibromoacetophenone was synthesized by the bromination of acetophenone in 80% yield, mp 33–35° (lit.[24] mp 35–36°). α-Bromocyclododecanone was prepared by the chromic acid oxidation of *trans*-2-bromo-1-hydroxycyclododecane, itself synthesized by the addition of hydrogen bromide to epoxycyclododecane (Aldrich) in 52% yield.[25]

α-Chloropropiophenone and α-chloroisobutyrophenone were prepared as previously described.[26] Diphenylphosphine was synthesized from the reduction of chlorodiphenylphosphine with lithium aluminum hydride[27] in 72% yield, bp 112–115° (0.5 mm). It was stored at 0–5°.

α-Mesyloxyacetophenone.—The following procedure is a general one for the conversion of α-bromo ketones to α-mesyloxy ketones. A mixture of α-bromoacetophenone (10.0 g, 0.0502 mol) and silver mesylate (10.0 g, 0.0502 mol) in acetonitrile (250 ml) was stirred for 24 hr in a 500 ml flask covered with aluminum foil. The solvent was then removed *in vacuo* and the resultant solid was slurried in hot benzene (250 ml). Filtration of silver bromide, evaporation of the solvent *in vacuo*, and recrystallization of the resultant solid from CCl_4 gave α-mesyloxyacetophenone (9.16 g, 0.045 mol, 88%). Spectral data for this compound as well as for other mesyloxy ketones is given in Table III. Analytical data for the α-mesyloxy ketones follows.

(24) F. Krohnke, *Chem. Ber.*, **83**, 53 (1950).

(25) L. I. Zakharkin and V. V. Kornevsi, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1817 (1962); *Chem. Abstr.*, **58**, 7841d (1963).

(26) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

(27) W. Kuchen and H. Buchwald, *Angew. Chem.*, **68**, 791 (1956).

Anal. Calcd for $C_9H_{10}O_4S$ (α-mesyloxyacetophenone): C, 50.46; H, 4.70; S, 14.96. Found: C, 50.20; H, 4.68; S, 14.96.

α-Mesyloxypropiophenone was recrystallized from cyclohexane.

Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.61; H, 5.29; S, 14.05. Found: C, 52.70; H, 5.35; S, 14.29.

α-Mesyloxyisobutyrophenone was recrystallized from cyclohexane.

Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.70; H, 5.80; S, 13.16.

α-Mesyloxydeoxybenzoin was recrystallized from ethyl acetate and cyclohexane.

Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.06; H, 4.85; S, 11.04. Found: C, 62.18; H, 5.00; S, 10.91.

α-Mesyloxycyclohexanone was recrystallized from cyclohexane.

Anal. Calcd for $C_7H_{12}O_4S$: C, 43.74; H, 6.29; S, 16.68. Found: C, 43.92; H, 6.21; S, 16.73.

α-Mesyloxycyclododecanone was recrystallized from methanol.

Anal. Calcd for $C_{13}H_{24}O_4S$: C, 56.49; H, 8.75; S, 11.60. Found: C, 56.57; H, 8.59; S, 11.57.

The following α-bromo ketones failed to be converted into α-mesyloxy ketones upon treatment with silver mesylate in acetonitrile (after the indicated time length): α-bromocamphor (16 weeks) and 2-bromodimedone (after 11 weeks).

The Conversion of α-Hydroxy Ketones into α-Mesyloxy Ketones.—The following procedure for the synthesis of α-mesyloxybenzylphenyl ketone was used for the conversion of α-hydroxy ketones into the corresponding mesyloxy ketones. Methanesulfonyl chloride (2.15 g, 0.0189 mol) in dry benzene (40 ml) was added dropwise with stirring over a 1-hr period to a mixture of benzoin (4.0 g, 0.0189 mol) and triethylamine (3.82 g, 0.0478 mol) in benzene (20 ml). After the mixture was stirred for an additional hour, triethylamine hydrochloride was filtered off, and the organic layer was washed with water, dried, evaporated *in vacuo*, and recrystallized from EtOAc–cyclohexane to give α-mesyloxybenzylphenyl ketone (3.80 g, 0.0131 mol, 69%). Other data for this compound and related syntheses are given in Table III.

The Reactions of α-Halo Ketones with Diphenylphosphine.—The following is a general procedure. To diphenylphosphine (0.450 g, 0.00242 mol) in a 5-mm nmr tube was added α-bromoacetophenone (0.481 g, 0.00242 mol) in CCl_4 (1 ml), causing an exothermic reaction. After 10 min, reaction was complete; nmr τ 7.70 (s, 3, $CH_3C{=}O$) and 2.0–3.0 (m, 5, phenyl H) indicated quantitative conversion into acetophenone, no absorption at 5.8 (s, 2, CH_2Br) indicated the absence of α-bromoacetophenone. In a similar experiment, ^{31}P nmr indicated only a sharp singlet at −72 ppm (relative to H_3PO_4) for bromodiphenylphosphine.[28]

Other examples are given in Table I. The reaction of *p*-nitro-α-bromoacetophenone with DPP was very exothermic and was accompanied by the formation of a deep red color and a reddish brown solid which was not readily characterized. A similar reaction occurred between DPP and *p*-nitroacetophenone.

The reaction of DPP with α-bromocyclohexanone was done in benzene, diethyl ether, ethyl acetate, glyme, and methanol at room temperature and at reflux. Oils were generally obtained which could be separated into diphenylphosphinic acid (identified by ir, tlc) and viscous hydrocarbons (alicyclic H by nmr). When the reaction was followed by ir (CH_2Cl_2), the 5.85-μ peak of α-bromocyclohexanone disappeared within several min at room temperature. The reaction of DPP with α-chlorocyclopentanone occurred rapidly to give unknown products and no cyclopentanone. The reaction of DPP (1 equiv) with α,α-dibromoacetophenone led to a mixture of acetophenone, α-bromoacetophenone, and α,α-dibromoacetophenone. A preferential removal of one bromine was not observed.

The Reaction of Benzyl Bromide with Diphenylphosphine.—Benzyl bromide (0.316 g, 0.00186 mol) in CCl_4 (1 ml) was added to DPP (0.323 g, 0.00173 mol) in an nmr tube. Little or no immediate reaction occurred. After 15 hr a white solid was present and the nmr spectrum had absorption at τ 2.4–3.0 (aromatic H) but no methyl group absorption; *i.e.*, toluene was absent. The solid was not characterized.

1-Hydroxy-1-diphenylphosphinoxy-2-chlorocyclohexane.—A mixture of DPP (2.21 g, 0.0119 mol) and α-chlorocyclohexanone (1.565 g, 0.0117 mol) in benzene (30 ml) was heated at reflux for 12 hr. White solid was formed. Upon exposure to the air more slowly precipitated to give 1-hydroxy-1-diphenylphosphinoxy-2-chlorohexane (**15**, 2.756 g, 0.00825 mol, 71%): mp 158–160° (recrystallization from toluene); ir ($CHCl_3$) 2.78, 3.0, 3.4, 6.95, 8.3, 8.55, 8.75, 8.95 μ; ir (KBr) 3.18 μ (H-bonded OH); mass spectrum (70 eV)[29] *m/e* (rel intensity, assignment) 334 (w, $M\cdot^+$), 316 (w, $M\cdot^+ - H_2O$), 298 (w, $M\cdot^+ - H^{35}Cl$), 201 (vs, $Ph_2PO\cdot^+$), 202 (s, $Ph_2POH\cdot^+$), 132 (s, $C_6H_9OCl\cdot^+$), 124 (s, $PhPO\cdot^+$), 97 (s, $C_6H_9O\cdot^+$), 88 (s, $C_4H_5Cl\cdot^+$), as well as the corresponding peaks for ^{37}Cl isomers for Cl-containing fragments; nmr ($CDCl_3$),[30] τ 2.50 (m, 10, aryl H), 5.70 [m, 1, C(Cl)H], 5.95 (s, 0.3, OH), 6.90 (s, 0.7, OH), 8.20 (m, 8, alicyclic H); OH peaks were exchanged with D_2O.

Anal. Calcd for $C_{18}H_{20}O_2ClP$: C, 64.57; H, 6.02; Cl, 10.58; P, 9.26. Found: C, 64.43; H, 6.14; Cl, 10.78; P, 8.99.

Attempts to dehydrate **15** with *p*-toluenesulfonic acid in benzene at reflux with azeotropic removal of water gave only starting material.

1-Hydroxy-1-diphenylphosphinoxycyclohexane.—Similar reaction of DPP with cyclohexanone (0.0165 mol each) in benzene at reflux for 20 hr gave 1-hydroxy-1-diphenylphosphinoxycyclohexane (2.97 g, 0.0099 mol, 60%): mp 159–161° (recrystallized from toluene); ir ($CHCl_3$), 2.78, 3.0 (broad), 3.40 (s), 6.95 (ms), 8.51 (s), 8.71 (s), 9.96 (s), 10.35 (m), μ; ir (KBr) 3.15 μ (H-bonded OH); nmr ($CDCl_3$)[30] τ 1.98 (m, 4, *o*-aryl H), 2.45 (m, 6, *m,p*-aryl H), 6.72 (s, 1, OH), 8.28 (m, 10, alicyclic H).

Anal. Calcd for $C_{18}H_{21}O_2P$: C, 72.06; H, 7.00; P, 10.35. Found: C, 72.08; H, 7.04; P, 10.07.

Relative Rates of Debromination of α-Bromo Ketones by Competition Experiments.—DPP was weighed into a 5-mm nmr tube. One equivalent of each of two α-bromo ketones was combined, dissolved in CCl_4, and added to the nmr tube. Reactions involving bromoacetophenones or bromopropiophenone were essentially instantaneous. Nmr spectra of the methylene groups of the unreacted bromoacetophenones and the methyl groups of the dehalogenated acetophenones were cleanly separated at a 50-Hz sweep width. The relative areas of the starting bromo ketones and of the product ketones were thus obtained (Table II), the average ratios were taken, and these were used to calculate relative reaction rates by use of the following equation.[31] Second-order rate relationships were assumed for the debromination reactions. For other competition reactions, the relative areas used were obtained as follows.

$$\frac{k_2\,(B)}{k_2\,(A)} = \frac{\log [B]_f/[B]_i}{\log [A]_f/[A]_i}$$

Competition Reaction between α-Bromoacetophenone and α-Bromopropiophenone with DPP.—A mixture of **1** and **2** (0.00197 mol each) in CCl_4 was added to DPP (0.00197 mol) to give complete reaction of DPP after several minutes: nmr integrated area ratio of propiophenone to α-bromopropiophenone was 1:6.7; *i.e.*, 0.00025 mol of **1** and 0.00172 mol of **2** was left. The relative rate ratio for **1**:**2** is 15.4.

Other Competition Experiments.—The competition reaction of α-bromopropiophenone (**2**) and α-bromoisobutyrophenone (**3**) with DPP (0.00197 mol each) gave an area ratio (nmr) of isobutyrophenone to **3** of 1:3.8 upon completion. The relative rate ratio for **2**/**3** is 6.8. A similar competition reaction between **1** and 2,4,6-trimethyl-α-bromoacetophenone (**10**) for DPP (0.000555 mol each) gave an area ratio (nmr) of **1**/**10** of 1:3.22 upon completion. The relative rate ratio for **1**/**10** is 5.3. The competition of **1** with α-chloroacetophenone (**4**) for DPP resulted in complete reaction of **1** and no reaction of **4**; *i.e.*, the relative rate ratio for **1**/**4** is large (see Discussion). Previously, less accurate competition experiments had shown that (a) DPP reacts more rapidly than does triphenylphosphine with **1** since at least 80% of the triphenylphosphine is left, none of the DPP is left, and no phenacyltriphenylphosphonium bromide is formed; (b) triphenylphosphine reacts more rapidly than does DPP with **4**

(28) (a) Kindly performed by Dr. Dorothy Denney, Rutgers University, on a Varian HA-100 nmr spectrometer at 40 MHz; (b) L. Maier, *Helv. Chim. Acta*, **46**, 2026 (1963).

(29) Done at Mellon Institute on a MS-9 mass spectrometer.

(30) The nmr spectrum was obtained with the aid of the Varian C-1024 time averaging computer.

(31) G. Russell in "Technique of Organic Chemistry," Vol. VIII, part I, 2nd ed, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961.

since 64% phenacyltriphenylphosphonium chloride is formed and no triphenylphosphine is left, but diphenylphosphine is left.

Attempts to Derivatize Bromo- or Chlorodiphenylphosphine from Dehalogenation Reactions.—Reaction of two equivalents of DPP with one equivalent of 1 led to acetophenone and diphenylphosphinic acid but no tetraphenyldiphosphine or the corresponding dioxide.[11b] In other experiments involving either bromodiphenylphosphine (from 1) or chlorodiphenylphosphine (from 4), addition of aniline or *t*-butylamine led to mixtures possibly containing anilino- or *t*-butylaminodiphenylphosphine. The products could not be purified to analytical purity and these experiments were abandoned.

The Reactions of α-Mesyloxy Ketones and Other Ketones with Diphenylphosphine.—The following serves as a general procedure with minor variations and other data given in Table IV. A mixture of α-mesyloxyacetophenone and DPP (0.0233 mol each) was heated at reflux in benzene for 240 hr under nitrogen and then left exposed to the air for 72 hr. Diphenylphosphinic acid, mp 193.0–196.0°, was removed by filtration and the residual solution was chromatographed through silica gel (20 g). Elution with benzene gave acetophenone (1.21 g, 0.0101 mol, 43%): ir (CH_2Cl_2) and nmr ($CDCl_3$) identical with a genuine sample's.

1-Hydroxy-1-diphenylphosphinoxy-2-mesyloxycyclohexane.—A mixture of α-mesyloxycyclohexanone (2.0 g, 0.010 mol) and DPP (2.32 g, 0.0125 mol) in benzene (5 ml) was stirred at room temperature for 168 hr. After removal of the solvent *in vacuo*, the resultant solid was dissolved in CH_2Cl_2 (25 ml) and washed with 5 *N* NaOH. The organic layer was dried and evaporated *in vacuo* to give 1-hydroxy-1-diphenylphosphinoxy-2-mesyloxycyclohexane (3.41 g, 0.00855 mol, 83.5%) after recrystallization from $CHCl_3$ (25 ml)–CH_3OH (3 drops): mp 147–148°; ir (CH_2Cl_2) 3.1–3.8 (broad), 7.3–7.7 (mesylate), 8.3–8.8 (mesylate), 10.2, 10.4, 10.7 μ.

Anal. Calcd for $C_{19}H_{23}O_6SP$: C, 57.85; H, 5.87; P, 7.85. Found: C, 57.60; H, 5.82; P, 7.93.

Registry No.—DPP, 829-85-6; **15**, 20187-69-3; **16**, 20187-70-6; **17**, 20187-71-7.

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Nor Steroids. VIII. Partial Synthesis and Chemical Studies of A-Nor Bile Acids[1,2]

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Methyl 3-keto-A-norcholanate (**6**) was reduced with several reagents to give the 3α- and 3β-hydroxy-A-nor compounds, with the former isomer predominating. The structural assignments were made on the basis of the nmr spectra and comparison with known model compounds. Similar studies were made with methyl 3,12-diketo-A-norcholanate (**12a**) to give A-nordeoxycholic acids. The benzilic acid rearrangement of methyl 3-hydroxy-4-keto-12α-acetoxy-5α-chol-2-enate (**16**) and lead tetraacetate cleavage of the product gave methyl 3-keto-12α-hydroxy-A-norcholanate (**15a**).

Despite a considerable amount of interest in recent years in the partial synthesis of ring-nor steroids and their biological activity, little work has been reported in the bile acid series. Many years ago Windaus[4] pyrolyzed 2,3- and 3,4-secocholanic acid dioic acid to 2-keto- and 3-keto-A-norcholanic acid, respectively. He also[5] prepared 2,6-diketo-A-norcholanic acid by the pyrolysis of 2,3-seco-6-ketocholane-2,3,24-trioic acid. Wieland[6] obtained 2,12-diketo-A-norcholanic acid and 3,12-diketo-A-norcholanic acid by pyrolysis of the corresponding secodeoxycholic acids. No reports could be found of the reduction of any of these keto compounds to the corresponding A-nor bile acids. The present work was undertaken to accomplish this and to explore further the chemistry of the A-nor compounds.

In order to gain some understanding of the stereochemical behavior of several common reducing agents toward the cholanic acid molecule, lithium aluminum hydride and sodium borohydride were used to reduce the 3-carbonyl group of 3-ketocholanic acid (**1**) in the six-membered A-ring series. Lithium aluminum hydride gave 12% of 3β-hydroxycholan-24-ol (**2**)[7] and 88% of 3α-hydroxycholan-24-ol (**3**),[8] both previously prepared by different routes. Sodium borohydride gave, after esterification of the reduction product, 10% of methyl 3β-hydroxycholanate (**4**) and 90% of methyl 3α-hydroxycholanate (**5**). (The above percentages are relative figures, not yields.) The upper, or β side of the molecule must therefore be less hindered, allowing easier approach of the hydride to the carbonyl group.

Methyl 3-keto-A-norcholanate (**6**) was studied next. It is interesting to note that the A-nor ketone has a deshielding effect on the C-19 methyl protons, δ 1.16, compared to the six-membered keto compound, δ 1.03. Reduction of the A-nor ketone with sodium borohydride gave 75% of the 3α-hydroxy compound **7a** and 25% of the 3β isomer **8a**. Reduction with lithium aluminum hydride gave a ratio of 54% of 3α-hydroxy-A-norcholan-24-ol (**9**) to 46% of 3β-hydroxy-A-norcholan-24-ol (**10**). Reduction with lithium borohydride gave a ratio of 62% of the 3α-hydroxy compound **7a** and 38% of the 3β compound **8a**. Reduction with lithium in liquid ammonia gave a ratio of 51% of the 3α-hydroxy compound **7a** and 49% of the 3β compound **8a**.

(1) For the previous paper in the series, see H. R. Nace and G. A. Crosby, *J. Org. Chem.*, **33**, 834 (1968).

(2) The major portion of this research was supported by the U. S. Public Health Service under Grant AM 05249-02. Grateful acknowledgment is hereby made.

(3) Abstracted from the Ph.D. Thesis of E. M. H., Brown University, 1966.

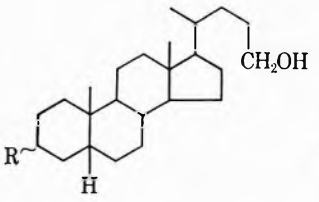
(4) A. Windaus, A. Bohne, and E. Schwartzkopf, *Z. Physiol. Chem.*, **140**, 177 (1924).

(5) A. Windaus and A. Bohne, *Ann.*, **442**, 7 (1925).

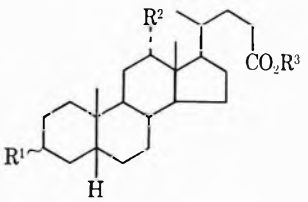
(6) H. Wieland and A. Kuhlenkampff, *Z. Physiol. Chem.*, **108**, 295 (1919).

(7) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **80**, 2729 (1958).

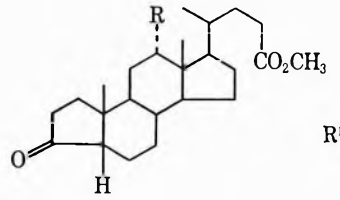
(8) L. F. Fieser and S. Rajagopalan, *ibid.*, **73**, 122 (1951).



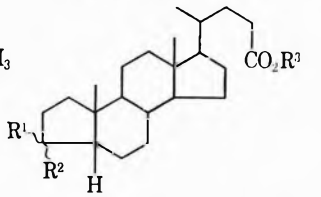
2, R = —OH
3, R = ···OH



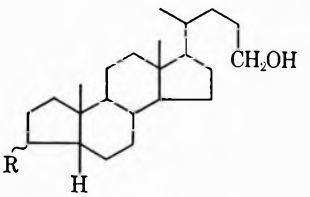
4, R^1 = —OH; R^2 = H; R^3 = CH_3
5, R^1 = ···OH; R^2 = H; R^3 = CH_3
11, R^1 = R^2 = ···OH; R^3 = H



6, R = H
15a, R = OH
15b, R = OAc



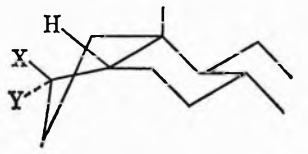
7a, R^1 = ···OH; R^2 = —H; R^3 = CH_3
b, R^1 = ···OH; R^2 = —D; R^3 = CH_3
c, R^1 = ···OAc; R^2 = —H; R^3 = CH_3
d, R^1 = ···OH; R^2 = R^3 = —H
8a, R^1 = —OH; R^2 = ···H; R^3 = CH_3
b, R^1 = —OH; R^2 = ···D; R^3 = CH_3
c, R^1 = —OAc; R^2 = ···H; R^3 = CH_3
d, R^1 = —OH; R^2 = ···H; R^3 = H



9, R = ···OH
10, R = —OH

The structural assignments for the reduction products are based on the characteristics of the nmr peaks for the hydrogens on the 3-carbon atom. Although the conformational analysis of a five-membered ring *cis*-fused to a six-membered ring is not completely understood, it appears that the two envelope models, A and B, represent the most stable conformations. Model A is preferred for two reasons. First, it explains

A



B

the fact that whether a substituent at position 3 is α or β has essentially no effect on the field position of the C-19 methyl hydrogens. Normally a difference of 2 cps or more in the field position of these protons is seen with inversion of conformation of a substituent at any given position of the A or B rings, owing to an electronic effect transmitted through space. Table I shows that for pairs of isomeric 3-substituted A-nor compounds the field position of the C-19 methyl hydrogens is virtually unchanged.

The fact that the conformation of a 3 substituent has no effect on the C-19 methyl hydrogens indicates that the 3 position is held remote from the methyl group,

TABLE I

FIELD POSITION OF THE C-19 METHYL HYDROGENS OF THE 3-HYDROXY-A-NOR ISOMERS

Compound	C-19 resonance, cps
Methyl 3α-hydroxy-A-norcholanate (**7a**)	60.0
Methyl 3β-hydroxy-A-norcholanate (**8a**)	61.0
Methyl 3α-hydroxy-3β-deuterio-A-norcholanate (**7b**)	58.5
Methyl 3β-hydroxy-3α-deuterio-A-norcholanate (**8b**)	59.0
Methyl 3α-acetoxy-A-norcholanate (**7c**)	59.0
Methyl 3β-acetoxy-A-norcholanate (**8c**)	59.0
3α-Hydroxy-A-norcholan-24-ol (**9**)	61.5
3β-Hydroxy-A-norcholan-24-ol (**10**)	62.5

as in model A. Model A is also preferred because Barton models show that model B involves considerable deformation, and thus strain, of ring B.

Using structure A, application of the Karplus equation[9] provides a basis for assignment of conformation of the 3-substituted A-nor isomers. Using Barton models and measuring the angles between the H–C–C^1 and C–C^1–H^1 planes, the various coupling constants shown in Table II were calculated.

TABLE II

COUPLING CONSTANTS CALCULATED WITH THE KARPLUS EQUATION FOR THE 3-HYDROXY-A-NOR-5β STRUCTURE A

	Φ_{YH}	J_{YH}	Φ_{YD}	J_{YD}	Φ_{YC}	J_{YC}
3β-OH(3α-H)	180°	11 cps	30°	6 cps	135°	7 cps
	Φ_{XH}	J_{XH}	Φ_{XD}	J_{XD}	Φ_{XC}	J_{XC}
3α-OH(3β-H)	45°	4 cps	90°	0.5 cps	15°	7.5 cps

From the coupling constants in Table II it is obvious that a 3α hydrogen is subject to larger coupling constants than a 3β hydrogen, which subtends relatively smaller dihedral angles with its neighboring hydrogens. Thus the α hydrogens (β substituted) should give broader peaks than the isomers with the β hydrogen (α substituted). Table III shows the position and shape of the 3 protons and allows assignment of structure for the various isomers.

TABLE III

FIELD POSITION AND SHAPE OF THE 3-HYDROGEN NMR PEAK OF 3-HYDROXY-A-NOR COMPOUNDS

Compd	3-Hydrogen peak Position	Shape
Methyl 3α-hydroxy-A-norcholanate (**7a**)	257	Sharp
Methyl 3β-hydroxy-A-norcholanate (**8a**)	254	Broad
Methyl 3α-acetoxy-A-norcholanate (**7c**)	318	Sharp
Methyl 3β-acetoxy-A-norcholanate (**8c**)	310	Broad
3α-Hydroxy-A-norcholan-24-ol (**9**)	257	Sharp
3β-Hydroxy-A-norcholan-24-ol (**10**)	254	Broad

Based on the above structural assignments, all of the hydride reductions of the norketone gave a preponderance of the 3α-hydroxy compound, showing that the β or upper side of the A ring offers less hindrance to approach of the hydride, as was observed for the six-membered A ring.

The deoxycholic acid series was studied next. Deoxycholic acid (**11**) was oxidized with nitric acid to

(9) M. Karplus and D. H. Anderson, *J. Chem. Phys.*, **30**, 6 (1959); A. D. Cross and P. Crabbé, *J. Amer. Chem. Soc.*, **86**, 1221 (1964).

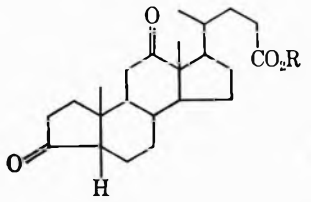
TABLE IV

NMR HYDROGEN ABSORPTIONS IN CYCLES PER SECOND OF THE ACETOXY-A-NOR COMPOUNDS[a]

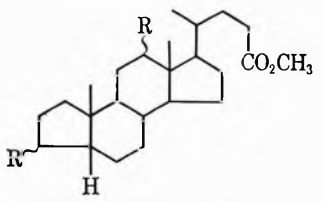
Compd	Hydrogen Configurations 3α	3β	12β
Methyl 3-keto-12α-acetoxy-A-norcholanate (**15b**)	···	···	304, sharp
Methyl-3α,12α-diacetoxy-A-norcholanate (**13b**)	···	···	305, sharp
Methyl-3α-acetoxy-A-norcholanate (7c)	···	318, sharp	···
Methyl 3β-acetoxy-A-norcholanate (8c)	310, broad	···	···
Methyl 3α,12α-diacetoxycholanate (from **11**)	···	···	305, sharp
Methyl 3-keto-12α-acetoxycholanate[b]	···	···	307, sharp

[a] Insufficient methyl 3β,12β-diacetoxy-A-norcholanate (**15b**) was available to obtain a spectrum. [b] Reference 22.

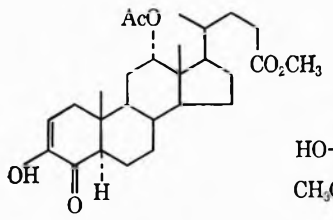
give the 12-keto-3,4-seconacid according to the procedure of Wieland and Kuhlenkampff,[6] and the seco acid was pyrolyzed to methyl 3,12-diketo-A-norcholanate (**12a**), after esterification of the pyrolysis product, in 14% yield. Again the field position of the C-19 methyl in the A-nor compound, δ 1.23, was shifted downfield from that of the C-19 methyl in methyl 3,12-diketocholanate, δ 1.12. Reduction of the 3,12-diketo-A-nor acid **12b** with excess sodium borohydride gave, after esterification, methyl 3β,12β-dihydroxy-A-norcholanate (**14a**) (6% yield), and methyl 3α,12α-dihydroxy-A-norcholanate (**13a**) (24% yield). If only one equivalent of hydride was used in the reduction, the major product, after esterification, was methyl 3-keto-12α-hydroxy-A-norcholanate (**15a**), also formed in small amounts with excess hydride.



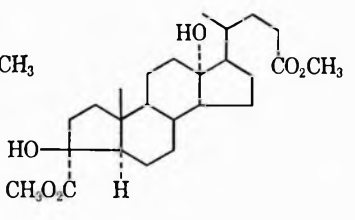
12a, R = CH_3
b, R = H



13a, R = ···OH
b, R = ···OAc
14a, R = —OH
b, R = —OAc



16



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The structure of these three products was established in the following manner. The 3β,12β isomer **14a** showed infrared absorption at 1003 cm^{-1} and nmr absorption at 254 cps (broad). Chang, Wood, and Holton[10] in a study of the isomeric 3,12-dihydroxycholanic acids, found that only the 12β-hydroxy isomer absorbed near 1000 cm^{-1}, while the other isomers absorbed in the region 1018–1036 cm^{-1}. It has been shown above that a 3α hydrogen (3β-hydroxy) shows a broad nmr peak centered at 254 cps (Table III). The 3α,12α isomer **13a** showed infrared absorption in the 1013–1036-cm^{-1} range but none near 1000 cm^{-1}, and nmr absorption at 237 (sharp, 12β hydrogen) and 256 cps (sharp, 3β hydrogen). The 3-keto-12α-hydroxy compound **15a** showed the C-19 methyl resonance at 70 cps [*cf.* methyl 3α-hydroxy-12-ketocholanate (61.0), methyl 3,12-diketocholanate (67.0), and methyl 3-keto-A-norcholanate (69.5)], the 12β hydrogen at 239 cps, and infrared absorption at 1035 cm^{-1}, consistent with a 12α-hydroxyl group. Brown and Ichikawa[11] reported that cyclohexanone is more readily reduced with sodium borohydride than is cyclopentanone, and Dauben and Boswell[12] reported the selective reduction of the 6-keto group of A-norcoprostane-2,6-dione with sodium borohydride to give the 2-keto-6-hydroxy compounds. The formation of **15a** above is thus consistent with these results.

The above structural assignments were confirmed by examination of the nmr spectra of the acetylated compounds, Table IV.

The synthesis of A-nordeoxycholic acid derivatives *via* the benzilic acid rearrangement of methyl 3-hydroxy-4-keto-12α-acetoxy-5α-chol-2-enate (**16**) was also studied. Oxygenation[13] of an alkaline solution of methyl 3-keto-12α-acetoxycholanate and esterification of the product gave the diosphenol **16** in 22% yield. It was assigned the structure shown and not the isomeric 3-keto-4-hydroxy-4-ene structure for two reasons. The ultraviolet spectrum showed λ_{max} 277.9 mμ (ε 24,000), and application of Woodward's rules for a conjugated system[14] gave a calculated value of 280 mμ for the structure shown, and a value of 297 mμ for the isomer. In addition, the nmr spectrum showed a vinyl proton at δ 6.0, in confirmation of the structure shown, and not possible for the isomer. The hydrogen at the 5-position was assigned the α configuration because of the greater stability of an A–B *trans* ring juncture for fused six-membered rings, and the ease of isomerization in a basic medium of a 4-keto compound.

The benzilic acid rearrangement was carried out by heating the diosphenol with potassium hydroxide in aqueous *n*-butanol and esterification of the rearrangement product to give methyl 3α-carbomethoxy-3β-hydroxy-12α-hydroxy-5α-A-norcholanate (**17**) in low yield (9%), and no other products from the reaction mixture could be characterized. The structure is assigned by analogy to the same reaction in the cholestane series[15] and is based on the assumption that the hydroxide addition intermediate[16] which is formed will be most stable when it involves the minimum

(10) F. C. Chang, N. F. Wood, and W. G. Holton, *J. Org. Chem.*, **30**, 1718 (1965).

(11) H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957).

(12) W. G. Dauben and G. A. Boswell, *J. Amer. Chem. Soc.*, **83**, 5003 (1961).

(13) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962).

(14) I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 58.

(15) H. R. Nace and M. Inaba, *J. Org. Chem.*, **27**, 4024 (1962).

(16) N. L. Wendler, D. Taub, and R. P. Graber, *Tetrahedron*, **7**, 173 (1959).

repulsive forces owing to 1,3-diaxial interactions and oxygen–oxygen dipoles. This assignment is also supported by the position of the C-19 methyl resonance which is roughly in the same field position as in the other 3-hydroxy-A-nor compounds, namely at 58.8 cps. If the ester group at the 3 position had the β configuration, it would be expected to have a large effect on the field position of the C-19 methyl, especially with the A–B *trans* ring fusion.

The diester **17** could not be cleaved to the A-nor-3 ketone with lead tetraacetate, but after hydrolysis the diacid was cleaved with lead tetraacetate to give, after esterification, methyl 3-keto-12α-hydroxy-A-norcholanate (**15a**) identical in melting point and infrared spectrum with the material described above.

Experimental Section

Melting points were determined with a Hershberg apparatus and Anschutz thermometers and are corrected. Microanalyses were done by Micro-Tech of Skokie, Illinois, and Schwarzkopf Microanalytical Laboratory, Woodside, New York, Deuterium analyses were done by Dr. Josef Nemeth, University of Illinois. The analytical samples were recrystallized to constant melting point. Ir spectra were determined with a Perkin-Elmer 141 spectrometer, ORD curves with a Cary 60 polarimeter, and uv spectra with a Bausch and Lomb 505 Spectrometer. Nmr spectra were determined in $CDCl_3$ with 30–35 mg of steroid per 0.6 ml of solvent, using TMS as an internal standard, and either a Varian HF-60 or a Varian A-60 spectrometer. The authors are indebted to Dr. G. O. Dudek and Dr. H. Janjagian and to Harvard University for the use of the latter instrument.

Acknowledgment is also made to the National Science Foundation for grants to the Chemistry Department for the purchase of the ir and uv spectrometers and the ord polarimeter.

Chromatographic separations were made using Baker Chromatographic Grade silica gel and Merck chromatographic grade alumina. The alumina was deactivated before use by allowing it to stand in the open air for 3 hr. The R_f values reported for tlc are travel distances on glass plates coated with a 500-μ thickness of Merck (Darmstadt) silica gel G, and refer to travel distances relative to a 10-cm solvent path. The solvent was 2:1 benzene–ether unless indicated otherwise. A solution of 2,4-dinitrophenylhydrazine in phosphoric acid and 95% ethanol was used for development, and the plates were baked at 70–90° for further development.

Reduction of 3-Ketocholanic Acid (1). A. With Lithium Aluminum Hydride.—To a solution of 250 mg (0.67 mmol) of the keto acid in 100 ml of a 1:1 mixture of benzene–petroleum ether was added 2 g of lithium aluminum hydride, and the mixture was stirred for 5 hr. Then an additional 1 g of hydride was added and the mixture was stirred overnight. After the addition of 100 ml of 30% sulfuric acid, the organic layer was washed with water, 10% $NaHCO_3$ solution, and water, dried ($MgSO_4$), and evaporated. The residue was taken up in benzene and chromatographed on 40 g of silica gel. Elution with 1:1 benzene–ether gave, after recrystallization from aqueous methanol, 12.3 mg (5%) of 3β-hydroxycholan-24-ol (**2**), mp 146–148°; $[\alpha]_D$ 24.2° (*c* 1.9, $CHCl_3$); ir (KBr) 3333 cm^{-1}; R_f 0.35; formed a precipitate with digitonin; nmr δ 0.66 (18-CH_3), 0.96 (19-CH_3); lit.[7] mp 150–151.5°.

Further elution with the same solvent gave, after recrystallization from aqueous methanol, 87 mg (36%) of 3α-hydroxy-cholan-24-ol (**3**), mp 175–176°; $[\alpha]_D$ 32.0° (*c* 2.2, $CHCl_3$); ir (KBr) 3333 cm^{-1}; R_f 0.2; gave no precipitate with digitonin; nmr δ 0.66 (18-CH_3), 0.93 (19-CH_3); lit.[8] mp 176–177°, $[\alpha]_D$ 44°.

Anal. Calcd for $C_{24}H_{42}O_2$: C, 79.49; H, 11.68. Found: C, 79.37; H, 11.66.

B. With Sodium Borohydride.—To a solution of 696 mg (1.85 mmol) of the keto acid in 30 ml of absolute ethanol (made basic by the addition of 3 ml of 1 *N* NaOH) was added 20 mg (2.1 mmol) of sodium borohydride dissolved in basic ethanol, and the resulting solution was boiled under reflux overnight. Then the solution was cooled, acidified with concentrated hydrochloric acid, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated, and the residue was esterified by allowing it to stand overnight in 10% methanolic HCl. After removal of the solvent, the residue was taken up in benzene and chromatographed on 40 g of silica gel. Elution with 10% ether–benzene gave, after recrystallization from aqueous methanol, 30.4 mg (7.8%) of methyl 3β-hydroxycholanate (**4**), mp 114–115° (lit.[17] mp 115–116°), R_f 0.6 (ether), gave a precipitate with digitonin.

Further elution with the same solvent gave, after recrystallization from aqueous methanol, 289 mg (74%) of methyl 3α-hydroxycholanate (**5**), mp 128–130°, $[\alpha]_D$ 28.3° (*c* 1.3, $CHCl_3$) [lit.[18] mp 130°, $[\alpha]_D$ 22° ($CHCl_3$)[19]], R_f 0.55 (ether), gave no precipitate with digitonin.

Methyl 3α- (7a) and 3β-Hydroxy-A-norcholanate (8a) by Sodium Borohydride Reduction of Methyl 3-Keto-A-norcholanate (6).—A solution of 270 mg (0.72 mmol) of **6** in 30 ml of ethanol was made basic with 1 *N* NaOH, a solution of 250 mg of sodium borohydride in the minimum amount of basic ethanol was added, and the resulting solution was boiled under reflux for 14 hr. Then the solution was acidified with concentrated hydrochloric acid, diluted with water, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), distilled, and the residue was esterified with 100 ml of 15% methanolic HCl. After removal of the solvent, the residue was taken up in benzene and chromatographed on alumina. Elution with 5% ether–benzene and recrystallization of the residue from aqueous MeOH gave 103 mg (38%) of methyl 3α-hydroxy-A-norcholanate (**7a**), mp 72–75°; $[\alpha]_D$ 28.0° (*c* 3.5, $CHCl_3$); ir (KBr) 3205, 1730 cm^{-1}; nmr δ 0.70 (18-CH_3), 1.00 (19-CH_3), 4.28 (sharp s, 1, 3β-H); (DMSO) 4.39 (s, 1, H on 3α-OH, disappears on the addition of D_2O); R_f 0.55

Anal. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.83; H, 10.67.

Further elution with the same solvent gave several mixed fractions followed by methyl 3β-hydroxy-A-norcholanate (**8a**), yield 35 mg (13%) after recrystallization from aqueous MeOH; mp 84–87°; $[\alpha]_D$ 39.5° (*c* 2.7, $CHCl_3$); ir (KBr) 3200, 1730 cm^{-1}; nmr δ 0.68 (18-CH_3), 1.02 (19-CH_3), 4.23 (broad s, 1, 3α-H); (DMSO) 4.20 (s, 1, H on 3β-OH, disappears on the addition of D_2O); R_f 0.35.

Anal. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.11; H, 10.65.

Reduction of Methyl 3-Keto-A-norcholanate (6) with Lithium Aluminum Hydride.—To a solution of 404 mg (1.08 mmol) of the norketone **6** in 200 ml of absolute ether was added 1 g of lithium aluminum hydride and the solution was boiled under reflux for 3 hr. Then 40 ml of 30% H_2SO_4 solution was added and the ether layer was removed, washed with water, $NaHCO_3$ solution, and water, dried ($MgSO_4$) and evaporated to give an oil. This was taken up in benzene and chromatographed on 40 g of silica gel. Elution with 25% ether–benzene gave, after recrystallization from aqueous methanol, 174 mg (46%) of 3α-hydroxy-A-norcholan-24-ol (**9**), mp 155–157°; $[\alpha]_D$ 18° (*c* 2.0, $CHCl_3$); ir (KBr) 3257 cm^{-1}; R_f 0.25; nmr δ 0.70 (18-CH_3), 0.99 (19-CH_3), 4.30 (sharp s, 3β-H).

Anal. Calcd for $C_{23}H_{40}O_2$: C, 79.25; H, 11.57. Found: C, 79.45; H, 11.67.

Further elution with the same solvent gave, after recrystallization from aqueous methanol, 146 mg (39%) of 3β-hydroxy-A-norcholan-24-ol (**10**), mp 185–186°; $[\alpha]_D$ 52° (*c* 1.8, $CHCl_3$); ir (KBr) 3225 cm^{-1}; R_f 0.15; nmr δ 0.70 (18-CH_3), 1.00 (19-CH_3), 4.25 (broad s, 3α-H).

When the reduction was carried out at room temperature for only 5 min, tlc analysis showed the presence of starting keto ester **6**, 3α-, and 3β-hydroxy-A-nor esters **7a** and **8a**, and no cholan-24-ols.

Reduction of the Keto Ester 6 with Lithium Aluminum Deuteride.—To an ether solution of 1.0 g (2.67 mmol) of the keto ester **6** was added 198 mg of lithium aluminum deuteride. After 1 min of stirring, 100 ml of 10% hydrochloric acid was added and the ether layer was removed, washed with 10% Na_2CO_3 solution, and water, dried ($MgSO_4$), evaporated, and the residue taken up in benzene and chromatographed on 60 g of alumina. Elution with benzene gave 20 mg of starting material, 42 mg of mixed material, and then, after recrystallization from aqueous methanol, 281 mg (28%) of methyl 3α-hydroxy-3β-deuterio-A-norcholanate

(17) K. Yamasaki and K. Kyogoku, *Z. Physiol. Chem.*, **235**, 43 (1935).

(18) W. Borsche and F. Hallwass, *Ber.*, **55**, 3324 (1922).

(19) F. C. Chang, R. T. Blickenstaff, A. Feldstein, J. R. Gray, G. S. McCaleb, and D. H. Sprunt, *J. Amer. Chem. Soc.*, **79**, 2164 (1957).

(**7b**), mp 84–85°; [α] D 9.9° (*c* 2.1, $CHCl_3$); ir (KBr) 3300, 2150, 1748 cm^{-1}; R_f 0.5; nmr δ 0.68 (18-CH_3), 0.98 (19-CH_3).

Anal. Calcd for $C_{24}H_{39}O_3D$: 2.50 atom % deuterium. Found: 2.48 atom % deuterium.

We are unable to explain the differences in melting point and [α] D between the deuterated and undeuterated material.

Further elution with benzene gave 387 mg of mixed material, and then, after recrystallization from aqueous methanol, 61 mg (6%) of methyl 3β-hydroxy-3α-deuterio-A-norcholanate (**8b**), mp 85–86°; [α] D 46° (*c* 1.8, $CHCl_3$); ir (KBr) 3400, 2150, 1745 cm^{-1}; R_f 0.3; nmr δ 0.66 (18-CH_3), 0.98 (19-CH_3).

Anal. Calcd for $C_{24}H_{39}O_3D$: 2.50 atom % deuterium. Found: 2.03 atom % deuterium.

Reduction of the Keto Ester 6 with Lithium Borohydride.—To a solution of 1.0 g (2.67 mmol) of the keto ester in 500 ml of ether was added 114 mg of lithium borohydride. After 1 min of stirring, 100 ml of 10% hydrochloric acid was added and the ether layer was removed, washed with water, dried ($MgSO_4$), and evaporated. The residue was taken up in benzene and chromatographed on 60 g of alumina. Elution with benzene gave 133 mg of starting material, 35 mg of mixed material, and then, after recrystallization from aqueous methanol, 341 mg (34%) of the α-hydroxy-A-nor ester **7a**, mp 84–85°; [α] D 28° (*c* 3.2, $CHCl_3$); R_f 0.55.

Further elution with benzene gave 154 mg of mixed material, and then, after recrystallization from aqueous methanol, 213 mg (21%) of the 3β-hydroxy-A-norester **8a**, mp 84–85°; [α] D 39.5° (*c* 2.5, $CHCl_3$); R_f 0.35.

Reduction of 3-Keto-A-norcholanic Acid with Lithium–Ammonia.—To a solution of 300 mg (0.83 mmol) of the nor acid (from **6**) in 12 ml of anhydrous ether, 6 ml of anhydrous methanol, and 50 ml of ammonia was added 1 g of lithium over a period of 30 min. The mixture was stirred under reflux for 15 min, the ammonia was then allowed to evaporate, and water was added. The mixture was acidified with 10% hydrochloric acid and extracted with ether. The extract was washed with water, dried ($MgSO_4$), evaporated, and the residue was esterified by boiling under reflux for 3 hr with 15% methanolic HCl. After removal of the solvent, the residue was taken up in benzene and chromatographed on 20 g of silica gel. Elution with benzene gave 50 mg of methylated starting material. Elution with 10% ether–benzene gave 132 mg (43%) of the 3α-hydroxy ester **7a**, followed by 124 mg (40%) of the 3β-hydroxy ester **8a**.

3α-Hydroxy-A-norcholanic Acid (7d).—A solution of 450 mg (1.2 mmol) of the 3α-hydroxy-A-nor ester **7a** in methanolic potassium hydroxide was allowed to stand overnight. Then acidification with hydrochloric acid gave 411 mg of the 3α-hydroxy acid **7d**, mp 135–137°; [α] D 27.0° (*c* 2.7, MeOH); ir (KBr) 1709 cm^{-1}; R_f 0.0.

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.56. Found: C, 75.53; H, 10.30.

3β-Hydroxy-A-norcholanic Acid (8d).—Treatment as above of 100 mg (0.265 mmol) of the 3β-hydroxy-A-norester **8a** gave 89 mg of the 3β-hydroxy acid **8d**, mp 223–224°; [α]D 42° (*c* 1.2, MeOH); ir (KBr) 1709 cm^{-1}; R_f 0.0.

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.56. Found: C, 75.22; H, 10.35.

A satisfactory analysis could not be obtained for this compound.

Methyl 3α-Acetoxy-A-norcholanate (7c).—A solution of 200 mg (0.53 mmol) of the 3α-hydroxy ester **7a** in 10 ml of acetic anhydride and 10 ml of anhydrous pyridine was boiled under reflux for 3 hr, cooled, diluted with water, and extracted with ether. The extract was washed with water, 10% sodium carbonate solution, and water, dried ($MgSO_4$), and evaporated. The residue was taken up in benzene and chromatographed on 20 g of alumina to give 117 mg of colorless oil which crystallized on standing neat in a refrigerator. Recrystallization from aqueous methanol gave the 3α-acetoxy-A-nor ester **7c**, mp 59–60°; [α]D 20° (*c* 1.6, $CHCl_3$); ir (KBr) 1745, 1730 cm^{-1}; R_f 0.7; nmr δ 0.68 (18-CH_3), 0.98 (19-CH_3), 5.30 (sharp s, 3β-H).

Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.61; H, 10.09.

Methyl 3β-Acetoxy-A-norcholanate (8c).—Treatment of the 3β-hydroxy ester **8a** as above gave the 3β-acetoxy-A-nor ester **8c**, mp 63–65°; [α] D 61° (*c* 0.8, $CHCl_3$); ir (KBr) 1745, 1740 cm^{-1}; R_f 0.7; nmr δ 0.65 (18-CH_3), 0.98 (19-CH_3), 5.17 (broad, 3α-H).

Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.64; H, 10.04.

Methyl 3,12-Diketo-A-norcholanate (12a).—Deoxycholic acid (**11**) (2.0 g, 5.1 mmol) was added to nitric acid in portions while the temperature was kept below 50° by ice-bath cooling. After the violent fuming stopped, water was added and the resulting precipitate was collected, yield 1.2 g. A 1.14-g sample of this material was heated in a sublimer at 290° (0.6 mm) to give 730 mg of material which was esterified by boiling under reflux for 3 hr with 15% methanolic HCl. Tlc of the product showed three spots, R_f 0.9, 0.5, and 0.45. The material was taken up in benzene and chromatographed on 60 g of alumina. Elution with benzene gave 22 mg of oil, R_f 0.8, whose ir spectrum showed unsaturation. Elution with 5% ether–benzene gave, after recrystallization from aqueous methanol, 261 mg (14%) of the 3,12-diketo-A-nor ester **12a** mp 143–145° (lit.[6] mp 149°); [α] D 180° (*c* 3.6, $CHCl_3$); ir (KBr) 1740, 1700 cm^{-1}; R_f 0.5; nmr δ 1.03 (18-CH_3), 1.23 (19-CH_3) [For methyl 3,12-diketocholanate, nmr δ 1.07 (18-CH_3), 1.12 (19-CH_3).]; ORD (*c* 0.9, MeOH) $[\Phi]_{450}$ 5.5°, $[\Phi]_{320}$ 151.6°, $[\Phi]_{309}$ 162.6°, $[\Phi]_{272}$ −93.4°, $[\Phi]_{250}$ −22.0°.

3,12-Diketo-A-norcholanic Acid (12b).—A solution of 500 mg (1.28 mmol) of the 3,12-diketo ester **12a** in 200 ml of methanol and 10 ml of 1 *N* methanolic KOH was boiled under reflux for 2 hr, then neutralized with hydrochloric acid, diluted with water, and the resulting precipitate collected and recrystallized from aqueous methanol. The 3,12-diketo acid **12b** had mp 170–175°; [α] D 167.8° (*c* 2.2, MeOH); R_f 0.0 (lit.[6] mp 197–198°). Despite repeated recrystallizations, the melting point could not be raised.

Reduction of 3,12-Diketo-A-norcholanic Acid (12b) with Sodium Borohydride.—To a solution of 1.2 g (3.2 mmol) of the acid in 100 ml of anhydrous methanol was added slowly 1 g of sodium borohydride, and then the solution was boiled under reflux for 1 hr. After cooling and acidification with dilute hydrochloric acid, the solution was extracted with ether and the extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was esterified by boiling under reflux for 1 hr with 15% methanolic HCl. After removal of the solvent the residue was taken up in benzene and chromatographed on 40 g of silica gel. Elution with 5% ether–benzene gave 122 mg of unsaturated materials, R_f 0.65 and 0.6. Elution with 15% ether–benzene gave 75 mg (6%) of methyl 3β,12β-dihydroxy-A-norcholanate (**14a**) mp after recrystallization from aqueous methanol, 128–130°; [α] D 27.6° (c 1.0, MeOH); ir (KBr) 3400, 3350, 1735 cm^{-1}; R_f 0.3; nmr δ 0.77 (18-CH_3), 1.08 (19-CH_3), 4.32 (broad, 3α-H).

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.19.

Further elution with the same solvent gave some mixed material, followed by 300 mg (24%) of methyl 3α,12α-dihydroxy-A-norcholanate (**13a**), mp after recrystallization from aqueous methanol, 145–147°; [α] D 37.8° (*c* 0.9, MeOH); R_f 0.1; nmr δ 0.77 (18-CH_3), 1.00 (19-CH_3), 3.95 (sharp, 12β-H), 4.27 (sharp, 3β-H).

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.33; H, 10.23.

It was found that if the reduction was carried out with only one equivalent of borohydride, the major product was methyl 3-keto-12α-hydroxy-A-norcholanate (**15a**), mp after recrystallization from aqueous methanol, 169–170°; [α] D 145° (*c* 0.7, MeOH); ir (KBr) 1740, 1710 cm^{-1}; R_f 0.2; nmr δ 0.75 (18-CH_3), 1.17 (19-CH_3), 3.98 (sharp, 12β-H).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.36; H, 9.94.

Methyl 3α,12α-Diacetoxy-A-norcholanate (13b).—A solution of 90.5 mg of the dihydroxyester **13a** in 10 ml of acetic anhydride and 10 ml of anhydrous pyridine was boiled under reflux for 3 hr, cooled, poured into water, and extracted with ether. The extract was washed with water and 10% $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was taken up in benzene and chromatographed on silica gel to give, after recrystallization from aqueous methanol, 39.5 mg of the diacetoxy compound **13b**, mp 109–110°; [α] D 82.6° (*c* 1.2, $CHCl_3$); ir (KBr) 1735 cm^{-1}; nmr δ 0.77 (18-CH_3), 0.98 (19-CH_3), 5.28 (sharp, 3β-H).

Anal. Calcd for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.36; H, 9.34.

Similar treatment of the 3-keto-12α-hydroxy ester **15a** also gave an oil which could not be recrystallized, but which was homogeneous to tlc, R_f 0.3; nmr δ 0.78 (18-CH_3), 1.00 (19-CH_3), 5.16 (12β-H).

Methyl 3α-Hydroxy-12-ketocholanate.—A solution of 700 mg (1.86 mmol) of 3α-hydroxy-12-ketocholanic acid[20] in 15% methanolic HCl was allowed to stand overnight, then the solvent was

(20) S. Bergstrom and G. A. D. Haslewood, *J. Chem. Soc.*, 540 (1939).

removed and the residue was recrystallized from aqueous methanol to give 250 mg (34%) of the ester, mp 114–116°; $[\alpha]$D 95.6° (*c* 2.8 MeOH) (lit. mp 110–111°; $[\alpha]$D 96 5°);[21] ir (KBr) 1735, 1700 cm^{-1}; R_f 0–0.1; nmr δ 1.02 (18- and 19-cH_3), 2.29 (broad, 3β-H); ORD (*c* 1.12, MeOH) $[\Phi]_{400}$ 133°, $[\Phi]_{350}$ 223°, $[\Phi]_{304}$ 580°, $[\Phi]_{255}$ 223°, $[\Phi]_{230}$ 534°.

Methyl 3-Hydroxy-4-keto-12α-acetoxy-5α-chol-2-enate (16).—To a solution of 447 mg (1.0 mmol) of methyl 3-keto-12α-acetoxy cholanate[22] in 100 ml of *t*-butyl alcohol (freshly distilled from calcium hydride) was added a solution of 1.12 g (10.0 mmol) of potassium *t*-butoxide in 80 ml of *t*-butyl alcohol. The resulting solution was stirred under 1 atm of oxygen until 11.2 ml (1.0 mmol) had been taken up, then it was acidified with hydrochloric acid, diluted with water, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), evaporated, and the residue was esterified by boiling under reflux for 3 hr in a 15% solution of methanolic HCl. After removal of the solvent, the residue was taken up in benzene and chromatographed on 20 g of silica gel. Elution with 5% ether–benzene gave the diosphenol **16** which was recrystallized from aqueous methanol to give 100 mg (22%), mp 160–162°; $[\alpha]$D 111° (*c* 3.9, MeOH); ir (KBr) 1730, 1725, 1660, 1625 cm^{-1}; R_f 0.45; uv λ_{max} (MeOH) 277.9 mμ (ϵ 24,000); nmr δ 1.96 (12-$OCOCH_3$), 5.08 (12β-H), 6.00 (t, 2-H).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75. Found: C, 69.75; H, 8.78.

Methyl 3α-Carbomethoxy-3β,12α-dihydroxy-A-nor-5α-cholanate (17).—To a solution of 1.95 g (4.2 mmol) of the diosphenol **16** in 100 ml of *n*-butyl alcohol was added a solution of 14 g of KOH and 10 ml of water, and the resulting solution was boiled under reflux for 3 days. After acidification with hydrochloric acid and dilution with water, the reaction mixture was extracted with ether and the extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was esterified by boiling under reflux for 3 hr with 15% methanolic HCl, the solvent was evaporated, and the residue was taken up in benzene and chromatographed on silica gel. Benzene eluted an oil which was crystallized from aqueous methanol to give 178 mg (9.4%) of the A-norhydroxy ester **17**, mp 53–54°; $[\alpha]$D 36° (*c* 1.7, MeOH); ir (KBr) 1730, 1720, 1018–1036 cm^{-1}; nmr δ 0.98 (19-CH_3), 3.58, 3.68 ($OCOCH_3$), 3.95 (12β-H).

Anal. Calcd for $C_{26}H_{42}O_6$: C, 69.30; H, 9.40. Found: C, 70.33; H, 9.51.

Methyl 3-Keto-12α-hydroxy-A-norcholanate (15a).—The diester **17**, 86 mg, was first hydrolyzed to the dihydroxy diacid in quantitative yield by warming in a solution of methanolic potassium hydroxide. Acidification with hydrochloric acid and dilution with water gave the crystalline diacid, mp 96–98°, which was dissolved in 5 ml of acetic acid and 2 ml of acetic anhydride. Lead oxide (Pb_3O_4), 287 mg, was added and the mixture was warmed on a steam bath until the red color disappeared, stirred overnight, diluted with water, and extracted with ether. The extract was washed with water, several times with 10% $NaHCO_3$ solution, and water, dried ($MgSO_4$), and evaporated. The residue was esterified by boiling under reflux for 3 hr with 15% methanolic HCl. Removal of the solvent and recrystallization of the residue gave 30 mg of the 3-keto-A-nor ester **15a**, identical in melting point and ir spectrum with the material described above.

The oxidation did not take place if the diester was used instead of the hydrolyzed material.

Registry No.—**2**, 20414-15-7; **3**, 20414-16-8; **6**, 20445-42-5; **7a**, 20414-17-9; **7b**, 20414-18-0; **7c**, 20414-19-1; **7d**, 20414-20-4; **8a**, 20414-21-5; **8b**, 20414-22-6; **8c**, 20414-23-7; **8d**, 20414-24-8; **9**, 20445-43-6; **10**, 20445-44-7; **13a**, 20414-25-9; **13b**, 20414-26-0; **14a**, 20414-27-1; **15a**, 20414-28-2; **16**, 20414-29-3; **17**, 20414-30-6.

(21) T. Reichstein and M. Sorkin, *Helv. Chim. Acta*, **25**, 797 (1942).
(22) T. Reichstein and V. Burchhardt, *ibid.*, **25**, 821 (1942).

Further Stereochemical Studies of the Catalytic Reduction of $\Delta^{1,4}$-3-Keto Steroids with Tritium[1a]

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The stereochemical distribution of label resulting from reduction of $\Delta^{1,4}$-steroids at C-1,2 with tritium gas using palladium–charcoal was studied. The tritium distribution at C-1 in 11β-hydroxyandrost-4-ene-3,17-dione and 11β,17,21-trihydroxypregn-4-ene-3,20-dione (cortisol) obtained from the corresponding Δ^1 compounds was analyzed using stereospecific chemical and enzymatic reactions. The distribution was found to be 76% β and 24% α. This is in general agreement with results obtained previously after reduction of a compound without an 11β-hydroxyl group. Analysis of testosterone-1,2-*t* using the C-1,2-dehydrogenase of *B. sphaericus* and the ring A aromatase (estrogen forming) enzyme system from human placenta indicated that the tritium distribution at C-2 was in a ratio of 1.4:1 ($\beta:\alpha$), considerably less than that at C-1, 3.4 : 1 ($\beta:\alpha$). A mechanism of reduction involving 1,4 addition to the enone system is discussed. The results are in agreement with our previous finding that estrogen formation in placenta involves *cis* elimination at C-1,2 (1β,2β).

Catalytic reduction of carbon–carbon double bonds with carrier-free tritium gas is a facile method for preparing pure radioactive compounds of high specific activity at relatively low cost. However, the distribution and orientation of tritium in the product is often not apparent. Owing to the instability of highly tritiated molecules and the dangers of contamination, physical measurements used for deuterated compounds are not made routinely on tritiated species. Instead, stereospecific reactions with diluted material and extrapolation of results obtained with deuterium often are used to determine the position labeled.[2] In previous publications, methods were discussed which enabled us to determine the distribution of tritium at positions 1,[3] 6, 7,[4,5] 11, and 12[6,7] of the steroid nucleus. The study of

(1) (a) This work was supported in part by U. S. Public Health Service Grants AM-6894, AM-3419, and Training Grant T01-AM05564. An abstract of portions of this work has appeared: H. J. Brodie, K. Raab, and M. Gut, *Excerpta Med. Int. Congr. Ser., 111, Int. Congr. Hormonal Steroids, 2nd, Milan, 1966*, Abstract No. 178. (b) McGill University Cancer Research Unit, Montreal. (c) Postdoctoral trainee in the Training Program for Steroid Biochemistry, 1963–1965; Pharma Research Canada, Pointe Claire, Quebec. (d) University of Tokyo, Tokyo, Japan.

(2) E. A. Evans, "Tritium and Its Compounds," Van Nostrand, New York, N. Y., 1966.
(3) H. J. Brodie, M. Hayano, and M. Gut, *J. Amer. Chem. Soc.*, **84**, 3766 (1962).
(4) S. Baba, H. J. Brodie, M. Hayano, G. Kwass, and M. Gut, *J. Org. Chem.*, **29**, 2751 (1964).
(5) H. J. Brodie, S. Baba, M. Gut, and M. Hayano, *Steroids*, **6**, 659 (1965).
(6) M. Hayano, M. Gut, R. I. Dorfman, O. K. Sebek, and D. H. Peterson, *J. Amer. Chem. Soc.*, **80**, 2336 (1958).
(7) M. Hayano, M. Gut, R. I. Dorfman, A. Schubert, and R. Siebert, *Biochim. Biophys. Acta*, **32**, 269 (1959).

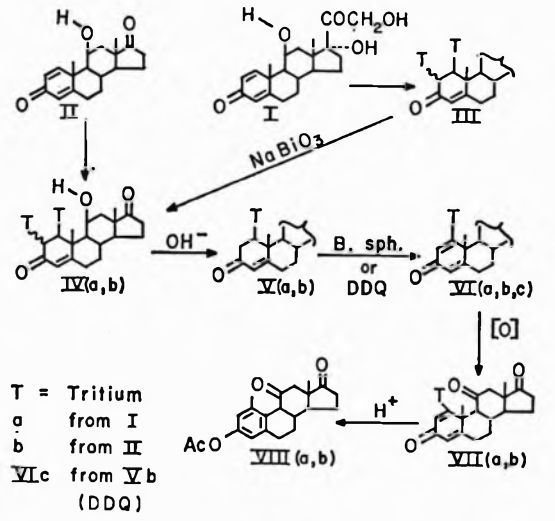
tritium introduction at C-1 initially was carried out in order to obtain estrogen precursors suitable for stereochemical studies, and we communicated that 17β-hydroxyandrosta-1,4-dien-3-one was reduced at the Δ^1-bond with palladium–carbon to give testosterone with the tritium at C-1 approximately 80% β, while the reduction of 5α-androst-1-ene-3,17-dione gave the saturated steroid with the label at C-1 over 90% α. The detailed methodology appeared in a subsequent paper dealing with the preparation of 19-hydroxy- and 19-nor steroids stereoselectively labeled at C-1β.[8]

Other steroids which are labeled at C-1,2 by reduction of $\Delta^{1,4}$ compounds contain the 11β-hydroxy function. They are used extensively for metabolic studies and it was of interest to determine whether the additional β substituent, 1,3 diaxial to the C-10 methyl group, has an effect on the stereochemistry of reduction of the Δ^1-bond. This paper reports on the reduction of such compounds. In addition, data are presented concerning the complete distribution of tritium in a commercial sample of testosterone-1,2-*t* prepared by similar reduction of 17β-hydroxyandrosta-1,4-dien-3-one.

Results

A. Tritium at C-1 in 11β-Hydroxy Compounds.—The two compounds chosen for reduction were prednisolone (I) (11β,17,21-trihydroxypregna-1,4-diene-3,20-dione) and 11β-hydroxyandrosta-1,4-diene-3,17-dione (II). The cortisol-1,2-*t* (III) from reduction of I with palladium–carbon catalyst[9] (Scheme I)

SCHEME I



was diluted with carrier and the side chain was cleaved with sodium bismuthate[10] to give 11β-hydroxyandrost-4-ene-3,17-dione-1,2-*t* (IVa). This and the same compound IVb obtained from the similar reduction of the Δ^1 bond of II were recrystallized to constant specific activity and then were equilibrated with base to remove enolizable tritium. After correction for stable tritium (see below), it was found that, whereas 45% of the tritium in IVb was enolizable to give Vb, only 24% was lost from IVa to give Va (Table I, line 3). Because of

(8) H. J. Brodie, *Tetrahedron*, **23**, 535 (1967).
(9) P. Osinski and A. Vanderhaeghe, *Rec. Trav. Chim.*, **79**, 216 (1960).
(10) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

TABLE I
CHANGES IN TRITIUM CONTENT AFTER INDICATED CONVERSIONS

	IV		V		VI[b]			VIII	
	a[a]	b	a	b	a	b	c	a	b
Relative *t* content	100	100	79	58	63	45	45	9.6	7.1
Relative reactive *t* content[c]	90	93	69	51	53	38	38	0	0
% "reactive" *t* lost from preceding step	...	...	24	45	23	25	25	100	100

[a] "a" compounds obtained from compound I. "b" compounds obtained from compound II. [b] Compounds a and b are from incubation with *B. sphaericus*. VIc is from DDQ reaction on Vb. [c] Relative amount of tritium in the molecule less the amount of stable tritium remaining in VIII (stable tritium). Thus Va contains 69% reactive tritium (79–9.6).

suggestions in review articles (ref 2, p 362)[11,12] that Δ^4-3 ketones form Δ^2-enols with difficulty,[13,14] a sample of 11β-hydroxyandrost-4-ene-3,17-dione was refluxed for 4 hr with potassium hydroxide in 98% deuterium-enriched methanol–water. Combustion analysis of the recovered steroid showed an incorporation of 6.5 atoms of deuterium, indicating that the seven enolizable hydrogens are exchangeable.

Compounds Va and Vb were incubated with respiring cultures of *B. sphaericus* to give the C-1,2 dehydrogenated products VIa and VIb with tritium losses from C-1 of 23 and 25% respectively (Table I, line 3). Since the C-1,2-dehydrogenase of *B. sphaericus* removes the 1α and 2β hydrogens,[15] the results show that the distribution of label at the C-1 was about 75% β and 25% α. The equilibrated material Vb from the reduction of 11β-hydroxyandrostadienedione (II) also was subjected to chemical dehydrogenation with DDQ (2,3-dichloro-5,6-dicyanoquinone), which also preferentially removes the 1α hydrogen[3,16] to give the Δ^1 analog VIc with substantially the same result (25% loss of tritium) (Table I, line 3). Jones oxidation[17] of a mixture of VIb and VIc to the 11 ketone VIIb and equilibration with base was accomplished without loss of tritium. After acid-catalyzed, dienone–phenol rearrangement to 3-acetoxy-1-methylestra-1,3,5(10)-triene-11,17-dione (VIIIb)[18] in which the C-10 methyl group migrates to displace the C-1 hydrogen,[19] 7% of the tritium originally present in 11β-hydroxyandrostenedione (IVb) remained. When Va was treated in the same manner to give VIIIa, 9.6% of the tritium originally in IVa remained (Table I, line

(11) P. Osinski, "Tritium in the Biological Sciences," Vol. II, International Atomic Energy Agency, Vienna, 1962, p 117.
(12) P. Osinski, *Atomlight*, No. 35, 6 (1964).
(13) These claims stem from a report[9] that the bismethylene dioxide of cortisol-1,2-*t* does not lose tritium on base treatment. Our results recorded here with 11β-hydroxyandrost-4-ene-3,17-dione (the large tritium loss in going from IVb to Vb and the 6.5 atoms of deuterium incorporation) and testosterone-1,2-*t* (43% *t* loss on base treatment) and our other reports[8,8] show that C-19 steroids readily exchange tritium at C-2 with base. In addition, Malhotra and Ringold[14] found that, with testosterone, base-catalyzed deuterium exchange occurs *preferentially* at the C-2β position.
(14) S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, **86**, 1997 (1964).
(15) H. J. Ringold, M. Hayano, and V. Stefanovic, *J. Biol. Chem.*, **238**, 1960 (1963).
(16) A. B. Turner and H. J. Ringold, *J. Chem. Soc., C*, 1720 (1967).
(17) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, 39 (1946).
(18) E. J. Bailey, J. Elks, J. F. Oughton, and L. Stephenson, *ibid.*, 4535 (1961).
(19) E. Caspi, P. K. Grover, and Y. Shimizu, *J. Amer. Chem. Soc.*, **86**, 2463 (1964).

Table II
Enzymatic Conversion of 1,2-*t*-4-^{14}C Substrates

Substrate[a]	^{3}H/^{14}C ratio (dpm)	System	Recovered substrate: Ratio	Recovered substrate: (% *t* change)	Product: Ratio	Product: (% *t* change)
A-1,2-*t*-4-^{14}C	25.3	*B. sph*, cell free	30.2	(+20)	10.8[b]	(−57)
A-1,2-*t*-4-^{14}C	23.6	*B. sph*, whole cell	24.6	(+4.2)	14.6[b]	(−38)
T-1,2-*t*-4^{14}C	26.5	Placental, supernate	26.3[c]	(∼0)	8.3[e]	(−69)
			27.6[d]	(+4.2)		

[a] A, androst-4-ene-3,17-dione; T, testosterone. [b] Androsta-1,4-diene-3,17-dione. [c] Androst-4-ene-3,17-dione. [d] Testosterone. [e] Estrone.

1). The remaining label in VIII represents stable tritium which, from the procedures used, is at one or more of positions 7, 8, 14, 15, 18, and 19. It has been subtracted from the total tritium in the samples to give the corrected value (Table I, line 2) of tritium at C-1 and, for compound IV, C-1 and C-2.

B. Tritium at C-1,2 in Testosterone-1,2-*t*.—A purified commercial sample of testosterone-1,2-*t*, prepared by the same general method as were the 11β-hydroxy compounds above, was analyzed for tritium at C-1,2 as previously described.[3,8] After Jones oxidation to androstenedione-1,2-*t* without loss of tritium and equilibration with base, C-1,2 dehydrogenation of the resultant androstenedione-1-*t* with *B. sphaericus* established that the distribution of tritium was 44% 1β, 17% 1α, and 43% enolizable. Conversion of androstenedione-1-*t* through the $\Delta^{4,6}$ and $\Delta^{1,4,6}$ intermediates to 3-acetoxy-1-methylestra-1,3,5(10),6-tetraen-17-one showed that 1% stable tritium was present in the original testosterone-1,2-*t*.

To obtain insight into the distribution of the 43% enolizable tritium, presumably at C-2, the testosterone-1,2-*t* was aromatized to estrone with a 10,000 × g supernate preparation from human placenta. In addition, androstenedione-1,2-*t* (prepared from testosterone-1,2-*t* by Jones oxidation without significant *t* loss) was C-1,2 dehydrogenated using a cell-free preparation from *B. sphaericus* and the whole-cell respiring organism. Different per cent tritium decreases were obtained in the products, as shown in Table II. With the bacterial cell-free preparation, the apparent tritium loss on C-1,2 dehydrogenation was 57%; from the respiring culture, an apparent loss of 38% was obtained in going to the $\Delta^{1,4}$-product. With the placental system, a 69% loss of tritium was obtained on conversion to product estrone.

Discussion

Results obtained for the reduction of the two 11β-hydroxy-$\Delta^{1,4}$-3-keto compounds I and II with tritium on palladium–charcoal catalyst show that attack occurs mainly from the β side to give products 75 to 77% tritiated at C-1β. This selectivity of tritium at C-1 approximates that obtained (78 to 83% 1β) when 17β-hydroxyandrosta-1,4-dien-3-one was reduced under similar conditions as reported here and elsewhere.[3,8] Thus, the 11β-hydroxy group has little effect on the stereochemistry of the reduction process at C-1. It is not clear why there was a relatively small 24% of enolizable tritium in IVa obtained from cortisol (III) compared with approximately 44% in the reduction of 11β-hydroxyandrosta-1,4-diene-3,17-dione and 17β-hydroxyandrosta-1,4-dien-3-one. Although our preparations were not analyzed for tritium loss during C-17,20 cleavage with bismuthate, Burstein, *et al.*,[20] found no loss in this step. The smaller amount is probably not related to the presence of the additional hydroxyl hydrogens on prednisolone which by catalytic exchange with tritium may provide hydrogen for addition at C-2, since the reduction of 6β-hydroxyprednisolone gave 37% exchangeable tritium.[20] It may be noted that in the reduction of a Δ^{11} bond, 30% of the label was at C-11 and 70% was at C-12.[6]

Both reduction products contained some stable tritium (9.6 and 7.1 from I and II respectively) which was not located in ring A. This is in contrast to the commercial sample of testosterone-1,2-*t*, in which 99% of the tritium was enolizable or at C-1. Since there was no tritium lost from the 9α,11α or 12 positions during conversion of VIb to equilibrated VII or after side-chain cleavage in going from I to III,[20] it is unlikely that a significant amount of this stable tritium arises from exchange. The possibility that during the dienone–phenol rearrangement (VII to VIII) some tritium migrated from C-1 to C-2 was considered unlikely since Burstein, *et al.*,[20] using cortisol prepared from the same prednisolone, also found 8% tritium at positions other than in ring A using a procedure involving direct equilibration of tritium from the C-1 position. Since starting material II was prepared from I, it is possible that the stable tritium arose from a small amount of undetected polyene in these compounds.

Testosterone-1,2-*t* was found to have 44% 1β, 13% 1α, and 43% exchangeable tritium. These values are in good agreement with those obtained[3,8] from samples of testosterone-1,2-*t* prepared in this laboratory, also by palladium–charcoal-catalyzed reduction, and should enable the stereochemical results obtained by us with the C-1 tritiated compound[8,21–23] to be correlated with those that may be obtained with commercial material. However, it is well to recall that the same type of reduction has been achieved recently with the soluble catalyst tris(triphenylphosphine)rhodium(I) chloride, which introduces the label about 85% stereoselectively at 1α and 2α.[24,25] From the nature of the reaction, it would be expected that the exchangeable tritium is located predominantly at C-2, arising from reduction of the Δ^1 bond. This is supported by our previous experience with testosterone-1,2-*t*[3,8] and 3β-hy-

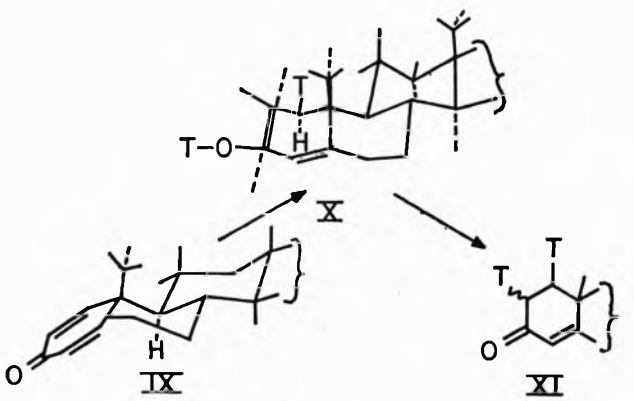
(20) S. Burstein, H. Kimball, and M. Gut, *Steroids*, **8**, 789 (1966).
(21) T. Morato, K. Raab, H. J. Brodie, M. Hayano, and R. I. Dorfman, *J. Amer. Chem. Soc.*, **84**, 2764 (1962).
(22) J. D. Townsley and H. J. Brodie, *Biochemistry*, **7**, 33 (1968).
(23) H. J. Brodie, G. Possanza and J. D. Townsley, *Biochim. Biophys. Acta*, **152**, 770 (1968).
(24) C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, **88**, 4537 (1966).
(25) H. J. Brodie, K. J. Kripalani and G. Possanza, *ibid.*, **91**, 1241 (1969).

droxyandrostan-17-one-5α,6α,7α-*t*[5] in which there was 0–3% exchange of tritium into stable[3,5,8] or enolic positions other than at a position α to the double bond being reduced.[5] After oxidation to androstenedione-1,2-*t* with negligible tritium loss, this material was incubated with a 10,000 × g supernate from *B. sphaericus*. The product, androsta-1,4-diene-3,17-dione, showed an apparent 57% loss of tritium (Table II). To be a true measure of tritium loss *due to conversion*, all tritium at C-2 would have to be eliminated, since 44% was at the unaffected 1β position. The 20% increase in the $^3H/^{14}C$ ratio of the recovered starting material suggests that the high *apparent* loss was due to the isotope effect operating at the C-1α and -2β positions,[26] retarding the conversion of tritiated (also at 1β and 2α) molecules to product. Further evidence for this conclusion was obtained when incubation of the androstenedione-1,2-*t* with a whole-cell preparation gave androsta-1,4-diene-3,17-dione, with only 38% loss of tritium. There was a much smaller 4% rise in the $^3H/^{14}C$ ratio in the recovered substrate, even though the percent conversion was appreciably higher. The reduced loss is apparently due to exchange which occurs in whole-cell preparations at the 2β and 1α positions,[26] decreasing the possibility of an isotope effect. The rates of exchange and dehydrogenation are competitive, so that some isotope effect of the type noted for the cell-free dehydrogenation is possible and the 38% loss represents a *maximum* amount of tritium at C-1α and C-2β. Since the tritium at the C-1α is 13% and the maximum amount at C-2 is 43%, the maximum amount at C-2β is 25% (38% total loss − 13% at C-1α); and by difference the amount at C-2α is 18%. This represents a tritium ratio 2β:2α of 1.4:1, much less than the 1β:1α ratio of 3.4:1.

The 69% tritium loss on conversion of testosterone-1,2-*t*-4-^{14}C to estrone supports this conclusion. We have established that aromatization with placental preparations involves elimination of the 1β[21,22] and the 2β[25] hydrogens. Since the 1β position originally contained 44% of the tritium, the additional 25% loss may be assigned to the 2β position, confirming that the β:α tritium ratio at C-2 is 1.4:1 (25:18).[27–29] In the aromatization, the first step, C-19 hydroxylation, does not require the involvement of the hydrogens at C-1 and C-2; and the C-19 hydroxy intermediate then metabolizes rapidly and completely under our incubation conditions, minimizing any isotope effect that may operate in the latter stages of the transformation to estrogen. Thus, the tritium decrease obtained in this case should reflect that lost at C-1β and C-2β. In further support of this, we could not detect an isotope effect involving the C-1β proton loss[22] during aromatization of androstenedione; and in the present experiment the recovered testosterone substrate and its C-17 oxidized metabolite, androstenedione, had essentially the original ratio, suggesting little isotope effect or exchange at C-2 also. It should be noted, however, that when deuterium labeling was used some exchange was observed.[25]

The large difference in the β:α ratio of tritium at C-1 and C-2 for testosterone 1,2-*t*, and perhaps the lower amount of tritium at C-2 compared with C-1, especially in the reduction of prednisolone (I) (see, however, reference 6), shows that the mechanism of C-1,2 hydrogenation of the $\Delta^{1,4}$-3-one system does not involve complete *cis* addition. The results support a mechanism involving 1,4 addition[30] to the Δ^1-3-one system. Inspection of Dreiding models suggests that the initial reduction at C-1 occurs predominately β because the planar structure of ring A (IX) is angled away from the C-10 methyl group and toward the C-9 hydrogen. A 1,4 addition gives X, which would probably accept hydrogen (tritium) at C-2 either from the catalyst surface or from the C-3 hydroxyl on collapse of the enol. In the addition to X, α attack appears to be favored, since the axis of the C-2 double bond is bent toward the C-10 methyl group. However, the steric preference for α attack might be opposed by an electronic factor favoring β (axial) addition. For either mechanism it is expected that the β:α ratio of tritium at C-2 would be less than at C-1 to the extent that 1,4 addition occurs.

SCHEME II



Experimental Section

Materials.—Testosterone-1,2-*t* (prepared[31] as described[9]) and testosterone-4-^{14}C were obtained from New England Nuclear Corporation. They were converted to androstenedione with chromic–sulfuric acid in acetone[17] (0–5°, 10 min). Prednisolone (I) was obtained commercially, and 11β-hydroxyandrosta-1,4-diene-3,17-dione (II) was prepared from it by sodium bismuthate oxidation.[10] Substrates for double-label experiments were purified separately by chromatography and then were combined to give the desired count ratio. The ratios remained constant when samples of the materials were purified by chromatography and crystallized following reverse isotope dilution.

Procedures involving solvents, chromatography, scintillation counting, ir, and uv spectroscopy have been reported.[8,22] Systems for chromatography are recorded as per cent by volume.

Reduction with Tritium Gas.[32]—To the solution of 0.1 mol of prednisolone (I) or 11β-hydroxyandrosta-1,4-diene-3,20-dione (II) in 3 ml of dioxane was added 20 or 30 mg of 10% palladium–charcoal and 0.1 or 0.15 mmol of carrier-free tritium gas re-

(26) R. Jerussi and H. J. Ringold, *Biochemistry*, **4**, 2113 (1965).

(27) In aromatizing 1,2-tritiated substrates, Bolte, *et al.*,[28] found a 56% loss of tritium in estrone after a placental perfusion; and Axelrod and Goldziehe,[29] with preparations of minced normal and polycystic ovaries, observed tritium changes of ~0 to −67% in several estrogen metabolites. Assuming that the substrates had tritium distributions similar to those reported here, it appears that the preparations and conditions affect the % tritium change; of course, this does not necessarily mean that different stereochemical mechanisms for estrogen biosynthesis are operating. The value closest to ours for tritium loss during aromatization (67 *vs* 69%) occurred with a pregnancy ovary where, as in our incubations, there was apparently an appreciable conversion to product.

(28) E. Bolte, S. Mancuso, G. Ericksson, N. E. Wiqvist, and E. Diczfalusy, *Acta Endocrinol.* (Copenhagen), **45**, 535 (1964).

(29) L. R. Axelrod and J. W. Goldzieher, *J. Clin. Endocrinol. Metab.*, **25**, 1275 (1965).

(30) H. Simon and O. Berngruber, *Tetrahedron Lett*, 4711 (1968), and references therein.

(31) L. Geller, New England Nuclear Corp., personal communication, 1968.

(32) For the precise procedure see K. L. Laumas and M. Gut, *J. Org. Chem.*, **27**, 314 (1962).

spectively. After stirring for 4 hr, the mixture was purified as indicated below.

11β,17,21-Trihydroxypregn-4-ene-3,20-dione-1,2-*t* (III).—Chromatography of the crude product on a Celite partition column, using methanol–water (1:1) as stationary phase and benzene as mobile phase, gave 700 mCi of product corresponding to $R_f = 0.22$.

11β-Hydroxyandrost-4-ene-3,17-dione-1,2-*t* (IVa).—Similar chromatography, with the stationary phase methanol–water (4:1) and the mobile phase toluene–ligroin (2:1), yielded 950 mCi, corresponding to $R_f = 0.6$. Specific activity data on the following transformations of 11β-hydroxy compounds are given in Table III, next to the appropriate numbers.

Base Equilibration.—11β-Hydroxyandrost-4-ene-3,17-dione-1,2-*t* (IVa, IVb) was diluted with carrier and refluxed under nitrogen for 2 hr with 0.25 *N* KOH in 67% aqueous methanol. The equilibrated materials Va and Vb were purified by tlc in 20% ethyl acetate–benzene and crystallized from acetone to constant specific activity. The equilibrations and purifications were repeated until constant specific activity was obtained (Table III, no. 2, 3, 9, 10, and 11).

C-1,2 Dehydrogenation with *B. sphaericus* (ATCC 7055) (VIa and VIb from Va and Vb).—After a 400-ml culture of *B. sphaericus* was grown for 48 hr,[33] approximately 135 mg of Va or Vb. (no. 4, 12) was added. After further incubation for 12 hr, VI was isolated, purified by preparative tlc in 20% acetone–benzene, and crystallized from acetone to constant specific activity (no. 4–5 and no. 12–13). Physical constants: mp 185–186°, $[\alpha]^{25}D$ (acetone) 120°, λ_{max}^{EtOH} 243 mμ (ε 14,950) (lit.[34] mp 181–182°, $[\alpha]^{25}D$ 138°, λ_{max}^{EtOH} 242 mμ (ε 15,200); ir identical with that of reference standard.

C-1,2 Dehydrogenation with DDQ (VIc from Vb).—A mixture of 170 mg of Vb (no. 12), 91 mg of 2,3-dichloro-5,6-dicyanoquinone (Aldrich, recrystallized from benzene), and 18 ml of benzene was refluxed for 20 hr. An additional 45 mg of reagent was added and refluxing was continued for another 10 hr. After filtering and washing the benzene with bicarbonate and water, evaporation gave 159 mg of crystals. Preparative tlc in 15% benzene–ethyl acetate and recrystallization as above gave VIc (no. 14) with double mp[35] 108–115° and 186–187°, as well as the other physical constants noted in the preceding section.

Androsta-1,4-diene-3,11,17-trione (VII) from 11β-Hydroxyandrosta-1,4-diene-3,17-dione-1-*t* (VI).—An acetone solution of 102 mg of VIb and VIc (no. 13 and 14) was treated with 1.6 ml of the Jones reagent[17] for 15 min at room temperature and then poured onto ice. After extraction with ethyl acetate and washing with aqueous bicarbonate and water, evaporation gave 87 mg of crystals. No loss of tritium was realized in the formation of this compound or after equilibration with base as above (no. 15). VIa was converted to VIIa in a similar fashion.

3β-Acetoxy-1-methylestra-1,3,5(10)-triene-11,17-dione (VIIIa and b) from Androsta-1,4-diene-3,11,17-trione (VIIa and b).[18]—To 70 mg of VIIa or VIIb (no. 15) dissolved in 2 ml of acetic anhydride was added 0.21 ml of a solution of 0.125 ml of 70% perchloric acid in 10 ml of acetic anhydride. The solution was allowed to stand at room temperature for 5 hr. After column and thin layer chromatography on silica gel, crystallization to constant specific activity gave materials no. 7 and 16, mp 203–210° (lit.[18] mp 203–208°) and with ir and uv spectra in agreement with the values reported. Approximately 10 mg was refluxed with base as above for 2 hr. Aliquots were taken before and after treatment, neutralized with HCl, and evaporated to dryness. The radioactivity was determined by scintillation counting. Before base treatment, the activity was 447 cpm, and after treatment, 443 cpm.

Deuterium incorporation into 11β-Hydroxyandrost-4-ene-3,17-dione.—Clean metallic potassium was treated with CH_3O-*d* (98%) and then diluted with 99.9% deuterated water to give 20 ml of a 2% base solution (w/v) in 50% aqueous methanol. To this was added 25 mg of steroid, and the mixture was refluxed under nitrogen for 4 hr. The mixture then was cooled, neutralized, and extracted with ethyl acetate. The dried residue was dissolved in methanol and evaporated to dryness several times to remove deuterium from the 11-hydroxyl group. Following purification by tlc and crystallization, combustion analysis (J. Nemeth, Urbana, Ill.) showed that it contained 24.94 atom % excess deuterium corresponding to 6.5 atoms per molecule.

TABLE III

STEREOCHEMICAL ANALYSIS OF TRITIUM IN 11β-HYDROXY COMPOUNDS. RECRYSTALLIZATION DATA

No.	Compd	Recrystn no.	dpm, μmol	Average
	Experiments with Prednisolone (I)			
1	IVa	1	24,700	
		2	26,300	
		3	25,300	25,400
2	Va (base equil of IVa)	1	21,400	
		2	21,600	21,500
3	Va (2nd equil of IVa)	1	20,300	
		2	19,900	20,100
4	Va (substr for *B. sph.*)	1	30,200	
		2	28,200	
			30,200	29,500
5	VIa	1	23,600	
			23,800	23,700
6	VIa (substr for VIa to VIIIa)	1	28,600	...
7	VIIIa	1	4,320	
		2	4,550	
			4,230	4,370
	Experiments with 11-β-hydroxyandrosta-1,4-diene-3,17-dione (II)			
8	IVb	1	77,900[a]	
		2	68,500	
		3	72,300	70,400
9	Vb (1st base equil of IVb)	1	41,800	
		2	47,500	
		3	48,400	47,900
10	Vb (2nd equil)	1	40,000	
		2	43,700	41,900
11	Vb (3rd equil)	1	40,900	
		2	41,300	41,100
12	Vb (for conversion to VIb and VIc)	1	11,900	
		2	12,200	12,000
13	VIb (*B. sph.*)	1	9,200	
		2	8,500	
		3	9,200	9,230
14	VIc (DDQ)	1	9,430	
		2	9,180	
		3	9,310	9,300
15	VIIb (from no. 13 and 14 followed by base treatment)	1	9,350	
		2	9,620	9,480
16	VIIIb	1	1,520	
		2	1,420	1,460

[a] Underlined values *not* used to compile average.

Testosterone-1,2-*t*.—Analysis carried out as previously reported[3,8] showed that 44% of the tritium was at C-1, 13% was at C-1α, and 43% was enolizable.

Incubations. 1. *B. sphaericus*.—The whole-cell incubation was carried out as detailed above, using 50 mg of androstenedione-1,2-*t*-4^{14}C, sp activity 7 × 10^4 dpm/mg ^{3}H and 2.96 × 10^3 dpm/mg ^{14}C (ratio 23.6:1) per 400 ml of culture medium. After extraction and preparative tlc in 28% acetone–hexane, androsta-1,4-diene-3,17-dione product and unconverted androstenedione were eluted. Conversion to product was 98%, judged by the relative amount of ^{14}C associated with the two zones. The $\Delta^{1,4}$ product was crystallized to constant ^{3}H and ^{14}C activities; ^{3}H/^{14}C ratio, first crystallization, 14.7:1; second, 14.4:1. The recovered substrate was purified successively in the ligroin–propylene glycol and Bush A paper systems; ratios, 24.7:1, 24.4:1.

(33) V. Stefanovic, M. Hayano, and R. I. Dorfman, *Biochim. Biophys. Acta*, **77**, 429 (1963).

(34) H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto, and E. B. Hershberg, *J. Amer. Chem. Soc.*, **77**, 4781 (1955).

(35) C. H. Gray, M. S. Green, N. J. Holness, and J. B. Lunnon, *J. Endocrinol.*, **14**, 146 (1956).

The cell-free incubations were carried in five 25-ml conical flasks for 6 hr at 30° using 2.5 mg of substrate with similar specific activities (ratio 25.3:1), 1 mg of menadione, and 5 ml of enzyme solution per flask.[26] After extraction and preparative tlc as above, androsta-1,4-diene-3,17-dione product and unreacted starting material were eluted; conversion was 23%. They were diluted with appropriate carriers and crystallization to constant specific activities and ratios: product, 10.8:1, 10.7:1; substrate, 29.5:1, 30.8:1.

2. A placental incubation[22] was carried out with a 10,000 × g supernate preparation prepared in phosphate buffer using 200 μg of testosterone-1,2-*t* (sp activity 2.5 × 10^4 dpm ^3H and 944 dpm ^{14}C per μg, ratio 26.5) per 20 g wet weight of tissue. After incubation in air at 37° for 1 hr in the presence of an NADPH generating system, the mixture was extracted with ethyl acetate. The extract was chromatographed in the ligroin–propylene glycol paper system for 12 hr, and then in the toluene–propylene glycol systems without elution. The material in the estrone–testosterone and androstenedione areas were purified further by tlc. The $^3H/^{14}C$ ratios in dpm of the estrone were 8.2:1 after tlc in 20% ethyl acetate–benzene, 8.6:1 after a second crystallization, 8.1:1 after partition between KOH and toluene, and 8.3:1 after thin layer chromatography and two crystallizations of the acetate. The conversion to estrone was about 40%, as judged from the radioscans of the chromatograms.

The testosterone after tlc, reverse isotope dilution, and recrystallization showed $^3H/^{14}C$ ratios of 27.0:1, 27.7:1, and 28.0:1. The androstenedione material after tlc in 20% ethyl acetate–benzene followed by reverse isotope dilution and crystallization after $^3H/^{14}C$ ratios of 26.5:1, 25.8:1, and 26.5:1. Results in this and the preceding section are summarized in Table II.

Registry No.—I, 50-24-8; II, 898-84-0; tritium, 10028-17-8.

Acknowledgment.—We are grateful to Mrs. Cynthia E. Hay for skilled technical assistance.

Chemistry of 3-(N-Acetylureido)-4,5-oxidoandrostan-17β-ol Acetates[1a]

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Epoxidation of 3-ureido-Δ⁴-androsten-17β-ol derivatives **1a** and **6a** afforded exclusively the *cis*-4,5-oxido derivatives **2a** and **7a**, whereas the unsaturated N-acetylureido compounds yielded a mixture of oxides with predominant formation of the *cis* oxides. The *trans*-ureido oxides **3** and **8** were prepared from the *cis*-3-hydroxy 4,5-oxides **4** and **10**. The hydroxyl group was epimerized through the mesylates to the *trans*-azido oxides **5** and **11**. Reduction of the azides with hydrazine hydrate gave the amines which were converted into the ureides with nitrourea. Dilute acid-catalyzed treatment of the *cis*-3-(N-acetylureido) oxides **2b** and **7b** proceeded slowly to the *trans*-diaxial opened products **12** and **13**. Neighboring-group participation of the N-acetylureido group was realized in the acid treatment of the *trans* oxides **3** and **8**.

In continuation of the study on the chemistry of C-3 ureido steroids,[2,3] the synthesis of isomeric 3-ureido- and 3-(N-acetylureido)-4,5-oxidoandrostanes and the participation of the ureido group on ring opening of the epoxide have been investigated.

Epoxidation of 3α-ureido-Δ⁴-androsten-17β-ol acetate (**1a**) gave almost exclusively the *cis* product, 3α-ureido-4α,5-oxido-5α-androstan-17β-ol acetate (**2a**), whereas the 3α-N-acetylureido derivative **1b** gave the epimeric α- and β-epoxides **2b** and **3b** in a 2:1 ratio. The α-epoxide **2b** could also be prepared from 3α-ureido-Δ⁴-androsten-17β-ol (**1c**) and *m*-chloroperoxybenzoic acid followed by acetylation. The configuration of the epoxides was assigned on the basis of nmr spectrometric evidence.[4] The proton at C-4 in both **2a** and **2b** appeared as a doublet at δ 3.01 (J = 4.5 cps) indicating an epoxide ring *cis* to the substituent at C-3. In **3b** the C-4 proton appeared as a singlet at δ 2.85, demonstrating the *trans* relationship of the epoxide with the C-3α-N-acetylureido group. The stereoselective introduction of the epoxide *cis* to the C-3 ureido group can be ascribed to the hydrogen bonding between $-N^1H$ and the carbonyl group of the peracid directing the reagent from the *cis* face of the steroid nucleus. Henbest and Wilson[5] have proposed such a transition complex for the stereoselective epoxidation of cyclic allyl alcohols. It has also been found that cyclic allyl acetamido and benzamido groups have similar strong directive influence on epoxidation.[6,7] The formation of an appreciable amount of the *trans* epoxide from the 3α-N-acetylureido derivative **1b** may be in part due to steric hindrance of the *cis* face by the bulkier group as well as preferential hydrogen bonding of the reagent with the more acidic $-N^3H$ placing the peracid in a less favorable position for epoxidation; consequently a larger proportion of the *trans*-β epoxide **3b** could be formed.

In order to prepare larger amounts of the *trans*-β epoxide **3**, the method employed by Ponsold[8] for the preparation of 3α-acetamido-4β,5-oxido-5β-cholestane was employed. The 4β,5β epoxide **4a** was stereoselectively introduced by *m*-chloroperoxybenzoic acid oxidation of Δ⁴-androstene-3β,17β-diol 17-monoacetate derived from testosterone acetate. Epimerization at C-3 was accomplished by mesylation to **4b** and treatment with sodium azide to give 3α-azido-4β,5-oxido-5β-androstan-17β-ol acetate (**5**). The α orientation of the azido group was demonstrated by the singlet at δ 2.88 due to the proton at C-4, indicating a *trans* relationship of the epoxide and the azido group.[4] Reduction of the azide with hydrazine hydrate in the presence of Raney nickel afforded the amine, which was converted to 3α-ureido-4β,5-oxide-5β-androstan-17β-ol acetate (**3a**) with nitrourea.[2] Attempts to form the N-acetyl derivative (**3b**) were unsuccessful.

(1) (a) This investigation was supported by a grant from the American Cancer Society and Grant CA-07304 from the National Cancer Institute, National Institutes of Health, U. S. P. H. S. (b) Visiting Scientist, 1966–1967. Institut de Chimie des Substances, Naturelles, Gif-sur-Yvette, France.

(2) A. Yagi, J. S. Liang, and D. K. Fukushima, *J. Org. Chem.*, **32**, 713 (1967).

(3) H. Kaufmann and D. K. Fukushima, *ibid.*, **32**, 1846 (1967).

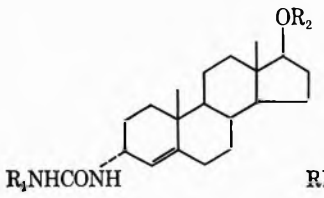
(4) D. J. Collins and J. J. Hobbs, *Tetrahedron Lett.*, 623 (1963).

(5) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(6) K. Ponsold and W. Preibach, *J. Prakt. Chem.*, **25**, 26 (1964).

(7) L. Goodman, S. Winstein, and R. Boschan, *J. Amer. Chem. Soc.*, **80**, 4312 (1958).

(8) K. Ponsold, *J. Prakt. Chem.*, **25**, 32 (1964).



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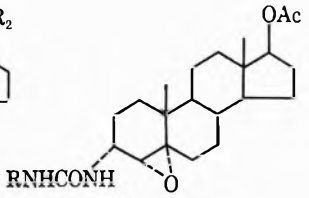
c, $R_1 = R_2 = H$



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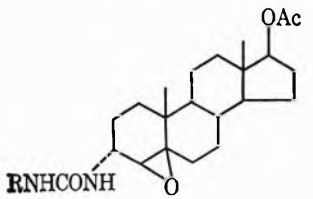

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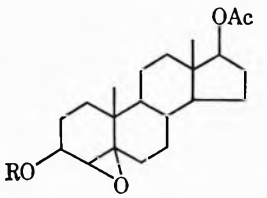

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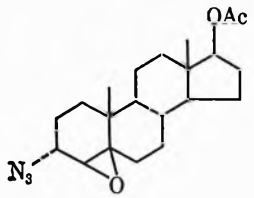

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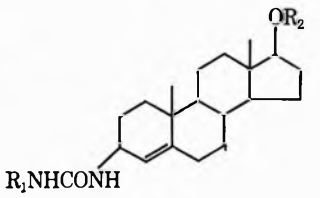

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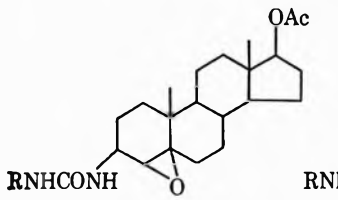

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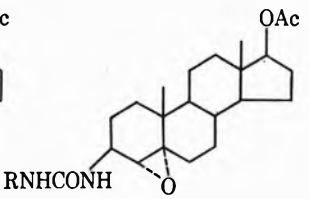

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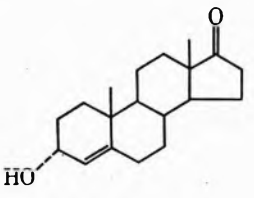
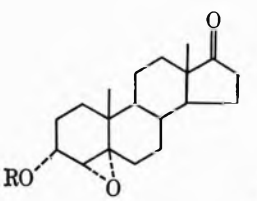


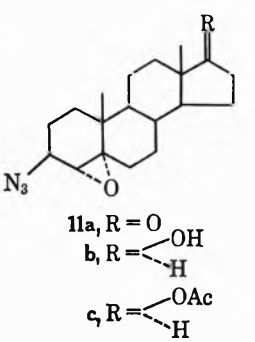
9

The 4,5 epoxides of the 3β-ureido derivatives were prepared in the same manner as the 3α epimers. The directive influence of hydrogen bonding between NH and the peracid was also evident for epoxidation of 3β-ureido-Δ⁴-androsten-17β-ol (**6a**). This yielded almost exclusively the *cis*-4β,5β epoxide despite the presence of the C-19 methyl group. The product was isolated as the N-acetylureido derivative **7b**. Only trace amounts of the *trans*-4α,5α epoxide **8b** was detected. Epoxidation of the 3β-(N-acetylureido)-Δ⁴-androsten-17β-ol acetate (**6b**) gave a higher proportion of the *trans* epoxide (*cis*:*trans*, 3:2) than that achieved with the 3α epimer **1b** in which the ratio was 2:1. This was probably due to the greater access of the peracid to the unsaturation from the less hindered α face in competition with the hydrogen bond assisted *cis*-β epoxide formation. The configuration of the oxirane ring in 3β-ureido-4β,5-oxido-5β-androstan-17β-ol acetate (**7a**), its N-acetyl derivative **7b**, and their 4α,5α epoxide isomers **8** was assigned by the splitting patterns of the C-4 protons.

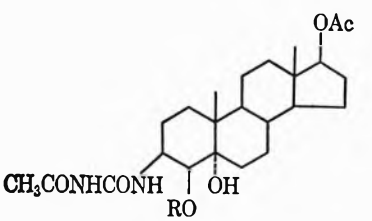
The *trans*-α epoxide, 3β-(N-acetylureido)-4α,5-oxido-5-androstan-17β-ol acetate (**8b**), could not be readily isolated from the 3:2 mixture (*cis*:*trans*) obtained from the epoxidation of unsaturated compound **6b**. Consequently, the synthesis of the *trans* epoxide **8** was undertaken by reactions analogous to those employed in the preparation of the *trans* epoxide of the 3α-ureide. The stereoselective introduction of the 4α,5α epoxide was achieved by the *m*-chloroperoxybenzoic acid treatment of 3α-hydroxy-Δ⁴-androsten-17-one (**9**) to yield 3α-hydroxy-4α,5-oxido-5α-androstan-17-one (**10a**). The *cis* configuration of the oxirane ring was verified by the doublet of the C-4 proton at δ 3.17 (J = 3.5 cps). Epimerization at C-3 was accomplished by formation of the mesylate **10b** and displacement with sodium azide to give 3β-azido-4α,5-oxido-5α-androstan-17-one (**11a**). The *trans* relationship was established from the chemical shift of the C-4 proton, a singlet at δ 2.92. The 17-carbonyl group of the azide **11a** was then reduced with sodium borohydride, and the alcohol **11b** was acetylated to give 3β-azido-4α,5-oxido-5α-androstan-17β-ol acetate (**11c**). The azido group in



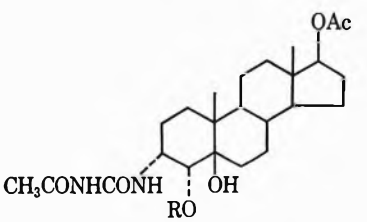
10a, R = H
b, $R = CH_3SO_2$



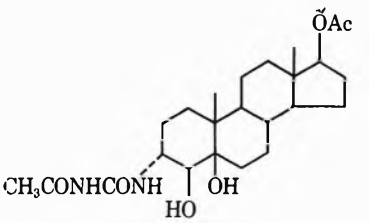
11a, R = O
b, R = OH, H
c, R = OAc, H



12a, R = H
b, $R = CH_3CO$



13a, R = H
b, $R = CH_3CO$



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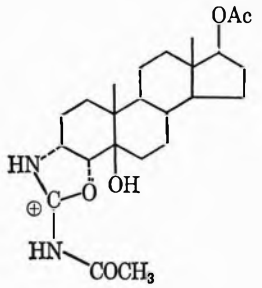
11c was next reduced with hydrazine hydrate to an amine, which was converted to 3β-ureido-4α,5-oxido-5α-androstan-17β-ol acetate (**8a**) with nitrourea. Although acetylation of the ureido group in the *cis* epoxy compounds proceeded readily, the preparation of the 3β-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (**8b**) from the ureide **8a** was unsuccessful, just as in the epimeric *trans*-3α epoxide **3b**. The reaction lead to a variety of products which were not characterized.

The acid-catalyzed opening of isomeric 3-acetoxy-4,5-oxido steroids has been studied by several investigators, and the participation of the acetoxyl group has been demonstrated.[9-13] In the accompanying paper, participation of the 3-acetamido group in the opening of the vicinal epoxide ring is described.[14] In the present study, treatment of 3α-ureido-4β,5-oxido-5β-androstan-17β-ol acetate (**3a**) and the 3β-ureido-4α,5α-oxido isomer **8a** with dilute sulfuric acid in acetone resulted in precipitation of a salt, which prevented further reaction. Upon neutralization with base, starting material was recovered. Therefore, the ring opening of the 4,5-oxides of the N-acetylureido derivatives was examined. Dilute sulfuric acid in acetone afforded *trans* diaxial ring opening of 3β-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (**7b**) to 3β(N-acetylureido)-5α-androstane-4β,5,17-triol 17-monoacetate (**12a**) in 2 days at room temperature. The β orientation of the hydroxyl group at C-4 was assigned from the appearance of the C-19 methyl protons signals downfield at δ 1.13. This downfield shift of the C-19 methyl protons was also evident in the acetylated product **12b** and is consistent with the presence of a 4β-OR group.

Opening of the oxirane ring of the *cis* α isomer, 3α-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (**2b**), required 16 days. The principal product was the *trans* diaxial product, 3α-(N-acetylureido)-5β-androstane-4α,5,17β-triol 17-monoacetate (**13a**).

trans diaxial opening of 4α,5α and 4β,5β oxides can occur in two directions, giving rise to 4β,5α-dihydroxy and 4α,5β-dihydroxy derivatives. The preferred opening would place the intermediate carbonium ion at the tertiary carbon, C-5, and thus the 4β,5β epoxide should give principally the 4β,5α dihydroxy derivative and the epimeric 4α,5α epoxide should give the 4α,5β-dihydroxy derivative. Both *cis*-N-acetylureido epoxides opened almost exclusively in the expected manner. Similar exclusive opening of *cis* oxides has been observed in the acetoxy and the acetamido series.

The anticipated backside participation of the neighboring ureido group was realized in the dilute acid treatment of the *trans* epoxides, 3β-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (**8b**) and the corresponding 3α derivative **3b**; the starting epoxide disappeared rapidly in the reaction. 3α-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (**3b**) did not afford the expected 4α,5β-dihydroxy derivative **13a**, but yielded instead a compound which had a nmr spectrum consistent with 3α-(N-acetylureido)-5β-androstane-4β,5,17β-triol 17-monoacetate (**14**). The protons of the C-19 methyl group appeared relatively far downfield, δ 1.27, indicating that the hydroxyl groups at C-4 and 5 were both in the β orientation. The *cis*-β-diol could arise by the participation of the N-acetylureido group with the formation of a cyclic intermediate such as



In aqueous solution with an acetoxy or an acetamido group at C-3, analogous cyclic intermediates react with the solvent to afford the vicinial hydroxyl group *cis* to the neighboring group; that is, the epoxides are opened to the diols with inversion at C-4. However, in the case of the N-acetylureido group, hydration of the carbonium ion of the cyclic intermediate is superseded by attack of the solvent at C-4 to give the β-hydroxyl group, resulting in *cis* opening of the epoxide. It may be also postulated that a six-membered cyclic intermediate is formed by attachment of the acetylureido group at C-5α. Such an intermediate, by *cis* opening of the epoxide, could also give rise to the same product **14** in the manner proposed above.

The other *trans* epoxide, 3β-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (**8b**), could not be prepared pure in sufficient amount for acid treatment. However, evidence of the participation of the N-acetylureido group was derived from the acid treatment of a 3:2 mixture (β:α oxide) with the *cis*-3β-(N-acetylureido)-4β,5β-oxide isomer. As measured by thin layer chromatography, the *trans*-α oxide disappeared within 16 hr, whereas the *cis*-β oxide required 48 hr for complete reaction. The sole product isolated and characterized was 3β-(N-acetylureido)-5α-androstane-4β,5,17-triol 17-monoacetate (**12a**) in 60% yield. However, since the pure *cis*-β oxide gave rise to this product in about 70% yield, the extent of formation of this product from the *trans*-α oxide could not be ascertained.

Experimental Section[15]

3α-Ureido-Δ⁴-androsten-17β-ol Acetate (1a) and 3α-(N-Acetylureido)-Δ⁴-androsten-17β-ol Acetate (1b).—A solution of 2.5 g of 3α-ureido-Δ⁴-androsten-17β-ol[3] (**1c**) in 90 ml of pyridine and 90 ml of acetic anhydride was allowed to stand at room temperature for 72 hr. It was poured into crushed ice containing 5% hydrochloric acid and extracted with methylene chloride. The extract was washed with base and water and dried, and the solvent was evaporated. The residue (2.8 g) showed four spots on chromatography on a thin layer of silica gel G in ethyl acetate–cyclo-

(9) D. J. Collins, *J. Chem. Soc.*, 3919 (1959).
(10) L. Fieser, T. Goto, and B. K. Bhattachanga, *J. Amer. Chem. Soc.*, **82**, 1700 (1960).
(11) S. Julia and J. P. Lavaux, *Bull. Soc. Chim. Fr.* 1223, 1238 (1963).
(12) J. M. Coxon, M. P. Hartshorn, and P. N. Kirk, *Tetrahedron*, **20**, 2531, 2547 (1964).
(13) S. Julia and B. Furer, *Bull. Soc. Chim. Fr.*, 1114 (1966).
(14) G. Lukacs and D. K. Fukushima, *J. Org. Chem.*, 000 (1969).

(15) Melting points were determined on a micro hot stage and are corrected. Nmr spectra were obtained on a Varian A-60 instrument in deuteriochloroform with tetramethylsilane as internal standard; the chemical shifts are given in δ ppm. Optical rotations were determined in chloroform at 24° unless otherwise stated. Infrared spectra were determined on a Beckman IR-9 spectrophotometer in potassium bromide dispersion; br = broad, sm = small, sh = shoulder. Thin layer chromatography, tlc, was carried out on a 250-μ layer of silica gel GF at 24°.

hexane (7:3). The compounds were separated on a column of 300 g of silica gel G with the above solvent mixture at 30 ml per fraction. Fractions 13–22 afforded 1.47 g of **3α-(N-acetylureido)-Δ⁴-androsten-17β-ol acetate (1b)** which after recrystallization from methanol melted at 219–221°; $[\alpha]_D$ 163°; tlc, R_f = 0.42 (ethyl acetate–cyclohexane 7:3); ir 3295, 3242, 3110, 1738, 1693, 1660 (sh),1548, 1502, 1245, 1042 cm⁻¹; nmr δ 0.82 (s), 1.01 (s), 2.03 (s), 2.12 (s), 4.47 (m), 4.63 (t, J = 8 cps), and 5.33 ppm (m).

Anal. Calcd for $C_{24}H_{36}N_2O_4$: C, 69.19; H, 8.71; N, 6.72. Found: C, 69.26; H, 8.81; N, 6.85.

Two minor products were eluted from the column with the same solvent system and were discarded. Elution with methanol–ethyl acetate (1:9) yielded 830 mg of **3α-ureido-Δ⁴-androsten-17β-ol acetate (1a)**. Recrystallization from methanol gave 1a, mp 208–211°; $[\alpha]_D$ 138° (ethanol); tlc, R_f = 0.07 (ethyl acetate–cyclohexane 7:3); ir 3500, 3350, 3290, 3220 (sh), 3080, 1733, 1678, 1645, 1605, 1580, 1550 (sh), 1248, 1045 cm⁻¹; nmr δ 0.82 (s), 1.00 (s), 2.02 (s), 4.05 (m), 4.63 (t, J = 8 cps), and 5.23 ppm (d, J = 5 cps).

Anal. Calcd for $C_{22}H_{34}N_2O_3$: C, 70.55; H, 9.15; N, 7.48. Found: C, 70.29; H, 8.87; N, 7.89.

3α-(N-Acetylureido)-4α,5-oxido-5α-androstan-17β-ol Acetate (2b) and Its 4β,5β Epimer (3b). A.—A solution of 218 mg of 3α-(N-acetylureido)-Δ⁴-androsten-17β-ol acetate (1b) and 220 mg of *m*-chloroperoxybenzoic acid in 15 ml of methylene chloride was stored at room temperature for 24 hr. It was washed with sodium carbonate solution and water and dried. Evaporation of the solvent and recrystallization of the residue from methanol–ethyl acetate afforded 59 mg of **3α-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (2b)**, mp 274°; $[\alpha]_D$ 76.1°; tlc, R_f = 0.25 (ethyl acetate–cyclohexane 7:3); ir 3308, 3243, 3125, 1735, 1715, 1698, 1540, 1505, 1250 (br), 1048 cm⁻¹; nmr δ 0.80 (s), 1.05 (s), 2.02 (s), 2.08 (s), 3.01 (d, J = 5 cps), 4.30 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{24}H_{36}N_2O_5$: C, 66.64; H, 8.39; N, 6.47. Found: C, 66.78; H, 8.35; N, 6.55.

Chromatography of the mother liquor on a thin layer of silica gel G with ethyl acetate–cyclohexane (7:3) yielded an additional 77 mg of the 4α,5α oxide 2b and 70 mg of **3α-(N-acetylureido)-17β-acetoxy-4β,5-oxido-5β-androstane (3b)**. Recrystallization from methanol–ethyl acetate gave 3b, mp 233.5–235.5°; $[\alpha]_D$ 38.8°; tlc, R_f = 0.37 (ethyl acetate–cyclohexane 7:3); ir 3290, 3250 (sh), 3135, 1735, 1700, 1545 (br), 1250, 1048, 1028 cm⁻¹; nmr δ 0.80 (s), 1.03 (s), 2.03 (s), 2.13 (s), 2.85 (s), 4.07 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{24}H_{36}N_2O_5$: C, 66.64; H, 8.39; N, 6.47. Found: C, 66.65; H, 8.13; N, 6.47.

B.—A solution of 50 mg of *m*-chloroperoxybenzoic acid in 3 ml of methylene chloride was added to 50 mg of 3α-ureido-Δ⁴-androsten-17β-ol in 3 ml of acetic acid. The mixture was stored at room temperature for 48 hr, and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride, washed with sodium carbonate solution and water, and dried. The product was acetylated with pyridine and acetic anhydride overnight at room temperature. Chromatography of the acetylated mixture on a thin layer of silica gel G in ethyl acetate–cyclohexane (7:3) afforded 16 mg of 2b, identical with the product described in method A.

3α-Ureido-4α,5-oxido-5α-androstan-17β-ol Acetate (2a).—A solution of 300 mg of 3α-ureido-Δ⁴-androsten-17β-ol acetate (1a) and 500 mg of *m*-chloroperoxybenzoic acid in 35 ml of methylene chloride was stored at room temperature overnight. As judged by thin layer chromatography, only a single product was obtained. The product (290 mg) was crystallized from methanol and from acetone–methanol to give 139 mg of **3α-ureido-4α,5-oxido-5α-androstan-17β-ol acetate (2a)**, mp 228–229.5°; $[\alpha]_D$ 79.6° (ethanol); tlc, R_f = 0.30 (methanol–ethyl acetate 1:9); ir 3430, 3340, 1740, 1678, 1658, 1625, 1592, 1550, 1245, 1048 cm⁻¹; nmr δ 0.82 (s), 1.05 (s), 2.02 (s), 3.01 (d, J = 4.5 cps), 4.21 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{22}H_{34}N_2O_4$: C, 67.66; H, 8.78; N, 7.18. Found: C, 67.66; H, 8.71; N, 7.08.

3α-Ureido-4β,5-oxido-5β-androstan-17β-ol Acetate (3a).—Testosterone acetate (10 g) was reduced with sodium borohydride in methanol at room temperature for 1 hr to give **Δ⁴-androstene-3β,17β-diol 17-monoacetate**; nmr δ 0.80 (s), 1.05 (s), 2.03 (s), 4.17 (m), 4.63 (t, J = 8 cps), 5.33 (br s). It was treated with an equal weight of *m*-chloroperoxybenzoic acid in 1 l. of methylene chloride at room temperature overnight to give **4β,5-oxido-5β-androstane-3β,17β-diol 17-monoacetate (4a)**, nmr δ 0.80 (s), 1.03 (s), 2.05 (s), 3.17 (d, J = 5 cps), 4.10 (m), and 4.66 ppm (t, J = 8 cps). The presence of a small amount of the 4α,5α epoxide was indicated by a singlet at δ 2.78.

A solution of 10 g of 4β,5-oxido-5β-androstane-3β,17β-diol 17-monoacetate (4a) and 7 ml of methanesulfonyl chloride in 130 ml of pyridine was allowed to stand at 5° for 3 hr. The mixture was poured into ice and extracted with methylene chloride. The extract was washed with water, sodium bicarbonate solution, and water, dried, and the solvent evaporated. Recrystallization from methanol afforded 11.6 g of **3β-methanesulfonoxy-4β,5-oxido-5β-androstan-17β-ol acetate (4b)**, ir 1733, 1360, 1242, 1175, 530 cm⁻¹; nmr δ 0.82 (s), 1.07 (s), 2.03 (s), 3.11 (s), 3.27 (d, J = 3.8 cps), 4.63 (t, J = 8 cps), and 5.18 ppm (m).

Anal. Calcd for $C_{22}H_{34}O_6S \cdot {}^1/_2H_2O$: C, 61.06; H, 8.20; S, 7.23. Found: C, 61.02; H, 8.10; S, 7.39.

The mesylate (11 g) was treated with 41 g of sodium azide in 580 ml of dimethyl sulfoxide at 90° for 90 min. The solution was poured into ice and water, extracted with methylene chloride, washed with water, and dried. Evaporation of the solvent and trituration with methanol afforded 6.63 g of **3α-azido-4β,5-oxido-5β-androstan-17β-ol acetate (5)**, mp 139.5–141.5°. The analytical sample from methanol melted at 141–142°; $[\alpha]_D$ −4.9°; tlc, R_f = 0.36 (ethyl acetate–benzene 1:19); ir 2110, 1735, 1248, 1045, 1023, 1018 cm⁻¹; nmr δ 0.82 (s), 1.03 (s), 2.03 (s), 2.88 (s), 3.75 (t, J = 8 cps), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{21}H_{31}N_3O_3$: C, 67.53; H, 8.37; N, 11.25. Found: C, 67.42; H, 8.45; N, 11.31.

A mixture of 1.0 g of the azide in 2.4 ml of hydrazine hydrate in 40 ml of ethanol and a small amount of W-2 Raney nickel was refluxed for 10 min. It was cooled and filtered, most of the ethanol was evaporated, and the residue was dissolved in ethyl acetate and washed with water. A solution of 500 mg of the crude amine and 480 mg of nitrourea in 40 ml of 50% ethanol was refluxed for 7 hr. The solution was concentrated to half its volume, ethyl acetate was added, and the extract was washed with water, sodium carbonate solution, and water. Recrystallization of the product from ethyl acetate–methanol afforded **3α-ureido-4β,5-oxido-5β-androstan-17β-ol acetate (3a)**, mp 223.5–226°; $[\alpha]_D$ 38.9° (ethanol); tlc, R_f = 0.36 (methanol–ethyl acetate 1:3); ir 3620, 3462, 3362, 3290, 1735 (sh), 1716, 1660, 1650 (sh), 1615, 1558, 1540 (sh), 1267, 1250 (sh), 1045, 1023 cm⁻¹; nmr δ 0.80 (s), 1.00 (s), 2.02 (s), 2.85 (s), 4.05 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{22}H_{34}N_2O_4 \cdot CH_3OH$: C, 65.37; H, 9.06; N, 6.63. Found: C, 65.89; H, 9.01; N, 7.10.

The N-acetylureido derivative **3b** could not be obtained by treatment with acetic anhydride and pyridine. There were many products, but none had the mobility on a thin layer chromatogram of the desired product **3b**.

3β-(N-acetylureido)-Δ⁴-androsten-17β-ol Acetate (6b).—A solution of 180 mg of 3β-ureido-Δ⁴-androsten-17β-ol (6c)[2] in 5 ml of pyridine and 5 ml of acetic anhydride was allowed to stand at room temperature overnight. The product was crystallized from methanol to give 131 mg of **3β-(N-acetylureido)-Δ⁴-androsten-17β-ol acetate (6b)**, mp 240–243°; $[\alpha]_D$ 2.3°; tlc R_f = 0.34 (ethyl acetate–cyclohexane 7:3); ir 3298, 3245, 3118, 1745, 1715, 1695, 1555, 1540 (sh), 1510, 1250, 1045, 1025 cm⁻¹; nmr δ 0.82 (s), 1.05 (s), 2.03 (s), 2.10 (s), 4.50 (m), 4.63 (t, J = 8 cps), and 5.21 ppm (nm).

Anal. Calcd for $C_{24}H_{36}N_2O_4$: C, 69.19; H, 8.71; N, 6.72. Found: C, 69.03; H, 9.11; N, 6.72.

3β-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol Acetate (7b).—A solution of 200 mg of 3β-ureido-Δ⁴-androsten-17β-ol (6a) and 200 mg of *m*-chloroperoxybenzoic acid in glacial acetic acid and 70 ml of methylene chloride was stored at room temperature overnight and then worked up as above for the 3α-epimer. The residue was acetylated with acetic anhydride in pyridine at room temperature for 4 days. The reaction mixture contained a small amount of a less polar product, R_f = 0.21, presumbably the 4α,5α oxide. Thin layer chromatography of the mixture on silica gel G in cylohexane–ethyl acetate (3:7) and recrystallization of the main product, R_f = 0.26, from methanol afforded 116 mg of **3β-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (7b)**, mp 246–248°; $[\alpha]_D$ −37.0° (chloroform); ir 3405 (sh), 3380, 3358, 3295, 1723, 1528, 1245, 1040 cm⁻¹; nmr δ 0.82 (s), 1.05 (s), 2.03 (s), 2.11 (s), 3.01 (d, J = 3.0 cps), 4.37 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{24}H_{36}N_2O_5$: C, 66.64; H, 8.39; N, 6.47. Found: C, 66.74; H, 8.18; N, 6.29.

A solution of 270 mg of 3β-(N-acetylureido)-Δ⁴-androsten-17β-ol acetate (**6b**) and 270 mg of *m*-chloroperoxybenzoic acid in 30 ml of methylene chloride was stored at room temperature overnight. Thin layer chromatography in cyclohexane–ethyl acetate (3:7) showed the presence of two products, R_f = 0.21 and 0.26, in relative yields of 2:3 respectively. The mixture was also verified by the relative intensities of the signals due to the C-4 protons in the nmr spectrum. The crude mixture could not be readily separated; only the *cis* oxide **7b** could be isolated in pure form.

3α-Hydroxy-4α,5-oxido-5α-androstan-17-one (10a).—A solution of 1.25 g of 3α-hydroxy-Δ⁴-androsten-17-one (**9**) and 1.25 g of *m*-chloroperoxybenzoic acid in 240 ml of methylene chloride was stored overnight at room temperature and worked up in the usual manner. Recrystallization of the product from ether–acetone afforded 876 mg of **3α-hydroxy-4α,5-oxido-5α-androstan-17-one (10a)**, mp 128–129°, 136–137.5°; $[\alpha]_D$ 174°; tlc, R_f = 0.37 (ethyl acetate); ir 3500, 1745, 1038 cm⁻¹; nmr δ 0.90 (s), 1.05 (s), 3.17 (d, J = 3.5 cps), and 3.95 ppm (m).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.29. Found: C, 74.20; H, 9.21.

From the mother liquor was obtained **3α-hydroxy-4β,5-oxido-5β-androstan-17-one**, mp 175.5–180.5°; tlc, R_f = 0.41 (ethyl acetate); ir 3460 (br), 1730, 1080, 1050 cm⁻¹; nmr δ 0.88 (s), 1.03 (s), 2.87 (s), and 3.97 ppm (t, J = 9 cps).

3β-Azido-4α,5-oxido-5α-androstan-17-one (11a).—A solution of 768 mg of 3α-hydroxy-4α,5-oxido-5α-androstan-17-one (**10a**) and 0.7 ml of methanesulfonyl chloride in 14 ml of pyridine was kept at 5° for 2.5 hr. The mixture was poured into ice and water and filtered. **3α-Methanesulfonoxy-4α,5-oxido-5α-androstan-17-one (10b)**, 903 mg, could not be crystallized without decomposition. Its mobility on tlc was R_f = 0.26 (cyclohexane–ethyl acetate 1:1); ir 1745, 1365, 1175, 910 cm⁻¹; nmr δ 0.87 (s), 1.03 (s), 3.03 (s), 3.23 (d, J = 4 cps), and 5.05 ppm (m). The mesylate **10b** was treated with 2.9 g of sodium azide in 40 ml of dimethylsulfoxide at 90° for 90 min. The reaction product was recrystallized from methanol and the mother liquor chromatographed on a thin layer of silica gel G to afford 696 mg of **3β-azido-4α,5-oxido-5α-androstan-17-one (11a)**, mp 129–129.5°; $[\alpha]_D$ 138°; tlc, R_f = 0.39 (cyclohexane–ethyl acetate 7:3), R_f = 0.53 (cyclohexane–ethyl acetate 1:1); ir 2105, 1743, 1058, 1015 cm⁻¹; nmr δ 0.87 (s), 1.10 (s), 2.92 (s), and 3.72 ppm (t, J = 9 cps).

Anal. Calcd for $C_{19}H_{27}O_2N_3$: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.28; H, 8.25; N, 12.76.

3β-Azido-4α,5-oxido-5α-androstan-17β-ol acetate (11c).—To a solution of 516 mg of 3β-azido-4α,5-oxido-5α-androstan-17-one (**11a**) in 30 ml of methanol was added 500 mg of sodium borohydride in 30 ml of methanol. Most of the methanol was removed *in vacuo* and the residue extracted with ethyl acetate. The product, 518 mg, was chromatographed on a thin layer of silica gel G in cyclohexane–ethyl acetate (1:1), and the major product was recrystallized from methanol to give **3β-azido-4α,5-oxido-5α-androstan-17β-ol (11b)**, mp 106–107.5°; $[\alpha]_D$ 66.0°; tlc, R_f = 0.41 (cyclohexane–ethyl acetate 1:1); ir 3330, 2100, 1075, 1057, 1035 cm⁻¹; nmr δ 0.77 (s), 1.10 (s), 2.92 (s), and 3.67 ppm (m).

Acetylation of 518 mg of the azide **11b** with acetic anhydride and pyridine and recrystallization from methanol afforded 479 mg of **3β-azido-4α,5-oxido-5α-androstan-17β-ol acetate (11c)**, mp 149.5–150°; $[\alpha]_D$ 49.7°; tlc, R_f = 0.46 (cyclohexane–ethyl acetate 7:3); ir 2480, 2195, 2100, 1745, 1250, 1048, 1045, 1022 cm⁻¹; nmr δ 0.82 (s), 1.10 (s), 2.03 (s), 2.90 (s), 3.73 (t, J = 9 cps), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{21}H_{31}N_3O_3$: C, 67.53; H, 8.37; N, 11.25. Found: C, 67.69; H, 8.10; N, 11.35.

3β-Ureido-4α,5-oxido-5α-androstan-17β-ol acetate (8a).—A mixture of 100 mg of 3β-azido-4α,5-oxido-5α-androstan-17β-ol acetate (**11c**), 0.5 ml of hydrazine hydrate, and a small amount of W-2 Raney nickel was stirred at room temperature for 1 hr. Most of the ethanol was removed, and the residue was extracted with ethyl acetate, affording 94 mg of **3β-amino-17β-acetoxy-4α,5-oxido-5α-androstane**. The product gave only one spot on thin-layer chromatography in the system *n*-butanol–acetic acid–water (4:1:5), R_f = 0.44. A solution of the 3β-amine and 150 mg of nitrourea in 24 ml of 50% ethanol was heated at 90° for 2 hr. The reaction mixture was worked up in the usual manner. Recrystallization from methanol–ether afforded 62 mg of **3β-ureido-4α,5-oxido-5α-androstan-17β-ol acetate (8a)**, mp 121–125°, 207–213°; $[\alpha]_D$ 21.5°; tlc, R_f = 0.34 (methanol–ethyl acetate 1:3); ir 3480, 3380, 3320 (sh), 1740, 1668, 1620, 1560, 1252, 1045, 1028 cm⁻¹; nmr δ 0.82 (s), 1.10 (s), 2.03 (s), 2.93 (s), 3.83 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{22}H_{34}N_2O_4 \cdot CH_3OH$: C, 65.37; H, 9.06; N, 6.63. Found: C, 65.65; H, 9.10; N, 6.96.

The N-acetyl derivative **8b** could not be derived by acetylation with acetic anhydride and pyridine.

Acid Treatment

3α-(N-Acetylureido)-4α,5-oxido-5α-androstan-17β-ol Acetate (2b).—A solution of 215 mg of 3α-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (**2b**) in 43 ml of acetone and 5.4 ml of 0.33 *N* sulfuric acid was allowed to stand at room temperature (22°) for 16 days, at which time no starting material remained. The acetone was removed *in vacuo* and the residue was extracted with ethyl acetate. The extract was washed with dilute sodium carbonate and saline solutions and dried, and the solvent was evaporated. The product, 216 mg, was chromatographed on 30 g of Celite 545 with the system benzene–2,2,4-trimethylpentane (3:1) methanol–water (4:1). Elution with the upper phase afforded 110 mg of **3α-(N-acetylureido)-5β-androstane-4α,5,17β-triol 17-monoacetate (13a)**, and 35 mg of a more polar product which could be derived from the monoacetate under the same acidic condition. Recrystallization of the triol monoacetate from acetone and methanol afforded 70 mg of **13a**, mp 171–176°; $[\alpha]_D$ 20.3° (ethanol); tlc, R_f = 0.22 (ethyl acetate); ir 3470 (br), 3135, 3120, 1700 (br), 1550, 1250, 1028 cm⁻¹; nmr δ 0.78 (s), 0.93 (s), 2.03 (s), 2.10 (s), 3.70 (m), 4.17 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{24}H_{38}N_2O_6 \cdot 1.5H_2O$: C, 60.35; H, 8.65; N, 5.87. Found: C, 60.21; H, 8.06; N, 5.75.

Acetylation of 70 mg of 3α-(N-acetylureido)-5β-androstane-4α,5,17β-triol 17-monoacetate (**13a**) with pyridine and acetic anhydride required 14 days at room temperature to go to completion. Chromatography on 20 g of Celite 545 in the system 2,2,4-trimethylpentane–benzene (5:3) and methanol–water (4:1) afforded 65 mg of the acetylated product. Recrystallization from acetone–petroleum ether gave 54 mg of **3α-(N-acetylureido)-5β-androstane-4α,5,17β-triol 4,17-diacetate (13b)**, mp 222–225°; tlc, R_f = 0.36 (ethyl acetate); ir 3465, 3290, 3140, 1750, 1735, 1700, 1552, 1495, 1250–1225, 1030, 600 cm⁻¹; nmr δ 0.78 (s), 0.93 (s), 2.03 (s), 2.07 (s), 2.13 (s), 4.50 (m), 4.63 (t, J = 8 cps), and 5.01 ppm (m).

Anal. Calcd for $C_{25}H_{40}N_2O_7$: C, 63.39; H, 8.19; N, 5.69. Found: C, 63.61; H, 8.52; N, 5.31.

3α-(N-Acetylureido)-4β,5-oxido-5β-androstan-17β-ol Acetate (3b).—A solution of 103 mg of 3α-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (**3b**) in 20 ml of acetone and 2.5 ml of 0.33 *N* sulfuric acid was allowed to stand at room temperature for 48 hr. No starting material remained at this time as judged by thin layer chromatography. The reaction product (18 mg) was recrystallized from methanol and gave a product, mp 163–163.5°, with the same mobility on paper and thin layer chromatography as 3α-(N-acetylureido)-5β-androstane-4α,5,17β-triol 17-monoacetate. The product had $[\alpha]_D$ −99° (ethanol), and the nmr spectrum was consistent with **3α-(N-acetylureido)-5β-androstane-4β,5,17β-triol 17-monoacetate (14)**, nmr δ 0.80 (s), 1.27 (s), 2.03 (s), 2.13 (s), 3.80 (m), 4.43 (m), and 4.63 ppm (t, J = 8 cps); ir 3600–3100, 1736, 1613, 1587, 1250, 1105, 1045, 990 cm⁻¹.

Anal. Calcd for $C_{24}H_{38}N_2O_6 \cdot {}^1/_2H_2O$: C, 62.72; H, 8.55; N, 6.10. Found: C, 63.03; H, 8.40; N, 6.10.

After acetylation of the product **14** with acetic anhydride and pyridine at room temperature for 4 days, at least 80% of the starting material remained; there was insufficient acetylated material to isolate and characterize.

3α-Ureido-4β,5-oxido-5β-androstan-17β-ol Acetate (3a).—A solution of 50 mg of 3α-ureido-4β,5-oxido-5β-androstan-17β-ol acetate (**3a**) in 8 ml of acetone and 0.85 ml of 0.25 *N* sulfuric acid gave a precipitate almost immediately. The mixture was allowed to stand at room temperature for 5 days and filtered. The precipitate was insoluble in ethyl acetate and in acetone. The precipitate was treated with 5% sodium carbonate solution, extracted with ethyl acetate, and washed with water. The mobility of the product on tlc and the infrared spectrum were identical with that of the starting material.

3β-(N-Acetylureido)-4β,5-oxido-5β-androstan-17β-ol Acetate (7b).—A solution of 31 mg of 3β-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (**7b**) in 6 ml of acetone and 0.74 ml

of 0.33 *N* sulfuric acid was allowed to stand at room temperature for 48 hr, at which time no starting material remained. The product was recrystallized from methanol to yield 23 mg of **3β-(N-acetylureido)-5α-androstane-4β,5,17β-triol 17-monoacetate (12a)**, mp 254–254.5°; $[\alpha]D$ 9.5° (ethanol); tlc, R_f = 0.21 (ethyl acetate); ir 3575, 3450, 3335, 3220, 3105, 1733, 1672, 1530, 1250 (br), 1050, 1028 cm^{-1}; nmr δ 0.77 (s), 1.13 (s), 2.03 (s), 2.10 (s), 3.50 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{24}H_{38}N_2O_6 \cdot {}^1/_2H_2O$: C, 62.72; H, 8.55; N, 6.10. Found: C, 62.48; H, 8.67; N, 6.06.

A solution of 56 mg of 3β-(N-acetylureido)-5α-androstane-4β,-5,17β-triol 17-monoacetate (**12a**) in 1 ml of pyridine and 1 ml of acetic anhydride was allowed to stand for 5 days at room temperature. The reaction product was separated by a preparative thin-layer chromatogram of silica gel G in ethyl acetate–cyclohexane (7:3) to give 55 mg of **3β-(N-acetylureido)-5α-androstane-4β,5,17β-triol 4,17-diacetate (12b)**. Recrystallization from methanol afforded diacetate **12b**, mp 233–234.5°; $[\alpha]D$ 15.7°; tlc, R_f = 0.22 (ethyl acetate–cyclohexane 7:3); ir 3600 (sh), 3490, 3300, 3150, 1745, 1720, 1695, 1548, 1505, 1245 (br), 1045, 1025 cm^{-1}; nmr δ 0.78 (s), 1.11 (s), 2.03 (s), 2.13 (s), 4.50 (m), 4.63 (t, J = 8 cps), and 4.97 ppm (m).

Anal. Calcd for $C_{26}H_{40}N_2O \cdot H_2O$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.41; H, 7.99; N, 5.38.

Mixture (3:2) of 3β-(N-Acetylureido)-4β,5-oxido-5β-androstan-17β-ol Acetate (7b) and 3β-(N-Acetylureido)-4α,5-oxido-5α-androstan-17β-ol Acetate (8b).—A solution of 100 mg of the 3:2 mixture of 3β-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (**7b**) and its 4α,5α-epoxide isomer **8b** in 20 ml of acetone and 2.5 ml of 0.33 *N* sulfuric acid was kept at room temperature. After 16 hr, the 4α,5α-epoxide isomer had completely disappeared as judged by thin layer chromatography. After 48 hr, no evidence for the presence of the 4β,5β epoxide was obtained and the mixture was worked up as usual. Recrystallization from methanol afforded 49 mg of **3β-(N-acetylureido)-5α-androstane-4β,5,17β-triol 17-monoacetate (12a)**, mp 256–257°. An additional 16 mg of **12a** was obtained from the mother liquor on preparative thin layer chromatography on silica gel G with ethyl acetate.

3β-Ureido-4α,5-oxido-5α-androstan-17β-ol Acetate (8a).—A solution of 12 mg of 3β-ureido-4α,5-oxido-5α-androstan-17β-ol acetate (**8a**) in 2 ml of acetone and 0.21 ml of 0.33 *N* sulfuric acid yielded a precipitate immediately. The mixture was allowed to stand for 48 hr. The starting material was recovered unchanged after neutralization with sodium carbonate solution.

Registry No.—**1a**, 20446-36-0; **1b**, 20446-37-1; **2a**, 20446-38-2; **2b**, 20446-39-3; **3a**, 20446-40-6; **3b**, 20446-41-7; **4a**, 17320-53-5; **4b**, 20446-43-9; **5**, 20446-44-0; **6b**, 20446-45-1; **7b**, 20446-46-2; **8a**, 20446-47-3; **10a**, 20446-48-4; **10b**, 20446-49-5; **11a**, 20446-50-8; **11b**, 20446-51-9; **11c**, 20446-52-0; **12a**, 20446-59-7; **12b**, 20446-53-1; **13a**, 20446-54-2; **13b**, 20446-55-3; **14**, 20446-56-4; Δ⁴-androstene-3β,17β-diol 17-monoacetate, 13903-65-6; 3α-hydroxy-4β,5-oxide-5β-androstan-17-one, 20446-58-6.

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Synthesis and Reactions of Isomeric 3-Acetamido-4,5-oxidoandrostan-17β-ol Acetates[1a]

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The *cis* and *trans* isomers of 3α- and 3β-acetamido-4,5-oxidoandrostan-17β-ol acetate have been synthesized. Dilute acid treatment of the isomeric pair of 3α-acetamido epoxides **4** and **5** afforded the same product, 3α-acetamido-4α,5β,17β-triol monoacetate **9a**, whereas the 3β-acetamido epoxides **7** and **8** yielded the 4β,5α,17β-triol monoacetate **10a**. Backside participation of the acetamido group in the opening of the *trans*-oxirane ring in the epoxides has been observed.

The backside neighboring-group participation of acylamino groups in substitution and addition reactions *via* an intermediate oxazolidine is well known.[2] However, the participation of the acylamino group in the opening of a vicinal oxirane ring has not been widely studied. In the present study, the synthesis and dilute acid treatment of the four isomers of 3-acetamido-4,5-oxidoandrostan-17β-ol acetate have been investigated.

The 3-acetamido-4,5 epoxides of the androstane series were prepared essentially in the same manner as those of the cholestane series described by Ponsold.[3] The *cis* epoxides, 3α-acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (**4**) and the 3β-acetamido-4β,5β-oxide **7**, were prepared from the corresponding 3-acetamido-Δ⁴-androsten-17β-ol acetates **3** and **6** with *m*-chloroperoxybenzoic acid. The configuration of the oxirane ring was verified by the doublet of the C-4 proton centered at δ 3.17 (J = 4 cps) and 3.08 (J = 4 cps) for **4** and **7** respectively.[4] The strong directive effect of the acylamino group on *cis* epoxidation of cyclic allylic derivatives have been amply noted.[2a,5] Similar effect of the ureido group has been reported in the previous paper.[6]

The *trans* epoxides, 3α-acetamido-4β,5-oxide-5β-androstan-17β-ol acetate (**5**) and 3β-acetamido-4α,5α-oxide **8**, were prepared from the 3β- and 3α-hydroxy-Δ⁴-androstene derivatives, respectively. Cyclic allylic alcohols are epoxidized stereoselectively to the *cis* oxides;[7] the C-3 hydroxyl group is then substituted by an azido group with epimerization *via* the intermediate methanesulfonoxy derivative. The preparation of 3α-azido-4β,5-oxido-5β-androstan-17β-ol acetate (**1a**)

(1) (a) This investigation was supported by a grant from the American Cancer Society and grant CA-07304 from the National Cancer Institute, National Institutes of Health, U. S. P. H. S. (b) Visiting scientist, 1966–1967. Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France.

(2) (a) S. Winstein and R. Boschan, *J. Amer. Chem. Soc.*, **72**, 4669 (1950). (b) L. Goodman, S. Winstein and R. Boschan, *ibid.*, **80**, 4312 (1958). (c) A. Hasegawa and H. Z. Sable, *J. Org. Chem.*, **31**, 4154 (1966).

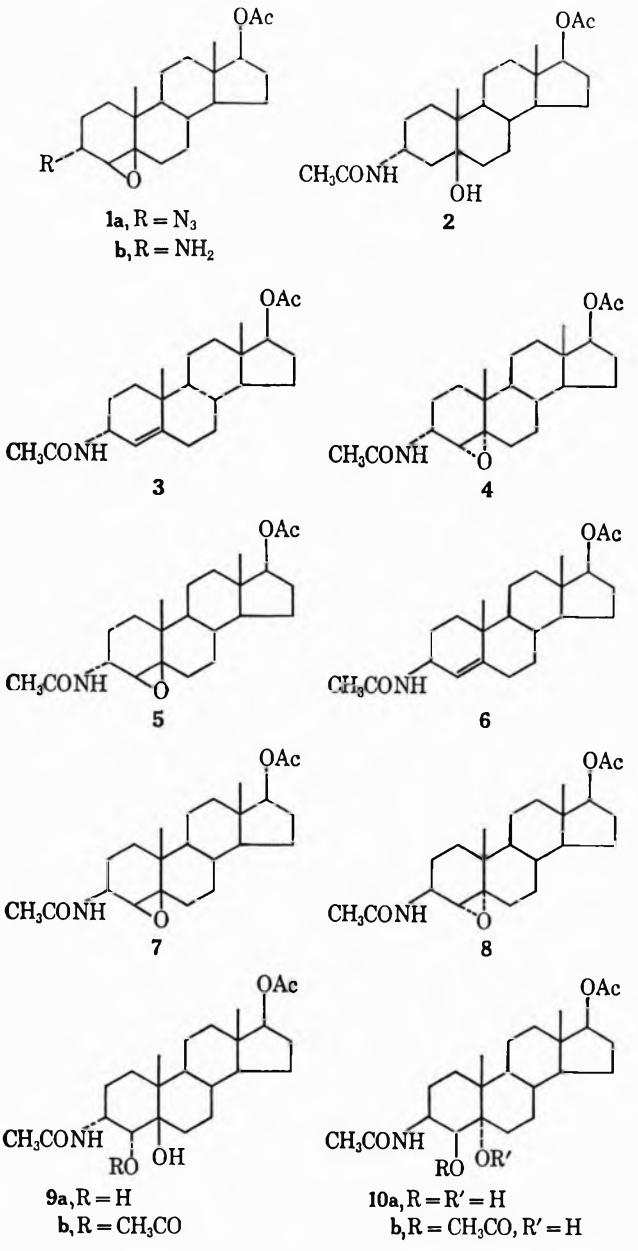
(3) K. Ponsold and J. Prakt, *Chemie*, **25**, 32 (1964).

(4) D. J. Collins and J. J. Hobbs, *Tetrahedron Lett.*, 623 (1963).

(5) K. Ponsold and W. Preibsch, *J. Prakt. Chem.*, **25**, 26 (1964).

(6) D. K. Fukushima, M. Smulowitz, J. S. Liang, and G. Lukacs, *J. Org. Chem.*, 2702 (1969).

(7) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).



and its isomer, 3β-azido-4α,5α oxide, in this manner has been described in the previous paper.[6] The azido groups were reduced with hydrazine hydrate in the presence of Raney nickel, and the amines acetylated to give 3α-acetamido-4β,5-oxido-5β-androstan-17β-ol acetate (**5**) and the 3β-acetamido-4α,5α oxide **8**. The *trans* configuration of the oxirane ring was verified by the singlet of the C-4 proton, δ 2.88, in both **5** and **8**.

3α-Amino-Δ^4 steroids are formed in small amounts by lithium aluminum hydride reduction of the corresponding unsaturated oximes;[8] the β epimer is the major product. In order to prepare large quantity of 3α-acetamido-Δ^4-androsten-17β-ol acetate (**3**) for the formation of the *cis* epoxide **4**, a stereoselective synthesis was conceived. 3α-Azido-4β,5-oxido-5β-androsten-17β-ol acetate (**1a**), an intermediate in the *trans* ureido and acetamido epoxides, was reduced with lithium aluminum hydride to the 3α-amino-5α-hydroxy derivative which was acetylated to give 3α-acetamido-5β-androstane-5,17β-diol 17-monoacetate (**2**). Dehydration of the 5β-hydroxyl group was achieved with thionyl chloride, leading to 3α-acetamido-Δ^4-androsten-17β-ol (**3**). The appearance of a doublet centered at δ 5.27 (J = 5 cps) demonstrated that the unsaturation was at 4,5 and that the proton at C-3 was in the equatorial β orientation. The Δ^4-3β-acetamido epimer **6** was prepared from testosterone oxime. Joska and Sorm[9] described the reduction of this oxime with zinc and acetic acid to a 3-amino-Δ^4-androsten-17β-ol, but these authors did not assign the orientation of the 3-amino groups. In a recent study it was demonstrated that this reduction led to the Δ^4-3β-amino epimer.[10] In the present study, the reduction product of testosterone oxime was acetylated and the product isolated as 3β-acetamido-Δ^4-androsten-17β-ol acetate (**6**). The vinyl C-4 proton of **6** appeared as a narrow multiplet centered at δ 5.20, affording evidence of the 3α-axial proton.

Ponsold[3] recently synthesized the four isomers of 3-acetamido-4,5-oxido cholestane. The acid cleavage of the *trans* acetamido epoxides, 3β-acetamido-4α,5-oxido-5α-cholestane and 3α-acetamido-4β,5-oxido-5β-cholestane, in which participation by the acetamido group would be expected, was not studied. Instead, the author treated the corresponding crude amino epoxide derived from the hydrazine hydrate reduction of the 3-azido-4,5-oxidocholestanes with 10% perchloric acid in dioxane at reflux for 1 hr. The products were partially acetylated and reported to be 3β-acetamido-4ξ,-5ξ-dihydroxycholestane and 3α-acetamido-4ξ,-5ξ-dihydroxycholestane. The orientation of the hydroxyl groups was not assigned. When the two *cis* epoxides, 3β-acetamido-4β,5-oxido-5β-cholestane and 3α-acetamido-4α,5-oxido-5α-cholestane, were opened with 2% sulfuric acid in acetone at reflux for 1 hr, two different 3-acetamido-4ξ,5ξ-dihydroxycholestanes were obtained. The assignment of the orientation of the hydroxyl groups were also not made in these compounds.

In order to get a clearer picture of the effect of the acetamido group on the cleavage of the vicinal oxirane ring, the four isomers of 3-acetamido-4,5-oxido-androstan-17β-ol acetate were treated with 0.2 N sulfuric acid in acetone at room temperature (22°). 3β-Acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (**8**) and its *cis* isomer, 3β-acetamido-4β,5β oxide **7**, gave the same product, 3β-acetamido-5α-androstane-4β,5,17β-triol 17-monoacetate (**10a**). The β orientation of the C-4 hydroxyl group was assigned from the nmr spectra of the triol monoacetate **10a** and the 4,17-diacetate **10b**; the signals of the C-19 methyl protons appeared downfield at δ 1.08 and 1.10, respectively, consistent with the presence of a 4β substituent. 3α-Acetamido-4β,5-oxido-5β-androstan-17β-ol acetate (**5**) and its *cis* isomer, 3α-acetamido-4α,5α oxide **4**, also gave a single product, 3α-acetamido-5β-androstane-4α,5,17β-triol 17-monoacetate (**9a**). The chemical shifts of the C-19 methyl protons in **9a** and the 4,17-diacetate **9b**, δ 0.92 and 0.97 respectively, provided evidence for the α orientation of the substituent at C-4. The oxirane ring can open *trans* diaxially in two directions. Several factors influence the direction of the cleavage: backside participation by the vicinal acetamido group,[3] electronegativity of the acetamido group,[2c,11] and the greater stability of a tertiary car-

(8) K. Ponsold and W. Preibsch, *J. Prakt. Chem.*, **23**, 173 (1964).

(9) J. Joska and F. Sorm, *Coll. Czech. Comm.*, **21**, 754 (1956).

(10) H. Kaufmann and D. K. Fukushima, *J. Org. Chem.*, **32**, 1846 (1967).

(11) R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Amer. Chem. Soc.*, **80**, 2237 (1958).

bonium ion. The backside participation by the acetamido group is not possible in the *cis* epoxides **4** and **7**. The weakly electronegative acetamido group would destabilize the developing carbonium ion at C-4 in the transition state and the preferred opening would be at C-5 to give the products **9a** and **10a**. The opening of the oxirane ring in this direction would be further enhanced by the fact that the carbonium ion at C-5 is tertiary. In the *trans* epoxides **5** and **8**, the neighboring-group effect of the vicinal acetamido group on the opening of the epoxide ring through an oxazolidine intermediate is quite evident. Not only are **9a** and **10a** the expected products from backside participation, but the rates of cleavage of the *trans* epoxides are more than twice as great as those of the *cis* epoxides.

Experimental Section[12]

3α-Acetamido-Δ⁴-androsten-17β-ol Acetate (3).—A solution of 500 mg of 3α-azido-4β,5-oxido-5β-androsten-17β-ol acetate (**1a**)[6] in 200 ml of ether was added dropwise to 1.5 g of lithium aluminum hydride in 500 ml of ether. The mixture was refluxed overnight and the excess reagent destroyed with 10% sulfuric acid. The organic phase was washed with dilute acid. The aqueous phase was neutralized with base and extracted with ethyl acetate. The product was acetylated with acetic anhydride and pyridine and chromatographed on a thin layer of silica gel G in the system ethanol–ethyl acetate (1:19). The acetamido derivative, 240 mg, was eluted with methanol–methylene chloride. Recrystallization from acetone afforded **3α-acetamido-5β-androstane-5,17β-diol 17-monoacetate (2)**, mp 256–256.5°; $[\alpha]D$ 61.8°; tlc, R_f = 0.20 (methanol–ethyl acetate 1:9); ir 3400 (sh), 3340, 1735, 1675, 1650 (sh), 1555, 1250, 1033 cm^{-1}; nmr δ 0.80 (s), 0.93 (s), 1.95 (s), 2.03 (s), 4.05 (m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.48; H, 9.29; N, 3.46.

To a solution of 786 mg of the crude 3α-acetamido derivatives **2** in 40 ml of pyridine maintained at 5° was added dropwise 0.5 ml of thionyl chloride. After 20 min, the reaction mixture was poured into ice–water, extracted with ethyl acetate, and washed with water. Evaporation of the solvent gave 839 mg of substance, which was purified by column chromatography using silica gel H. Elution with ethyl acetate–cyclohexane (7:3) yielded 397 mg of **3α-acetamido-Δ⁴-androsten-17β-ol acetate (3)**. Recrystallization from acetone–hexane gave the analytical sample of **3**, mp 152.5–153°; $[\alpha]D$ 132°; tlc, R_f = 0.18 (ethyl acetate–cyclohexane 7:3); ir 3280 (sh), 3255, 1735, 1663, 1635, 1555, 1528, 1250, 1045 cm^{-1}; nmr δ 0.83 (s), 1.03 (s), 1.98 (s), 2.03 (s), 4.30 (m), 4.63 (t, J = 9 cps), 5.27 (d, J = 5 cps).

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 74.37; H, 9.57; N, 3.61.

3α-Acetamido-4α,5-oxido-5α-androstan-17β-ol Acetate (4).—A solution of 256 mg of 3α-acetamido-Δ⁴-androsten-17β-ol acetate (**3**) and 250 mg of *m*-chloroperoxybenzoic acid in 270 ml of methylene chloride was kept at room temperature overnight. A single product, 255 mg, was obtained as judged by thin layer chromatography. Recrystallization from acetone–petroleum ether afforded 135 mg of **3α-acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (4)**, mp 169–170.5°; $[\alpha]D$ 61.1°; tlc, R_f = 0.25 (ethanol–ethyl acetate 1:19); ir 3398, 1732, 1682, 1520, 1253, 1080, 1040, 1030, 1012 cm^{-1}; nmr δ 0.83 (s), 1.08 (s), 1.98 (s), 2.03 (s), 3.17 (d, J = 4 cps), 4.25 (m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{35}NO_4$: C, 70.91; H, 9.06; N, 3.60. Found: C, 71.19; H, 8.79; N, 3.61.

3α-Acetamido-4β,5-oxido-5β-androstan-17β-ol Acetate (5).—3α-Azido-4β,5-oxido-5β-androstan-17β-ol acetate (**1a**) (1.0 g) was reduced with hydrazine hydrate in the presence of Raney nickel as previously described.[3,6] The crude 3β-amine **1b** had the following chemical shifts: δ 0.83 (s), 1.05 (s), 2.03 (s), 2.75 (s), 3.21 (s), 4.63 (t, J = 9 cps). The amine, 839 mg, was acetylated with acetic anhydride and pyridine to give 963 mg of **3α-acetamido-4β,5-oxido-5β-androstan-17β-ol acetate (5)**. Recrystallization from acetone–petroleum ether and methanol yielded **5**, mp 197–199.5°; $[\alpha]D$ 42.6°; tlc, R_f = 0.24 (ethanol–ethyl acetate 1:19); ir 3265, 3070, 1738, 1640, 1555, 1248, 1048, 1025 cm^{-1}; nmr δ 0.83 (s), 1.05 (s), 2.00 (s), 2.03 (s), 2.88 (s), 4.00 (br m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{35}NO_4$: C, 70.91; H, 9.06; N, 3.60. Found: C, 70.43; H, 9.00; N, 3.44.

3β-Acetamido-4β,5-oxido-5β-androstan-17β-ol Acetate (7).—Testosterone oxime was reduced with zinc and acetic acid[9] and the resulting 3β-amino-Δ⁴-androsten-17β-ol was acetylated with pyridine and acetic anhydride to give **3β-acetamido-Δ⁴-androsten-17β-ol acetate (6)**. Recrystallization from methanol yielded **6**, mp 236–237°; $[\alpha]D$ −1.8°; tlc, R_f = 0.19 (ethyl acetate–cyclohexane 7:3); ir 3295, 1735, 1642, 1548, 1245, 1043 cm^{-1}; nmr δ 0.80 (s), 1.05 (s), 1.98 (s), 2.03 (s), 4.30 (m), 4.63 (t, J = 9 cps), 5.20 (n m).

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.44; N, 3.74. Found: C, 74.09; H, 9.26; N, 3.66.

A solution of 250 mg of 3β-acetamido-Δ⁴-androsten-17β-ol acetate (**6**) and 250 mg of *m*-chloroperoxybenzoic acid in 30 ml of methylene chloride was kept at room temperature overnight. A single product, 246 mg, was obtained as judged by thin layer chromatography. Recrystallization from ether–petroleum ether afforded 170 mg of **3β-acetamido-4,5-oxido-5β-androstan-17β-ol acetate (7)**, mp 127–129°; $[\alpha]D$ −9.4°, tlc, R_f = 0.34 (ethanol–ethyl acetate 1:19); ir 3300 (sh), 3260, 1738, 1655, 1635, 1545, 1248, 1045 cm^{-1}; nmr δ 0.82 (s), 1.03 (s), 1.98 (s), 2.03 (s), 3.08 (d, J = 4 cps), 4.40 (m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{35}NO_4$: C, 70.91; H, 9.06; N, 3.59. Found: C, 70.88; H, 9.37; N, 3.56.

3β-Acetamido-4α,5-oxido-5α-androstan-17β-ol Acetate (8).—Acetylation of the 3β amine[6] obtained by the reduction of 3β-azido-4α,5-oxido-5α-androstan-17β-ol acetate with hydrazine hydrate in the presence of Raney nickel afforded **3β-acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (8)**. Recrystallization from acetone–petroleum ether gave mp 229–233.5°; $[\alpha]D$ 13.1°; ir 3315, 1738, 1648, 1548, 1245, 1045, 1025, 535 cm^{-1}; nmr δ 0.82 (s), 1.13 (s), 2.00 (s), 2.03 (s), 2.88 (s), 4.00 (m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{35}NO_4$: N, 3.60. Found: N, 3.78.

Acid Treatment

3α-Acetamido-4α,5-oxido-5α-androstan-17β-ol Acetate (4).—A solution of 196 mg of 3α-acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (**4**) in 40 ml of acetone and 4 ml of 0.2 *N* sulfuric acid was kept at room temperature (22°) for 8 days, at which time approximately 20% of the starting material still remained as judged by thin layer chromatography. The reaction mixture was extracted with ethyl acetate and washed with dilute base and water. The extract was dried and the solvent was evaporated to give 190 mg of residue. Preparative thin layer chromatography on silica gel G in methanol–ethyl acetate (1:9) afforded 30 mg of starting material and 75 mg of a more polar product. Recrystallization of the latter from ethyl acetate afforded 63 mg of **3α-acetamido-5β-androstane-4α,5,17β-triol 17-monoacetate (9a)**, mp 268.5–271°, $[\alpha]D$ 48.8° (ethanol); tlc, R_f = 0.31 (methanol–ethyl acetate 1:9); ir 3630, 3365, 1740, 1655 (sh), 1630, 1245, 1045, 1025, 1015 cm^{-1}; nmr δ 0.78 (s), 0.92 (s), 1.95 (s), 2.03 (s), 3.67 (d, J = 3 cps), 4.17 (m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.53; N, 3.43. Found: C, 67.82; H, 9.27; N, 3.00.

Acetylation of 25 mg of 3α-acetamido-5β-androstane-4α,5,17β-triol 17-monoacetate (**9a**) with acetic anhydride and pyridine at room temperature for 2 days afforded 24 mg of 3α-acetamido-5β-androstane-4α,5,17β-triol 4,17-diacetate (**9b**). Recrystallization from acetone–petroleum ether yielded 15 mg of **9b**, mp 230–231°; ir 3450, 3330, 1738, 1715, 1645, 1550, 1270, 1250, 1045, 1039 cm^{-1}; nmr δ 0.80 (s), 0.97 (s), 1.90 (s), 2.03 (s), 2.15 (s), 4.50 (m), 4.63 (t, J = 9 cps), 5.17 (m).

3α-Acetamido-4β,5-oxido-5β-androstan-17β-ol Acetate (5).—A solution of 32 mg of 3α-acetamido-4β,5-oxido-5β-androstan-17β-ol acetate (**5**), in 5 ml of acetone and 0.5 ml of 0.2 *N* sulfuric acid was kept at room temperature (22°) overnight, after which time

(12) Melting points were determined on a micro hot stage and are corrected. Nmr spectra were obtained on a Varian A-60 instrument in deuteriochloroform with tetramethylsilane as internal standard; the chemical shifts are given in δ ppm. Optical rotations were determined in chloroform at 24° unless otherwise stated. Infrared spectra were determined on a Beckman IR-9 spectrophotometer in potassium bromide dispersion; br = broad, sm = small, sh = shoulder. Thin layer chromatography, tlc, was carried out on a 250-μ layer of silica gel GF at 24°.

no starting material remained. The reaction mixture, 26 mg, was recrystallized from ethyl acetate to give **3α-acetamido-5β-androstane-4α,5,17β-triol 17-monoacetate (9a)** identical with that obtained from the *cis*-3α-acetamido-4α,5α oxide **4**.

3β-Acetamido-4β,5-oxido-5β-androstan-17β-ol Acetate (7).—A solution of 168 mg of 3β-acetamido-4β,5-oxido-5β-androstan-17β-ol acetate (**7**) in 25 ml of acetone and 2.5 ml of 0.2 *N* sulfuric acid at room temperature for 4 days, after which time no starting material remained. Recrystallization of the reaction product, 160 mg, from methanol–ethyl acetate gave 88 mg of **3β-acetamido-5α-androstane-4β,5,17β-triol 17-monoacetate (10a)**, mp 290° dec, subl; $[\alpha]_D$ −15.6° (ethanol); tlc, R_f = 0.30 (methanol–ethyl acetate 1:9); ir 3430, 3355, 1730, 1716, 1648, 1632, 1523, 1250, 1038, 1023, 960, 945 cm^{-1}; nmr δ 0.75 (s), 1.08 (s), 1.87 (s), 1.98 (s) (deuteriochloroform and dimethyl sulfoxide-d_6).

Anal. Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.53; N, 3.43. Found: C, 67.52; H, 9.22; N, 3.47.

Acetylation of 48 mg of 3β-acetamido-5α-androstane-4β,5,17β-triol 17-monoacetate (**10a**) with acetic anhydride and pyridine at room temperature for 3 days afforded 48 mg of **3β-acetamido-5α-androstane-4β,5,17β-triol 4,17-diacetate (10b)**. Recrystallization from acetone–petroleum ether afforded **10b**, mp 312–313°; $[\alpha]_D$ −30.0° (ethanol); tlc, R_f = 0.58 (methanol–ethyl acetate 1:3); ir 3508, 3330, 1745, 1722, 1660, 1553, 1268, 1233, 1045, 1025 cm^{-1}; nmr δ 0.78 (s), 1.10 (s), 1.90 (s), 2.01 (s), 2.03 (s), 4.63 (br m), 5.02 (d, J = 4 cps).

Anal. Calcd for $C_{25}H_{39}NO_6$: C, 66.78; H, 8.74; N, 3.11. Found: C, 66.88; H, 8.89; N, 3.22.

3β-Acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (8).—A solution of 11 mg of 3β-acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (**8**) in 5 ml of acetone and 0.5 ml of 0.2 *N* sulfuric acid was kept at room temperature (22°) for 24 hr, after which time no starting material remained. Recrystallization from acetone–petroleum ether gave **3β-acetamido-5α-androstane-4β,5,17β-triol 17-monoacetate (10a)**, mp 300° dec, subl. The product was identical with that obtained by the dilute sulfuric acid treatment of the corresponding *cis*-3β-acetamido-4β,5β oxide **7**.

Registry No.—**2**, 20429-62-3; **3**, 20429-63-4; **4**, 20445-48-1; **5**, 20429-64-5; **6**, 20588-73-5; **7**, 20429-66-7; **8**, 20429-67-8; **9a**, 20429-68-9; **9b**, 20429-69-0; **10a**, 20429-70-3; **10b**, 20429-71-4.

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Polar and Steric Effects in Acyl Phosphate Monoanion and Dianion Reactions

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The rate constants for hydrolysis of a series of aliphatic acyl phosphates have been determined at 60°. Complete pH–rate profiles for three of the derivatives, isobutyryl, trimethylacetyl, and 3,3-dimethylbutyryl phosphate, were obtained as well as the monoanion and dianion hydrolytic rate constants for isovaleryl phosphate. The values of ΔS^* were uniformly close to zero, consistent with the postulated unimolecular mechanism of hydrolysis of acyl phosphates. A decrease in the rate of hydrolysis was observed for the monoanion and dianion reactions as steric bulk and electron donation in the acyl group, as measured by the Taft σ^* constants, were increased. Second-order rate constants for reaction of pyridine with the monoanions and dianions were also correlated with σ^* constants. The ρ^* for k_{pyr} (monoanion) was +2.0 and for k_{pyr} (dianion) was +6.1. Imidazole and morpholine did not catalyze the hydrolysis of trimethylacetyl phosphate or 3,3-dimethylbutyryl phosphate.

Detailed mechanistic studies of acyl phosphate dianion,[2–4] monoanion,[2–4] and acid-catalyzed[5] hydrolysis reactions have been carried out. Acetyl phosphate monoanion and dianion hydrolysis takes place with unimolecular decomposition to metaphosphate,[4] but reaction with various nucleophiles can be observed.[3,4] Various tertiary amines and pyridine will attack at phosphorus, but imidazole and primary amines attack at the carbonyl group. There seems to be no relationship between the pK_a of the attacking amine and the position of attack.[6] As a consequence, it was thought that steric influences might be of extreme importance in these reactions. A study of the effects of increased steric size of the acyl group in acyl phosphate reactions was therefore undertaken.

Experimental Section

Materials.—Dilithium acetyl phosphate was purchased from CalBiochem Corp. and was used without further purification. All of the remaining aliphatic acyl phosphates were prepared by the method of Lipmann and Tuttle,[7] and isolated as the disodium salts as previously reported.[5] β-Chloropropionyl phosphate was analyzed as the disilver salt. *Anal.* Calcd for $C_3H_4ClO_5PAg_2$: C, 8.96; H, 1.00; P, 7.70. Found: C, 8.79; H, 0.89; P, 7.53. The acyl phosphates were stored in a desiccator at −4°, and fresh samples were prepared periodically.

Dioxane was purified by the method of Fieser[8] and was stored frozen. Deuterium oxide (99.8%) was obtained from Bio-Rad Laboratories. The remainder of the chemicals were reagent grade.

Kinetic Measurements.—The hydroxamic acid assay was used exclusively for the kinetic runs as described by Di Sabato and Jencks.[4] All rates were run in duplicate to at least 75% completion, with less than 5% deviation between the two rate constants in all cases. Each run was initiated by adding the acyl phosphate to the preequilibrated buffer solution making it approximately 2×10^{-3} *M* in acyl phosphate. Rate constants did not change when the acyl phosphate concentration was varied 50%. At appropriate time intervals, aliquots were removed and introduced into the hydroxylamine solution. The resulting mixture was then stoppered and shaken. Development time for complete formation of the hydroxamate was experimentally determined for each compound. At least nine points were employed for a rate determination, and infinity points were taken at ten half-lives. Temperature was controlled to ±0.1° by a Princo thermoregulator in a stirring-water bath. Pseudo-first-order rate constants (k_{obsd}) were calculated with an Oliuetti-Underwood Programma 101 using a computer program designed to calculate a least-

(1) This study represents part of the work to be submitted by D. R. Phillips in partial fulfillment of the requirements for the Ph.D. degree, University of Southern California.

(2) D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **74**, 2286 (1952).

(3) J. H. Park and D. E. Koshland, Jr., *J. Biol. Chem.*, **233**, 986 (1958).

(4) G. Di Sabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4393, 4400 (1961).

(5) D. R. Phillips and T. H. Fife, *ibid.*, **90**, 6803 (1968).

(6) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966.

(7) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **153**, 571 (1944).

(8) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 284.

squares evaluation of the slope and intercept of a plot of ln $[(OD_0 - OD_\infty)/OD_t - OD_\infty)]$ *vs.* time.

Results

Rate constants for hydrolysis of the acyl phosphates at 60° and at various pH values are given in Table I. The pH–rate profiles for three branched acyl phosphates are presented in Figure 1. The lines are theoretical and were calculated from eq 1 employing the values of $k_{monoanion}$, $k_{dianion}$, and the second-order rate constant

$$k_{obsd} = k_{monoanion}\frac{(AcP^-)}{(AcP)_{total}} + k_{dianion}\frac{(AcP^{2-})}{(AcP)_{total}} + k_{OH}\frac{(AcP^{2-})(OH^-)}{(AcP)_{total}} \quad (1)$$

for hydroxide ion catalysis, k_{OH}, in Table II. The pK_a values were determined by measuring the pH of a half-neutralized solution of the disodium salt. The experimental pK_2 values at 25° are 4.86, 5.02, and 5.11 for isobutyryl phosphate, trimethylacetyl phosphate, and 3,3-dimethylbutyryl phosphate, respectively. These values were used as pK_2 of the compounds at 60°. pK_1 for the compounds could not be determined by this method due to rapid hydrolysis of all the compounds below pH 2. For this reason, theoretical lines were not continued below pH 3.

TABLE I

OBSERVED RATE CONSTANTS FOR HYDROLYSIS OF ALIPHATIC ACYL PHOSPHATES AT VARIOUS pH VALUES (60° AND μ = 0.6 WITH KCl)

No.	Acyl group[b]	Buffer[a] (*M*)	pH 60°	$k_{obsd} \times 10^3$ min^{-1}
1	Isobutyryl	HCl (0.299)		159.4
		HCl (0.101)		93.5
		HCl	1.98	61.7
		Formate	3.57	56.9
		Acetate	5.02	36.3
		Imidazole	5.83	20.4
		Tris	8.83	14.5
		KOH	10.60	16.3
		KOH (0.0679)		82.2
2	Trimethylacetyl	HCl (0.497)		85.3
		HCl (0.299)		65.3
		HCl (0.101)		47.9
		HCl	1.98	37.7
		Formate	2.85	35.4
		Formate	3.48	33.7
		Acetate	4.61	28.1
		Acetate	5.02	22.8
		Acetate	5.51	13.7
		Imidazole	5.65	11.5
		Imidazole	6.61	3.97
		Imidazole	7.63	3.04
		Tris	8.83	3.14
		KOH (0.0679)		10.2
		KOH (0.170)		21.2
		KOH (0.424)		51.9
		KOH (0.501)		75.8
3	3,3-Dimethylbutyryl	HCl (0.299)		188.6
		HCl (0.101)		78.4
		HCl	1.98	64.6
		Formate	3.48	63.7
		Acetate	4.61	46.5
		Imidazole	5.65	15.7
		Imidazole	6.61	8.98
		Tris	8.83	8.78
		KOH	10.66	8.68
		KOH (0.0679)		15.6
		KOH (0.170)		26.7
		KOH (0.424)		48.8
		KOH (0.501)		61.0

[a] Buffer concentration was 0.05 *M* except where indicated. [b] Registry numbers are as follows: 1, 19926-78-4; 2, 19926-68-2; 3, 19926-69-3.

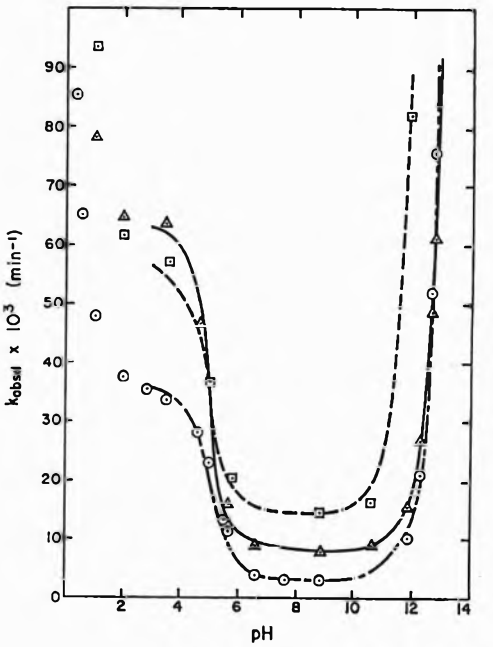


Figure 1.—Plot of k_{obsd} at 60° for hydrolysis of acyl phosphates *vs.* pH: ⊡, isobutyryl phosphate; ⊙, trimethylacetyl phosphate; △, 3,3-dimethylbutyryl phosphate.

TABLE II

RATE CONSTANTS FOR SPONTANEOUS AND HYDROXIDE ION CATALYZED HYDROLYSIS OF ACYL PHOSPHATES AT 60° (μ = 0.6 WITH KCl)

No.	Acyl group[b]	$k_{monoanion} \times 10^3$ min^{-1}	$k_{dianion} \times 10^3$ min^{-1}	k_{OH}, l. mol^{-1} min^{-1}
1	Acetyl	128.0[a]	58.5[a]	15.7
2	Isobutyryl	56.9	14.5	1.0
3	Isovaleryl	57.6	16.9	
4	Trimethylacetyl	36.0	3.14	0.115
5	3,3-Dimethylbutyryl	63.7	8.78	0.10

[a] Value calculated employing the activation energy reported in ref 4. [b] Registry numbers are as follows (monoanion and dianion, respectively): 1, 19926-70-6, 19926-71-7; 2, 19926-72-8, 19926-73-9; 3, 19926-74-0, 19926-75-1; 4, 19926-76-2, 19926-77-3; 5, 19926-43-4, 19926-44-4.

The rate constants at various temperatures for trimethylacetyl phosphate and 3,3-dimethylbutyryl phosphate are reported in Table III. Activation parameters are also tabulated, calculated at 39.0°. For comparative purposes, the literature values for acetyl phosphate[4] are presented.

The effects of changing ionic strength and organic solvent can be seen in Table IV. For monoanion and dianion reactions of both trimethylacetyl phosphate and 3,3-dimethylbutyryl phosphate the rate is slightly increased by changing the ionic strength from 0.6 to 2.0 *M*. Similar effects are noted when the solvent is changed from water to 50% dioxane–water. The rate constant for hydrolysis of the dianion of trimethylacetyl phosphate is, however, doubled in 50% dioxane–H_2O and a rate decrease is observed for the dianion of 3,3-

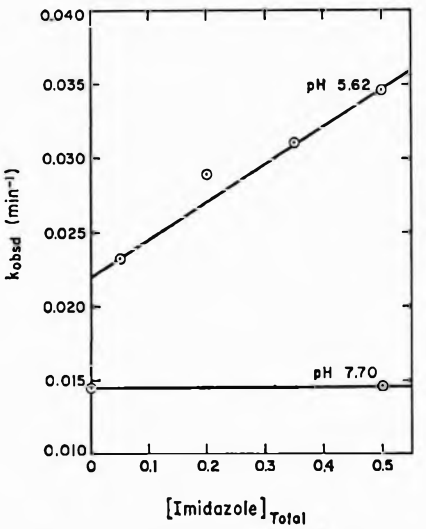


Figure 2.—Plot of k_{obsd} for hydrolysis of isobutyryl phosphate at 60° and μ = 0.6 *vs.* total imidazole concentration (moles per liter).

TABLE III

RATE CONSTANTS FOR THE HYDROLYSIS OF ACYL PHOSPHATES AT VARIOUS TEMPERATURES AND THE ACTIVATION PARAMETERS CALCULATED AT 39.0°

Acyl group	Temp, °C	k_{obsd}, min^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
Monoanion				
Trimethylacetyl[a]	25	0.00055	22.9 ± 0.3	−4.4 ± 0.8
	60	0.0337		
	70	0.107		
	80	0.286		
3,3-Dimethylbutyryl[b]	40	0.00617	23.4 ± 0.1	−2.0 ± 0.4
	50	0.0214		
	60	0.0637		
	65	0.111		
	70	0.184		
Acetyl	39	0.0127		
Acetyl	60	0.128[c]	22.5[d]	−3.6[d]
Isobutyryl[b]	60	0.0569		
Isovaleryl[b]	60	0.0576		
Chloropropionyl[b]	39	0.00512		
Dianion				
Trimethylacetyl[e]	55	0.00205	27.7 ± 0.5	+5.4 ± 1.3
	60	0.00314		
	65	0.00736		
	70	0.0107		
	75	0.0222		
	80	0.0425		
3,3-Dimethylbutyryl[e]	50	0.00274	25.7 ± 0.1	+1.1 ± 0.5
	60	0.00878		
	65	0.0170		
	70	0.0304		
	75	0.0508		
Acetyl	39	0.0056		
Acetyl	60	0.0585[e]	25.4[d]	+3.7[d]
Isobutyryl[e]	60	0.0145		
Isovaleryl[e]	60	0.0169		
Chloropropionyl	39	0.00814		

[a] Rates were measured at pH 3.48, where the monanion is the predominant species, in 0.05 *M*, formate buffer, μ = 0.6 with KCl. [b] Rates were measured at pH 3.57, where the monoanion is the predominant species, in 0.05 *M* formate buffer, μ = 0.6 with KCl. [c] Value calculated from activation energy reported in ref 4. [d] Reference 4. [e] Rates were measured at pH 8.83 in 0.05 *M* Tris buffer, μ = 0.6 with KCl.

dimethylbutyryl phosphate.[9] The rate constants for hydrolysis of the monoanion and dianion of trimethylacetyl phosphate in deuterium oxide were also measured and are also reported in Table IV. Comparing these values to those determined in H_2O, D_2O solvent isotope effects (k_{D_2O}/k_{H_2O}) of 1.27 and 1.10 were obtained.

(9) It should be noted that the pK_2 values of the acyl phosphates may be considerably different in the mixed solvent than in water. Also, the effect of solvent on the rate constant includes its effect on the ratio of activity coefficients of the initial state and the transition state. It is probable that the observed differences between trimethylacetyl and 3,3-dimethylbutyryl phosphate indicate that these ratios are affected differently upon going from water to 50% dioxane–H_2O.

TABLE IV

HYDROLYSIS OF TRIMETHYLACETYL PHOSPHATE AND 3,3-DIMETHYLBUTYRYL PHOSPHATE WHEN SUBJECTED TO VARIOUS SOLVENT CONDITIONS AT 60° IN 0.05 *M* BUFFER AT IONIC STRENGTH 0.6 WITH KCl, EXCEPT WHERE INDICATED

Acyl group	μ	Buffer	Solvent	pH or pD[a]	k_{obsd}, min^{-1}
Trimethylacetyl	0.6	Formate	D_2O	3.30	0.0438
	2.0	Formate	H_2O	3.47	0.0390
	0.6	Formate	50% dioxane–H_2O	4.57	0.049
	0.6	Tris	D_2O	7.93	0.00345
	2.0	Tris	H_2O	8.82	0.00416
	0.6	Tris	50% dioxane–H_2O	8.96	0.00866
3,3-Dimethylbutyryl	2.0	Formate	H_2O	3.47	0.0655
	0.6	Formate	50% dioxane–H_2O	4.57	0.0814
	2.0	Tris	H_2O	8.82	0.0102
	0.6	Tris	50% dioxane–H_2O	8.96	0.00582

[a] pD values were determined from pH meter readings employing the glass electrode correction formula of T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

The second-order rate constants for pyridine catalysis are presented in Table V and show a decrease for the more highly branched compounds. No detectable reaction could be observed between imidazole or morpholine and the branched acyl phosphates. There was no catalysis at pH 5.65, 6.12, or 7.50 by 0.5 *M* imidazole nor at pH 8.10 by 0.5 *M* morpholine. However, a pronounced imidazole catalysis was observed in the case of isobutyryl phosphate at pH 5.62 where the monoanion would be at high concentration although no catalysis was observed at pH 7.70 where little monoanion would be present. A plot of k_{obsd} *vs.* total imidazole concentration is shown for isobutyryl phosphate in Figure 2.

TABLE V

SECOND-ORDER RATE CONSTANTS FOR PYRIDINE CATALYSIS OF THE HYDROLYSIS OF ACYL PHOSPHATES AT 60.0° AND μ = 0.60 WITH KCl

	k, l. mol^{-1} min^{-1}		
Acyl group	Pyridine[a]	Imidazole	Morpholine[b]
Monoanion			
Acetyl	0.163[c]		
Isobutyryl	0.114[c]	1.68	
Trimethylacetyl	0.0375[c]	*b*	
3,3-Dimethylbutyryl	0.0590[c]	*b*	
Dianion			
Acetyl	0.0412[d]		
Isobutyryl	0.0060[d]	*b*	*b*
Trimethylacetyl	0.00060[d]	*b*	*b*
3,3-Dimethylbutyryl	0.00134[d]	*b*	*b*

[a] Rate constants determined at four concentrations from 0.5 to 0.05 *M* amine. [b] No detectable reaction in 0.5 *M* amine. [c] In pyridine buffer, pH 5.22. [d] In 0.05 *M* Tris buffer, pH 8.89.

The pK_a of pyridine was determined at 60° and an ionic strength of 0.6 by half-neutralization and was found to be 4.75. The pK_a of imidazole at 60° was found to be 6.58 by extrapolation of values determined at a number of other temperatures.[10]

(10) J. B. Milstien and T. H. Fife, *J. Amer. Chem. Soc.*, **90**, 2164 (1968).

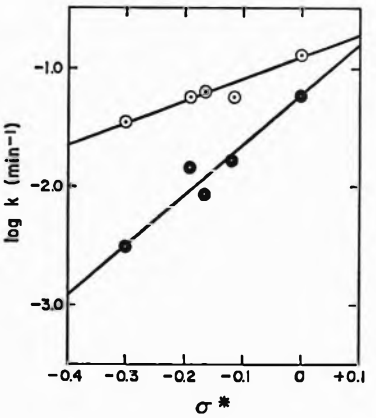
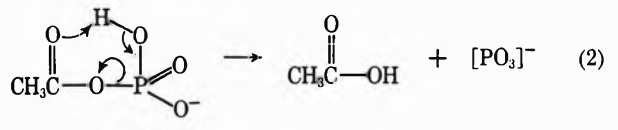


Figure 3.—Plot of log k at 60° for hydrolysis of acyl phosphate monoanions (⊙) and dianions (●) *vs.* σ^*.

Discussion

On the basis of present evidence it is likely that the monoanion and the dianion of acetyl phosphate hydrolyze by the unimolecular mechanisms 2 and 3, respectively.[4] The D_2O solvent isotope effect (k_{D_2O}/k_{H_2O} = 0.94) for acetyl phosphate monoanion is in accord with an internal proton transfer that is either complete or partially rate determining.[11,12] Likewise, in the present study this ratio for trimethylacetyl phosphate monoanion was found to be 1.27. Salt effects and solvent effects are also similar for these compounds.



In general, increased branching decreases the rate of both monoanion and dianion hydrolysis. This rate decrease could be due to either steric or electronic factors, or to a combination of both. As seen in Table III, the entropies of activation for the branched compounds and acetyl phosphate are very similar, with ΔS^* for the monoanion of trimethylacetyl phosphate and the dianion of 3,3-dimethylbutyryl phosphate being only slightly more negative than the corresponding values for acetyl phosphate. Steric hindrance to solvation could lead to large rate reductions with increasing size of the acyl group, but it can be concluded from the similar entropies of activation that this is not an important factor.

Inductive effects in the aliphatic series could be quite important in producing the rate retardations observed for the highly branched compounds. Di Sabato and Jencks[4] found that the dianion rate of substituted benzoyl phosphates is facilitated by electron-withdrawing substituents (ρ = +1.2), while the hydrolysis of monoanions is relatively insensitive to electron withdrawal (ρ = −0.2). When the logarithms of the rate constants at 60° for the aliphatic series are plotted *vs.* the Taft σ^* constants,[13] a straight line relationship is obtained as shown in Figure 3. The value of ρ^* is +1.8 for the monoanion hydrolysis reaction and +4.3 for the dianion reaction. Thus, while the order of reactivity is in accord with inductive effects being of great importance, still the large magnitude of the ρ^* values might indicate that steric factors are indeed of some importance. Data obtained at 39° were also plotted *vs.* σ^* in order to incorporate more compounds.[14] This plot is shown in Figure 4. It can be seen that the same general relationship between the alkyl-substituted compounds is obtained at 39° as at 60°. However, inclusion of compounds having acyl groups with positive σ^* values, benzoyl, β-chloropropionyl, and chloroacetyl, makes it appear that the actual ρ^* values are approximately zero for the monoanion reaction and +2.2 for the dianion reaction. The large apparent ρ^* values when only alkyl-substituted derivatives are considered are due mainly to acetyl phosphate hydrolyzing considerably faster than expected in comparison with the other compounds. A possible explanation is that the $\rho^*\sigma^*$ plots are actually curved (dotted line in Figure 4) in which case the importance of steric factors in the hydrolytic reaction would be evident since linear $\sigma\rho$ plots are obtained with the benzoyl phosphates.[4]

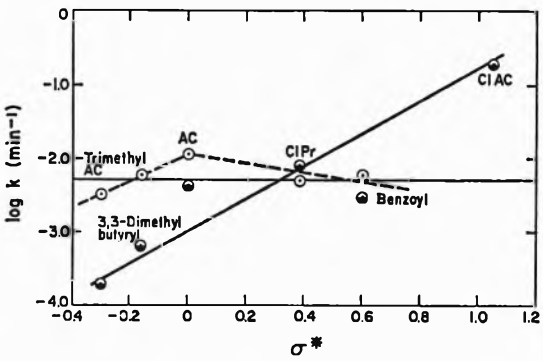


Figure 4.—Plot of log k at 39° for hydrolysis of acyl phosphate monoanions (⊙) and dianions (◒) *vs.* σ^*. Constants for benzoyl phosphate were from ref 4.

When the second-order rate constants, k_{pyr} (monoanion) and k_{pyr} (dianion) for the reaction of the acyl phosphates with pyridine at 60° are plotted against Taft's σ^* constants (Figure 5), reasonably straight lines are obtained with large ρ^* values of +2.0 and +6.1. Steric hindrance to approach of the nucleophile should only account for a part of the differences in the second-order rate constants since pyridine has been shown to attack predominantly at phosphorus when it reacts with either the monoanion or the dianion of acetyl phosphate.[3,4] Thus, two atoms, oxygen and the carbonyl carbon, separate the reaction center from the point of branching thereby reducing greatly the magnitude of any steric effect. This can be illustrated by the similar Taft E_s constants[13] for the groups—n-C_3H_7 (−0.36), i-C_5H_{11} (−0.35), t-$C_4H_9CH_2CH_2$ (−0.34)—although in this comparison replacement of the carbonyl carbon and the oxygen by two saturated carbon atoms may

(11) A. J. Kirby and A. G. Varvoglis, *J. Amer. Chem. Soc.*, **89**, 415 (1967).

(12) Solvent isotope effects of about unity might be expected if a zwitterionic species was involved as an intermediate since D_2O would have compensating effects on the equilibrium concentrations of monoanion and the zwitterion.

(13) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 556.

(14) For chloroacetyl phosphate, $k_{dianion}$ is 0.190 min^{-1} at 39.0° and μ = 0.6. Elemental analysis on this compound was not possible due to its rapid partial hydrolysis in aqueous solutions during the isolation procedure.

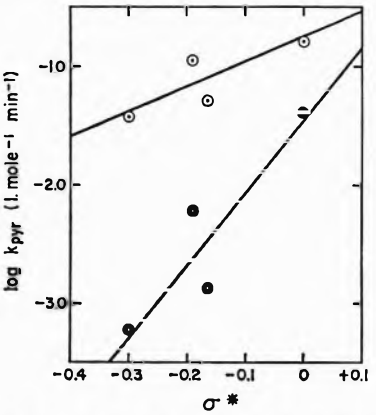
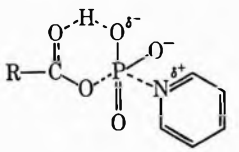


Figure 5.—Plots of log k_{pyr} at 60° for acyl phosphate monoanions (⊙) and dianions (●) *vs.* σ^*.

not be exact. In the case of β-glycerol phosphate[15] the C–O–P bond distance is similar to the C–C–C distance, but with acyl phosphates the C–O–P distance could be shorter because of resonance interaction between oxygen and the carbonyl group. It is therefore possible that steric and inductive effects are both affecting the nucleophilic attack of pyridine.

The value of ρ^* for the reaction of acyl phosphate dianions with pyridine is larger than for the dianion hydrolytic reaction. Inductively electron-donating groups would not only make it more difficult for the carboxylate anion to leave, as in the hydrolytic reaction, but would also impede the attack of pyridine. Also, ρ^* for the pyridine-catalyzed hydrolysis of acyl phosphate dianions is much larger than the ρ^* for the pyridine catalysis of acyl phosphate monoanion hydrolysis. This observation can be attributed to a proton-transfer step taking place in the monoanion reaction with pyridine, as in the hydrolytic reaction.[4] Thus the probable transition state for the pyridine reaction with the monoanion would appear as shown in I. A pentacovalent intermediate could also be forming, and the kinetic data do not eliminate this possibility.



I

Pyridine has been shown not to catalyze the hydrolysis of phenyl phosphate monoanions,[16] although weak catalysis was observed in the hydrolysis of *p*-nitrophenyl phosphate dianion.[17] The facile pyridine reaction with the monoanion of acyl phosphates may be due to the ease of proton transfer with these compounds, and in addition, the low pK_a of the carboxyl leaving group, compared with 9.9 for phenol and 7.1 for *p*-nitrophenol, should greatly facilitate the reaction. These differences in pK_a undoubtedly strongly influence the pyridine reaction with the dianion of acyl phosphates since proton transfer does not, of course, take place in the dianion reaction.

Reactions of acyl phosphates which occur at the carbonyl carbon center are subject to normal steric effects. Imidazole and morpholine, two amine bases which attack at the carbonyl of acetyl phosphate,[4] show no observable reaction with trimethylacetyl phosphate and 3,3-dimethylbutyryl phosphate. Hydroxide ion, a much smaller nucleophile, will catalyze the hydrolysis of the dianionic species of these two compounds, although at a reduced rate in comparison with acetyl phosphate, the relative rate ratios being acetyl 1.0, trimethylacetyl 0.0073, and 3,3-dimethylbutyryl phosphate 0.0064. The fact that imidazole is a good catalyst for the hydrolysis of isobutyryl phosphate at a pH value where the monoamion is at high concentration, but not at higher pH, indicates that the monoanion is the kinetically significant species with attack by the free base of imidazole taking place. A nucleophilic reaction involving the conjugate acid of imidazole and the dianion would not be expected on chemical grounds.[4] The monoanionic species should be considerably more reactive than the dianion in reactions involving attack of a nucleophile at the carbonyl since HPO_4^{2-} is a much better leaving group than PO_4^{3-}.

An important observation is that inductive and/or steric influences at the carbonyl carbon will not change the position of attack of amines. The relatively rapid acylation of imidazole by acetyl phosphate could possibly conceal a slower reaction at phosphorus, but the present data show that this is not the case. Imidazole will not preferentially attack at phosphorus even when relatively high electron density (trimethylacetyl phosphate) or large steric hindrance (3,3-dimethylbutyryl phosphate) occurs at the carbonyl carbon, no catalysis by imidazole being detected with those compounds. It is not clear why imidazole is such a poor nucleophile toward phosphorus in these compounds in comparison to pyridine.

Some enzymes which exhibit acyl phosphatase activity have histidine at their active sites. In the case of glyceraldehyde-3-phosphate dehydrogenase,[3] it has been suggested that histidine might attack at the carbonyl, as observed in the nonenzymatic reaction of imidazole with acetyl phosphate. However, when succinyl phosphate is utilized by succinic thiokinase, the acyl phosphate transfers the phosphoryl group to the enzyme to form a phosphoryl enzyme.[18] The phosphorylated group in the enzyme has been identified as 3-phosphohistidine.[18,19] The chemical data indicate that a phosphoryl group cannot be transferred directly from an acyl phosphate to histidine. Transfer must then be mediated through an intermediate carrier or else the enzyme, in an unknown manner, is inducing a change in mechanism from that normally seen in the nonenzymatic reactions.

Acknowledgment.—This study was supported by a research grant from the National Institutes of Health. Support for D. R. Phillips was provided by National Institutes of Health Research Training Grant GM-197.

(15) M. Ul-Haque and C. N. Caughlan, *J. Amer. Chem. Soc.*, **88**, 4124 (1966).
(16) J. D. Chanley and E. Feageson, *ibid.*, **85**, 1181 (1963).
(17) A. J. Kirby and W. P. Jencks, *ibid.*, **87**, 3209 (1965).
(18) J. S. Nishimura, *Biochemistry*, **6**, 1094 (1967).
(19) D. E. Hultquist, R. W. Moyer, and P. D. Boyer, *ibid.*, **5**, 322 (1966).

Hofmann Elimination of Heterocycles Containing Bridgehead Hydrazines. I. 2,6-Benzodiazonine and Dibenzo[*c*,*h*][1,6]diazecine[1a] Derivatives

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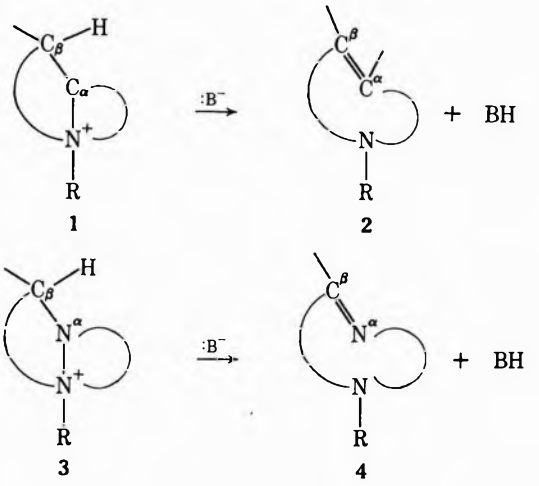
Received October 25, 1968

Treatment of the methyl halide salts of the bridgehead hydrazines, 5-(*p*-chlorophenyl)-2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazine (**9**) and 5,7,12,14-tetrahydrophthalazino[2,3-*b*]phthalazine(**19**), with sodium methoxide–methanol gave the medium-sized heterocycles 1-(*p*-chlorophenyl)-6-methyl-4,5,6,7-tetrahydro-3H-2,6-benzodiazonine (**10**) and 6-methyl-5,6,7,14-tetrahydrodibenzo[*c*,*h*][1,6]diazecine (**22**). The lithium aluminum hydride reduction of 2-(4-chlorobutyl)-4-*p*-chlorophenylphthalazin-1(2H)-one (**5e**) resulted in an unusual N–N cleavage and ring formation to give 2-pyrrolidinomethylbenzhydrylamine (**16**).

The base elimination (Hofmann elimination[2]) of heterocycles containing a quaternary bridgehead nitrogen atom has been demonstrated[3] to be a useful technique for preparing medium-sized nitrogen-containing rings. In a simplified model system **1** this reaction occurs by the removal of a proton from a carbon atom β to the quaternary nitrogen atom to give the unsaturated amine **2**. In all cases reported[2,3] to date the α atom in this system has been carbon (**1**, C_α) and the resultant product has been an olefin amine (**2**, $C_\beta{=}C_\alpha$). Replacement of the α atom in this system by N (**3**, N_α) suggests that this reaction can be modified to produce imino amines such as **4**.



If such a transformation could be accomplished this would allow a convenient preparation of medium-sized heterocycles containing at least two nitrogen atoms. In this paper we report the successful application of the generalized reaction **3** → **4** in the preparation of the 2,6-benzodiazonine and dibenzo[*c*,*h*][1,6]diazecine ring system and an unusual lithium aluminum hydride reduction of a phthalazinone.

The reaction of *o*-(4-chlorobenzoyl)benzoic acid with 3-hydrazinopropanol in toluene gave 3-hydroxypropylphthalazinone **5**. Reduction of this compound with excess lithium aluminum hydride[4] in refluxing tetrahydrofuran for 96 hr afforded the tetrahydrophthalazine **6a** (Scheme I). Treatment of **6a** with thionyl chloride followed by distillation gave the pyrazolo[1,2-*b*]phthalazine **7a**. This compound was also obtained when the chloropropylphthalazinone **5b**, obtained from **5a** and thionyl chloride, was reduced with lithium aluminum hydride. In addition a small amount of a polar, water-soluble chloride was obtained. Spectral and analytical data indicate that this substance is probably the imminium salt **8a**. Treatment of **7a** with methyl iodide gave a quaternary salt that could be assigned as the N-4 or N-11 derivative. The nmr spectrum of this compound gave a single methyl signal and the $ArCH_2N$ protons relative to the ArCHAr′N proton have undergone a larger downfield shift indicating that the quaternary N is at N-11 (**9**). Inspection of models also indicate that methylation at N-11 is sterically more favorable. When **9** was treated with sodium methoxide in refluxing methanol an unsaturated amine was isolated. This compound gave a typical benzophenonimine ultraviolet[5] spectrum, an $ArCH_AH_BN$ quartet, a CH_3N singlet, six aliphatic and eight aromatic protons in agreement with structure **10**, the Hofmann elimination product resulting from removal of the benzhydryl β hydrogen in **9**. The products resulting from β elimination[6] at positions C-2 and C-3 were not detected. Attempted reduction of the C=N bond in **10** with lithium aluminum hydride in refluxing tetrahydrofuran (96 hr) resulted in recovered starting material. The platinum-catalyzed hydrogenation of **10** in acetic acid proceeded easily to give the desired **11**.

The reduction of the hydroxybutylphthalazinone **5c** with lithium aluminum hydride resulted in a mixture of dihydro- and tetrahydrophthalazines **12a** and **6b** with the former predominating. The tetrahydro compound **6b** underwent dehydrogenation to **12a** at a rate sufficient to exclude it as a useful intermediate to prepare the pyrazinophthalazine **7b**. In an attempt to utilize **12a** as an intermediate to prepare **7b** it was treated with thionyl chloride with the hope of obtaining the imminium salt **8b** rather than the spiro salt **13**. In order to distinguish between **13** and **8b** the model quaternary salt **13b** was prepared by partial lithium aluminum hydride reduction of **5d** to the imine **12b** followed by treat-

(1) (a) Portions of this paper were presented by W. J. Houlihan and R. E. Manning at the First International Congress of Heterocyclic Chemistry, the University of New Mexico, Albuquerque, N. M., June 1967. (b) Sandoz Ltd., Basle, Switzerland. (c) To who inquiries should be sent.

(2) A. C. Cope, *Org. Reactions*, **11**, Chapter 5 (1960).

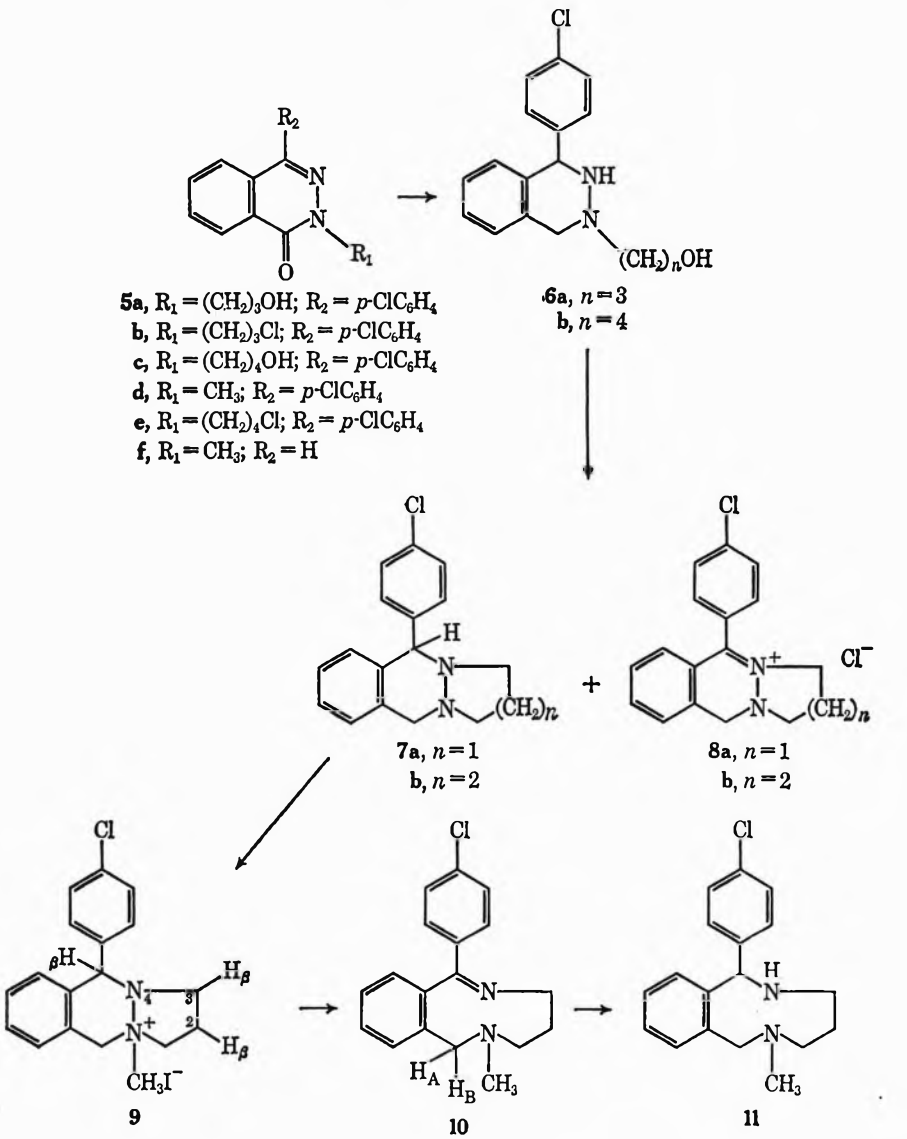
(3) See ref 2 and E. Gellert, T. R. Govindachari, M. V. Laksmikanthan, *J. Chem. Soc.*, 1008 (1962); M. G. Reinecke, L. R. Kray, and R. F. Francis, *Tetrahedron Lett.*, 3549 (1965; L. A. Paquette and L. D. Wise, *J. Amer. Chem. Soc.*, **87**, 1561 (1965); *J. Org. Chem.*, **30**, 228 (1965); L. A. Paquette and M. K. Scott, *ibid.*, **33**, 2379 (1968).

(4) The lithium aluminum hydride reduction of the C=N bond in phthalazinones has been reported to be sluggish: Yu. S. Shabarov, N. I. Vasil'er, N. K. Mamaeva, and R. Ya. Levina, *J. Gen. Chem. USSR*, **33**, 1182 (1963).

(5) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold Ltd., London, 1954.

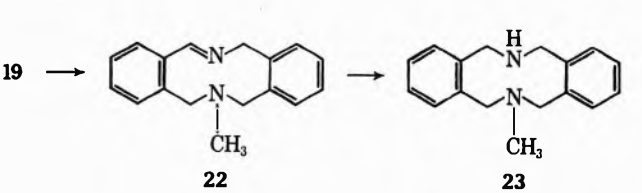
(6) For some comments on the olefin(s) expected from the β elimination of quaternary ammonium salts, see ref 2 and D. V. Banthrope, "Elimination Reactions," Elsevier Publishing Co., Amsterdam, The Netherlands, 1963.

SCHEME I

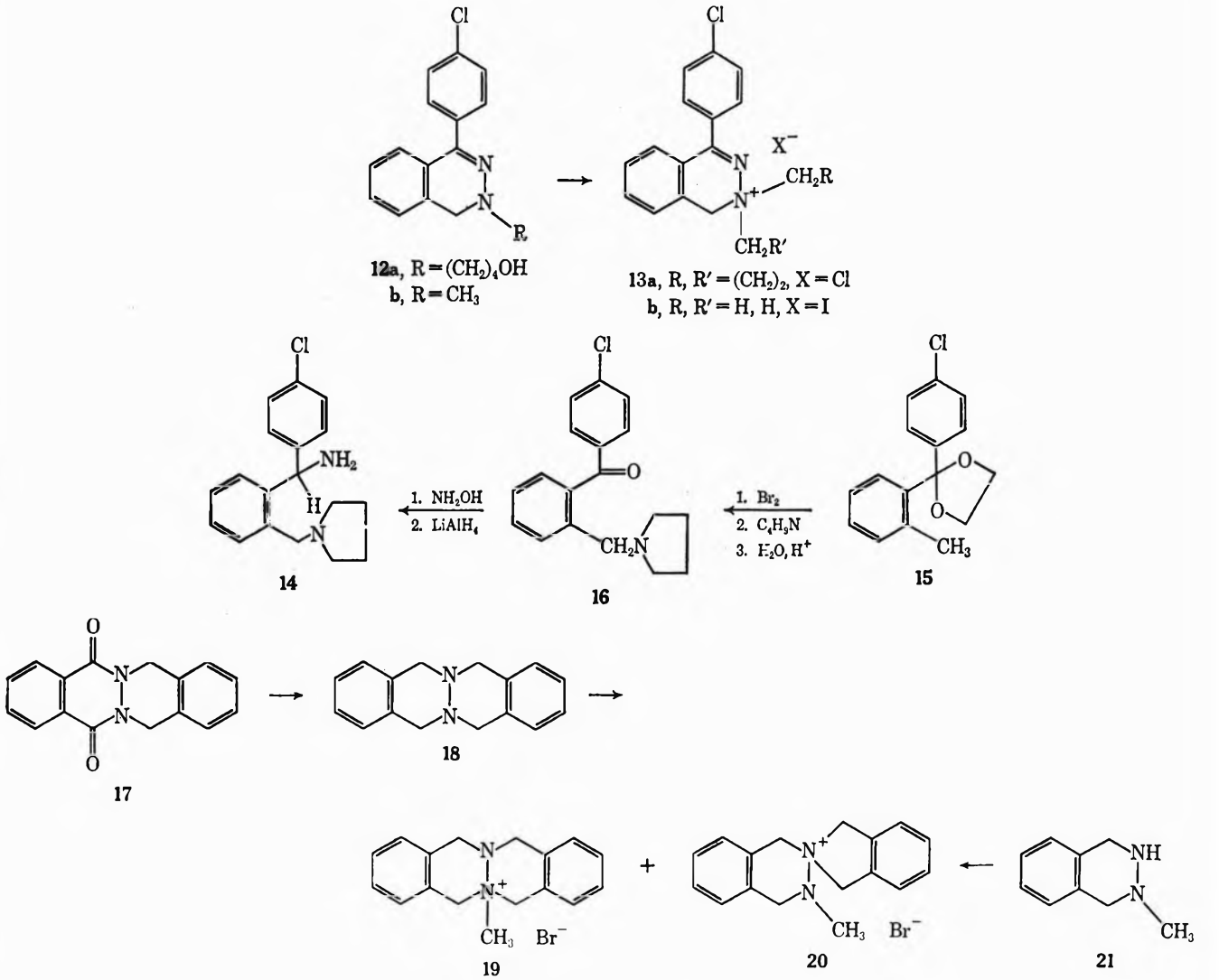


ment with methyl iodide. The structure of **13b** was confirmed by an nmr spectrum that gave a 6 H singlet indicating $^{+}N(CH_3)_2$ rather than $=N^{+}(CH_3)N(CH_3)-$. Comparison of the position of the nmr benzyl singlet in **13b** (δ 5.52) and the salt (δ 5.73) obtained from **12a** and thionyl chloride indicated that both were in a similar environment. These data, together with the result that **12b** methylated only on the tertiary amine nitrogen, indicate the spiro salt **13**. In an additional attempt to prepare **7b**, the chlorobutylphthalazone **5e** was treated with lithium aluminum hydride under conditions that converted **5b** into **7a**. Instead of **7b** a diamine that formed a monoacetyl derivative and gave two D_2O exchangeable hydrogens was obtained. On the basis of nmr data and possible mechanistic pathways, structure **14** was postulated for this compound. This assumption was then synthetically established by lithium aluminum hydride reduction of the oxime of the pyrrolobenzophenone **16** to **14** (Scheme II). The ketone was prepared by monobromination of the ketal **15**, followed by treatment with pyrrolidine and acid hydrolysis.

Lithium aluminum hydride reduction of the known dione **17** gave the tetracycle **18** which on treatment with methyl bromide afforded the quaternary salt **19**. The same compound was obtained when the tetrahydrophthalazine **21**, obtained from lithium aluminum hydride reduction of **5f**, was treated with α,α'-dibromo-*o*-xylene. In addition a second quaternary salt was isolated from this reaction that has been assigned the spiro salt **20**. When **19** was treated with sodium methoxide in refluxing methanol the dibenzo[*c*,*h*][1,6]diazecine **22** was obtained. The structure of **22** was established by nmr and ultraviolet data. Platinum-catalyzed hydrogenation of **22** in acetic acid gave **23**.



Scheme II



Experimental Section[7]

2-(3-Hydroxypropyl)-4-*p*-chlorophenylphthalazin-1(2H)-one (5a).—A mixture of 54 g (0.60 mol) of 3-hydrazinopropanol,[8] 130.5 g (0.50 mol) of 2-*p*-chlorobenzoylbenzoic acid, and 2000 ml of toluene was stirred and refluxed in a flask equipped with a Dean–Stark tube. After the level of the water layer was constant (19.0 ml) the solvent was removed *in vacuo* and the residue crystallized from methanol–water to give 143 g (91%) of **5a**: mp 104–106°; ir (KBr) 2.98 (OH), 6.07 μ (C=O); nmr ($CDCl_3$) δ 2.07 (2 H, quintet, J = 6 cps, CCH_2C), 3.65 (3 H, t, J = 6 cps, CH_2OH, 1 H, D_2O exchangeable), 4.43 (2 H, t, J = 6 cps, NCH_2), 7.30–7.90 (8 H, m, C_6H_4 and C_6H_4Cl).

Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.9; H, 4.8; Cl, 11.3; N, 8.9. Found: C, 65.2; H, 5.0; Cl, 11.3; N, 8.7.

1-*p*-Chlorophenyl-3-(3-hydroxypropyl)-1,2,3,4-tetrahydrophthalazine (6a).—A slurry of 84.5 g (2.20 mol) of lithium aluminum hydride and 2500 ml of diethyl ether (nitrogen atmosphere) was stirred and refluxed (96 hr) through a Soxhlet apparatus containing 100.0 g (0.32 mol) of **5a**. After cooling in an ice bath the reactants were treated with 169 ml of 2 *N* sodium hydroxide, 253 ml of water, and 150 g of anhydrous sodium sulfate. The salts were filtered off and washed with ether. The filtrate was concentrated *in vacuo* to give 91.9 g of **6a** as an oil: R_f 0.50, $CHCl_3$–CH_3OH (95:5); nmr ($CDCl_3$) δ 1.72 (2 H, quintet, J = 6.0 cps, $-CCH_2C-$), 2.68 (2 H, t, J = 6.0 cps, CH_2N), 3.48 (2 H, t, J = 6.0 cps, CH_2OH), 3.66 (2 H, D_2O exchangeable, NH, OH), 3.27 (2 H, s, $ArCH_2N$), 51.3 (1 H, s, –CHN), 6.83–7.43 (8 H, m, C_6H_4, C_6H_4Cl).

Anal. Calcd for $C_{17}H_{19}ClN_2O$: C, 67.3; H, 6.3; Cl, 11.7. Found: C, 67.0; H, 6.3; Cl, 11.9.

5-(*p*-Chlorophenyl)-2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazine (7a) and (*p*-Chlorophenyl)-1,2,3,11-tetrahydropyrazolo[1,2-*b*]phthalazinium Chloride (8a). A. From Thionyl Chloride Treatment of 6a.—A solution of 6.0 g (0.02 mol) of **6a**, 2.4 g (0.20 mol) of thionyl chloride, and 50 ml of chloroform was stirred and refluxed for 18 hr. The solution was washed with 2 *N* Na_2CO_3, water, dried ($MgSO_4$), filtered, and concentrated to give 4.7 g (83%) of **7a**: mp 123–125° (ether–pentane); nmr ($CDCl_3$) δ 1.99 (2 H, m, CCH_2C), 2.28–3.07 (3 H, m, CH_2-$NNCH_A$), 3.32 (1 H, m, CH_BN), 3.72 (H_A), 4.14 (H_B, q, J = 14 cps, $ArCH_AH_BN$), 4.48 (1 H, s, ArCHAr'), 6.64–7.37 (8 H, m, C_6H_4, C_6H_5Cl).

Anal. Calcd for $C_{17}H_{17}ClN_2$: C, 71.7; H, 6.0; Cl, 12.4; N, 9.8. Found: C, 71.5; H, 6.0; Cl, 12.4; N, 9.7.

Treatment of **7a** in ether with anhydrous HCl gave the hydrochloride **7** (hygroscopic), mp 189–192° (CH_2Cl_2–ether).

Anal. Calcd for $C_{17}H_{18}Cl_2N_2$: C, 63.6; H, 5.6; Cl, 22.1; N, 8.7. Found: C, 63.2; H, 6.0; Cl, 22.4; N, 8.6.

B. From Lithium Aluminum Hydride Reduction of 5b.—Following the $LiAlH_4$ Soxhlet procedure given above, 50.0 g (0.15 mol) of **5b**, 28.5 g (0.75 mol) of $LiAlH_4$, and 2000 ml of diethyl ether (reflux 48 hr) gave 43.7 g of oil. Crystallization

(7) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and have not been corrected. Proton nmr spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in parts per million from an internal $SiMe_4$ standard. Infrared spectra were determined using a Perkin-Elmer Infracord. Ultraviolet spectrum were determined in 95% C_2H_5OH on a Beckman Model DB or a Cary Model 15 spectrometer. Mass spectra were determined on a Consolidated Electronics Co. mass spectrometer Model 21-103 C, equipped with an all-glass heated inlet. Thin layer chromatography (tlc) was determined on glass plates coated with silica gel HF-254, Merck AG.

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of the oil from ether afforded 19.6 g of **7a**, mp 123–125°. Chromatography of the filtrate on silica gel (developed with $CHCl_3$–CH_3OH 95:5) gave 16.1 g of **7a** (total yield 83%) and 2.0 g of **8a**: mp 203–205° (CH_3OH–ether–pentane); nmr ($CDCl_3$) δ 2.38 (2 H, quintet, J = 7 cps, $-CCH_2C-$), 3.90 (2 H, t, J = 6.0 cps, CH_2N), 4.55 (2 H, t, J = 7 cps, CH_2N^+), 5.00 (2 H, s, $ArCH_2N$), 6.90–8.00 (8 H, m, C_6H_4, C_6H_4Cl).

Anal. Calcd for $C_{17}H_{16}Cl_2N_2$: C, 63.9; H, 5.0; Cl, 22.3; N, 8.8. Found: C, 63.6; H, 5.2; Cl, 22.1; N, 8.5.

2-(3-Chloropropyl)-4-*p*-chlorophenylphthalazin-1(2H)-one (5b).—A mixture of 15.8 g (0.04 mol) of **5a**, 8.9 g (0.075 mol) of thionyl chloride, and chloroform (250 ml) was stirred and refluxed for 20 hr in a nitrogen atmosphere. The solution was washed with 2 *N* sodium bicarbonate (100 ml), saturated sodium chloride (100 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue gave 13.1 g (97%) of **5b**: mp 112–113° (ether); ir (KBr) 6.05 μ (C=O); uv maxima 245 mμ (ϵ 17,425), 295 (10,560); nmr ($CDCl_3$) δ 2.35 (2 H, quintet, J = 6.0 cps, CCH_2C), 3.63 (2 H, t, J = 6.0 cps, CH_2Cl), 4.43 (2 H, J = 6.0 cps, CH_2N), 7.43–7.96 (8 H, m, C_6H_4 and C_6H_4Cl).

Anal. Calcd for $C_{17}H_{14}Cl_2N_2O$: C, 61.3; H, 4.2; Cl, 21.3; N, 8.4. Found: C, 61.5; H, 4.3; Cl, 21.5; N, 8.2.

5-*p*-Chlorophenyl-11-methyl-2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalainium Iodide (9).—A solution of 12.0 g (0.042 mol) of **7a**, 12.0 g (0.084 mol) of methyl iodide, and 250 ml of dry tetrahydrofuran was stirred at room temperature for 18 hr. The resultant solid was filtered to give 16.7 g (93%) of **9**: mp 215–217° (CH_2Cl_2–C_6H_6); nmr ($CDCl_3$) δ 2.48 (2 H, m, CCH_2C), 3.28 (2 H, m, NCH_2C), 3.63 (3 H, s, N^+CH_3), 3.95 (H_A), 4.78 (H_B, m, $NC^+H_ACH_BC$), 4.97 (H_A'), 5.67 (H_B', q, J = 14 cps, $ArCH_AH_B'N^+$), 5.42 (1 H, s, ArCHAr'N), 6.78–7.54 (8 H, m, C_6H_4, C_6H_4Cl).

Anal. Calcd for $C_{18}H_{20}ClIN_2$: C, 50.7; H, 4.7; I, 29.0; N, 6.6. Found: C, 50.7; H, 4.8; I, 29.4; N, 6.4.

1-(*p*-Chlorophenyl)-6-methyl-4,5,6,7-tetrahydro-3H-2,6-benzodiazonine (10).—To a freshly prepared solution of 4.0 g (0.17 mol) of sodium in 100 ml of dry methanol maintained under a nitrogen atmosphere there was added 16.0 g (0.037 mol) of **9** in 150 ml of dry methanol. The solution was refluxed for 24 hr and then the solvent removed *in vacuo*. The residue was treated with 100 ml of chloroform and 50 ml of water. The chloroform was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 5.8 g (52%) of oily **10**: uv maxima 253 mμ (16,000); nmr ($CDCl_3$) δ 1.68 (2 H, m, CCH_2C), 2.28 (3 H, s, NCH_3), 2.68 (2 H, m, NCH_2C), 3.08 (H_A), 3.78 (H_B, t-d, J = 10 cps, J' = 4.0 cps, $C{=}NCH_AH_B$), 3.32 (H_A), 3.58 (H_B, q, J = 14 cps, $ArCH_AH_B$), 6.87–7.68 (8 H, m, C_6H_4, C_6H_4Cl).

Treatment of a tetrahydrofuran solution of **10** with dry hydrogen chloride gave the dihydrochloride of mp 215–217° (CH_2Cl_2–CCl_4).

Anal. Calcd for $C_{18}H_{21}Cl_3N_2$: C, 58.2; H, 5.7; Cl, 28.6; N, 7.5. Found: C, 57.9; H, 5.8; Cl, 28.9; H, 7.3.

1-*p*-(Chlorophenyl)-6-methyl-2,3,4,5,6,7-hexahydro-1H-2,6-benzodiazonine (11).—A mixture of 5.4 g of **10**, 0.6 g of platinum oxide, and 100 ml of acetic acid was hydrogenated (50 psi, 26°) on a Parr hydrogenation apparatus. After hydrogen uptake (theory 17.0 psi; actual 16.2 psi) had ceased (18 hr) the catalyst was filtered off and the filtrate concentrated *in vacuo*. The residue was made basic with 2 *N* Na_2CO_3, extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated *in vacuo* to give 4.3 g (78%) of **11**: mp 132–134° (ether–pentane); ir ($CHCl_3$) 2.92 (NH); nmr ($CDCl_3$) δ 1.58 (2 H, m, $-CCH_2C-$), 2.32 (3 H, s, NCH_3), 2.50 (H_A), 3.47 (H_B, m, CH_AH_B), 2.98 (H_A'), 4.45 (H_B', J = 13 cps, $ArCH_AH_B'N$), 3.78 (1 H, D_2O exchangeable, NH), 5.58 (1 H, s, CHN), 6.50 (1 H, m, C_6H), 6.90–7.75 (7 H, m, C_6H_3, C_6H_4Cl).

Anal. Calcd for $C_{18}H_{21}ClN_2$: C, 71.8; H, 7.0; Cl, 11.9; N, 9.3. Found: C, 72.1; H, 7.1; Cl, 11.7; N, 9.6.

2-(4-Hydroxybutyl)-4-*p*-chlorophenylphthalazin-1-(2H)-one (5c).—Following the procedure used to prepare **5** a mixture of 31 g (0.03 mol) of 4-hydrazinobutanol,[8] 73 g (0.28 mol) of 2-*p*-chlorobenzoylbenzoic acid, and 400 ml of toluene gave 70.8 g (77%) of **5c**: mp 116–118° ($CHCl_3$–pentane); ir (KBr) 3.00 (OH), 6.06 μ (C=O); nmr ($CDCl_3$) δ 1.45–2.10 (4 H, m, CCH_2CH_2C), 2.83 (1 H, D_2O exchangeable, OH) 3.72 (2 H, t, J = 6.0 cps, CH_2OH), 4.33 (2 H, t, J = 6.0 cps, CH_2N), 7.42–7.92 (7 H, m, C_6H_3, $C_6H_3C_6H_4Cl$), 8.42 (1 H, m, HC=CCO).

Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.8; H, 5.2; Cl, 10.8; N, 8.05; O, 9.7. Found: C, 65.4; H, 5.3; Cl, 11.2; O, 9.7.

2-(4-Hydroxybutyl)-4-*p*-chlorophenyl-1,2-dihydrophthalazine (12a) and 1-(*p*-Chlorophenyl)-3-(4-hydroxybutyl)-1,2,3,4-tetrahydrophthalazine (6b).—Following the procedure for **6a**, 50.0 g (0.15 mol) of **5c**, 28.8 g (0.76 mol) of lithium aluminum hydride and 1500 ml of diethyl ether (reflux 96 hr) gave 47.8 g of oil containing two components, R_f 0.4 and 0.6 ($CHCl_3$–CH_3OH, 95:5). Crystallization from ether–pentane gave 20.1 g of **12a**: mp 76°; R_f 0.6; ir (CH_2Cl_2) nmr ($CDCl_3$) δ 1.84 (4 H, m, CCH_2CH_2C), 2.40 (1 H, D_2O exchangeable, OH), 3.21 (2 H, t, J = 6.0 cps, CH_2N), 3.57 (2 H, t, J = 6.0 cps, CH_2O), 3.93 (2 H, s, $ArCH_2$), 7.05–7.70 (8 H, m, C_6H_4, C_6H_4Cl). The filtrate from **12a** was chromatographed on silica gel (500 g, C_6H_6–$CHCl_3$, 50:50 eluent) to give (1) 18.8 g of **12a** (total, 38.9 g) and (2) 6.2 g of **6b** as an oil: nmr ($CDCl_3$) δ 1.66 (4 H, m, CCH_2CH_2C), 2.57 (2 H, t, J = 6.0 cps, CH_2N), 3.00 (2 H, D_2O exchangeable, NH, OH), 3.42 (2 H, t, J = 6.0 cps, CH_2O), 5.18 ((1 H, s, ArCHAr'), 6.80–7.58 (8 H, m, C_6H_4, C_6H_4Cl). When **6b** was rechecked by tlc *ca.* 2 hr after it was isolated the presence of **12a** (R_f 0.6) was detected. Further evaluation after 4 and 8 hr revealed that the intensity of the R_f 0.6 spot (**12a**) had increased.

Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.7; H, 6.1; Cl, 11.3. Found: C, 68.3; H, 6.1; Cl, 11.3.

Anal. Calcd for $C_{18}H_{21}ClN_2O$: C, 68.1; H, 6.6; Cl, 11.2. Found: C, 68.2; H, 6.5; Cl, 11.0.

4-(*p*-Chlorophenyl)spiro[phthalazine-2(1H)-1′-pyrrolidinium] Chloride (13).—A solution containing 2.0 g (0.0063 mol) of **12a**, 0.91 g (0.0076 mol) of thionyl chloride, and 20 ml of dry chloroform was stirred and refluxed for 18 hr. The solution was washed with saturated $NaHCO_3$ and H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. There was obtained 1.6 g (76%) of **13**: mp 149–150° (CH_2Cl_2–pentane); nmr ($CDCl_3$) δ 2.42 (4 H, m, CCH_2CH_2C), 3.78 (2 H, m, CH_2N^+), 5.73 (2 H, s, $ArCH_2N^+$), 7.32–7.98 (8 H, m, C_6H_4, C_6H_4Cl).

When **13** was dissolved in $CHCl_3$–CCl_4 it crystallized as **13**·CCl_4, mp 129–130°. The nmr of **13**·CCl_4 was identical with pure **13**.

Anal. Calcd for $C_{18}H_{18}Cl_2N_2$: C, 64.9; H, 5.4; Cl, 21.3; N, 8.4. Found: C, 64.7; H, 5.8; Cl, 21.0; N, 8.7.

Anal. Calcd for $C_{19}H_{18}Cl_6N_2$: C, 46.9; H, 3.7; Cl, 43.7; N, 5.7. Found: 46.5; H, 3.8; Cl, 43.4; N, 5.8.

4-*p*-Chlorophenyl-2-methylphthalzin-1(2H)-one (5d).—Following the procedure given in the preparation of **5a**, 130.5 g (0.50 mol) of 2-*p*-chlorobenzoylbenzoic acid, 27.6 g (0.60 mol) of methylhydrazine and 750 ml of toluene gave 117.2 g (87%) of **5d**: mp 152–154° (CCl_4–$CHCl_3$); ir (KBr) 6.01 μ (C=O); nmr ($CDCl_3$) δ 3.88 (3 H, s, CH_3), 7.50–7.90 (7 H, m, C_6H_4, C_6H_3), 8.41 (1 H, m, CH=CCO).

Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.4; H, 4.1; Cl, 13.1. Found: C, 66.5; H, 4.0; Cl, 13.4.

4-*p*-Chlorophenyl-2-methyl-1,2-dihydrophthalazine (12b).—Following the procedure given in the preparation of **6a**, 50.0 g (0.185 mol) of **5d**, 13.4 g (0.348 mol) of $LiAlH_4$, and 1500 ml of diethyl ether (reflux 80 hr) gave 41.3 g (81%) of **12b**: mp 137–138° (CH_2Cl_2–pentane); ir (CH_2Cl_2) 6.01 μ (C=N); nmr ($CDCl_3$) δ 3.08 (3 H, s, NCH_3), 3.92 (2 H, s, CH_2N), 7.10–7.70 (8 H, m, C_6H_4, C_6H_4Cl).

Anal. Calcd for $C_{15}H_{13}ClN_2$: C, 70.2; H, 5.1; N, 10.9. Found: C, 70.1; H, 5.4; N, 10.7.

4-*p*-Chlorophenyl-2,2-dimethyl-1,2-dihydrophthalazinium Iodide (13b).—A mixture of 8.0 g (0.03 mol) of **12b**, 8.7 g (0.062 mol) of methyl iodide, and 200 ml of dry tetrahydrofuran were stirred for 56 hr at room temperature and then diluted with 250 ml of dry diethyl ether to give 7.4 g (60%) of **13b**: mp 163–166°; nmr ($CDCl_3$–C_2D_6SO) δ 3.67 (6 H, s, $CH_3NC^+H_3$), 5.52 (2 H, s, $ArCH_2N^+$), 7.40–7.80 (8 H, m, C_6H_4Cl, C_6H_4).

Anal. Calcd for $C_{15}H_{16}ClIN_2$: C, 48.2; H, 4.0; I, 31.8. Found: C, 48.4; H, 3.8; I, 31.5.

2-(4-Chlorobutyl)-4-*p*-chlorophenylphthalazin-1(2H)-one (5e).—Following the procedure given for the preparation of **5b** a mixture of 50.0 g (0.15 mol) of **5c**, 27.0 g (0.23 mol) of thionyl chloride, and 400 ml of chloroform gave 51.5 g (97%) of **5e**: mp 148–151° (CH_2Cl_2–ether); ir (KBr) 6.05 μ (C=O); nmr ($CDCl_3$) δ 1.85 (4 H, m, CCH_2CH_2C), 3.68 (2 H, t, J = 6.0 cps, CH_2Cl), 4.40 (2 H, t, J = 6.0 cps, CH_2N), 7.38–7.89 (8 H, m, C_6H_4Cl, C_6H_4).

Anal. Calcd for $C_{18}H_{16}Cl_2N_2O$: C, 62.3; H, 4.6; Cl, 20.4; N, 8.1. Found: C, 62.0; H, 4.9; Cl, 20.2; N, 8.0.

2-(Pyrrolidinomethyl)benzhydrylamine (14). A. From Lithium Hydride Reduction of 5e.—Following the procedure for **6a** 50.0

g (0.14 mol) of **5e**, 16.4 g (0.43 mol) of lithium aluminum hydride, and 1500 ml of diethyl ether (refluxed 56 hr) gave 40.3 g of oil. The oil was taken up in CH_2Cl_2 and washed with 2 *N* HCl (200 ml, twice). The acid layer was made alkaline with 50% NaOH, extracted with $CHCl_3$, dried ($MgSO_4$), filtered, and concentrated to give 33.0 g (83%) of **14** as an oil: R_f 0.2 ($CHCl_3$–CH_3OH, 95:5); ir (CH_2Cl_2) 2.87, 2.98 μ (NH_2); nmr $CDCl_3$) δ 1.67 (2 H, m, CCH_2CH_2C), 2.18 (2 H, D_2O exchangeable, NH_2) 2.42 (4 H, m, CH_2NCH_2), 3.32 (H_A), 3.72 (H_B, q, J = 12.0 cps, $ArCH_2N$), 5.52 (1 H, s, ArCHAr'), 7.00–7.32 (8 H, m, C_6H_4, C_6H_4Cl).

A solution of **14** in anhydrous THF was treated with dry HCl to give the dehydrochloride **14** of mp 220° (hygroscopic).

Anal. Calcd for $C_{18}H_{23}Cl_3N_2$: C, 57.8; H, 6.1; Cl, 28.6; N, 7.5. Found: C, 58.1; H, 6.4; Cl, 28.3; N, 7.2.

B. From Lithium Aluminum Hydride Reduction of 16 Oxime.—A mixture of 7.0 g (0.023 mol) of **16**, 7.0 g (0.10 mol) of hydroxylamine hydrochloride, 5.6 g (0.10 mol) of potassium hydroxide, and 200 ml of 95% ethanol was stirred and refluxed for 6 hr. The solvent was removed *in vacuo* and the residue treated with 50 ml of water and 150 ml of methylene chloride. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give 6.5 g of crude **16** oxime as an oil: R_f 0.15 ($CHCl_3$–CH_3OH; 95.5; 22 R_f 0.85); ir (CH_2Cl_2) no C=O band.

Anal. Calcd: N, 4.6. Found: N, 4.7.

Following the procedure given in A, 6.5 g (0.023 mol) of crude **16** oxime, 1.75 g (0.046 mol) of lithium aluminum hydride, and 200 ml of diethyl ether (refluxed 14 hr) gave 2.8 g of **14**. Comparison of the ir and nmr spectrum of **14** prepared from **5e** showed them to be identical.

2-*p*-Chlorophenyl-2-*o*-tolyl-1,3-dioxolane (15).—A mixture of 50.0 g (0.22 mol) of 2-*p*-chlorobenzoyltoluene, 26.8 g (0.43 mol) of ethylene glycol, 5.0 g of *p*-toluenesulfonic acid, and 300 ml of benzene was stirred and refluxed in a flask equipped with a Dean–Stark tube until (25 hr) the "water layer" (19 ml) in the side arm remained constant. The solution was washed with 150 ml of 2 *N* NaOH, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue gave 43.0 g (71%) of **15**: bp 135–137° (0.10 mm); $n^{20}D$ 1.5842; nmr ($CHCl_3$) δ 2.17 (3 H, s, CH_3), 4.02 (4 H, A_2B_2, OCH_2CH_2O), 7.05–7.88 (8 H, m, C_6H_4, C_6H_4Cl).

Anal. Calcd for $C_{16}H_{15}ClO_2$: C, 69.9; H, 5.5; Cl, 12.9. Found: C, 69.7; H, 5.4; Cl, 12.8.

4-Chloro-2′-pyrrolidinomethylbenzophenone (16).—To a stirred refluxing mixture of 82.5 g (0.30 mol) of **15**, 34.8 g (0.42 mol) of anhydrous $NaHCO_3$, and 500 ml of carbon tetrachloride, irradiated with a high-intensity light source, there was added a solution of 48 g (0.30 mol) of bromine and 200 ml of carbon tetrachloride at such a rate that the bromine color faded rapidly. After 1 additional hr of reflux the mixture was cooled to *ca.* 30° and treated with a solution of 42.6 g (0.60 mol) of pyrrolidine in 200 ml of carbon tetrachloride. After 18 hr the salts were filtered off and the filtrate was saturated with anhydrous HCl. The solvent was decanted and the oily residue (59.7 g, crude ketal amine) was refluxed for 20 hr in a solution of 300 ml of methanol, 30 ml of water, and 60 ml of concentrated hydrochloric acid. The cooled solution was made basic with 2 *N* Na_2CO_3, extracted with methylene chloride, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue gave 22.8 g (25%) of **16**: mp 69–71° (CH_3OH–H_2O); ir (CH_2Cl_2) 5.98 (C=O); nmr ($CDCl_3$) δ 1.45 (4 H, m, CCH_2CH_2C), 2.21 (4 H, m, CH_2NCH_2), 3.60 (2 H, s, $ArCH_2N$), 7.32 (4 H, s, C_6H_4Cl), 7.50 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{18}H_{18}ClNO$: C, 72.1; H, 6.1; Cl, 11.8; N, 4.7; O, 5.3. Found: C, 72.0; H, 6.1; Cl, 11.7; N, 4.6; O, 5.6.

A solution of **16** in diethyl ether–methylene chloride was treated with anhydrous HCl to give the hydrochloride of **16**, mp 201–204°.

Anal. Calcd for $C_{18}H_{19}Cl_2NO$: C, 64.3; H, 5.7; Cl, 21.1; N, 4.2. Found: C, 64.2; H, 5.7; Cl, 20.9; N, 4.2.

7H,12H-Phthalazino[2,3-*b*]phthalazine-5,14-dione (17).—Following the procedure of Hatt and Stephenson,[9] α,α'-dibromo-*o*-xylene and phthalazine-1,4-dione gave **17**: mp 195–196° (lit.[9] mp 196.5–197.5°); uv λ_{max}^{EtOH} 232 mμ (ϵ 11,250), 236 (11,100), 308 (5900); nmr ($CDCl_3$) δ 5.32 (4 H, s, CH_2NNCH_2), 7.32 (4 H, s, C_6H_4), 7.75 and 8.23 (4 H, A_2B_2, COC_6H_4CO).

5,7,12,14-Tetrahydrophthalazino[2,3-*b*]phthalazine (18).—Following the procedure used to prepare **7a** a mixture of 6.0 g (0.023 mol) of **17**, 1.7 g (0.035 mol) of lithium aluminum hydride, and absolute tetrahydrofuran (24 hr reflux) gave 2.5 g (46%) of **18**: mp 127–129° (lit.[10] mp 132–133°); uv maxima 252 mμ (ϵ 575), 258 (690) 266 (895), 273 (975); nmr[11] ($CDCl_3$) δ 3.98 [8 H, s, $(CH_2)_2NN(CH_2)_2$], 7.09 (8 H, A_2B_2, C_6H_4, C_6H_4). The mass spectrum exhibits a molecular ion peak at *m/e* 236 ($C_{16}H_{16}N_2$) with abundant fragment peaks at *m/e* 132 ($M^+ - CH_2C_6H_4CH_2$), 118 ($CH_2C_6H_4CH_2N$), and 104 ($CH_2C_6H_4CH_2$).

Treatment of **18** in dry THF with anhydrous HBr gave the hydrobromide of **18**, mp 253–256° (CH_2Cl_2–ether).

Anal. Calcd for $C_{16}H_{17}BrN_2$: C, 60.6; H, 5.4; Br, 25.2; N, 8.8. Found: C, 60.1; H, 5.5; Br, 25.2; N, 8.5.

6-Methyl-5,7,12,14-tetrahydrophthalazino[2,3-*b*]phthalazinium Iodide (19) and 1,2,3′,4′-Tetrahydrospiro[isoindoline-2,2′-(1′H)-phthalazinium] Bromide (20). A. From 18 and Methyl Bromide.—A solution of 5.0 g of **18** in 50 ml of dry THF was cooled in an ice bath and treated with a stream of methyl bromide gas for 0.3 hr. After stirring 18 hr at room temperature the resultant solid was filtered off to give 5.9 g of **19**: mp 218–219°; nmr (C_2D_6SO) δ 3.52 (3 H, s, NC^+H_3) 4.32 ($2H_A$), 4.72 ($2H_B$, q, J = 8.0 cps, $ArCH_AH_BNCH_ACH_BAr$), 5.15 (4 H, s, $ArCH_2N^+CH_2Ar$), 7.10–7.56 (8 H, m, C_6H_4, C_6H_4).

Anal. Calcd for $C_{17}H_{19}BrN_2$: C, 61.6; H, 5.8; Br, 24.1; N, 8.5. Found: C, 61.5; H, 5.9; Br, 23.9; N, 8.4.

B. From 21 and α,α'-Dibromo-*o*-xylene.—A mixture of 10.7 g (0.075 mol) of **21**, 19.2 g (0.072 mol) of α,α'-dibromo-*o*-xylene, 20.0 g (0.15 mol) of anhydrous K_2CO_3, and 100 ml of acetone was stirred and refluxed for 52 hr. The acetone was decanted off and the remaining solid was treated with about 100 ml of water and 100 ml of $CHCl_2$ and then stirred for 2 hr. The insoluble material was filtered off to give 7.5 g (31%) of **19**: mp 215–217°; nmr identical with **19** obtained in procedure A. On standing for about 48 hr there was obtained 4.7 g of solid, mp 157–165°. Recrystallization (CH_2Cl_2–ether) gave 4.2 g (18%) of **20**: mp 142° dec; nmr (C_2D_6SO) δ 3.08 (3 H, s, NCH_3), 4.12 (2 H, s), 4.32 (2 H, s, $ArCH_2N$), 5.12 (2 H, s, CH_2N^+), 7.00–8.00 (8 H, m, C_6H_4, C_6H_4).

Anal. Calcd for $C_{17}H_{19}BrN_2$: C, 61.6; H, 5.8; Br, 24.1; N, 8.5. Found: C, 61.5; H, 5.8; Br, 24.2; N, 8.9.

2-Methyl-1,2,3,4-tetrahydrophthalazine (21).—From 60 g (0.40 mol) of 2-carboxybenzaldehyde, 23 g (0.50 mol) of methylhydrazine, and toluene there was obtained 50 g (81%) of 2-methylphthalazine-1(2H)-one (**5f**): mp 110–111° (toluene, lit.[12] mp 113–115°); uv maxima, 225 mμ (ϵ 14,855), 244 (5905), 253 (5905), 287 (6855), 313 (3045); nmr ($CHCl_3$) δ 3.80 (3 H, s, CH_3), 6.28 (4 H, m, C_6H_4), 8.08 (1 H, s, CH=N).

Following the procedure given to prepare **7a** a mixture of 35.0 g (0.22 mol) of **5f**, 10.0 g (0.22 mol) of lithium aluminum hydride, and ether (1200 ml) gave 28.6 g (92%) of **21**: bp 140–141° (25 mm); $n^{20}D$ 1.5613; nmr ($CHCl_3$) δ 2.40 (1 H, D_2O exchangeable, NH), 2.55 (3 H, s, CH_3), 3.57 (2 H, s, CH_2NMe), 4.06 (2 H, s, CH_2N), 7.06 (4 H, m, C_6H_4). Th3 hydrochloride of **21** prepared in the usual manner had mp 160–162° (CH_2Cl_2–ether).

Anal. Calcd for $C_9H_{13}ClN_2$: C, 58.5; H, 7.1; Cl, 19.1; N, 15.2. Found: C, 58.7; H, 7.1; Cl, 18.9; N, 14.9.

6-Methyl-5,6,7,14-tetrahydrodibenzo[*c*,*h*][1,6]diazecine (22).—To a freshly prepared solution of 1.5 g (0.065 mol) of sodium in 40 ml of dry methanol maintained under a nitrogen atmosphere there was added 7.0 g (0.021 mol) of **19** in 50 ml of dry methanol. The solution was refluxed for 192 hr and the solvent was removed *in vacuo*. The residue was treated with 100 ml of water and 100 ml of chloroform. The chloroform layer was washed with 2 *N* HCl (100 ml, twice) and the acid layer was made basic (2 *N* NaOH), extracted with CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 4.3 g (85%) of **22**: mp 219–222° (CH_2Cl_2–CH_3OH); ir (KBr) 6.12 μ (C=N); uv maxima 250 mμ (ϵ 9800); nmr ($CDCl_3$–C_2D_6SO) δ 1.92 (3 H, s, CH_3N), 4.34 (2 H, s, CH_2N), 4.38 (2 H, s, CH_2N), 4.48 (2 H, s, $=NCH_2$), 7.21–7.44 (7 H, m, C_6H_4, C_6H_3), 8.08 (1 H, m, HC=CC=N), 8.81 (1 H, s, CH=N).

Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.6; H, 7.3; N, 11.2. Found: C, 81.1; H, 7.3; N, 11.2.

6-Methyl-5,6,7,12,13,14-hexahydrodibenzo[*c*,*h*][1,6]diazecine (23).—A mixture of 1.0 g of **22**, 0.1 g of platinum oxide, and 50 ml of acetic acid was hydrogenated as in the preparation of **11** to give 0.80 g (79%) of **23**: mp 162–164° (CH_3OH); ir (CH_2Cl_2) 3.03 μ (NH); nmr ($CDCl_3$) δ 1.92 (3 H, s, NCH_3), 3.03 (1 H,

(9) H. H. Hatt and E. F. M. Stephenson, *J. Chem. Soc.*, 658 (1943).

(10) H. H. Hatt and E. F. M. Stephenson, *ibid.*, 199 (1952).

(11) The effect of temperature on the nmr spectrum of **18** has been reported by B. Junge and H. A. Staab, *Tetrahedron Lett.*, 709 (1967).

(12) R. Gompper, *Chem. Ber.*, **93**, 198 (1960).

D_2O exchangeable, NH), 3.61 (4 H, s, CH_2NCH_2), 3.83 (4 H, s, CH_2NCH_2), 7.13–7.50 (8 H, m, C_6H_4, C_6H_4).

Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.9; H, 8.0; N, 11.1. Found: C, 80.9; H, 8.2; N, 11.1.

Registry No.—**5a**, 20072-33-7; **5b**, 20072-34-8; **5c**, 20072-35-9; **5d**, 4725-83-1; **5e**, 20072-37-1; **6a**, 20072-38-2; **6b**, 20072-39-3; **7a**, 20072-40-6; **7** hydrochloride, 20072-41-7; **8a**, 20072-42-8; **9**, 20072-43-9; **10**, 20072-44-0; **10**, dihydrochloride, 20072-45-1; **11**, 20072-46-2; **12a**, 20072-47-3; **12b**, 20072-48-4; **13a** 20126-04-9; **13b**, 20072-49-5; **14**, 20072-50-8; **14**, dihydrochloride, 20072-51-9; **15**, 20072-52-0; **16**, 20072-53-1; **16** hydrochloride, 20072-54-2; **17**, 13152-91-5; **18**, hydrobromide, 20126-05-0; **19**, 20072-56-4; **20**, 20126-06-1; **21**, 20072-57-5; **21** hydrochloride, 20072-58-6; **22**, 20072-59-7; **23**, 20072-60-0.

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A Novel N–CH_2–N Bridging Reaction[1a]

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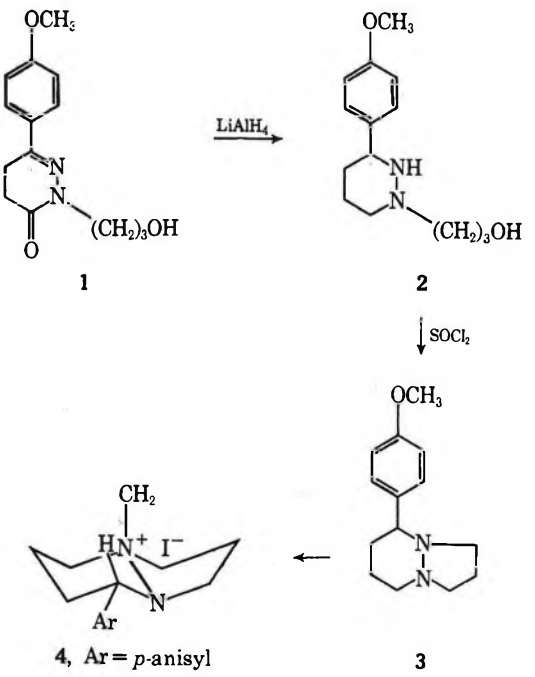
Received December 30, 1968

Treatment of the methyl iodide salts (**4** and **10**) of the bridgehead hydrazines, 2-*p*-anisyl-1,6-diazabicyclo[4.3.0]nonane (**3**) and 2-*p*-anisyl-1,6-diazabicyclo[4.4.0]decane (**9**), with refluxing sodium methoxide–methanol resulted in the formation of the N–CH_2–N bridged derivatives 2-*p*-anisyl-1,6-diaza[4.3.1]decane (**12**) and 2-*p*-anisyl-1,6-diaza[4.4.1]undecane (**14**). The same hydrazine salts when treated with sodium–ammonia gave the medium-sized ring compounds 6-*p*-anisyl-1-methyl-1,5-diazacyclononane (**13**) and 5-*p*-anisyl-1-methyl-1,6-diazacyclodecane (**15**). The formation of the NCH_2N derivatives is postulated to occur by a 1,2 shift (**17**) analogous to a Stevens rearrangement.

In the preceding paper[2] from our laboratories it was reported that the 2,6-benzodiazonine and dibenzo[*c*,*h*][1,6]diazecine ring systems could be prepared by the base elimination of the appropriate bridgehead hydrazine quaternary salts from 2,3,5,10-tetrahydro-1H-pyrazolo[1,2-*b*]phthalazine and 5,7,12,14-tetrahydrophthalazino[2,3-*b*]phthalazine. The present work reports our findings in the attempt to extend the synthetic usefulness of this reaction to the preparation of 1,5-diazacyclononane and 1,6-diazacyclodecane ring systems from the appropriate bridgehead hydrazine quaternary salts.

The synthesis of the required bridgehead hydrazine intermediates **3** and **9** are given in Schemes I and II. When **3** was allowed to react with methyl iodide it gave a sharp melting quaternary salt in nearly quantitative yield. The nmr of this compound gave a single methyl signal (δ 3.62) indicating that the methylation had occurred stereoselectively. Recent findings on the quaternization of piperidine[3a] and other cyclic nitrogen derivatives[3b] have shown that the methylation of these systems occurs stereoselectively with the incoming methyl group occupying an axial position. By analogy with this work we have assigned structure **4**, with an axial methyl group and an equatorial anisyl group, as the most probable conformational form.[4] Additional support for the methyl assignments will be given below.

SCHEME I



When the mixed anhydride from 3-*p*-anisylpropionic acid (**5**) and ethyl chloroformate was allowed to react with hexahydropyridazine it gave a hydrazide that could be represented by **6** or its ring tautomer (**6a**). The ir of this compound gave carbonyl bands at 5.97 and 6.10 μ and a uv maximum at 228 mμ indicating that the tautomeric form **6** predominates. Treatment of a toluene solution of **6** with acid gave the unsaturated lactam **7**. The position of the double bond was determined from uv and nmr data. Catalytic hydrogenation of **7** afforded **8** which on further reduction with lithium aluminum hydride gave **9**. Reaction of **9** with methyl iodide gave a quaternary salt that gave a nmr spectrum with a single methyl signal (δ 3.62). By ar-

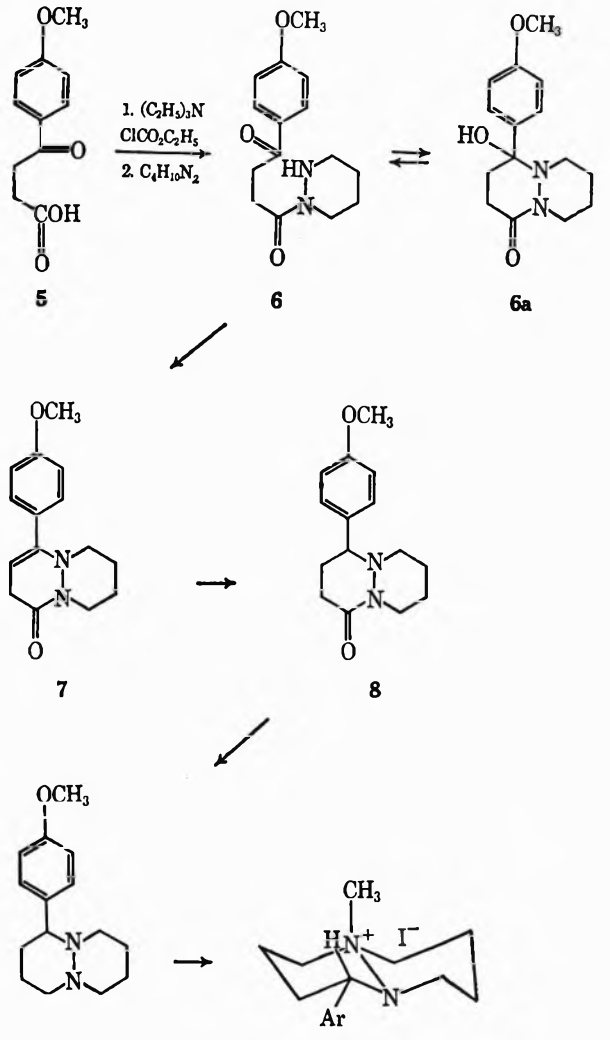
(1) (a) Portions of this paper were presented by W. J. Houlihan and R. E. Manning at the First International Congress of Heterocyclic Chemistry, The University of New Mexico, Albuquerque, N. M., June 1967. (b) Sandoz Ltd., Basel, Switzerland. (c) To whom inquiries should be sent.

(2) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **34**, 2715 (1969).

(3) (a) Y. Kawazoe and M. Tsuda, *Chem. Pharm. Bull. Tokyo*, **15**, 1405 (1967); D. K. Brown, J. McKenna, J. M. McKenna, J. M. Stuart, and B. G. Hutley, *Chem. Commun.*, 380 (1967); H. O. House, B. A. Tefertiller, and C. G. Pitt, *J. Org. Chem.*, **31**, 1073 (1966). (b) H. O. House and C. G. Pitt, *ibid.*, 31, 1062 (1966); H. O. House and B. Terfertiller, *ibid.*, **31**, 1068 (1966); C. D. Johnson, R. A. Y. Jones, A. R. Katritzky, C. R. Palmer, K. Schofield, and R. J. Wells, *J. Chem. Soc.*, 6797 (1965).

(4) We have presumed that the indicated chair conformations (trans-fused) predominate in all compounds containing a six-membered ring since inspection of models reveals no apparent reason why the usual order of stability (chair > boat) should be reversed.

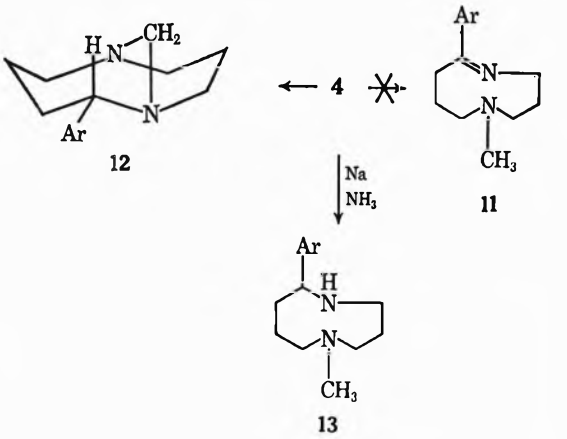
Scheme II



guments analogous with the assignment of structure **4** we propose formula **10** for this compound.

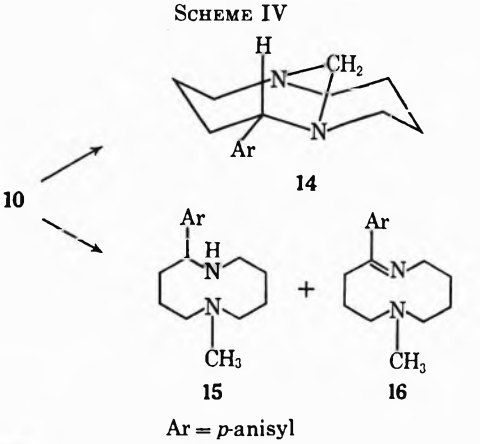
Treatment of **4** with a refluxing sodium methoxide–methanol solution gave a novel $C_{15}H_{22}N_2O$ compound. The uv spectrum of this substance gave only isolated anisyl absorption thereby ruling out structure **11**, the compound expected to be formed by analogy with the examples given in the preceding paper.[2] The nmr spectrum gave a broad 2 H singlet at δ 4.12 in addition to a OCH_3 singlet (δ 3.72) and 13 aliphatic and 4 aromatic protons. The low-field position and absence of splitting for the 2 H signal at 4.12 suggests a CH_2 grouping attached to two polar atoms that are devoid of H. Such an arrangement is present in the 1,6-diazabicyclo-[4.3.1]decane structure **12** with the NCH_2N group[5] being assigned to the δ 4.12 singlet. When **4** was treated with a sodium–ammonia reducing system under conditions used to cleave $\geqslant C-\overset{+}{N}\leqslant$ bonds there resulted a $\geqslant N-\overset{+}{N}\leqslant$ cleavage to form the desired 1,5-diazacyclononane **13**. Alternative structures where a $CH_2{}^+N\leqslant$ cleavage occurred were ruled out since the nmr spectrum of **13** did not contain any CH_3C group. (See Scheme III.)

Scheme III

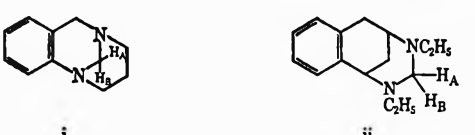


The treatment of **10** with refluxing sodium methoxide–methanol resulted in a $C_{16}H_{24}N_2O$ compound that gave isolated anisyl absorption in the uv region and an nmr spectrum with a 2 H AB pattern at δ 4.08 (H_A) and 4.42 (H_B, J = 15.0 cps), attributed to an NCH_2N group,[5] a OCH_3 singlet, 15 aliphatic and 4 aromatic protons. These data are in agreement with the 1,6-diazabicyclo[4.4.1]decane **14**. Treatment of **10** with the sodium–ammonia reducing system gave two novel compounds. The major product gave ir and nmr data consistent with the $N-N^+$ cleavage product **15**. The ir spectrum of the minor component gave a C=N bond at 6.05 μ, uv maxima at 226, 276 and 283 mμ, and nmr signals corresponding to an NCH_3 singlet (δ 2.27), 17 aliphatic and 4 aromatic protons. This compound has been assigned as the Hofmann elimination[6] product **16**. Further evidence for this structure was obtained by catalytic reduction to **15**. (See Scheme IV.)

Scheme IV

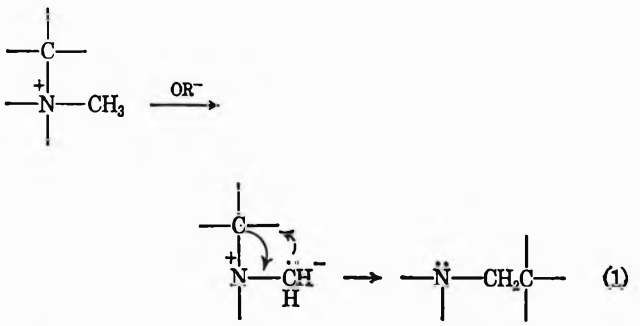


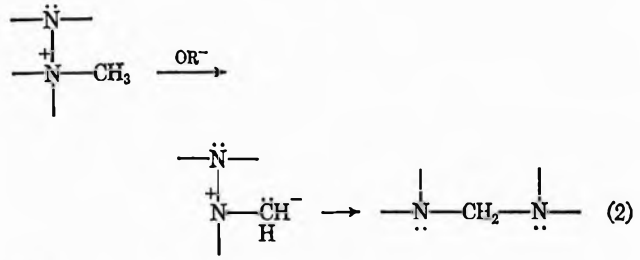
(5) The nmr signal of the NCH_2N grouping in the ring system i and ii is reported to occur as AB quartets at 3.95 (H_A), 4.26 (H_B, J = 13 cps) and 3.30 (H_A), 3.85 (H_B, J = 10.5 cps), respectively: S. Shiotani and K. Mitsuhashi, *J. Pharm. Chem. Jap.*, **14**, 608 (1966).



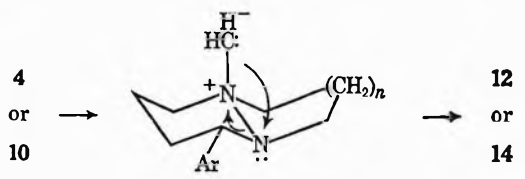
(6) The formation of Hofmann elimination products from –C—N^+ systems under sodium–ammonia reducing conditions has been reported: A. C. Cope, *Org. Reactions*, **11**, Chapter 5 (1960).

The formation of **12** and **14** from **4** and **10** represents a 1,2 shift analogous to the Stevens rearrangement[7] where an NN^+C system rather than an CN^+C system is undergoing rearrangement. In simplified form these transformations may be represented by eq 1 and 2.



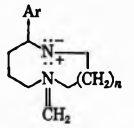


The formation of Stevens rearrangement rather than Hofmann elimination[8] products from **4** and **10** is probably due to the unfavorable steric conditions for β-H elimination. Inspection of models of **4** and **10** reveal that attack of methoxide ion on the axial benzyl hydrogen is sterically unfavorable owing to crowding of this site by the axial N^+CH_3 group. The H atoms on the N^+CH_3 group are readily accessible to methoxide ion to form the anion **17** which has the proper geometrical orientation to undergo a 1,2 shift to **12** or **14**.



17, Ar = *p*-anisyl
$n = 1, 2$

(7) The Stevens rearrangement has been postulated to occur by (a) an ion-pair mechanism [R. A. W. Johnstone and T. S. Stevens, *J. Chem. Soc.*, 4487 (1955); E. F. Jenny and A. Melzer, *Tetrahedron Lett.*, 3507 (1966)], (b) a stepwise internal nucleophilic displacement mechanism [C. R. Hauser and S. W. Cantor, *J. Amer. Chem. Soc.*, **73**, 1437 (1951)] that has recently been proposed to involve (c) a concerted cyclic process [H. E. Zimmerman in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 378–391; E. Grovenstein, Jr., and G. Wentworth, *J. Amer. Chem. Soc.*, **89**, 1852, (1967)] and (d) carbene pathway [A. G. Anderson and M. T. Wills, *J. Org. Chem.*, **33**, 537 (1968)]. The pathway given in eq 2 corresponds to the stepwise nucleophilic displacement (eq 1). We do not consider that this is the only possible pathway for forming **12** and **14**. Ion-pair intermediates such as iii are also possible.



iii, $n = 1,2$
Ar = *p*-anisyl

(8) For a recent discussion on the Hofmann elimination in cyclic hydrocarbons, see M. P. Cooke, Jr., and J. L. Coke, *J. Amer. Chem. Soc.*, **90**, 5556 (1968).

Experimental Section[9]

4-*p*-Anisyl-2-(3-hydroxypropyl)-5,6-dihydropyridazin-1(2H)-one (1).—A mixture of 20.8 g (0.10 mol) of 3-*p*-anisoylpropionic acid, 13.5 g (0.15 mol) of 3-hydrazinopropanol,[10] and 250 ml of toluene was stirred and refluxed in a flask equipped with a Dean–Stark tube until the "water" level in the side arm remained constant. The solvent was removed *in vacuo* and the residue gave 21 g (81%) of **1**: mp 117–118°; ir (KBr) 6.05 μ (C=O).

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.1; H, 6.9; N, 10.7. Found: C, 64.0; H, 6.7; N, 10.6.

3-*p*-Anisyl-1-(3-hydroxypropyl)hexahydropyridazine (2).—A slurry of 14.3 g (0.376 mol) of lithium aluminum hydride and 1500 ml of diethyl ether (nitrogen atmosphere) was stirred and refluxed (72 hr) through a Soxhlet apparatus containing 50.0 g (0.19 mol) of **1**. After cooling in an ice bath the reactants were treated with 28.6 ml of 2 *N* sodium hydroxide, 42.9 ml of water, and 50 g of anhydrous sodium sulfate. The salts were filtered off and the filtrate was concentrated *in vacuo* to give 46 g of **2** as an oil: nmr ($CDCl_3$) δ 1.87 (6 H, m, CH_2CH_2, CH_2), 2.28–3.24 (4 H, m, CH_2NCH_2), 3.63 (2 H, t, J = 6.0 cps, CH_2OH), 3.73 (3 H, s, OCH_3), 3.82 (2 H, D_2O exchangeable, NH, OH), 3.88 (1 H, m, ArCHN), 7.10 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.2; H, 8.8. Found: C, 67.4, H, 8.7.

2-*p*-Anisyl-1,6-diazabicyclo[4.3.0]nonane (3).—A mixture containing 50.0 g (0.20 mol) of **2**, 35.7 g (0.30 mol) of thionyl chloride, and 500 ml of dry chloroform was refluxed for 18 hr. The solution was washed with 100 ml of 2 *N* $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 47.5 g of oil. Distillation gave 33.2 g (72%) of **3**: bp 150–152° (2.0 mm); $n^{20}D$ 1.5507; nmr ($CDCl_3$) δ 1.52–3.40 (13 H, series of overlapping multiplets), 3.78 (3 H, s, OCH_3), 7.08 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.4; H, 8.6. Found: C, 72.7; H, 8.5.

A solution of **3** in diethyl ether was treated with anhydrous HCl to give the hydrochloride of **3**, mp 135–138° (hygroscopic).

Anal. Calcd for $C_{14}H_{21}ClN_2O$: C, 62.6; H, 7.9; N, 10.4. Found: C, 62.2; H, 8.0; N, 10.3.

5-*p*-Anisyl-1-methyl-1,6-diazonia[4.3.0]nonane Iodide (4).—A solution containing 24.2 g (0.102 mol) of **3**, 29.6 g (0.204 mol) of methyl iodide, and 500 ml of dry ether was stirred at room temperature for 15 hr. The solid was filtered off and gave 37.6 g (98%) of **4**: mp 194–197°; nmr ($CDCl_3$) δ 1.68–3.28 (9 H, series of overlapping multiplets), 3.62 (3 H, s, CH_3N^+), 3.66 (2 H, m, CH_2N^+), 3.78 (3 H, s, OCH_3), 4.32 (2 H, m, CH_2N^+), 7.10 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{15}H_{23}IN_2O$: C, 48.1; H, 6.2; N, 7.5. Found: C, 48.0; H, 6.4; N, 7.2.

1-(3-*p*-Anisoylpropionyl)hexahydropyridazine (6).—To a stirred, ice cooled solution of 50.6 g (0.243 mol) of 3-anisoylpropionic acid, 24.6 g (0.243 mol) of triethylamine, and 500 ml of dry chloroform there was added dropwise (0.7 hr; internal temperature 10 ± 5°) a solution of 26.5 g (0.243 mol) of ethyl chloroformate in 150 ml of chloroform. After stirring 1 additional hr a solution of 20.8 g (0.275 mol) of hexahydropyridazine[11] [nmr, $CDCl_3$, δ 1.68 (4 H, m, CH_2CH_2), 2.90 (4 H, m, CH_2NNCH_2), 3.38 (2 H, D_2O exchangeable, NHNH)] in 150 ml of chloroform was added dropwise (0.3 hr). The ice bath was removed and the reaction was stirred for 18 hr at room temperature, washed with 100 ml of 2 *N* Na_2CO_3 and 150 ml of water, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 56.0 g (84%) of **6** as an oil: R_f 0.70 ($CHCl_3$–CH_3OH, 95:5); ir (CH_2Cl_2) 5.97 (C=O), 6.10 μ (CON); nmr ($CDCl_3$) δ 1.63 (4 H, m, CCH_2CH_2C), 2.83 (1 H, D_2O exchangeable, NH), 2.72–3.40 (5 H, m, $ARCOCH_2$, CH_2NNCH_A), 3.61 (3 H, m, CH_2CONCH_B), 3.82 (3 H, s, OCH_3), 7.42 (4 H, A_2B_2, C_6H_4).

(9) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and have not been corrected. Proton nmr spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in parts per million from an internal $(CH_3)_4Si$ standard. Infrared spectrum were determined on a Perkin-Elmer Infracord spectrophotometer. Ultraviolet spectrum were carried out on a Cary Model 15 spectrometer. Mass spectra were determined on a Consolidated Electronics Co. mass spectrometer, Model 21-103C, equipped with an all-glass heated inlet. Thin layer chromatography was determined on glass plates coated with silica gel HF-254, Merck AG.

(10) G. Gever, *J. Amer. Chem. Soc.*, **76**, 1283 (1954).

(11) P. Baranger and J. Levisalles, *Bull. Soc. Chim. Fr.*, 704 (1957).

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.2; H, 7.2; N, 10.1. Found: C, 65.0; H, 7.0; N, 10.0.

5-*p*-Anisyl-1,6-diazabicyclo[4.4.0]dec-4-en-2-one (7).—A mixture containing 56.0 g of **6**, 2.5 g of *p*-toluenesulfonic acid, and 750 ml of toluene was stirred and refluxed in a flask equipped with a Dean–Stark tube. After the "water" level in the side arm remained constant (18 hr) the solution was washed with 100 ml of 1 *N* Na_2CO_3 and 50 ml of water, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 33.4 g (63%) of **7**: mp 119–121° (CH_2Cl_2–diethyl ether); ir (KBr) 6.08 μ (C=O); uv maximum 246 mμ (18,300); nmr ($CDCl_3$) δ 1.68 (4 H, m, CCH_2CH_2C) 3.02 (4 H, m, CH_2NNCH_2), 3.78 (3 H, s, OCH_3), 3.83 (2 H, m, CH_2CO), 5.18 (1 H, t, J = 4 cps, HC=C), 7.12 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.7; H, 7.0; N, 10.9; O, 12.4. Found: C, 69.6; H, 7.3; N, 10.7; O, 12.3.

5-*p*-Anisyl-1,6-diazabicyclo[4.4.0]decan-2-one (8).—A mixture of 14.0 g of **7**, 0.7 g of platinum oxide and 75 ml of acetic acid was hydrogenated (50 psi; room temperature) on a Parr hydrogenation apparatus until 1 equiv of hydrogen was absorbed (2.0 hr). The catalyst was filtered off, the filtrate concentrated *in vacuo*, and the residue treated with 100 ml of 2 *N* $NaHCO_3$ and 100 ml of chloroform. The organic layer was washed with water, dried ($MgSO_4$), filtered, and concentrated to give 12.7 g (90%) of **8**: bp 220° (kugelrohr, 0.5 mm); ir (CH_2Cl_2) 6.10 μ (C=O); nmr ($CDCl_3$) δ 1.58 (4 H, m, CCH_2CH_2C), 1.90–3.50 (7 H, overlapping multiplets, CH_ANNCH_2, $ArCCH_2CH_2CO$), 3.70 (3 H, s, OCH_3), 3.92 (1 H, t, J = 5.0 cps, ArCHN), 4.28 (1 H, m, CH_BNCO), 7.08 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.2; H, 7.7; N, 10.8; O, 12.3. Found: C, 68.7; H, 8.0; N, 10.7; O, 12.5.

A solution of **8** in tetrahydrofuran was treated with anhydrous HCl to give the hydrochloride of **8**, mp 174–176°.

Anal. Calcd for $C_{15}H_{21}ClN_2O_2$: C, 60.5; H, 7.1; N, 9.4; O, 10.8. Found: C, 60.5; H, 7.5; N, 9.1; O, 11.0.

A solution of 1.0 g (0.004 mol) of **8**, 1.8 g (0.008 mol) of methyl iodide, and 60 ml of dry diethyl ether when stirred at room temperature for 52 hr (tlc gave only **8**) and refluxed for 18 hr gave after work-up only recovered **8**.

2-*p*-Anisyl-1,6-diazabicyclo[4.4.0]decane (9).—To a stirred slurry (nitrogen atmosphere) of 6.7 g (0.176 mol) of lithium aluminum hydride and 500 ml of dry diethyl ether there was added dropwise a solution of 22.8 g (0.088 mol) of **8** in 250 ml of dry diethyl ether. After 96-hr reflux the mixture was cooled in an ice bath, treated with 13.4 ml of 2 *N* NaOH, 20 ml of water, and 50 g of anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Distillation of the residue gave 17.8 (82%) of **9**: bp 205° (16 mm); mp 66–68° (pentane); nmr ($CDCl_3$) δ 1.62 (8 H, overlapping multiplets, CCH_2CH_2C, CH_2CH_2CAr), 1.90–3.32 [7 H, overlapping multiplets, $CH_2N(CH_2)N(CH_2)CHAr$], 3.73 (3 H, s, OCH_3), 7.01 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.1; H, 9.0; N, 11.4; O, 6.5. Found: C, 73.1; H, 9.3; N, 11.6; O, 6.9.

A solution of **9** in diethyl ether treated with anhydrous HCl gave the hydrochloride of **9**, mp 153–156°.

Anal. Calcd for $C_{15}H_{23}ClN_2O$: C, 63.7; H, 8.2; Cl, 12.5. Found: C, 63.5; H, 8.4; Cl, 12.7.

5-*p*-Anisyl-1-methyl-1,6-diazonia[4.4.0]decane Iodide (10).—A solution of 12.7 g (0.052 mol) of **9**, 14.7 g (0.104 mol) of methyl iodide, and 125 ml of dry diethyl ether was stirred for 50 hr at room temperature. The resultant solid was filtered off to give 18.2 g (91%) of **10**: mp 212–215° (CH_2Cl_2–ether); nmr ($CDCl_3$) δ 1.68–3.28 (11 H, overlapping multiplets, $CH_2CH_2CHNCH_2$-CH_2CH_2), 3.62 (3 H, s, CH_3N^+), 3.66 (2 H, m, $CH_AN^+CH_A$), 3.78 (3 H, s, OCH_3), 4.32 ($CH_BN^+CH_B$), 7.10 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{16}H_{25}IN_2O$: C, 49.5; H, 6.5; N, 7.2. Found: C, 49.1; H, 6.7; N, 7.2.

2-*p*-Anisyl-1,6-diazabicyclo[4.3.1]decane (12).—To a freshly prepared solution of 4.6 g (0.20 g-atom) of sodium in 150 ml of anhydrous methanol (nitrogen atmosphere) there was added a solution of 25 g (0.067 mol) of **4** in 200 ml of anhydrous methanol. After 48 hr at reflux the solvent was removed *in vacuo* and the residue treated with 100 ml of water and 150 ml of methylene chloride. The organic layer was concentrated *in vacuo* and the residue treated with 250 ml of pentane, filtered, and the filtrate concentrated *in vacuo* to give 10.6 (62%) of **12**: bp 192–195° (0.25 mm); nmr ($CDCl_3$) δ 1.05 (1 H, d–m, J = 12 cps, CH_AN), 1.50–3.56 [12 H, overlapping multiplets, $ArCH(CH_2)_3NCH_2CH_2$-CH_BN], 3.72 (3 H, s, OCH_3), 4.12 (2 H, s, NCH_2N), 7.03 (4 H, A_2B_2, C_6H_4); *m/e* 256 ($C_{15}H_{22}N_2O$).

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.1; H, 9.0; N, 11.4. Found: C, 72.8; H, 9.1; N, 11.4.

6-*p*-Anisyl-1-methyl-1,5-diazacyclononane (13).—To a mixture of 5.0 g (0.013 mol) of **4** in *ca.* 100 ml of anhydrous ammonia, cooled in a Dry Ice–acetone bath, there was added in small portions 0.76 g (0.033 g-atom) of sodium over a 0.2-hr period. The system turned brown, then blue, and finally colorless in *ca.* 0.3 hr after the addition was completed. The ammonia was allowed to evaporate and the residue was treated with 50 ml of ice–water and then 50 ml of chloroform. The organic layer was extracted with 1 *N* HCl (50 ml, twice) and the acid layer made basic with 2 *N* NaOH, extracted with chloroform, dried ($MgSO_4$), filtered, and concentrated to give 2.8 g (87%) of **13**: bp 183–185° (0.5 mm); ir (CH_2Cl_2) 2.98 μ (NH); nmr ($CDCl_3$) δ 1.46–1.80 (4 H, m, two CH_2 groups), 1.78 (1 H, D_2O exchangeable, NH), 2.03–3.33 (8 H, m, 4 CH_2 groups), 2.32 (3 H, s, HCN_3), 3.72 (1 H, m, ArCHN), 3.75 (3 H, s, OCH_3), 7.02 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.6; H, 9.7; N, 11.3. Found: C, 72.4; H, 9.8; N, 11.1.

A solution of **13** in diethyl ether was treated with anhydrous HCl to give the dihydrochloride of **13**, mp 187–188° (hygroscopic).

Anal. Calcd for $C_{15}H_{26}Cl_2N_2O$: C, 56.1; H, 8.2; N, 8.7. Found: C, 56.1; H, 8.4; N, 8.8.

2-*p*-Anisyl-1,6-diaza[4.4.1]undecane (14).—To a freshly prepared solution of 1.7 g (0.074 g-atom) of sodium in 50 ml of anhydrous methanol (nitrogen atmosphere) there was added a solution of 9.0 g (0.023 mol) of **10** and 60 ml of methanol. The solution was refluxed 96 hr, concentrated *in vacuo*, and the residue treated with 75 ml of water and 75 ml of pentane. The organic layer was dried (Na_2SO_4), filtered, concentrated *in vacuo*, and distilled (kugelrohr; 1.0 mm, 200–220°) to give 4.4 g (90%) of **14** as an oil: nmr ($CDCl_3$) δ 1.33–3.27 [14 H, overlapping multiplets, $(CH_2)_3N(CH_2)_4N$], 3.70 (1 H, m, ArCHN), 3.75 (3 H, s, OCH_3), 4.08 (H_A), 4.42 (H_B, AB, J = 15.0 cps, NCH_AH_BN), 7.00 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{16}H_{24}N_2O$: C, 73.8; H, 9.3; N, 10.8. Found: C, 73.4; H, 9.5; N, 10.8.

A solution of **14** in anhydrous diethyl ether was treated with dry HCl to give the hydrochloride of **14**: mp 187–189° (hygroscopic); nmr ($CDCl_3$) δ 1.98 [8 H, m, $(CCH_2CH_2C)_2$], 2.60–3.80 [6 H, $CH_2NCN^+(CH_2)CH_2$], 3.72 (3 H, s, OCH_3), 3.81 (1 H, m, ArCHN), 4.62 (H_A), 4.93 (H_B, A_2B_2, J = 15.0 cps, $^+NCH_AH_BN$), 6.98 (4 H, A_2B_2, C_6H_4), 9.20 (1 H, D_2O exchangeable, ^+NH).

Anal. Calcd for $C_{16}H_{25}ClN_2O$: C, 61.6; H, 8.4; Cl, 12.0. Found: C, 61.7; H, 8.7; Cl, 12.3.

5-*p*-Anisyl-1-methyl-1,6-diazacyclodecane (15) and 5-*p*-Anisyl-1-methyl-1,6-diazacyclodec-4-ene (16).—Following the procedure used to prepare **13** a mixture of 9.0 g (0.023 mol) of **10**, 1.3 g (0.055 g-atom) of sodium, and ~200 ml of anhydrous liquid ammonia gave 7.2 g of basic material, R_f 0.2 and 0.5 ($CHCl_3$–CH_3OH, 90:10). Chromatography on silica gel (100 g; eluent $CHCl_3$–CH_3OH, 98:2) gave 1.8 g of **16** as an oil: R_f 0.5; ir (CH_2Cl_2) 6.05 μ (C=N); uv maxima 226 mμ (9030), 276 (1805), 283 (1435); nmr ($CDCl_3$) δ 1.63 (8 H, m, four CH_2 groups), 2.27 (3 H, s, NCH_3), 2.32 (6 H, m, CH_2NCH_2, $=NCH_2$), 3.72 (3 H, s, OCH_3), 6.98 (4 H, A_2B_2, C_6H_4) and 4.7 g of **15** as an oil, R_f 0.2; ir (CH_2Cl_2) 2.75, 3.08 and 3.13 μ (NH); nmr ($CDCl_3$ δ 1.71 (8 H, m, four CH_2 groups), 2.25 (3 H, s, NCH_3), 2.05–2.54 (6 H, m, CH_2NCH_2, $N'CH_2$), 3.50 (1 H, m, ArCHN), 3.71 (3 H, s, OCH_3), 5.02 (1 H, D_2O exchangeable, NH), 7.00 (4 H, A_2B_2, C_6H_4).

Anal. Calcd for $C_{16}H_{24}N_2O$: C, 73.9; H, 9.2; N, 10.8. Found: C, 73.7; H, 9.1; N, 10.6.

Registry No.—**1**, 20072-61-1; **2**, 20072-62-2; **3**, 20072-63-3; hydrochloride of **3**, 20072-64-4; **4**, 20126-07-2; **6**, 20072-65-5; **7**, 20072-66-6; **8**, 20072-67-7; hydrochloride of **8**, 20072-68-8; **9**, 20072-69-9; hydrochloride of **9**, 20072-71-3; **10**, 20072-72-4; **12**, 20072-73-5; **13**, 20072-70-2; dihydrochloride of **13**, 20072-74-6; **14**, 20072-29-1; dihydrochloride of **14**, 20072-30-4; **15**, 20072-31-5; **16**, 20072-32-6.

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A Darzens Aziridine Synthesis[1]

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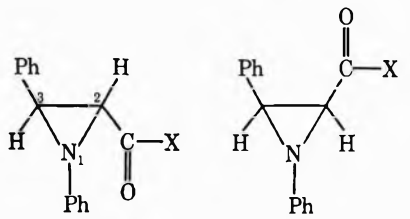
A procedure has been developed which allows successful extension of the Darzens synthesis to the preparation of aziridine esters and amides. The stereochemical course of the condensation yields the unexpected result of preferential formation of *trans* ester and *cis*-amide. The significance and a possible explanation of this result are discussed. The chemistry of these aziridines has been briefly investigated and found to be dominated by the ease with which these compounds form azomethine ylides.

The unexpected reactions and stereochemical behavior which we encountered in our studies of 2-chloro-1,3-diphenylaziridines have focused our interest on exploring the chemistry of related functionally substituted aziridines.[2,3] Although a number of precursors to functionally substituted aziridines were considered, aziridine esters appeared to offer the greatest versatility. In order to correlate our results with our previous work, we chose to prepare *cis*- and *trans*-1,3-diphenyl-2-aziridinecarboxylic acid derivatives (**1** and **2**).



1 **2**

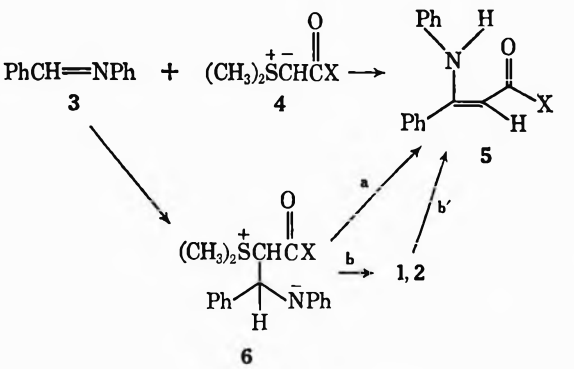
a, X = OC_2H_5
b, X = $N(C_2H_5)_2$

Attempts to extend conventional procedures for aziridine synthesis were unsuccessful when applied to the preparation of **1** and **2**. Our search for alternative routes to these compounds has resulted in the discovery that the Darzens condensation[4] can be extended to the synthesis of **1** and **2**.

Reaction of benzalaniline (**3**) and ethyl chloroacetate in ether (sodium methoxide as base) or in benzene (potassium *t*-butoxide as base) failed to yield the desired product. The combination of dimethoxyethane as solvent and potassium *t*-butoxide as base, however, resulted in the formation of **1a** in 29% yield. Examination of the crude reaction mixture by nmr spectroscopy showed that no more than 10% of the isomeric *cis* adduct (**2a**) was formed. In a similar manner, 2-chloro-N,N-diethylacetamide could be condensed with **3** to give *cis* amide **2b** as the major product in 58% yield. A second product was also isolated in 7% yield and identified as the *trans* isomer **1b**. Analysis of the crude reaction mixture showed a similar ratio (approximately 9:1) of *cis* to *trans* products. The failure of these aziridines to isomerize under the reaction conditions (see Experimental Section) indicates that these product ratios are kinetically controlled. This rather remarkable change in the stereochemistry of the major product from *trans* to *cis* will be discussed below. The structure and stereochemistry of these products were established by their elemental analyses and nmr spectra (Table I).

$$\underset{\mathbf{3}}{PhCH{=}NPh} + ClCH_2CO_2Et \rightarrow \mathbf{1a}$$

The isolation of aziridines **1a**, **2a** and **2b** is interesting in view of a recent publication concerning the reaction of benzalaniline (**3**) with sulfonium ylides (**4**).[5] The main product of these reactions were cinnamic acid derivatives **5**. Careful inspection (see Experimental Section) revealed that **5** was not formed as a by-product in the aziridine synthesis. Conversely, aziridines **1b** and **2b** were not detected in the synthesis of **5b**.



3 **4** **5** **6**

It was concluded by the authors that the initially formed betaine (**6**) underwent initial closure (b) to aziridine (**1**, **2**) which rapidly opened (b′) to the observed product. An alternative mechanism (a) which bypassed the aziridine ring was excluded by means of an alternative (carbenoid) reaction with **3** which also yielded **5**.

In view of this reported instability of aziridines **1** and **2**, we undertook a brief examination of their thermal stability and sensitivity toward base. Although no reaction occurred at room temperature in carbon tetrachloride, *trans*-aziridine **1a** underwent isomerization in this solvent at 80°. After 10 hr, equilibrium (50:50) was established between **1a** and a new substance which could not be obtained in pure crystalline form. Structure **2a** was assigned to this compound on the basis of its nmr spectrum (Table I). In a similar manner, **1b** could be equilibrated in carbon tetrachloride at 80° to a 52:48 mixture of **1b** and **2b** respectively.

These isomerizations in the absence of base are most reasonably explained in terms of intermediate azo-

(1) Acknowledgement: Support of this research by National Science Foundation Grants GP-5531 and GP-8044 is gratefully acknowledged.

(2) J. A. Deyrup and R. B. Greenwald, *J. Amer. Chem. Soc.*, **87**, 4538. (1965).

(3) J. A. Deyrup and R. B. Greenwald, *Tetrahedron Lett.*, 5091 (1966).

(4) M. S. Newman and B. J. Magerlein, *Org. Reactions*, **5**, 413 (1949); H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, 1965, p 240.

(5) A. J. Speziale, C. C. Tung, K. W. Ratts, and A. Yao, *J. Amer. Chem. Soc.*, **87**, 3460 (1965).

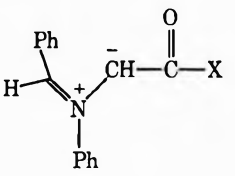
TABLE I

NMR SPECTRA OF CONDENSATION PRODUCTS[a]

Compd	ArH	C-3 H[b]	C-2 H[b]	CH_2	CH_3
1a	6.7–7.4	3.72 (2.0)	3.08 (2.0)	4.07	1.08
2a	6.7–7.6	3.44 (7.0)	3.04 (7.0)	3.80	0.92
2b	6.8–7.5	3.42 (7.5)	3.07 (7.5)	2.9–3.5	4–1.1
1b	6.7–7.4	3.90 (2.0)	3.07 (2.0)	3.0–3.8	0.8–1.4

[a] Chemical shifts are expressed in δ, ppm, with respect to internal TMS. Values in parantheses are for $J_{2,3}$. [b] The assignment of C-2 and C-3 is tentatively based on the greater deshielding effect of a C_6H_5 over a CO_2R group. [c] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 53.

methine ylide **7**.[6] In order to confirm the intermediacy of this dipolar species, aziridines **1a**, **1b**, and **2b** were



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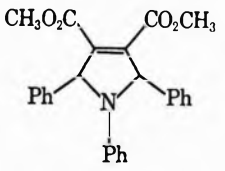
heated in carbon tetrachloride in the presence of a twofold excess of a dipolarophile (dimethyl acetylenedicarboxylate). In each case a single 1:1 adduct was obtained.

Previous reactions of aziridines with alkynes (*via* azomethine ylides) have produced 2-pyrrolines,[7] 3-pyrrolines,[6b,8] and mixtures of both.[6a] Especially relevant to this work is the adduct formed from 1,2,3-triphenylaziridine and dimethyl acetylenedicarboxylate.[8] This symmetrical adduct has been definitely assigned the 3-pyrroline structure (**8**) on the basis of the single OCH_3 and ring proton peaks in its nmr spectrum. The unsymmetrical 2-pyrroline isomer (**9**) would be expected



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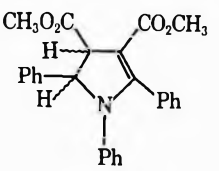

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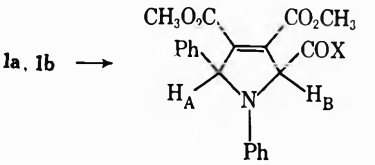
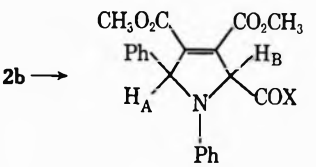
to show two separate OCH_3 peaks as well as different (and coupled) ring protons. Similar nmr spectral symmetry arguments can not be extended to the adducts from **1a**, **1b**, and **2b**. The difference in the chromophoric systems of N-phenyl-2- and 3-pyrrolines allows ultraviolet spectral comparison of these adducts with **8**. The great similarity of the uv spectra of **8** (λ_{max}^{EtOH} 242 mμ, log ϵ 4.29; 288 mμ, log ϵ 3.26), the adduct from **1a** (λ_{max}^{EtOH} 240 mμ, log ϵ 4.37; 284 mμ, log ϵ 3.27), and the adduct from **2b** (λ_{max}^{EtOH} 242 mμ, log ϵ 4.35; 288 mμ, log ϵ 3.25) thus allows assignment of the 3-pyrroline structure to them.[9] The stereospecificity of adduct formation also suggests that the initial adduct has not undergone 1,3-hydride migration to a 2-pyrroline isomer. A concerted 1,3 shift is not thermally allowed, and stereospecific two-step isomerization seems unlikely.

The verification by Huisgen that aziridines open *via* a conrotatory process in thermal reactions[6b] allows assignment of structures **10** and **11** to the products of the reactions described in this paper. An unusual feature of the nmr spectra of these compounds in the magnitude (3.5–7 Hz) of the long range coupling constants J_{AB}.



$J_{AB} = 3.5$ Hz

10



$J_{AB} = 7$ Hz

11

Although efficient coupling does not normally occur through four σ bonds,[7,11] the presence of the nitrogen atom[12] and possible contributions of the homoallylic type[13] could contribute to the size of J_{AB}.[14]

Both the esters and the amides were unaffected by base in ethanol and dimethoxyethane at 25°. At higher temperatures (80°), alcoholic base converted ester **1a** into benzaldehyde and ethyl 2-anilinoacetate. These products were presumably formed in the reaction of **7** with trace amounts of water present in the solvent.[15] A solution of potassium *t*-butoxide and **1b** or **2b** in *t*-butyl alcohol at 82° produced an equilibrium mixture of **2b** and **1b** (65:35). Although no attempts were made to ascertain the role (if any) of base in this latter equilibrium, it is clear that aziridines **1** and **2** are not precursors of **5**. We conclude, therefore, that the reaction of sulphonium ylides with imines proceeds *via* path a and does not involve intermediacy of aziridine (path b). The details of the mechanism by which the unsaturated product **5** is formed is an interesting but as yet unsettled question. A number of possible mechanisms can be considered.[16]

The stereochemical course of these Darzens condensations is unusual and deserves further comment. The

(6) R. Huisgen, W. Scheer, G. Szeimies, and H. Huber, *Tetrahedron Lett.*, 397 (1966); (b) R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).

(7) A. Padwa and L. Hamilton, *J. Heterocyclic Chem.*, **4**, 118 (1967).

(8) H. W. Heine and R. Peavy, *Tetrahedron Lett.*, 3123 (1965).

(9) The position and relative intensities of these maxima are in qualitative agreement with models for similar aniline chromophores.[10]

(10) A. T. Bottini and C. P. Nash, *J. Amer. Chem. Soc.*, **84**, 734 (1962).

(11) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden Day, Inc., San Francisco, Calif., 1964, pp 115.

(12) *Cf.* reference 11, p 121.

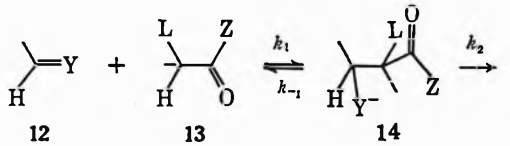
(13) Reference 11, p 110.

(14) Professor R. Huisgen has kindly informed us of his observation of similar long range coupling constants in 3-pyrrolines.

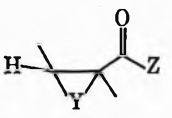
(15) Similar reactions and conclusions have been observed in the chemistry of the N-alkyl aziridine esters; P. B. Woller and N. H. Cromwell, *J. Heterocyclic Chem.*, **5**, 579 (1968).

(16) *Cf.* E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

Darzens condensation between halo esters and carbonyl compounds has been investigated by Zimmerman.[17] He concluded that the aldol intermediate **14** (Y = O, Z = OR) is formed rapidly and reversibly prior to rate-determining cyclization ($k_{-1} > k_2$). The stereochemistry of the product **15** is, therefore, determined by the k_2 (*trans*)/k_2 (*cis*) ratio. This ratio for Y = O, Z = OR was



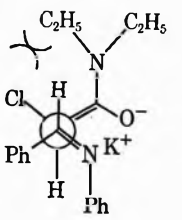
12 **13** **14**



15

observed to be greater than unity. In order to explain this result, Zimmerman noted that overlap of the C–O π orbital with the departing halide is greatest in the transition state which leads to the *trans* product ("overlap control").

The preferred formation of *trans*-aziridine **1a** is in agreement with Zimmerman's picture of the Darzens condensation. In contrast, there is no reason to expect overlap control of k_2 to favor the *trans* ester (**1a**) and the *cis* amide (**2b**). The stereochemistry of **2b** must, therefore, be determined in the condensation of **12** and **13** to give **14**. In other words, k_2 is greater than k_{-1} and k_1 (*cis*) is greater than k_1 (*trans*). The suggested inversion in magnitude of rate constants k_2 and k_{-1} is not unreasonable in view of the decreased stability of enolate anion (**9**)[18] and the increased nucleophilicity of the heteroatom in **14**. In order to understand the stereochemical control of this reaction, it is necessary to consider the transition state leading to the aldol intermediate (as opposed to the relative stability of these intermediates). We would like to suggest that the preferred geometry for the reaction between enolate anion **13** (Z = NR_2) and imine (Y = NR′) will find the cation more or less symmetrically disposed between the developing (on nitrogen) and dispersing (acyl oxygen) negative charge. This restriction allows two possible arrangements (**16** and **17**) which have minimal incipient eclipsing interactions. The bulk of the diethylamino group and its probable coplanarity with the enolate anion π system stands in opposition to the bulk of the chloro group. For this reason, **17** would appear to be the preferred arrangement. Bond formation from **17** would produce **18**, which is the diastereomeric precursor to **2b**. The extent to which these considerations are applicable to the Darzens and similar condensations is under further study.[19]



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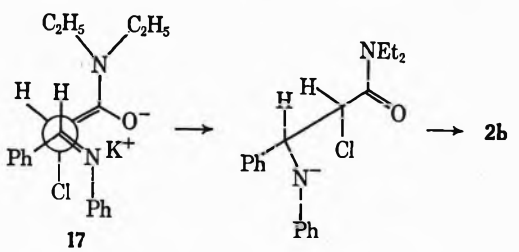

17 **18** **2b**

Experimental Section

cis- and *trans*-1,3-Diphenyl-2-azairidinecarboxylic Acid Diethylamide.—A mixture of 9.05 g (0.05 mol) of benzaldehyde anil and 7.87 g (0.07) mol) of potassium *t*-butoxide in 200 ml of dimethoxyethane was cooled to −40° under nitrogen. This mixture was stirred and maintained at this temperature while a solution of 10.47 g (0.07 mol) of 2-chloro-N,N-diethylacetamide in 125 ml of dimethoxyethane was added over a 2-hr period. The reaction was allowed to warm to room temperature over a 30-min period and concentrated to a small volume *in vacuo* at 35°. The residue was diluted with water and ether. After removal of the ether layer, the aqueous fraction was extracted with two portions of ether, and the combined extracts were dried ($MgSO_4$). Filtration and evaporation of the ether yielded 16.32 g of crude material.[21] This material was chromatographed on deactivated alumina with initial elution by petroleum ether followed by benzene. In this way two pure fractions were obtained which, after recrystallization from benzene–petroleum ether, were identified as the *trans* isomer, mp 90–92° (7%), and the *cis* isomer, mp 80.5–82.5° (58%).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.76; H, 7.60; N, 9.61 (*trans*); C, 77.41; H, 7.73; N, 9.30 (*cis*).

Inspection (nmr spectral and thin layer) of the other fractions did not reveal any 3-anilino-N,N-diethylcinnamamide.

Ethyl *trans*-1,3-Diphenyl-2-aziridinecarboxylate.—A mixture of 42.5 g (0.25 mol) of benzaldehyde anil and 39.2 g (0.35 mol) of potassium *t*-butoxide in 250 ml of dimethoxyethane was cooled to −40° under nitrogen. To this stirred mixture at −40° was added, over a 3-hr period, a solution of 45.3 g (0.35 mol) of ethyl chloroacetate. The reaction was allowed to warm to room temperature for 1 hr, and then evaporated *in vacuo*. The residue was diluted with water and extracted several times with ether. The ether extracts were dried and concentrated to give 66.85 g of an oil.[22] This oil was diluted with petroleum ether and cooled; yield 19.4 g (29%) of solid, mp 80–83°. Recrystallization from ethanol gave colorless prisms: mp 82–84°; ir (Nujol) 1730 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.62; H, 6.29; N, 5.45.

Preparation of 3-Anilino-N,N-diethylcinnamamide.—This compound was prepared in 48% yield (mp 90–92°), 91–92°)[5] according to the previously published procedure. Careful chromatographic investigation of the mother liquors failed to reveal either of the isomeric aziridines.

Stability of Products to Reaction Conditions.—A solution of 40 mg (0.35 mmol) of potassium *t*-butoxide and 74 mg (0.25 mmol) of *trans*-amide **1b** in 5 ml of dimethoxyethane was allowed to stand at room temperature for 2 hr. The solution was then evaporated, diluted with water, and extracted with chloroform. The thin-layer chromatogram of these extracts showed **1b** and no other products. The chloroform was then evaporated. The weight of the residue and its nmr spectrum demonstrated that **1b** had been recovered quantitatively.

(17) H. E. Zimmerman and L. Abramjian, *J. Amer. Chem. Soc.*, **82**, 5459 (1960).

(18) A. J. Spezialle and H. W. Frazier, *J. Org. Chem.*, **26**, 3176 (1961).

(19) In contrast to our observed k_1 (*cis*)/k_1 (*trans*), a recent report of the Darzens condensation between **12** (Y = O) and **3** (Z = NR_2) explained the approximately equal (isolated) yields of *cis* and *trans* in terms of an expectation that k_1 (*cis*) ≈ k_1 (*trans*) (ref 20). Alternatively, their result could reflect a fortuitous combination of almost equally rapid aldolization and cyclization steps.

(20) C. C. Tung, A. J. Speziale, and H. W. Frazier, *J. Org. Chem.*, **28**, 1514 (1963).

(21) The nmr spectrum of this crude material revealed none of the *trans* isomer. The complexity of the spectrum in the region of the ring protons might (conservatively) prevent detection of less than 10% *trans* isomer.

(22) The nmr spectrum of this crude product showed no detectable amount (less than 10%) of the *cis* isomer.

A solution of *trans* ester **1a** (125 mg, 0.5 mmol) and potassium *t*-butoxide (112 mg, 1 mmol) in 10 ml of ethanol was allowed to stand at room temperature for 3 hr. Thin layer analysis of this solution indicated that no change had occurred.

Ring Opening of Ethyl *trans*-1,3-Diphenyl-2-aziridinecarboxylate (CCl_4).—A solution of 268 mg (1 mmol) of the aziridine ester and 4 mg of NaOEt in 20 ml of ethanol was refluxed for 3 days. The solution was then evaporated, diluted with water, and extracted with ether. The ether extracts were dried and concentrated to give 250 mg of oil which had a strong odor of benzaldehyde. The nmr spectrum of this oil was identical to the nmr spectrum of a 50:50 mixture of benzaldehyde and ethyl 2-anilinoacetate. This assignment was confirmed by isolation of the latter compound.

Equilibration of *cis*- and *trans*-Diethylamides (*t*-BuOH).—A solution of 235 mg of the *cis* amide was heated at reflux with 10 mg of potassium *t*-butoxide in 10 ml of *t*-butyl alcohol. After 3 days, tlc analysis revealed no further change. The solution was evaporated, diluted with water, and extracted with ether. The residue was examined by nmr spectroscopy, which indicated *cis* and *trans* isomer in an 65:35 ratio, respectively. A solution of 160 mg of the *trans*-amide and 8 mg of potassium *t*-butoxide in 8 ml of *t*-butyl alcohol was treated in a similar manner and produced the same 65:35 distribution.

Equilibration of Ethyl *trans*-1,3-Diphenyl-2-aziridinecarboxylate.—A solution of 1 g of this ester in 25 ml of CCl_4 was refluxed for 10 hr. An nmr spectrum of an aliquot was identified as a 50:50 mixture of *cis*- and *trans*-aziridine esters. This ratio had not changed after 9 hr of additional reflux. The solvent was then removed and the residue was diluted with petroleum ether. The majority of the *trans* isomer could be removed by filtration. The nmr spectrum of the residue was in agreement (see Table I) with that expected for the *cis* isomer. All attempts to obtain this material in a crystalline form have been unsuccessful.

Equilibration of *trans*-Diethylamide 1b (CCl_4).—A solution of 80 mg of **7** in 25 ml of CCl_4 was refluxed for 3 days. The solution was evaporated and the percentages of **2b** and **1b** determined as 52:48 (respectively) by nmr spectroscopy.[23]

Reaction of *cis*-1,3-Diphenyl-2-aziridinecarboxylic Acid Diethylamide with Dimethyl Acetylenedicarboxylate.—A solution of 294 mg (1 mmol) of the aziridine and 282 mg (2 mmol) of the dipolarophile was refluxed in 30 ml of carbon tetrachloride for 24 hr. Evaporation at reduced pressure yielded a solid which was recrystallized from benzene–petroleum ether to give 330 mg (76%) of a solid: mp 139–140°; nmr ($CDCl_3$) δ 6.3–7.5 (m, 10 H), 6.18 (d, 1 H, J = 7 Hz), 6.12 (d, 1 H, J = 7 Hz), 3.76 (s, 3 H), 3.60 (s, 3 H), 3.1–3.8 (m, 4 H), and 0.8–1.4 ppm (m, 6 H).

Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.69; H, 6.47; N, 6.42. Found: C, 68.81; H, 6.46; N, 6.28.

Reaction of *trans*-1,3-Diphenyl-2-aziridine Carboxylic Acid Diethylamide with Dimethyl Acetylenedicarboxylate.—A solution of 294 mg (1 mmol) of the aziridine and 282 mg (2 mmol) of the dipolarophile was refluxed in 30 ml of carbon tetrachloride for 24 hr. Evaporation at reduced pressure yielded a solid which was recrystallized from benzene–cyclohexane to give 350 mg (80%) of a solid: mp 148–149°; nmr ($CDCl_3$) δ 6.3–8.1 (m, 10 H), 5.77 (d, 1 H, J = 4 Hz), 5.40 (d, 1 H, J = 4 Hz), 3.76 (s, 3 H), 3.60 (s, 3 H), 3.1–4.1 (m, 4 H), and 1–1.5 ppm (m, 6H).

Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.66; H, 6.53; N, 6.31.

Examination of the crude reaction mixture from the reaction of the *cis*- and *trans*-aziridines failed to reveal detectable amounts of isomeric contamination.

Reaction of Ethyl *trans*-1,2-Diphenyl-2-aziridinecarboxylate with Dimethyl Acetylenedicarboxylate.—A solution of 500 mg (1.9 mmol) of this aziridine and 530 mg (3.7 mol) of the dipolarophile was refluxed in 30 ml of carbon tetrachloride for 3 days. The solvent was removed and the residue recrystallized from ethanol to give 500 mg (64%) of solid: mp 120–121°; nmr (CCl_4) δ 6.4–7.8 (m, 10 H), 5.70 (d, J = 3.5 Hz, 1H), 5.22 (d, J = 3.5 Hz, 1 H), 4.35 (q, J = 7Hz, 2 H), 3.76 (s, 3 H), 3.60 (s, 3 H), and 1.37 ppm (t, J = 7 Hz).

Anal. Calcd for $C_{23}H_{23}NO_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.31; H, 5.56; N, 3.23.

No isomers could be detected in the crude reaction mixture. Another experiment with equimolar amounts of the two reactants produced the same stereochemical result. In contrast, reflux of an equimolar mixture of the two reactants in toluene for 3 hr produced a mixture of two adducts. The second adduct was recognized as isomeric to the first: nmr (CCl_4) δ 6.14 (d, J = 7.5 Hz, 1 H), and 5.81 ppm (d, J = 7.5 Hz, 1 H). This second adduct was not characterized further.

Registry No.—**1a**, 20414-50-0; **1b**, 20414-51-1; **2a**, 20414-52-2; **2b**, 20414-53-3; **10b**, 20414-54-4; **11b**, 20414-55-5; **11a**, 20414-56-6.

Acknowledgments.—The author wishes to express his appreciation to Miss Karyl Barron (National Science Foundation Summer Research Participation Program, 1968) for the preparation of several of the above compounds.

(23) This shift in equilibrium constant **2b/1b** with change in solvent is in qualitative agreement with solvent effects observed in aziridine ketone equilibrations: R. E. Lutz and A. B. Turner, *J. Org. Chem.*, **33**, 516 (1968).

Reactions of Phenylchlorodiazirine with Nucleophiles and Substituted Acetylenes[1,2]

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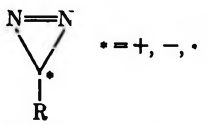
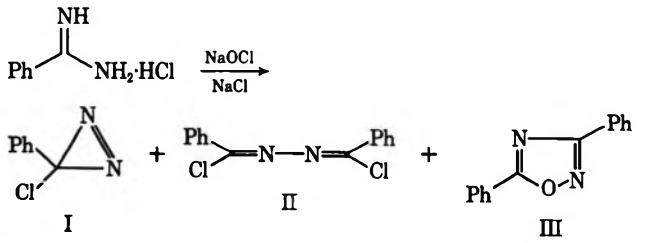
The chemistry of phenylchlorodiazirine (I) has been investigated with emphasis on the nucleophilic attack on the nitrogen–nitrogen double bond and the formation and chemistry of phenylchlorocarbene. Treatment of I with phenyllithium afforded diphenylbenzamidine, whereas reaction with methyllithium gave acetophenone. The reaction of I with sulfonium and phosphonium ylides was also studied. Like other diazirines, phenylchlorodiazirine decomposes thermally to produce phenylchlorocarbene, which may be trapped with triphenylphosphine, tri-*n*-butyltin hydride, and substituted acetylenes.

Among the numerous heterocyclic ions which have been prepared, the diazirinium ion is of particular interest. The heterocyclic cation is isoelectronic with the cyclopropenyl cation[4] and consequently would be predicted to be stable according to Hückel's 4n + 2 rule.[5,6] Although this rule strictly applies only to monocyclic hydrocarbons, heterocyclic aromatics possessing this number of π electrons are considered to meet the criteria of aromaticity.[7] Extended Hückel calculations have indicated however, that the diazirinium cation is unstable with respect to a distortion to a diazomethane cation.[8] In an attempt to gain some insight into the

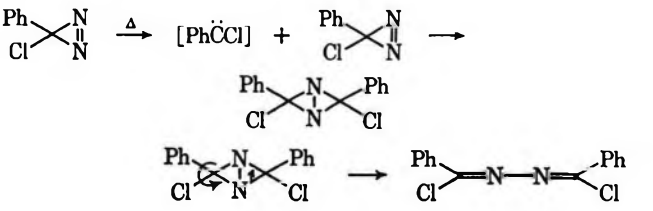


chemical and physical properties of the diazirinium ion system, the chemistry of 3-chlorophenyldiazirine has been investigated. The results of some attempts to generate the anion and radical from a 3-halodiazirine are reported in this paper.

3-Chlorophenyldiazirine (I) was available from the reaction of benzamidine hydrochloride with an aqueous sodium hypochlorite solution.[6] In addition to diazirine I (60%), smaller quantities of 1,4-diphenyl-1,4-dichloro-2,3-diaza-1,3-butadiene (II) (4%) and 3,5-diphenyl-1,2,4-oxadiazole (III) (3%) were formed.

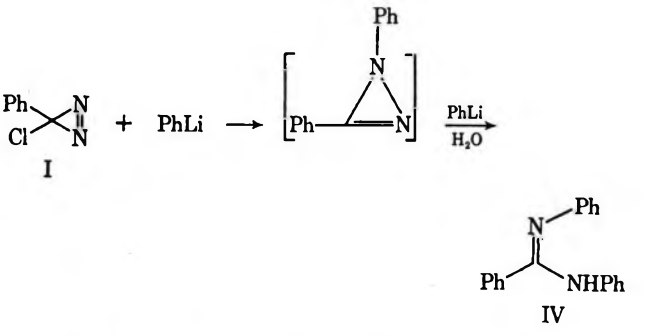


Like other diazirines, phenylchlorodiazirine decomposes thermally to produce phenylchlorocarbene.[9–11] Once formed, the carbene reacts with excess starting diazirine (I) to give a transient diazabicyclo[1.1.0]-butane intermediate.[12] Subsequent bond reorganization readily rationalizes the formation of azine II. In



fact, thermolysis of I in benzene gives II in excellent yield. Similarly, irradiation of I in pentane yields II and a mixture believed to be the insertion products of phenylchlorocarbene with *n*-pentane. Evidently II is a secondary product formed from partial decomposition of I under the original reaction conditions.

With the hope of documenting the transient existence of the diazirinyl anion, we set out to examine the metal exchange reactions of phenylchlorodiazirine. Treatment of I with phenyllithium in ether afforded diphenylbenzamidine (IV) in excellent yield. Isolation of the



amidine suggests that the reaction occurs by attack of phenyllithium on the N–N double bond followed by chloride ion loss and subsequent reaction of the initially formed intermediate with excess phenyllithium. Previous reports by Schmitz[13] have demonstrated the facile addition of related organometallics to diazirines and provide reasonable chemical analogy for the first step. It seems as though the initial intermediate undergoes further reaction with phenyllithium at a faster rate than

(1) We gratefully acknowledge support of this research by the Public Health Service Grant GM 13990-02.

(2) For a preliminary report of this work, see A. Padwa and D. Eastman, *Tetrahedron Lett.*, 4035 (1967).

(3) Alfred P. Sloan Foundation Fellow, 1968–1970.

(4) R. Breslow, H. Hover, and H. W. Chang, *J. Amer. Chem. Soc.*, **84**, 3168 (1962).

(5) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists" John Wiley & Sons, Inc., New York, N. Y., 1961, p 256.

(6) W. H. Graham, *J. Amer. Chem. Soc.*, **87**, 4396 (1965).

(7) R. Breslow, J. Brown, and J. J. Gajewski, *ibid.*, **89**, 4383 (1967).

(8) R. Hoffmann, *Tetrahedron*, **22**, 539 (1966).

(9) H. M. Frey and I. D. R. Stevens, *J. Chem. Soc.*, 1700 (1965).

(10) R. A. Mitsch, *J. Amer. Chem. Soc.*, **87**, 758 (1965).

(11) R. A. Moss, *Tetrahedron Lett.*, 4905 (1967).

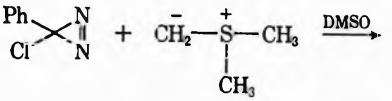
(12) The formation of oxadiazole III may also originate from the transient diazabicyclo[1.1.0]butane.

(13) E. Schmitz, "Advances in Heterocyclic Chemistry," Vol. II, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1965, p 129.

does starting material.[14] This explanation accounts for the large amount (50%) of starting material that can be recovered when equivalent quantities of phenyllithium were used. When a 2 mol excess of phenyllithium was employed, a near quantitative yield of IV could be obtained.

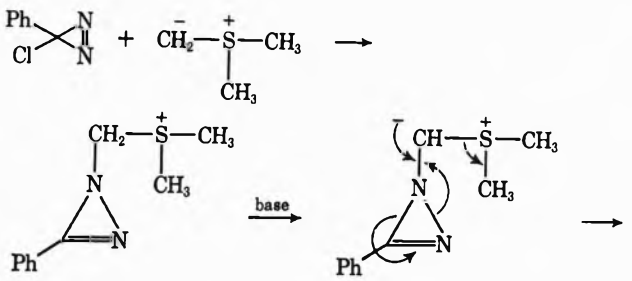
The reaction course followed by treating I with methyllithium in ether proved to be dramatically different. The major product obtained in this case was identified as acetophenone. Careful examination of the residue revealed no detectable amount of dimethylbenzamidine. It appears that the major difference in reaction of I with the two lithium compounds used is related to the direction of addition across the carbon–nitrogen double bond of the initial intermediate. If phenyllithium simply adds across the carbon–nitrogen double bond in the observed direction, then the only phenyl group with which the anion is conjugated is one which is also present in the starting material and which could function just as well in the methyllithium reaction. It therefore appears that attack by phenyllithium is accompanied by ring opening, since the amidine anion which results does indeed have the extra phenyl stabilization in this case. In contrast, methyllithium prefers to undergo stepwise addition at the carbon atom end, since the related amidine anion would be devoid of this overlap. The formation of acetophenone may be readily explained by a hydrolytic fission of the diaziridine upon acid hydrolysis.[14]

With the above results in hand, we considered it relevant to explore the reactivity of I with other nucleophilic reagents. To this end we undertook the study of the reaction of I with dimethylsulfonium ylide. The reaction was observed to proceed quite readily at room temperature. Removal of the solvent followed by vapor phase chromatography of the residue afforded mostly benzonitrile and dimethyl sulfide, with lesser quantities of benzaldehyde and benzal chloride.

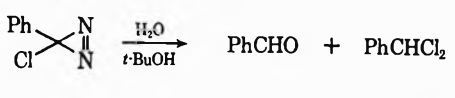


PhCN + CH_3SCH_3 + PhCHO + $PhCHCl_2$

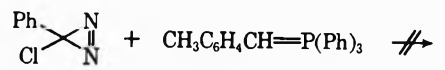
Although no detailed mechanistic study was undertaken, it is possible to formulate a reasonable path for the formation of benzonitrile based on the mechanism previously outlined. As discussed above, initial nucleophilic attack on nitrogen followed by chloride ion loss would lead to a strained sulfonium salt. Removal of a proton from the salt followed by ring cleavage readily accounts for the observed products. The formation of the remaining products obtained from the above reaction may be attributed to the decomposition of unreacted starting material upon aqueous work-up. When phenylchlorodiazirine (I) was treated with aqueous *t*-butanol, benzaldehyde and benzal chloride were the only two products isolated. It seems reasonable to assume that phenylchlorocarbene inserts into the O–H bond of solvent, and the reactive chloro ether so produced undergoes solvolysis under the reaction conditions.



PhCN + HCN + CH_3SCH_3

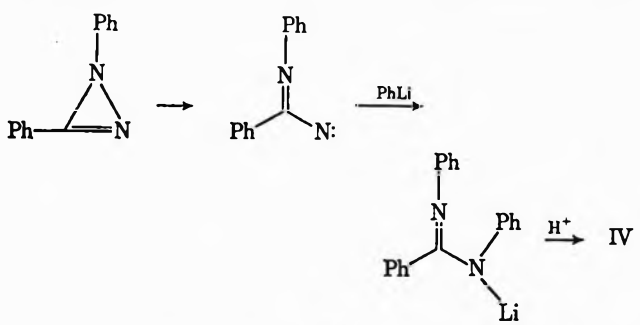


In the expectation that a study of the reaction of I with other ylides might illuminate the mechanism for nitrile formation, phenylchlorodiazirine was treated with a phosphonium ylide. Treatment of I with *p*-toluylmethylene triphenylphosphorane for 2 hr at room temperature produced small amounts of benzal chloride and benzonitrile (4%). The remaining organic products were brown to black tars with ill-defined spectra, unresolved by careful chromatography. In view of the difficulty of isolating characterizable products from this reaction, we abandoned further study of the reaction of I with phosphonium ylides.

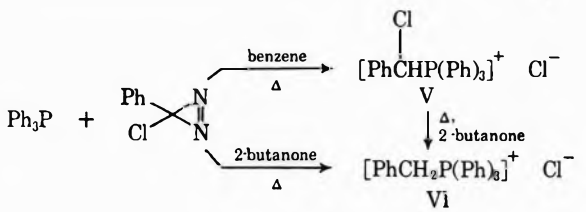


In an attempt to further demonstrate the generality of nucleophilic attack on the nitrogen double bond, phenylchlorodiazirine was treated with triphenylphosphine under two different sets of conditions. In the first case, which utilized benzene as the solvent, a 28% yield of α-chlorobenzyltriphenylphosphonium chloride

(14) A referee has suggested that since the initial intermediate is antiaromatic it may rearrange to a nitrene which in turn may rapidly react with phenyllithium to give the observed product. This could explain the unexpected direction of addition of phenyllithium to the C=N double bond and also its faster rate of addition relative to I.



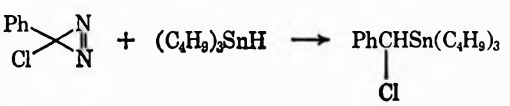
(V) was obtained. The second set of conditions used 2-butanone as solvent and resulted in the formation of benzyltriphenylphosphonium chloride (VI). It was noted



that refluxing V in 2-butanone for 2 hr resulted in the formation of VI. The above reactions apparently proceed by thermal decomposition of I to phenylchlorocarbene, which is subsequently trapped by triphenylphosphine.[15,16] It is interesting to note that the behavior of I with triphenylphosphine is substantially different from the diazirine ring-opening defluorination reaction observed with difluorodiazirine.[17] The reaction seems to be more closely related to the behavior of bis(trifluoromethyl)diazirine with trivalent organophosphorous derivatives.[18]

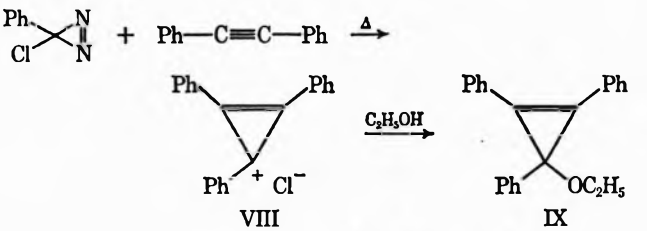
As a result of the above experiments, it is possible at this time to draw some conclusions concerning the reactivity of I with nucleophilic reagents. It is obvious from the results on hand that the reaction of phenylchlorodiazirine occurs readily with carbanions and less readily with nucleophilic reagents. As discussed in some detail by Mitsch,[17] a major factor responsible for nucleophilic attack on a diazirine is the electron availability of the nucleophilic reagent. In no case was there any evidence for diaziridinyl anion formation. It appears that the heterocyclic 4-π-electron system, like the cyclopropenyl anion,[19] is quite unstable and resists formation.

In connection with our attempts to generate the diaziridinyl anion, we felt it desirable to obtain data on the stability of the related 3-π-electron system. Accordingly, we set out to examine the reaction of tri-*n*-butyltin hydride with I in the hope of documenting the transient existence of the radical. It is generally accepted that the reaction of alkyl halides with organotin hydrides proceeds by a free-radical chain mechanism.[20] Furthermore, it is known that the reduction of alkyl chlorides with tin hydrides occurs more readily than addition to multiple double bonds.[21] The reaction between I and tri-*n*-butyltin hydride in refluxing ether gave α-chlorobenzyl tri-*n*-butyltin hydride (VII). The

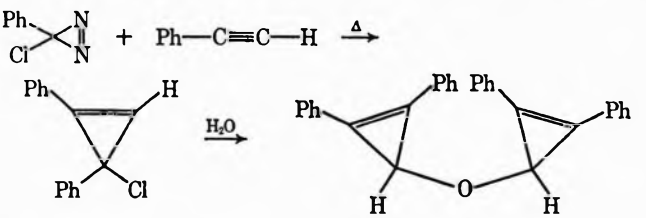


structure of the product was confirmed by nmr and mass spectroscopy. The nmr spectrum ($CDCl_3$) showed a broad multiplet between τ 8.70 and 9.10, a singlet at τ 5.31 for the benzylic proton, with the expected tin satellites (J_{SnH} = 23 cps), and a singlet at τ 2.80 ppm for the aromatic hydrogens. The mass spectroscopically determined molecular weight was 416, and there were peaks at *m/e* 379 and 381 corresponding to the loss of chlorine. The formation of this product is readily accounted for by the insertion of phenylchlorocarbene into the tin–hydrogen bond. The insertion of dichlorocarbene into a tin–hydrogen bond has already been reported on by Seyferth and Burlitch and provides reasonable chemical analogy for the above reaction.[22] It appears that the decomposition of I to phenylchlorocarbene precludes diaziridinyl-radical formation.

Inasmuch as both heat and light caused phenylchlorodiazirine (I) to lose nitrogen, it became of further interest to investigate the reaction of phenylchlorocarbene with reagents possessing π bonds. Graham has already reported on the reaction of I with cyclohexene.[6] Treatment of I with diphenylacetylene in refluxing benzene produced a single component in high yield which was subsequently identified as *sym*-triphenylcyclopropenyl chloride (VIII). The structure of this material was fully established by conversion to 1,2,3-triphenylcyclopropenyl ethyl ether (IX) by refluxing in ethanol. Compound IX was converted to the known triphenylcyclopropenyl bromide[23] by saturating an ethereal solution of IX with hydrogen bromide.



Similarly, the reaction of I with phenylacetylene gave 1-chloro-1,2-diphenylcyclopropene, which could be converted to the known bis-Δ'-1,2-diphenylcyclopropenyl ether[24] by recrystallizing the chloride from aqueous ethanol. The formation of the cyclopropenyl chlorides



in high yields suggests that this method can be effectively utilized for the preparation of these small-ring carbocyclic systems.

Experimental Section[25]

Preparation of Phenylchlorodiazirine (I).—3-Chlorophenyldiazirine was prepared by a slight modification of the procedure

(15) A. J. Speziale, G. J. Marco and K. W. Ratts, *J. Amer. Chem. Soc.*, **82**, 1260 (1960).
(16) D. Seyferth, S. O. Grim and T. O. Read, *ibid.*, **82**, 1510 (1960).
(17) R. A. Mitsch, *ibid.*, **89**, 6297 (1967).
(18) D. M. Gale, W. J. Middleton, and C. G. Krespan, *ibid.*, **88**, 3617 (1966).
(19) R. Breslow and P. Dowd, *ibid.*, **85**, 2729 (1963).
(20) H. G. Kuivila, L. W. Menapace, and C. R. Warner, *ibid.*, **84**, 3584 (1962).
(21) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968).
(22) D. Seyferth and J. B. Burlitch, *J. Amer. Chem. Soc.*, **85**, 2667 (1968).
(23) R. Breslow and H. W. Chang, *ibid.*, **83**, 2367 (1961).
(24) D. G. Farnum and M. Burr, *ibid.*, **82**, 2651 (1960).
(25) All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and Alfred Bernhardt Laboratories, Hohenweg, Germany. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. All infrared spectra were determined in carbon tetrachloride as solvent unless otherwise stated. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. Ethyl alcohol (95%) was used as the solvent unless otherwise stated. The nuclear magnetic resonance spectra were determined at 60 Mc with the Varian Associates high resolution spectrometer. Tetramethylsilane was used as an internal standard.

of Graham.[6] To a solution of 53 g of lithium chloride and 37 g of benzamidine hydrochloride in 800 ml of dimethylsulfoxide and 600 ml of hexane was added rapidly and with stirring 310 g of sodium chloride in 1800 ml of a 7% sodium hypochlorite solution. The reaction mixture was cooled in an ice bath and vigorous mechanical stirring was employed throughout the addition. After stirring for an additional 15 min, the hexane layer was removed and the aqueous layer was washed with several portions (100 ml) of ether. The combined washings were dried over sodium sulfate and the solvent was removed under reduced pressure. Distillation of the residue gave 12 g (60%) of phenylchlorodiazirine, bp 33–35° (0.5 mm). Spectral ir peaks appeared at 6.38, 11.01, 13.22, and 14.51 μ; uv λ_{max} 388 mμ.

The residue from the distillation was chromatographed on a 3 × 98 cm silica gel column. The column was eluted with benzene, and the eluent, in 50 ml of fractions, was concentrated and dried *in vacuo*. Fractions 2 and 3 contained 0.3 g of 1,4-diphenyl-1,4-dichloro-2,3-diaza-1,3-butadiene (II): mp 121–122° (lit.[26] mp 122–123°); ir 6.25, 8.25, and 10.91 μ. The identity of this product was further confirmed by heating 0.1 g of the dichloroazine in 50 ml of aqueous ethanol for 16 hr to give 2,5-diphenyl-1,3,4-oxadiazole, mp 135–136° (lit.[27] mp 135–136°). Fractions 4 and 5 contained 0.4 g of 3,5-diphenyl-1,2,4-oxidiazole, mp 105–106 (lit.[28] mp 108°). Verification of this product was obtained by comparison with an authentic sample prepared by a procedure described by Clarke.[29]

Photolysis of I in Pentane.—A solution of 600 mg of I in 200 ml of pentane was irradiated with an internal, water-cooled mercury arc lamp (Hanovia, Type L, 450 w) with a Pyrex filter for 1 hr. At the end of this time, the solution was evaporated to dryness to give a red oil which partially solidified on standing. The solid was separated from the crude oil by filtration and was subsequently identified as 1,4-diphenyl-1,4-dichloro-2,3-diaza-1,3-butadiene (0.15 g, 28%). The red oil was taken up in methylene chloride and filtered through a column of carbon black. The solvent was removed *in vacuo*, leaving a yellow oil (0.55 g, 71%). The oil was tentatively identified as a mixture of isomeric phenyl hexylchlorides as evidenced by infrared and nmr spectroscopy.

Thermal Decomposition of Phenylchlorodiazirine.—A solution of 1.0 g of I in 70 ml of benzene was refluxed for 3 hr. Removal of the solvent left a white solid that was identified as 1,4-diphenyl-1,4-dichloro-2,3-diaza-1,3-butadiene (0.95 g). The above procedure was repeated using 60 ml of *t*-butyl alcohol. Evaporation of the solvent and analysis of the residue by glpc using a 6 ft × 0.25 in. 10% DEGS on Chromsorb W (60–80 mesh) at 110° revealed the presence of benzaldehyde (65%) and benzal chloride (35%). These materials were identified by comparison with authentic samples.

Reaction of I with Organometallics.—To a solution of 4.6 g of I in 200 ml of ether was added slowly and with stirring 0.06 mol of phenyllithium in ether. The reaction mixture was stirred for an additional 30 min and was then quenched by the addition of water. The ether layer was separated and the aqueous layer was extracted with three 50-ml portions of ether. The ethereal extracts were combined and dried over sodium sulfate. Removal of the solvent left a white solid, which was recrystallized from ethanol to give 8.0 g of N,N-diphenylbenzamidine, mp 145–146°. Proof of structure was obtained by hydrolysis to aniline and benzanilide and also comparison with an authentic sample.[30] When equivalent quantities of phenyllithium and I were used, the yield of N,N-diphenylbenzamidine diminished (45%) and starting material (50%) could be recovered. The procedure outlined above was repeated using phenylmagnesium bromide. Again N,N-diphenylbenzamidine was the only detectable product. Repetition of the above procedure using methyllithium afforded acetophenone without any detectable formation of dimethylbenzamidine.

Reaction of I with Dimethylsulfonium Methylide.—Dried dimethyl sulfoxide (10 ml) and sodium hydride (0.32 g) were reacted in a nitrogen atmosphere at 60° until the hydrogen evolution ceased. The solution was cooled to −10° and enough anhydrous tetrahydrofuran was added to keep the solution from solidifying.[31] To the above solution was added 2.7 g of trimethylsulfonium iodide in 10 ml of dimethyl sulfoxide. The reaction mixture was stirred for 5 min, and then 1.0 g of phenylchlorodiazirine was added dropwise with vigorous stirring. The mixture was allowed to stir at room temperature for 2 hr and was then poured onto 500 g of crushed ice. The aqueous solution was extracted three times with 100-ml portions of ether. The ethereal extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. Analysis of the residue by glpc using a 6 ft × 0.25 in. DEGS on Chromosorb W at 120° revealed the presence of three components. These products were assigned as benzaldehyde (5%), benzonitrile (25%), and benzal chloride (5%). These materials were identified by retention time and infrared comparisons with authentic samples. The formation of dimethyl sulfide was evident from its characteristic odor.

Reaction of I with *p*-Toluylmethylenetriphenylphosphorane.—A mixture of 9.2 g of *p*-methyl-α-bromotoluene and 13.1 g of triphenylphosphine in 300 ml of benzene was heated to reflux for 2 hr. The resultant white precipitate was removed by filtration, washed with cold benzene, and dried. To a suspension of 2.84 g of triphenyl-*p*-methylbenzylphosphonium bromide in 30 ml of ether was added an equivalent amount of butyllithium in hexane. To the above solution was added 1.0 g of phenylchlorodiazirine in 10 ml of ether. The mixture was allowed to stir at room temperature for 2 hr. At the end of this time the mixture was poured onto ice and the aqueous layer was extracted with several portions of ether. The ethereal extracts were dried over sodium sulfate and the solvent was removed under reduced pressure. Analysis of the resulting residue by glpc on a 6 ft × 0.25 in. 10% DEGS column (Chromosorb W) at 110° revealed the presence of benzal chloride and benzonitrile (4%). No detectable quantities of *p*-tolylnitrile were evident. The bulk of the reaction product appeared to be a tarry phosphorus-containing mixture.

Reaction of I with Triphenylphosphine. A. In Benzene.—A solution of 1.0 g of I and 1.7 g of triphenylphosphine in 60 ml of benzene was refluxed for 3 hr. The solvent was removed under reduced pressure and the crude oil was shaken for several hours with 80 ml of acetone. The resultant white precipitate (0.4 g) was purified by trituration with refluxing acetone. This material was identified as α-chlorobenzyltriphenylphosphonium chloride: mp 258–259°; ir 6.95 and 9.01 μ.

Anal. Calcd for $C_{25}H_{21}Cl_2P$: C, 70.93; H, 5.00. Found: C, 70.64; H, 5.01.

Evaporation of the combined acetone washings left 1.2 g of a hygroscopic yellow solid whose infrared spectrum indicated a mixture of the phosphonium salt and triphenylphosphine oxide.

B. In 2-Butanone.—A solution of 1.0 g of I and 1.7 g of triphenylphosphine in 70 ml of 2-butanone was refluxed for 2 hr. The resultant white precipitate was crystallized from chloroform–acetone to give benzyltriphenylphosphonium chloride. When a 0.1 g sample of α-chlorobenzyltriphenylphosphonium chloride and 0.1 g of triphenylphosphine was heated to reflux in 70 ml of 2-butanone, a quantitative yield of benzyltriphenylphosphonium chloride was obtained.

Reaction of I with Tributyltin Hydride.—Tri-*n*-butyltin hydride was synthesized by the method of Kuivila and Beumel[32] and purified by distillation before use. A mixture of 1.0 g of I and 2.0 g of tri-*n*-butyltin hydride in 100 ml of ether was refluxed for 3 days. The reaction mixture was poured into a 10% sulfuric acid solution and the aqueous layer was extracted with ether. The ether was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The crude residue was chromatographed on a 3 × 50 cm Florisil column. The column was eluted with 400 ml of benzene and the eluent, in 50-ml fractions, was concentrated and dried *in vacuo*. Fraction 4 contained 1.6 g of a yellow oil. The oil was subjected to a molecular distillation at 120° (0.5 mm). The clear oil obtained was assigned as α-chloro-benzyltri-*n*-butyltin hydride, as evidenced by its nmr and mass spectral data: ir 3.45, 6.23, 6.71, 6.82, 7.25, 9.30, 11.40, 13.05, and 14.40 μ. The nmr spectrum ($CDCl_3$) has a broad multiplet between τ 8.70 and 9.10 (27 H), a singlet at τ 5.31 (with satellite peaks due to tin–hydrogen coupling, J = 23 cps), and a singlet at τ 2.80 (5 H). The mass spectrum (60 eV) has parent peaks at m/e 414 and 416, as well as peaks at m/e 379 and 381 corresponding to the loss of chlorine.

Reaction of I with Diphenylacetylene.—A mixture of 1.0 g of I and 1.17 g of diphenylacetylene in 70 ml of benzene was heated to reflux for 4 hr. The solvent was removed *in vacuo* and the colorless oil obtained was solidified upon standing. The crude

(26) E. Gunther, *Chem. Ber.*, **21**, 517 (1888).
(27) R. Stolle, *J. Prakt. Chem.*, **73**, 278 (1906).
(28) E. Beckman, *Chem. Ber.*, **22**, 1589 (1889).
(29) K. Clarke, *J. Chem. Soc.*, 4251 (1954).
(30) A. J. Hill and M. V. Cos, *J. Amer. Chem. Soc.*, **48**, 3214 (1926).
(31) E. J. Corey and M. Chaykovky, *ibid.*, **87**, 1353 (1965).
(32) H. G. Kuivila and O. F. Beumel, *ibid.*, **83**, 1246 (1961).

solid was placed on a porous plate to remove the residual oils. The colorless solid obtained rapidly decomposed upon standing to a dark oil. The structure of this material was concluded to be *sym*-triphenylcyclopropenyl chloride from the following data. Crystallization of the solid from ethanol–water gave 1,2,3-triphenylcyclopropenyl ethyl ether as white prisms: mp 121–122°; ir (KBr) 5.50 μ; uv (95% ethanol) 317 (ϵ 21,800), 302 (ϵ 22,100) 228 (ϵ 26,500), and 223 mμ (ϵ 27,600). The nmr spectrum ($CDCl_3$) has a triplet at τ 8.77 (3 H), a quartet at τ 6.32 (2 H), and a multiplet at τ 2.60–2.25 ppm (15 H).

Anal. Calcd for $C_{23}H_{20}O$: C, 88.42; H, 6.45. Found: C, 88.29; H, 6.54.

A 0.5-g sample of 1,2,3-triphenylcyclopropenyl ethyl ether in 50 ml of ether was saturated with hydrogen bromide gas at 0° and was allowed to stand overnight at room temperature. The resulting solid that precipitated was crystallized from acetonitrile to give 0.33 g of triphenylcyclopropenyl bromide. The bromide was identified by comparison of infrared and mixture melting point with those of an authentic sample.[23] The ir spectrum of the bromide was almost identical with that of the original solid.

Reaction of I with Phenylacetylene.—A mixture of 1.0 g of I and 0.7 g of phenylacetylene in 70 ml of benzene was refluxed for 4 hr. The solvent was removed under reduced pressure to give a yellow oil which solidified upon standing. The oily solid was placed on a porous plate to give 0.9 g of a yellow solid. If the crude material is not purified immediately, violent decomposition occurs and a dark oil is produced. The yellow solid was crystallized from cold pentane to give 1-chloro-1,2-diphenylcyclopropene: mp 82–85°; ir 5.50 μ; uv (acetonitrile) λ_{max} 316 (ϵ 23,400), 301 (ϵ 29,600), and 288 mμ (ϵ 23,400). The nmr spectrum ($CDCl_3$) has a singlet at τ 5.05 (1 H) and a multiplet between τ 2.27 and 2.61 (10 H).

The structure of this material was further confirmed by briefly heating the solid in an aqueous ethanol solution. Removal of the solvent and crystallization of the white solid from benzene–hexane gave 0.15 g of bis-Δ'-1,2-diphenylcyclopropenyl ether, mp 164–166° (lit.[24] 163–165). The spectroscopic data obtained were in complete agreement with that reported by Breslow.[33]

Registry No.—I, 4460-46-2; V, 20420-97-7; VII, 20420-98-8; IX, 13668-03-6; 1-Chloro-1,2-diphenylcyclopropene, 20421-00-5.

Acknowledgment.—The authors are indebted to the U. S. Public Health Service (Grant GM 13990-02) for generous support of this research.

(33) R. Breslow, J. Lockhart, and H. W. Chang, *J. Amer. Chem. Soc.*, **83**, 2375 (1961).

Olefin–Tetracyanoethylene Oxide Adducts and Some of Their Derivatives[1a]

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Received January 14, 1969

The reaction of tetracyanoethylene oxide with methyl erucate (methyl *cis*-13-docosenoate) and methyl brassidate (methyl *trans*-13-docosenoate) gave 2,2,5,5-tetracyano-3-(11-carbomethoxyundecyl)-4-octyltetrahydrofurans (**2** and **3**) in good yields. In methanol containing 5% hydrogen chloride, both **2** and **3** undergo partial and selective methanolysis to give 2,5-dicyano-2,5-dicarbomethoxytetrahydrofuran derivatives (**4** and **5**). The newly formed carbomethoxy groups are *trans* to their adjacent alkyl groups. Both **2** and **3** also are partially and selectively hydrolyzed on the surface of silica gel to give 2,5-dicyano-2,5-dicarbamoyltetrahydrofuran derivatives (**10** and **11**) in good yields. The newly formed carbamoyl groups have a *cis* relationship to each other.

Adducts of tetracyanoethylene oxide (TCNEO, **1**) *via* the unusual *cis* cycloaddition to olefins, acetylenes, and aromatics[2–4] are products having potential for further modifications to provide compounds of diverse functionality. We have prepared TCNEO adducts **2** and **3** of methyl erucate and methyl brassidate, the respective *cis* and *trans* isomers of methyl 13-docosenoate. Homogeneity of each adduct was determined by tlc on silica gel, on which the two can be readily resolved. The adducts were isomeric 2,2,5,5-tetracyano-3-(11-carbomethoxyundecyl)-4-octyltetrahydrofurans, as judged by ir, nmr, and elemental analyses.

Esters.—In contrast with the complete methanolysis of TCNEO adducts obtained by somewhat different conditions,[2] we found that both adducts may undergo partial and selective methanolysis. Reaction at room temperature with methanol containing 5% hydrogen chloride converts **2** and **3** to **4** and **5**, respectively, in 90% yield. Their ir and nmr spectra are consistent for dicyanodicarbomethoxytetrahydrofuran derivatives.

The methanolysis products of the two TCNEO adducts could have their respective ring substituents in several different geometric configurations. However, most of these can be excluded as likely possibilities. Since the cycloaddition of TCNEO to olefins is *cis*,[2,3] we may reasonably assume that the ring alkyl substituents have a *cis* relationship in compounds **2** and **4** and a *trans* relationship in compounds **3** and **5**. Chemical shift values for the ring protons, when compared with literature values,[2] are consistent with this interpretation. Nmr analyses of both methanolysis products **4** and **5** show that the six protons associated with the carbomethoxy groups on the rings occur as a sharp singlet[5] (τ 6.09 and 6.08, respectively). Thus, in both **4** and **5**, the two carbomethoxy groups on the ring appear to be in magnetically equivalent environments. The two ring protons in **4** and **5** are also magnetically equivalent (multiplets at τ 7.20 and 7.37, respectively). These observations imply that, in compounds **4** and **5**, one carbomethoxy is attached at position **2** and the other at position **5**. If *gem* functions were present, the ring protons could be expected to have greatly different chemical shift values due to the marked difference in diamagnetic anisotropy of the cyano and carbomethoxy groups. Also, each carbomethoxy group should have identical geometric relationships with its adjacent ring alkyl substituent. Apparently the methanolysis reaction has considerable stereoselectivity.

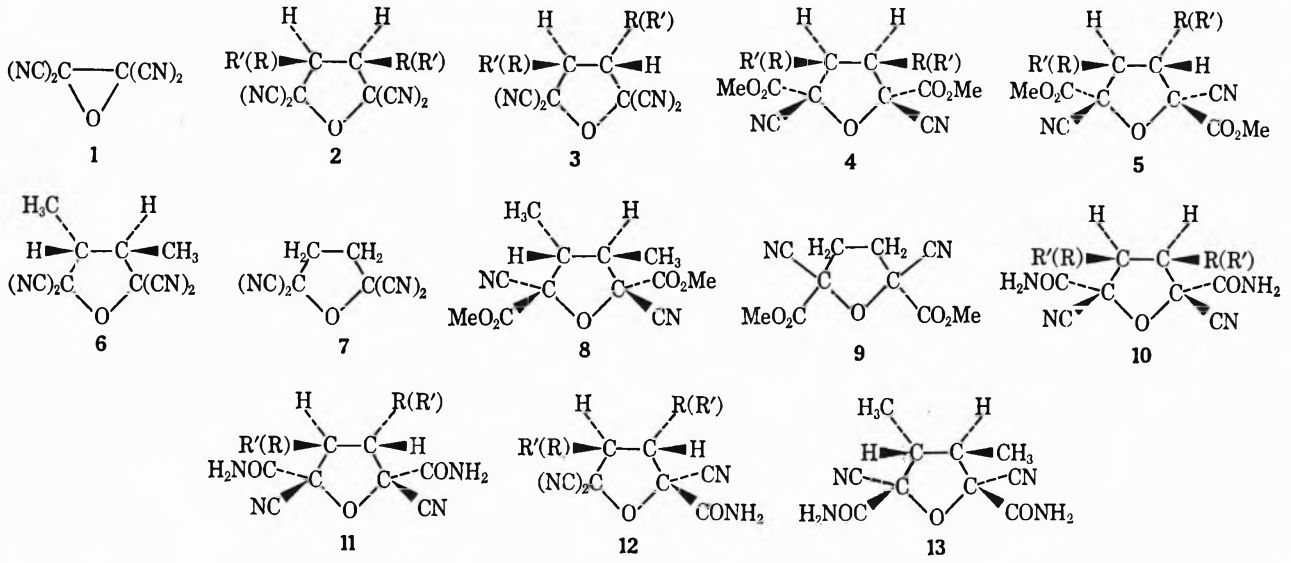
(1) (a) Presented in part at the 58th Annual Meeting of the American Oil Chemists' Society, New Orleans, La., May 7–10, 1967. (b) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) W. J. Linn and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 3657 (1965).

(3) W. J. Linn, *ibid.*, **87**, 3665 (1965).

(4) P. Brown and R. C. Cookson, *Proc. Chem. Soc.*, 185 (1964).

(5) The band width at half peak height is approximately 1 Hz.



R = $CH_3(CH_2)_7$-
R′ = $MeO_2C(CH_2)_{11}$-

The nmr spectrum of an admixture of **4** and **5** showed singlets at τ 6.10 and 6.07 corresponding to the ring carbomethoxy groups of the respective compounds. Evidently the small differences observed between these signals in the separate spectra are real, and, in addition to being attached to different carbon atoms, it is probable for steric reasons that the newly formed carbomethoxy groups are *trans* to their adjacent alkyl groups. For each, the present nmr data do not rule out the possibility that the carbomethoxy groups are *cis* to their adjacent alkyl groups.

On steric grounds, one might assume that carbomethoxy groups would be generated in these selective methanolysis reactions from nitrile groups that are *trans* to adjacent alkyl groups. Therefore, the two products would have the structures as shown for **4** and **5**. To test this hypothesis and to gain greater insight into the steric course of the reaction, two model compounds were prepared by methanolysis of the known[2] *trans*-3,4-dimethyl-2,2,5,5-tetracyanotetrahydrofuran (**6**) and 2,2,-5,5-tetracyanotetrahydrofuran (**7**).

The diester product **8** from **6** gives a six-proton singlet at τ 6.03,[5] corresponding to carbomethoxy protons. According to our reasoning, the carbomethoxy groups should be generated *trans* to their adjacent methyl groups. In contrast, the four cyano groups of **7** should have equivalent reactivity. If a monoester species actually is formed, the methanolysis of the second nitrile group might occur selectively so as to favor formation of the product with *trans* carbomethoxy groups. In fact, the nmr spectrum of product **9** shows two sharp bands corresponding to the carbomethoxy protons. The major band[5] occurs at τ 6.03, which is coincident with that of *trans*-dimethyl compound **8**. We believe that the second band[5] at τ 6.06 is due to the isomer of **9** having *cis* carbomethoxy groups.

Additional support for the conclusions concerning products of the selective methanolysis is provided in the following section on amides.

Amides.— In early phase of our investigation, we attempted to purify reaction product **2** from TCNEO and methyl erucate by chromatography on silica gel. The yield of adduct by this procedure was considerably less than anticipated, and almost all fractions contained some amide as determined by ir. A large amount of product of greater polarity than the starting material could be removed from the silica gel columns, and the ir spectrum of this polar fraction revealed bands corresponding to amide absorption. Since the initial mixture had no amide absorption in the ir, the hydrolysis reaction probably occurred during a short residence time on silica gel.

This fact was established by spotting pure adduct **2** on a tlc plate, waiting about 2 min, and then spotting the pure adduct in a second place on the plate. The chromatogram was developed with an irrigant (chloroform/acetonitrile) containing about 1% acetic acid to eliminate streaking. The first applied material was resolved into two spots, while the second was homogeneous. In the absence of acetic acid, streaking occurred with the pure adduct. This streaking implies that hydrolysis occurs during development of the chromatogram.

For larger scale reactions, adducts **2** and **3** were mixed neat with silica gel. Adduct **2** reacted more readily than did adduct **3**, which did not react appreciably during conventional tlc. These reaction differences probably reflect steric inhibition exerted by the bulky *trans* alkyl groups present in **3**. We observed that silica gel was not unique in its ability to catalyze this reaction. Neutral alumina and washed sand also hydrolyzed the nitriles to amides.

Although examples described in the Experimental Section involve addition of water to the silica gel, the reactions proceed equally well on silica gel samples activated as received from the suppliers or water-washed silica gels activated by heating for several hours at 120°. Acetonitrile, malononitrile, and 1,11-undecanedinitrile yielded little or no amide when treated with silica gel; therefore, this silica-catalyzed hydrolysis of nitriles is not general in scope. In its facility, this reaction parallels the solid phase catalysis reported by Cook, Forbes, and Khan.[6] They found that a variety of nitriles are

(6) M. J. Cook, E. J. Forbes, and G. M. Khan, *Chem. Commun.*, 121 (1966).

converted to amides when agitated in methylene chloride with solid manganese dioxide. In contrast, the hydrolysis of nitriles to amides in solution frequently involves quite rigorous acid or alkali treatment.

Diamide **10** was obtained from **2**, and in addition to diamide **11**, a small yield of monoamide **12** was isolated from the reaction mixture after silica gel treatment of **3**.

Diamide products **10** and **11** have nmr spectra consistent with 2,5-dicyano-2,5-dicarbamoyltetrahydrofuran derivatives. The alkyl substituents must be oriented as in **2** and **3**. The two ring protons in **10** and **11** appear to be in magnetically equivalent environments (multiplets at τ 7.31 and 7.34, respectively). In contrast, the amide protons are in different environments. Amide **10** has two broad singlets of nearly equal intensity, whereas amide **11** has three broad singlets of unequal intensity (τ 3.31, 1.5 H; τ 2.57, 0.6 H; and τ 2.20, 0.9 H). The signal for the fourth proton may be so broad that it is not detected.

These hydrolysis reactions probably involve compound interaction with water adsorbed on the silica gel surface. If the tetranitrile compounds are adsorbed at the silica surface and then displaced by solvent or by desorption and diffusion, the amide groups should be generated with a *cis* relationship in most of the diamide molecules formed. Therefore, amide groups in **10** should be in a greatly different environment from those in **11**. In product **10**, amide groups would be *trans* to their adjacent alkyl groups, whereas in product **11** one amide group would be *trans* and the other would be *cis* to its adjacent alkyl group. In a study that has some parallel to ours, Ciganek[7] has reported a selective hydrolysis of 7,7-dicyanonorcaradiene with alkaline hydrogen peroxide.

In an effort to determine whether the amide groups in **10** and **11** are *cis* or *trans*, both products were allowed to react with methanol containing 5% hydrogen chloride under the same conditions used to prepare **4** and **5**. The reaction with **10** was not complete, but the corresponding ester was isolated by column chromatography. This ester had ir and nmr spectra identical with those of **4**. In contrast, the amide groups of **11** were not converted to ester groups in a clear-cut manner. A small sample of amide **11** gave several products (at least six by tlc). The major one probably contains two nitrile groups, one amide group, and one ester group on the tetrahydrofuran ring. Its ir spectrum showed amide bands of lower intensity than in the parent compound **11**. The other major change in the spectrum was an increase in intensity and broadening of the absorption band at 1250–1290 cm^{-1}. The nmr spectrum, compared to that of the parent amide **11**, showed a diminution of the three amide bands and of the deshielded methylene multiplet at about τ 8.0. A band also appeared at τ 6.05, but it was not of sufficient intensity to account for one new methoxyl group per molecule.

Hydrogen-Bonding Studies.—Additional insight into the suggested selectivity in the nitrile hydrolysis is gained by ir spectra of amide products **10**, **11**, and **12** at concentration levels ranging from 0.02 to 0.0004 *M*.

Band assignments were made in accordance with the discussion by Jones and Sandorfy.[8] The tetrahydrofuran monoamide trinitrile, **12**, is without detectable associated N–H stretching bands at concentrations of 0.02 to 0.0004 *M* in chloroform solution. In carbon tetrachloride solution, **12** has appreciable associated N–H bands only at the 0.02 *M* concentration.

These data suggest that in either chloroform or carbon tetrachloride, amide **12** occurs mainly, if not entirely, as the monomer at concentrations of 0.004 *M* or less. Also, at least in chloroform, there is no detectable N–H intramolecular association with π bonds of the nitriles or with electron pairs of ring oxygen.

It seems likely that at concentrations of less than 0.004 *M*, at any rate, the appreciable N–H association found for amides **10** and **11** is due to intramolecular hydrogen bonding. This bonding must involve interaction between the two amide groups. From this interpretation, it follows that the two amide groups in both **10** and **11** must be *cis* as shown.

It has been suggested that the association bands of amides chiefly involve $-N-H\cdots O{=}C-$ rather than $-NH\cdots N-$ linkages.[8] This bonding would require one carbonyl oxygen to achieve a preferred conformation projecting over the plane of the tetrahydrofuran ring. The amide group *cis* to its adjacent alkyl group in compound **11** should experience steric interactions causing restricted rotation about its carbon–carbon bond. This restricted rotation, together with hydrogen bonding effects, should cause considerable preference for one conformation.

For **11** and **12**, there is a two-proton multiplet corresponding to a greatly deshielded methylene. The multiplets centered at τ 7.94 and 7.97, respectively, are probably deshielded by amide carbonyl.[9] In addition to a preferred conformation of the amide groups, this deshielding effect would require a preferred orientation of one alkyl group. Presumably this alkyl group is on the same side of the tetrahydrofuran ring as the amide groups. Spectra of more model compounds would be needed for an unambiguous assignment of the deshielded proton pair. However, examination of molecular models prompts the suggestion that the methylene in question is β to the tetrahydrofuran ring. Both diester **8** and diamide **13** give AX_3 $A'X'_3$ spectra[10] with their respective dimethyl multiplets occurring with nearly identical chemical shift values of τ 8.63 and 8.66. Since the methyl proton shift values of both **8** and **13** are $X_3X'_3$ spectra rather than M_3X_3, we conclude that protons of substituents α to the ring are essentially affected equally by amide groups. Therefore, it seems unlikely that the preferentially deshielded methylenes (τ 7.94 and 7.97) of compounds **11** and **12** are those α to the tetrahydrofuran ring.

Quenched Infrared Nitrile Absorptions.—Compounds **4**, **5**, **8-11**, and **13**, which have either two disubstituted cyano acetamides or two disubstituted methyl cyano acetate groups, lack ir absorption bands owing to the nitrile groups (*ca.* 2250 cm^{-1}). Such nitriles (one substituent is an ether oxygen) have been discussed

(7) E. Ciganek, *J. Amer. Chem. Soc.*, **89**, 1458 (1967).

(8) R. N. Jones and C. Sandorfy, "Techniques of Organic Chemistry, Chemical Applications of Spectroscopy," Vol. IX, W. West, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p 509 ff.

(9) G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967).

(10) For discussions of $AX_3A'X'_3$ spectra, see A. A. Bothner-By and C. Naar-Colin, *ibid.*, **84**, 743 (1962), and F. A. L. Anet, *ibid.*, **84**, 747 (1962).

in the literature, and there is ample precedent for the absence of nitrile absorption.[11-13]

Experimental Section

Melting points were taken on a Fisher–Johns[14] block. Ir spectra were determined with an infracord Model 337 spectrophotometer; nmr spectra were determined with a Varian A-60 or an HA-100 spectrometer on solutions containing tetramethylsilane. Fractionation and purity of materials were monitored by tlc on silica gel. Spots were developed by charing with chromic acid at about 160°. TCNEO (1) was prepared by the action of aqueous hydrogen peroxide on tetracyanoethylene in acetonitrile as described by Linn, Webster, and Benson.[15] Adducts of 1 with olefins were prepared in toluene by the procedure of Linn and Benson.[2]

2,2,5,5-Tetracyano-3-(11-carbomethoxyundecyl)-4-octyltetrahydrofurans (2 and 3).—A typical preparation of adduct from methyl erucate (methyl *cis*-13-docosenoate) is described as follows: 0.6 g of TCNEO was refluxed for 16 hr with 1.7 g of methyl erucate in toluene. The solvent was removed *in vacuo* and the residue was partitioned countercurrently between hexane and acetonitrile. Adduct 2 (2.1 g, 100%) was obtained from the acetonitrile phases: ir (neat) 2250 (C≡N), 1730 (C=O), 1075, 1018 cm^{-1}; nmr (CCl_4) τ 9.10 (t, 3, CH_3), 8.0–8.95 (m, 34, CH_2), 7.76 (t, 2, CH_2CO), 6.83 (m, 2, ring CH), and 6.38 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{29}H_{44}N_4O_3$: C, 70.13; H, 8.93; N, 11.28. Found: C, 70.68; H, 9.00; N, 11.13.

Adduct 3 (0.65 g, 92%) was prepared by reaction of TCNEO (0.20 g) with methyl brassidate (0.53 g) (methyl *trans*-13-docosenoate): ir (neat) 2250 (C≡N), 1730 (C=O), 1115, 1068, 1010 cm^{-1}; nmr (CCl_4) τ 9.12 (t, 3, CH_3), 7.90–8.90 (m, 34, CH_2), 7.79 (t, 2, CH_2CO), 7.22 (m, 2, ring CH), and 6.42 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{29}H_{44}N_4O_3$: C, 70.13; H, 8.93; N, 11.28. Found: C, 70.36; H, 8.95; N, 11.21.

Chromatography of adduct 3 and in particular of adduct 2 on thin layers of silica gel revealed that the adducts react with silica gel.

2,5-Dicyano-2,5-dicarbomethoxy-3-(11-carbomethoxyundecyl)-4-octyltetrahydrofurans (4 and 5).—The erucate adduct 2 (0.332 g), chilled in an ice bath, was mixed with 10 ml of 5% hydrogen chloride in methanol. The mixture became homogeneous after about 10 min; then it was held at room temperature for 20 hr. Volatile solvent was removed *in vacuo*, water (5 ml) was added, and the product was extracted with four 5-ml portions of ether. The solvent was removed *in vacuo* to give 0.332 g of 4. Chromatography on silica gel and two treatments with charcoal gave 0.238 g of 4: ir (neat) 1750 (C=O, broad), 1092, 1070, 797 cm^{-1}; nmr (CCl_4) τ 9.10 (t, 3, CH_3), 8.0–8.9 (m, 34, CH_2), 7.76 (t, 2, CH_2CO), 7.20 (m, 2, ring CH), 6.39 (s, 3, OCH_3) and 6.09 ppm (s, 6, OCH_3).

Anal. Calcd for $C_{31}H_{50}N_2O_7$: C, 66.16; H, 8.96; N, 4.98. Found: C, 65.34; H, 8.83; N, 4.96.

The brassidate adduct 3 (0.193 g) was esterified as above to give 0.198 g of 5. Chromatography on silica gel gave 0.132 g of pure 5: ir (neat) 1750 (C=O, broad), 1120, 1075, 1045, 815, 790, 780 cm^{-1}; nmr (CCl_4) τ 9.12 (t, 3, CH_3), 8.0–9.0 (m, 34, CH_2), 7.78 (t, 2, CH_2CO), 7.37 (m, 2, ring CH), 6.40 (s, 3, OCH_3), and 6.08 ppm (s, 6, OCH_3).

Anal. Calcd for $C_{31}H_{50}N_2O_7$: C, 66.16· H, 8.96; N, 4.98. Found: C, 67.01; H, 9.06; N, 4.84.

***trans*-3,4-Dimethyl-2,5-dicyano-2,5-dicarbomethoxytetrahydrofuran (8).**—*trans*-3,4-Dimethyl-2,2,5,5-tetracyanotetrahydrofuran (6, 0.124 g) was let stand with methanol containing 5% hydrogen chloride as described before. The crude product (0.141 g) was chromatographed on silica gel. Selected fractions were combined to give 0.134 g of pure 8: mp 111.5–114°; ir (Fluorolub mull) 1770 and 1745 (C=O), 1050, 1028, 812 cm^{-1}; nmr ($CDCl_3$) τ 8.63 (m, 6, CH_3), 7.41 (m, 2, CH), and 6.03 ppm (s, 6, OCH_3).

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.33; H, 5.48; N, 10.54.

2,5-Dicyano-2,5-dicarbomethoxytetrahydrofuran (9).—2,2,5,5-Tetracyanotetranydrofuran (7, 0.168 g) was let stand with methanol containing 5% hydrogen chloride as described previously. The crude product (0.203 g) was purified by silica gel chromatography to give selected fractions of pure 9 (0.144 g): ir (neat) 1760 (broad, C=O), 1089, 1049, 796 cm^{-1}; nmr ($CDCl_3$) τ 7.14 (s, 4, CH_2) 6.06 and 6.03 ppm, major band (2s, 6, OCH_3).

Anal. Calcd for $C_{10}H_{10}N_2O_5$: N, 11.76. Found: N, 10.77.

2,5-Dicyano-2,5-dicarbamoyl-3-(11-carbomethoxyundecyl)-4-octyltetrahydrofuran (10 and 11).—Erucate adduct 2 (0.314 g) was mixed with 5 g of 30–60 mesh silica gel and 1.0 g of water, and then left for 18 hr. The product was fractionated on a silica gel column. Similar fractions were combined and then decolorized in an acetone slurry of charcoal. Decolorized 10 (0.238 g, 70%) was further purified by silica gel chromatography to give 0.120 g of pure amorphous solid. The solid, which was opalescent to transparent on the melting point block, became more transparent as the temperature increased and fluid at 72.5°: ir ($CHCl_3$) 3509, 3479, 3400, 3330, 3284, 3170, 1710 (broad, C=O), 1590, 1082 cm^{-1}; nmr ($CDCl_3$) τ 9.12 (t, 3, CH_3), 7.9–8.9 (m, 34, CH_2), 7.69 (t, 2, CH_2CO), 7.31 (m, 2, ring CH), 6.32 (s, 3, OCH_3), 2.25 and 2.89 ppm [2s (broad), 4, NH_2].

Anal. Calcd for $C_{29}H_{48}N_4O_5$: C, 65.38; H, 9.08; N, 10.52. Found: C, 65.91; H, 9.27; N, 10.36.

The brassidate adduct 3 (0.211 g) was mixed with silica gel as above except that the contact time was 120 hr. Tlc of the products revealed six spots. The major material (11, 0.106 g, 47%) was isolated by chromatography on silica gel. One additional fractionation gave selected fractions (0.042 g) of pure 11. The nearly transparent amorphous solid became rapidly fluid at 103°: ir ($CHCl_3$) 3510, 3480, 3397, 3332, 3292, 3176, 1720 (broad, C=O), 1592, 1117, 1072, 1028 cm^{-1}; nmr ($CDCl_3$) τ 9.12 (t, 3, CH_3), 8.05–8.95 (m, 32, CH_2), 7.94 (m, 2, CH_2), 7.71 (t, 2, CH_2CO), 7.34 (m, 2, ring CH), 6.36 (s, 3, OCH_3), and 3.31, 2.57, 2.20 ppm [3s (broad), 3, NH_2].

A small sample (0.011 g) of product 12, which has a higher R_f than 11, was isolated from some chromatographic fractions as a semisolid: ir (neat) 3440, 3352, 3290, 3188, 2247 (C≡N), 1720 (broad C=O), 1594, 1114, 1065, 1020 cm^{-1}; nmr ($CDCl_3$) τ 9.12 (t, 3, CH_3), 8.05–8.90 (m, 32, CH_2), 7.97 (m, 2, CH_2), 7.00–7.82 [overlapping m and t (7.70), 4, ring CH and CH_2CO], 6.36 (s, 3, OCH_3), 3.90 and 3.62 ppm [2s (broad), 2 (1.6), NH_2].

***trans*-3,4-Dimethyl-2,5-dicyano-2,5-dicarbamoyltetrahydrofuran (13).**—*trans*-3,4-Dimethyl-2,2,5,5-tetracyanotetrahydrofuran (6, 0.114 g) was stored with silica gel as described before. Chromatography on a silica gel column gave 0.126 g of 13: mp 197–199° with some sublimation beginning at 180°; ir (Fluorolub mull) 3470, 3445, 3335, 3255, 3190, 1710, 1685, 1590, 1064, 1040, 1010, 803, 770 cm^{-1}; nmr ($CD_3C{\equiv}N$) τ 8.66 (m, 6, CH_3), 7.56 (m, 2, CH), 3.55, 3.05, 2.44 ppm [3s (broad), 4, NH_2].

Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.82; H, 5.43; N, 23.81.

Registry No.—2, 20407-00-5; 3, 20462-29-7; 4, 20407-01-6; 5, 20407-02-7; 8, 20407-03-8; 9, 20407-05-0; 10, 20407-07-2; 11, 20407-10-7; 12, 20407-11-8; 13, 20407-12-9.

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(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958, p 265.

(12) N. Latif and N. Mishriky, *Can. J. Chem.*, **44**, 1271 (1966).

(13) H. Sterk and H. Junek, *Monatsh. Chem.*, **99**, 810 (1968).

(14) The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

(15) W. J. Linn, O. W. Webster, and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 3651 (1965).

Pyranylidene Iminium Salts. I. Iminium Salts Derived from Alkyl-Substituted Pyrylium Salts and Their Hydrolysis Products

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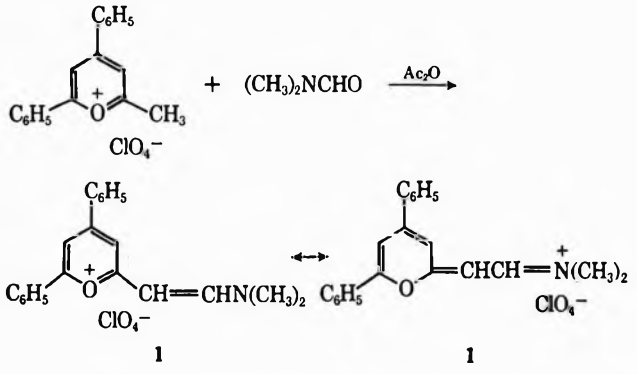
Pyrylium salts containing an active methyl group give monoiminium salts with N,N-dimethylformamide in acetic anhydride and bisiminium salts with the Vilsmeier complex. Methylene pyrylium salts yield monoiminium salts with the Vilsmeier complex. Monoiminium salts are obtained from alkylpyrylium salts and either N,N-dimethylthioacetamide in acetic anhydride or N,N-dialkylamides in the presence of phosphorus oxychloride. Vinylogs of certain of the monoiminium salts are obtained from alkylpyrylium compounds and diethylaminoacrolein in acetic anhydride. The iminium salts are hydrolyzed to give, in most cases, aldehydes and ketones. The hydrolysis products obtained from the iminium salt derived from 2-methyl-4,6-diphenylpyrylium perchlorate are 2-formylmethylidene-4,6-diphenyl-2H-pyran, 4-dimethylamino-2-phenylbenzophenone, and 4-methoxy-2-phenylbenzophenone.

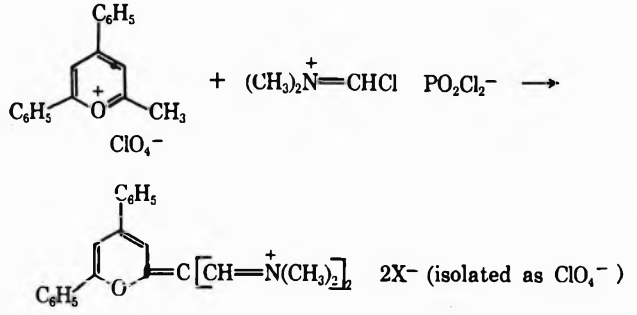
As suggested by the results of earlier work with *p*-dimethylaminobenzaldehyde,[1] it was not surprising to learn than N,N-dimethylformamide reacted with 2-methyl-4,6-diphenylpyrylium perchlorate in acetic anhydride to yield the expected 2-N,N-dimethylaminovinyl derivative **1**.[2] The generality of the reaction with



1 **1**

N,N-dimethylformamide was demonstrated by the formation of the related compounds **2**–**7** (see Table I). Attempts to extend the reaction through the use of N,N-dimethylacetamide under the same conditions were unsuccessful.[3] However, N,N-dimethylthioacetamide furnished the desired iminium derivatives readily, as shown by the synthesis of **9**–**12** (Table I). Vinylogs related to **1** were prepared either through the use of dialkylaminoacrolein or its closely related methoxyiminium derivative[4] (see **13**–**18** in Table I).

Under Vilsmeier–Haack conditions, 2 mol of N,N-dimethylformamide–phosphorous oxychloride complex reacted with 1 mol of the methyl pyrylium salts to give bisiminium salts (**19**–**23**, Table I) as illustrated below for **19**. Similar behavior has been observed in other

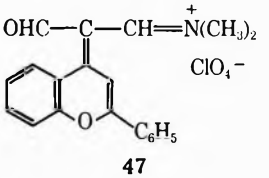


19

instances.[5] Other N,N-disubstituted amides and phosphorous oxychloride led to monoiminium salts (see **9**–**12** and **24**–**29**, Table I). We feel that the course of bisiminium salt formation is accounted for by Scheme I. The facts that methylpyrylium salts gave bisiminium salts and that monoiminium salts gave bisiminium salts with the Vilsmeier reagent suggested that this reagent reacts more readily with monoiminium salts than with methylpyrylium salts. Ethylpyrylium salts reacted with the Vilsmeier reagent to form monoiminium salts, and isopropylpyryliam salts failed to react. The formation of monoiminium salts by the reaction of the phosphorous oxychloride complex of other N,N-disubstituted amides with methylpyrylium salts may be the result of steric effects.

Iminium salts are usually readily hydrolyzed to aldehydes, and the Vilsmeier–Haack procedure often yields an aldehyde owing to hydrolysis of the intermediate iminium salt during the work-up. The iminium salts described in this paper are quite stable, but they are hydrolyzed by strong bases. In most cases, hydrolysis of various iminium salts gave the expected aldehydes or ketones, and the hydrolysis products, **30**–**46**, are recorded in Table II.

The bisiminium salt **20** was hydrolyzed by methanolic potassium hydroxide to give the bisaldehyde **44**. Hydrolysis of **21** by the same procedure gave the monoaldehyde **47**. A possible explanation for the failure of



47

21 to yield a bisaldehyde on hydrolysis is that **47** is stabilized by resonance to such an extent that the imino bond is no longer reactive. When **20** was heated with

(1) R. Wizinger and K. Wagner, *Helv. Chim. Acta*, **34**, 2290 (1951).

(2) We will use the iminium structures for the compounds described in this paper.

(3) Only 4-methylflavylium perchlorate gave a product with dimethylacetamide in acetic anhydride, and the product was shown to be the pyrylium cyanine dye 4-[3-(4H-flaven-4-ylidene)-2-methyl-1-propenyl]-flavylium perchlorate rather than an iminium salt.

(4) H. Brodereck, F. Effenberger, and G. Simchen, *Chem. Ber.*, **96**, 1350 (1963).

(5) Z. Arnold, *Coll. Czech. Chem. Comm.*, **28**, 863 (1963); H. V. Hansen, J. A. Caputo, and R. I. Meltzer, *J. Org. Chem.*, **31**, 3845 (1966).

TABLE I
METHODS OF PREPARATION AND PHYSICAL PROPERTIES OF IMINIUM SALTS

Compd number	Structure[a]	Method of preparation	Yield, %	Empirical formula	Anal. Calcd, % C	Anal. Calcd, % H	Anal. Found, % N or Cl	Solvent of recrystallization	Mp, °C	Absorption spectra in acetonitrile, λ,mμ (ε × 10⁻³)
1	A-1	A	38	$C_{21}H_{20}ClNO_5$	62.8	5.0	3.5	alcohol	243–244	239 (17.6) 476 (21.2)
					62.9	5.3	3.4			316 (40.7)
2	A-2	A and C	73; 67	$C_{22}H_{22}ClNO_5$	63.5	5.3	3.4	acetonitrile	261–262	241 (15.2) ~366 (9.9)
					63.2	5.2	3.1			313 (21.8) 380 (16.2)
										356(9.6)
3	C-1	A	91	$C_{24}H_{24}ClNO_5$	65.2	5.5	(Cl) 8.0	acetic	275	238 (16.6) 353 (9.5)
					65.5	5.7	(Cl) 8.3	anhydride		305 (30.0) 493 (18.5)
4	B-1	A	90	$C_{21}H_{20}ClNO_5$	62.8	5.0	3.5	acetonitrile	261–262	226 (15.7) 422 (41.5)
					63.0	5.1	3.7			~252 (12.7) 443 (39.8)
										~264 (12.3) 544 (13.9)
										336 (17.1)
5	D-1	A	76	$C_{19}H_{18}ClNO_5$	60.7	4.8	(Cl) 9.5	formic and	240–241	241 (19.3) 428 (39.5)
					60.5	5.0	(Cl) 9.8	acetic acid		268 (8.3) 450 (31.3)
										320 (14.2)
6	D-2	A	42	$C_{19}H_{18}ClNO_4S$	58.2	4.6	(S) 8.2	acetonitrile	186–187	244 (23.0) 326 (13.2)
					58.5	4.7	(S) 8.2			264 (16.2) 464 (35.8)
										284 (8.3)
7	E-1	A and C	82; 70	$C_{20}H_{20}ClNO_5$	61.6	5.2	(Cl) 9.1	acetonitrile	279–280	217 (42.2) 350 (7.2)
					61.3	4.9	(Cl) 8.9			254 (23.2) 368 (6.7)
										288 (14.7) 462 (27.0)
										327 (11.1) 468 (28.1)
										518 (14.7)
8[b]	A-3	A	42	$C_{22}H_{20}ClNO_6$	61.5	4.7	3.3	acetonitrile	240–241	255 (25.6) ~310 (12.0)
					61.7	4.7	3.1			280 (23.2)
9	A-4	B and D	39; 54	$C_{22}H_{22}ClNO_5$	63.5	5.3	3.4	acetonitrile	242–244	237 (15.3) 466 (20.3)
					63.5	5.1	3.2			310 (32.3) 484 (19.6)
10	B-2	B and D	43; 60	$C_{22}H_{22}ClNO_5$	63.5	5.3	(Cl) 8.5	acetonitrile	302–303	247 (13.2) 328 (10.7)
					63.7	5.0	(Cl) 8.3			273 (10.2) 420 (24.0)
11	C-2	B	46	$C_{25}H_{26}ClNO_5$	65.8	5.7	3.1	acetic	212–213	239 (16.2) 374 (5.9)
					65.8	5.6	2.9	anhydride		278 (18.0) 465 (9.0)
										360 (6.3)
12	D-3	B and D	90; 81	$C_{20}H_{20}ClNO_6$	61.6	5.2	3.6	acetonitrile	195–196	237 (19.2) 310 (13.8)
					61.4	5.4	3.3			274 (6.2) 522 (27.1)
13	A-5	E	52	$C_{25}H_{26}ClNO_6$	65.8	5.8	3.1	acetonitrile	201–202	263 (18.2) ~397 (15.2)
		F	78		66.0	5.9	3.0			~300 (14.4) 558 (36.1)
										325 (26.8) 595 (35.4)
14	B-3	E	96	$C_{25}H_{26}ClNO_6$	65.8	5.8	3.1	acetonitrile	210–211	234 (14.7) 340 (14.9)
					66.1	5.6	2.9			248 (14.2) 516 (76.3)
										274 (5.1) 549 (72.5)
										285 (4.9)
15	B-4	E	88	$C_{25}H_{26}ClNO_4S$	63.6	5.6	3.0	ethyl alcohol	185–186	243 (20.0) 339 (10.4)
					63.6	5.4	2.8			286 (6.5) 540 (67.0)
										302 (6.2) 576 (54.6)
16	C-3	E	66	$C_{28}H_{30}ClNO_5$	67.7	6.3	2.8	ethyl alcohol	240–241	262 (14.4) 424 (15.9)
		F	89		67.9	6.0	2.7			326 (24.9) 570 (34.8)
										~340 (20.1) 605 (26.1)
										408 (12.2) ~652 (18.9)
17	D-4	E	72	$C_{28}H_{28}Cl_2NO_6$	59.5	5.0	(Cl) 15.3	acetonitrile	250–251	248 (21.6) 513 (50.5)
					59.7	5.2	(Cl) 14.9			320 (17.5) ~543 (33.2)
										~333 (14.4) 715 (2.1)
18	F-1	E	81	$C_{27}H_{26}ClNO_6$	67.6	5.5	(Cl) 7.4	acetonitrile	207–207.5	244 (32.8) 367 (13.0)
					67.9	5.7	(Cl) 7.4			268 (23.6) 518 (50.5)
										301 (7.7)
19	A-6	C	83	$C_{24}H_{26}Cl_2N_2O_9$	51.7	4.7	(Cl) 12.7	acetonitrile	240–241	244 (13.5) 343 (31.4)
					51.5	5.0	(Cl) 12.9			315 (32.4) 472 (24.0)
20	B-5	C	94	$C_{24}H_{26}Cl_2N_2O_9$	51.7	4.7	(Cl) 12.7	formic acid +	265–266	268 (13.9)
					51.4	5.0	(Cl) 12.7	acetic acid		355 (25.9)
										430 (46.0)
21	D-5	C	73	$C_{22}H_{24}Cl_2N_2O_9$	49.7	4.6	(Cl) 13.5	acetic anhydride	209–210	~243 (20.4) 428 (15.7)
					50.0	4.7	(Cl) 13.5			~266 (17.4) 453 (15 4)
										313 (31.2)
22	D-6	C	78	$C_{22}H_{24}Cl_2N_2O_8S$	48.3	4.4	5.1	acetic anhydride	249–250	267 (17.4) 400 (17.2)
					48.3	4.2	4.9			303 (27.4) 520 (11.9)
23	A-7	C	90	$C_{26}H_{30}Cl_2N_2O_{11}$	50.6	4.9	4.5	acetonitrile	235–236	266 (14.3) 407 (36.2)
					50.4	4.6	4.2			310 (19.0) 479 (28.0)
24	B-6	D	84	$C_{27}H_{24}ClNO_6$	67.8	5.1	2.9	acetonitrile	260–261	255 (14.4) 432 (40.4)
					67.4	5.2	3.2			340 (14.4) 453 (40.0)
25	B-7	D	93	$C_{28}H_{22}ClNO_6$	64.6	5.2	3.3	acetonitrile	272–273	253 (10.2) 423 (42.6)
					64.5	5.2	3.1			280 (8.8) 445 (33.3)
										335 (15.6)
26	A-8	D	66	$C_{27}H_{24}ClNO_6$	67.8	5.1	2.9	acetonitrile	255–256	245 (18.6)
					67.8	5.2	2.7			318 (26.4)
										500 (16.3)
27	A-9	D	50	$C_{28}H_{22}ClNO_6$	64.6	5.2	3.3	pyridine +	229–230	275 (101.0)
					64.5	5.3	3.1	methyl alcohol		465 (20.0)
28	D-7	D	51	$C_{28}H_{22}ClNO_5$	66.4	4.9	3.1	acetonitrile	241–242	238 (22.0)
					66.4	4.6	2.9			320 (14.2)
										445 (35.4)
29	D-8	D	95	$C_{21}H_{20}ClNO_5$	62.8	5.0	3.5	acetonitrile	226–227	238 (19.0)
					62.8	5.1	3.2			317 (16.5)
										430 (36.7)

[a] The structures are given in Chart I, and to aid in finding these structures they have been designated in the tables by a capital letter to indicate the heterocyclic nucleus followed by a number to give the position of the compound in the listings below these nuclei. [b] Prepared from 2-methyl-4,6-diphenylpyrylium perchlorate and N-methylacetamide by procedure A.

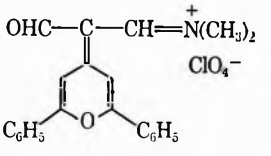
TABLE II

HYDROLYSIS PRODUCTS OF IMINIUM SALTS

Compd number	Structure	Method of preparation	Yield, %	Empirical formula	Anal. Calcd, % C	Anal. Calcd, % H	Anal. Found, % N or S	Solvent of recrystallization	Mp, °C	Absorption spectra in acetonitrile, λ,mμ (ε × 10⁻³)
30	A-10	H	82	$C_{19}H_{14}O_2$	83.2	5.1		ligroin	125–126	224 (13.5) 327 (10.0)
					83.4	5.3		(bp 63–75°)		286 (33.4) 445 (9.7)
31	A-11	H	52	$C_{20}H_{16}O_2$	83.3	5.6		ethyl alcohol	170–171	228 (15.2) 340 (13.4)
					83.4	5.8				283 (30.2) 4
32[a]	C-4	H and I	62; 74	$C_{22}H_{18}O_2$	84.0	5.8		benzene +	165–166	227 (13.9) 352 (8.0)
					83.7	5.5		ligroin		282 (26.2) 443 (9.9)
								(bp 63–75°)		340 (9.9)
33	B-8	H and I	90; 87	$C_{19}H_{14}O_2$	83.2	5.1		ethyl ether	89–90	241 (11.8) 298 (18.0)
					83.3	5.4				272 (12.5) 370 (26.0)
34	D-9	H	80	$C_{17}H_{12}O_2$	82.2	4.9		methyl alcohol	110–111	244 (21.8)
					81.9	4.8				295 (15.7)
										374 (21.4)
35	D-10	H	81	$C_{17}H_{12}OS$	77.2	4.6	(S) 12.1	methyl alcohol	89–90	255 (27.2)
					77.7	4.5	(S) 11.9			299 (13.4)
										401 (19.7)
36	E-2	J	74	$C_{18}H_{14}O_2$	82.4	5.4		methyl alcohol	172–173	257 (21.8) 342 (13.2)
					82.3	5.3				267 (20.8) 357 (10.8)
										278 (20.4) 404 (14.0)
										327 (10.4) 419 (16.5)
										438 (12.9)
37	A-12	H	44	$C_{20}H_{16}O_2$	83.3	5.6		ethyl alcohol	115–117	...
					83.2	5.8				
38	B-9	H	69	$C_{20}H_{16}O_2$	83.3	5.6		ethyl alcohol	109–110	230 (12.2) 297 (18.0)
					83.0	5.9				270 (12.9) 375 (24.7)
39	C-5	I	64	$C_{23}H_{20}O_2$	84.1	6.2		ethyl alcohol	142–143	...
					84.0	6.4				
40	D-11	I	78	$C_{18}H_{14}O_2$	82.4	5.4		methyl alcohol	111–112	243 (25.4)
					82.3	5.6				296 (15.3)
										380 (18.2)
41	B-10	I	51	$C_{21}H_{16}O_2$	84.0	5.4		acetonitrile	165–166	245 (13.9)
					83.9	5.9				302 (13.9)
										421 (39.2)
42	C-6	I	63	$C_{24}H_{20}O_2$	84.7	5.9		acetonitrile	196–197	242 (17.6) 365 (15.0)
					84.5	6.2				255 (18.3) 384 (15.8)
										270 (19.8) 470 (13.6)
										~345 (12.8) ~510 (11.6)
43	F-2	I	67	$C_{23}H_{16}O_2$	85.2	5.0		acetonitrile	171–172	...
					84.9	5.1				
44	B-11	K	88	$C_{20}H_{14}O_3$	79.5	4.7		acetonitrile	234–235	...
					79.6	4.9				
45[b]	B-12	K	96	$C_{25}H_{18}O_2$	85.7	5.2		ethyl alcohol	158–159	222 (19.4) 305 (16.4)
					85.4	5.5				247 (17.9) 410 (33.4)
46[c]	D-12	K	97	$C_{23}H_{16}O_2$	85.2	5.0		ethyl alcohol	129–130	250 (22.5)
					85.0	4.9				295 (15.9)
										405 (26.4)
47	D-13	L	24	$C_{20}H_{18}ClNO_6$	59.5	4.5		acetonitrile	234–235	...
					59.6	4.4				
48	B-13	J	31	$C_{22}H_{20}ClNO_6$	61.5	4.7	3.3	acetic acid	224–225	...
					61.2	5.0	3.3			
49	G-1	see Experimental Section		$C_{21}H_{19}NO$	83.7	6.4	4.7	isopropyl alcohol	145–146	...
					83.6	6.4	4.7			
50	G-2	see Experimental Section		$C_{20}H_{16}O_2$	83.3	5.6		ligroin	93–94	...
					83.3	5.8		(bp 63–75°)		
53	G-3	see Experimental Section		$C_{23}H_{21}NO_2$	80.4	6.2	4.1	butyl alcohol	152	...
					80.2	6.2	4.0			
54	G-4	see Experimental Section		$C_{24}H_{23}NO$	84.5	6.8	4.1	ligroin	110	...
					84.5	6.6	4.2	(bp 63–75°)		

[a] H. D. Kirmer and R. Wizinger, *Helv. Chim. Acta*, **44**, 1766 (1961). [b] H. Strzelecka, *Ann. Chim.*, 201 (1966). [c] J. A. VanAllan, G. A. Reynolds, and T. H. Regan, *J. Org. Chem.*, **32**, 1897 (1967).

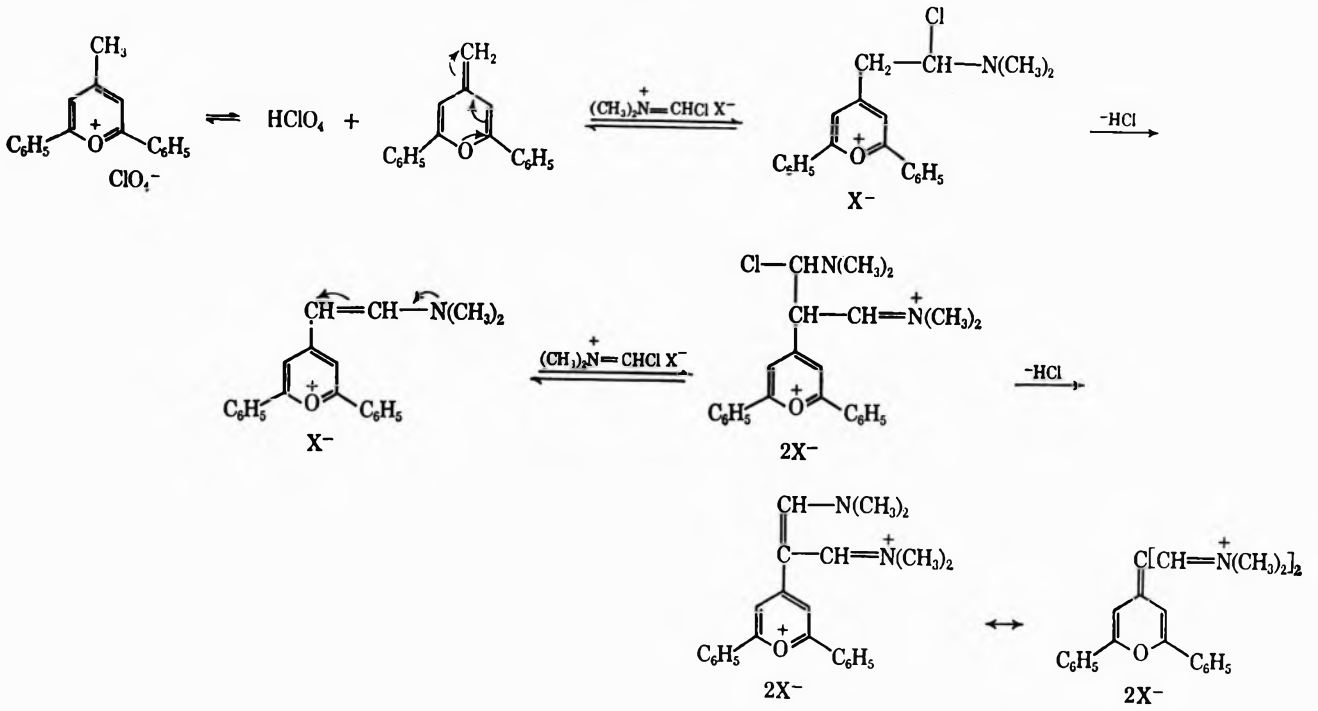
aqueous pyridine rather than methanolic potassium hydroxide, only one of the iminium groups was hydrolyzed, and compound **48** was obtained.



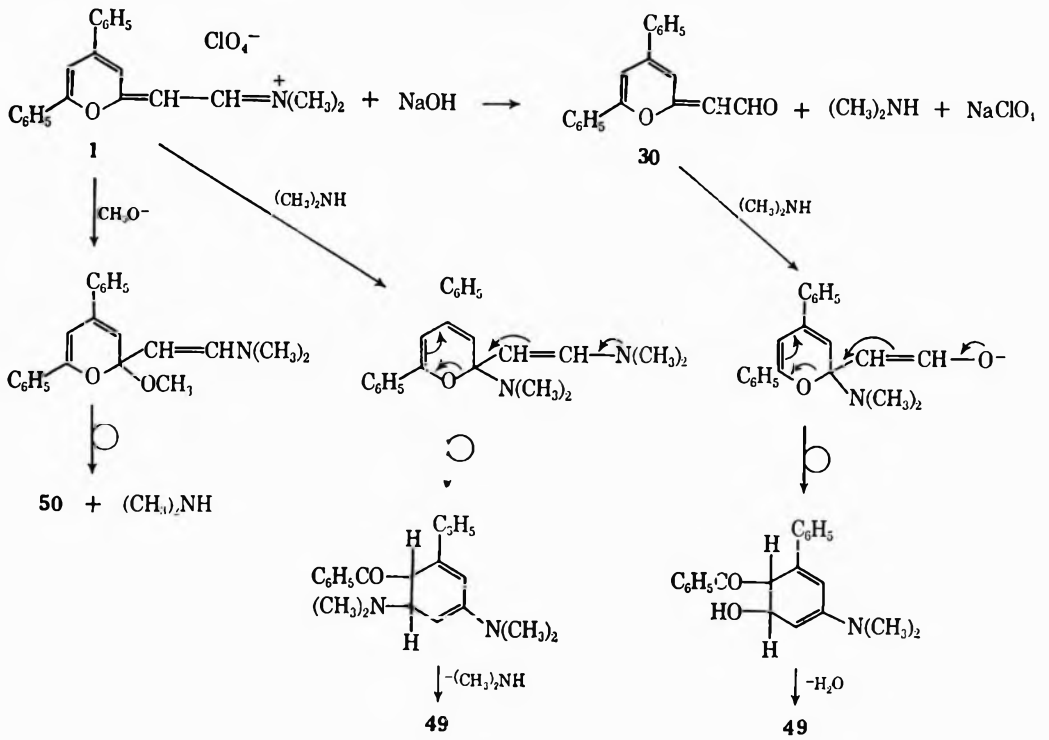
48

Alkaline hydrolysis of the iminium salt **1** gave rise to a mixture of products, and the reaction conditions were found to change the reaction path. The methods which were used for the hydrolysis of **1** are (a) a mixture of **1**, 2% aqueous sodium hydroxide, and ether was stirred for 24 hr; (b) a mixture of **1**, 2% sodium hydroxide, and chloroform was stirred for 3 hr; (c) a solution of **1** in 5% methanolic potassium hydroxide was refluxed for 1 hr. On the basis of the other hydrolyses described in this paper, it was expected that the product would be the aldehyde **30** (Scheme II). Although **30** was the major product from procedure a, it was a minor product from procedure b and was not obtained by procedure c. The principal product isolated by procedure b was 4-dimethylamino-2-phenylbenzophenone (**49**), and procedure c gave a mixture of **49** and 4-methoxy-2-phenylbenzophenone (**50**). The structural assignments for **49** and **50** were made on the basis of the elemental analysis and nmr, ultraviolet, infrared, and mass spectra.

SCHEME I



SCHEME II



The absorption maxima for **49** and **50** are compared with those of 4-dimethylaminobenzophenone (**51**) and 4-methoxybenzophenone (**52**) in Table III; the similarity of the spectra of the related compounds is apparent. The carbonyl stretching vibrations for these compounds are also recorded in Table III.

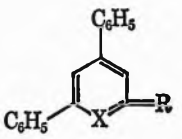
The mass spectrometric analyses of **49** and **50** were consistent with the proposed structures, and some of the major fragmentations are (**49**) M (*m/e*) 301, *m/e* 224, 180, 152; (**50**) M (*m/e*) 288, *m/e* 211, 168, 140, 139 105.

The nmr spectra of **49** and **50** demonstrated that a 1,2,4-trisubstituted phenyl ring was present in these compounds. The 100-MHz spectrum of **49** in benzene-d_6 has absorption at τ 7.49 (s, 6 H, NMe_2) and from τ 3.6 to 2.5 (complex m, 13 H, ArH). The substitution pattern on the central ring is clearly seen, however, from the typical ABX pattern characteristic of

CHART I

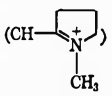
STRUCTURES OF COMPOUNDS IN TABLES II AND III

A



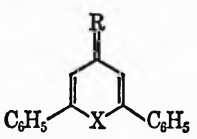
R

1 (CHCH=N$^+$(CH$_3$)$_2$)
2 (C(CH$_3$)CH=N$^+$(CH$_3$)$_2$)
8 (CHCH=N$^+$(CH$_3$)COCH$_3$)
9 (CHC(CH$_3$)=N$^+$(CH$_3$)$_2$)
13 (CHCH=CHCH=N$^+$(C$_2$H$_5$)$_2$)
19 (C[CH=N$^+$(CH$_3$)$_2$]$_2$)
23 (*p*-methoxy in both phenyls; R as in **19**)
26 (CHC(C$_6$H$_5$)=N$^+$(CH$_3$)$_2$)

27 

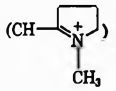
30 (CHCHO)
31 (C(CH$_3$)CHO)
37 (CHCOCH$_3$)

B



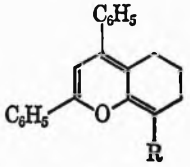
R

4 (CHCH=N$^+$(CH$_3$)$_2$)
10 (CHC(CH$_3$)=N$^+$(CH$_3$)$_2$)
14 (CHCH=CHCH=N$^+$(C$_2$H$_5$)$_2$)
15 (X = S; R as in **14**)
20 (C[CH=N$^+$(CH$_3$)$_2$]$_2$)
24 (CHC(C$_6$H$_5$)=N$^+$(CH$_3$)$_2$)

25 

33 (CHCHO)
38 (CHCOCH$_3$)
41 (CHCH=CHCHO)
44 (C[CHO]$_2$)
45 (CHCOC$_6$H$_5$)
48 (C(CHO)CH=N$^+$(CH$_3$)$_2$)

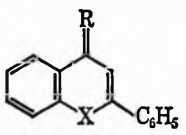
C



R

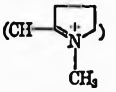
3 (CH=N$^+$(CH$_3$)$_2$)
11 (C(CH$_3$)=N$^+$(CH$_3$)$_2$)
16 (CH=CHCH=N$^+$(C$_2$H$_5$)$_2$)
32 (CHO)
39 (COCH$_3$)
42 (CH=CHCHO)

D



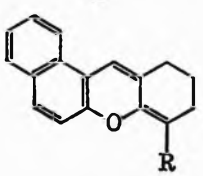
R

5 (CHCH=N$^+$(CH$_3$)$_2$)
6 (X = S; R as in **5**)
12 (CHC(CH$_3$)=N$^+$(CH$_3$)$_2$)
17 (4′-chloro; R is CHCH=CHCH=N$^+$(C$_2$H$_5$)$_2$)
21 (C[CH=N$^+$(CH$_3$)$_2$]$_2$)
22 (X = S; R as in **21**)
28 (CHC(C$_6$H$_5$)=N$^+$(CH$_3$)$_2$)

29 

34 (CHCHO)
35 (X = S; R as in **34**)
40 (CHCOCH$_3$)
46 (CHCOC$_6$H$_5$)
47 (C(CHO)CH=N$^+$(CH$_3$)$_2$)

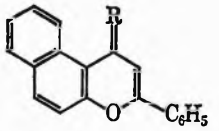
E



R

7 (CH=N$^+$(CH$_3$)$_2$)
36 (CHO)

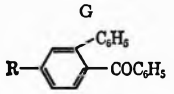
F



R

18 (CHCH=CHCH=N$^+$(C$_2$H$_5$)$_2$)
43 (CHCH=CHCHO)

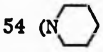
G



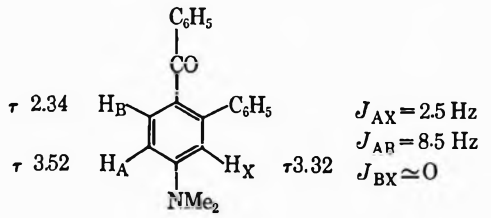
R

49 (N(CH$_3$)$_2$)
50 (OCH$_3$)

53 

54 

1,2,4-trisubstituted benzenes. Compound **50** has a singlet at τ 6.76 (3 H, OCH$_3$) and a complex multiplet from τ 3.4 to 2.2 (13 H, ArH). As expected for this compound, the signals for the protons *ortho* to the methoxy group are at lower field than the analogous protons for **49** and the H$_x$ signal falls on the side of a



49

complex absorption. The assignments for the protons of **50** are H$_A$, τ 3.28; H$_B$, τ 2.54; H$_X$, τ 3.09; J_{AB} = 8.5 Hz; J_{AX} = 2.5 Hz; $J_{BX} \simeq 0$.

Scheme II shows a reaction path which accounts for the formation of **30**, **49**, and **50** from the hydrolysis of **1**.

To test the proposed reaction scheme, **1** and dimethylamine were heated in alcohol for a short time and **49** was isolated in high yield. The same results were obtained when the aldehyde **30** was treated with dimethylamine. The substitution of other secondary amines for dimethylamine in these reactions also gave aminobenzophenone derivatives. For example, **1** and morpholine gave 4-morpholino-2-phenylbenzophenone (**53**), and **1** and piperidine gave 4-piperidino-2-phenylbenzophenone (**54**). The reaction of **1** with sodium methoxide in methanol gave **50** and a small amount of **49**. The reaction of **1** with 5% potassium hydroxide in methanol gave about 75% **49** and 25% **50**, and, when 25% methanolic potassium hydroxide was used, approximately equal amounts of **49** and **50** were formed. We were unable to isolate 4-hydroxy-2-phenylbenzophenone from any of our experiments. This result may be due to the low nucleophilicity of the hydroxide ion or because attack of hydroxide at the 2 position of the pyran ring is reversible. The results described above are consistent with nucleophilic attack of secondary amine or methoxide ion at the 2 position of the pyran ring followed by rearrangement as shown in Scheme II. The dimethylamine, which is necessary for the formation of **49**, is produced by the hydrolysis of the iminium bond and also from the final aromatization step.

Probably the formation of the aldehyde **30** by procedure a is the result of the poor solubility of **30** in ether, which prevents subsequent reaction to form rearranged products.

TABLE III

ABSORPTION MAXIMA OF BENZOPHENONE DERIVATIVES

Compd	λ_{max}, mμ	$\epsilon \times 10^{-3}$	Solvent	CO vibration, μ
49	241	25.6	acetonitrile	6.08
	346	11.1		
51[a]	247	15.7	alcohol	6.1
	355	20.6		
50	245	24.3	acetonitrile	6.05
	285	7.8		
	249	9.0		
52[b]	283	16.0	alcohol	6.05
	288	16.55		

[a] H. Szmant and C. McGinnis, *J. Amer. Chem. Soc.*, **74**, 241 (1952). [b] E. Moriconi, W. O'Connor, and W. Forbes, *ibid.*, **82**, 5454 (1960).

Experimental Section

The methods of preparation of the various classes of compounds are described as general procedures. The compounds are listed in Tables I and II along with the methods of preparation and some physical properties.

Preparation of Monoiminium Salts. Procedure A.—A mixture of 5 g of alkylpyrylium perchlorate, 3 ml of N,N-dimethylformamide, and 100 parts of acetic anhydride was refluxed for 15 min. The mixture was cooled, and if no product separated, ether was added to precipitate the crude product, which was collected and recrystallized.

Procedure B.—A mixture of 0.02 mol of alkylpyrylium salt, 0.02 mol of N,N-dimethylthioacetamide, and 30 ml of acetic anhydride was refluxed for 30 min and chilled, and the product was collected and recrystallized.

Procedure C.—A solution of the Vilsmeier complex was prepared from 2 ml of phosphorous oxychloride and 10 ml of cold N,N-dimethylformamide, 0.01 mol of the alkylpyrylium perchlorate was added, and the solution was heated for 30 min on a steam bath. The reaction mixture was poured onto ice and the solid was collected.

Procedure D.—This procedure was the same as C, except that N,N-dimethylacetamide, N,N-dimethylbenzamide, and N-methylpyrrolidinone were used rather than dimethylformamide.

Procedure E.—A mixture of 2 g of alkylpyrylium perchlorate, 2 ml of diethylaminoacrolein, and 50 ml of acetic anhydride was stirred at room temperature for 2 hr. It was then diluted with ether and chilled, and the solid was collected.

Procedure F.—A mixture of 0.01 mol of active methyl compound, 0.012 mol of N,N-diethyl-N-(1-methoxy-1-propen-3-ylidene)-ammonium methylsulfate,[4] 2 ml of N,N-diisopropylethylamine, and 25 ml of alcohol was heated on a steam bath for 15 min and chilled, and the solid was collected.

Preparation of Bisiminium Salts. Procedure G.—This procedure was the same as C, except that the amount of N,N-dimethylformamide was doubled.

Preparation of Monoaldehydes. Procedure H.—A mixture of 0.01 mol of the monoiminium salt, 75 ml of 2% aqueous sodium hydroxide, and 75 ml of ether was stirred for 24 hr. The ether phase was separated. In some cases the aldehyde was sparingly soluble in ether and additional ether was added. The ether extracts were dried, the solvent was removed, and the residue was recrystallized.

Procedure I.—A mixture of 0.01 mol of monoiminium salt and 50 ml of 5% methanolic potassium hydroxide was heated on a steam bath for 0.5 hr and chilled, and the solid was collected.

Procedure J.—A mixture of 0.01 mol of iminium salt, 25 ml of pyridine, and 2 ml of water was refluxed for 1 hr, cooled, and diluted with water, and the solid which separated was collected.

Preparation of Bisaldehydes. Procedure K.—Procedure H was duplicated with a bisiminium salt.

Procedure L.—Procedure I was employed with a bisiminium salt.

4-[3-(4H-Flaven-4-ylidene)-2-methyl-1-propenyl]flavylium Perchlorate.—A mixture of 3 g of 4-methylflavylium perchlorate, 3 ml of N,N-dimethylacetamide, and 25 ml of acetic anhydride was refluxed for 0.5 hr and chilled, and the dark solid was collected and recrystallized from acetonitrile to give 2.4 g of the cyanine dye.

Anal. Calcd for $C_{32}H_{23}ClO_6$: C, 71.3; H, 4.3; Cl, 6.6. Found: C, 71.6; H, 4.3; Cl, 6.6.

4-Dimethylamino-2-phenylbenzophenone (49).—(a) A mixture of 2 g of the iminium salt **1**, 50 ml of chloroform, and 50 ml of 2% aqueous sodium hydroxide was stirred for 3 hr. The organic phase was separated and the solvent was removed. Analysis of the residue by vpc showed that it consisted of 62% **49** and 38% aldehyde **30**. These two compounds were readily separated by preparative vpc, or they could be fractionally crystallized from isopropyl alcohol to give **49**, and the alcohol-soluble fraction was then crystallized from ligroin (bp 63–75°) to give **30**.

(b) A mixture of 1 g of **1** or 1 g of the aldehyde **30**, 5 ml of 25% aqueous dimethylamine, and 50 ml of alcohol was heated on a steam bath for 0.5 hr and diluted with water, and the solid was collected and recrystallized to give **49** in 85% yield (from **1**) and 88% yield (from **30**).

4-Methoxy-2-phenylbenzophenone (50).—(a) A mixture of 12 g of **1** and 100 ml of 5% methanolic potassium hydroxide was heated on a steam bath for 1 hr and poured into water, and the solid was extracted into benzene. The benzene extract was dried ($MgSO_4$) and the solvent removed. The residue as analyzed by vpc consisted of 75% **49** and 25% **50**. Distillation of the residue followed by crystallization of the distillation fractions did not completely separate **49** and **50**. The two products were separated by preparative vpc, yielding 5.1 g of **49** and 1 g of **50**.

When this procedure was repeated using 100 ml of 25% methanolic potassium hydroxide, the reaction mixture consisted of approximately equal parts of **49** and **50**, as shown by vpc.

(b) A mixture of 2 g of **1**, 4 g of sodium methoxide, and 75 ml of methanol was heated on the steam bath for 1 hr, cooled, and diluted with water, and the sticky solid was collected and recrystallized to give **50** in 87% yield.

4-Morpholino-2-phenylbenzophenone (53).—A mixture of 2 g of **1**, 3 ml of morpholine, and 25 ml of alcohol was heated on a steam bath for 15 min and poured into water, and the solid was collected and recrystallized to give 1.2 g of **53**.

4-Piperidino-2-phenylbenzophenone (54).—This compound was prepared as described for **53**, piperidine being substituted for morpholine; yield 1.3 g.

Registry No.—**1**, 20439-71-8; **2**, 20439-72-9; **3**, 20439-73-0; **4**, 20439-74-1; **5**, 20439-75-2; **6**, 20420-95-5; **7**, 20439-76-3; **8**, 20439-77-4; **9**, 20439-78-5; **10**, 20439-79-6; **11**, 20439-80-9; **12**, 20439-81-0; **13**, 17203-20-2; **14**, 17203-19-9; **15**, 17203-24-6; **16**, 17203-21-3; **17**, 17203-22-4; **18**, 17203-23-5; **19**, 20439-85-4; **20**, 20439-86-5; **21**, 20439-87-6; **22**, 20439-88-7; **23**, 20420-94-4; **24**, 20399-80-8; **25**, 20399-81-9; **26**, 20399-82-0; **27**, 20399-83-1; **28**, 20399-84-2; **29**, 20399-85-3; **30**, 20399-86-4; **31**, 20399-87-5; **32**, 20399-88-6; **33**, 20399-89-7; **34**, 20399-90-0; **35**, 20399-91-1; **36**, 20399-92-2; **37**, 20399-93-3; **38**, 1914-17-6; **39**, 20399-95-5; **40**, 20399-96-6; **41**, 17203-26-8; **42**, 17202-98-1; **43**, 17202-97-0; **44**, 20400-00-4; **45**, 1914-13-2; **46**, 10385-47-4; **47**, 20400-03-7; **48**, 20400-04-8; **49**, 20400-05-9; **50**, 20400-06-0; **53**, 20400-07-1; **54**, 20400-08-2.

Acknowledgment.—We wish to acknowledge the assistance of Dr. T. H. Regan and Mr. R. L. Young for the determination and interpretation of the nmr spectra; to Mr. D. P. Maier for the mass spectral data; and to Mr. D. H. Miles for the determination of the electronic spectra.

Azlactone Formation in the Isoxazolium Salt Method of Peptide Synthesis

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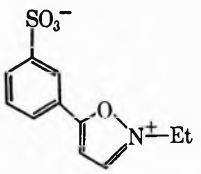
The reaction of hippuric acid with isoxazolium salts to give enol esters has been found to be accompanied by azlactone formation. The extent of the side reaction with N-*t*-butyl-5-methylisoxazolium perchlorate (**7**) decreases with increasing basicity of the medium, although the ester (**12**) from **7** itself decomposes to azlactone in the presence of strong base. The ester **12** free of azlactone may be obtained by use of 2-picoline as the reaction solvent to maintain a medium of intermediate base strength. The peptide reagent N-ethyl-5-phenylisoxazolium 3′-sulfonate (**1**) does not give appreciable azlactone in the normal procedure for its use because the low rate of solution of the reagent fortuitously controls the basicity of the reaction mixture.

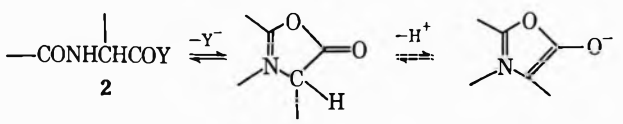
In the investigation[1] of the use of N-ethyl-5-phenylisoxazolium 3′-sulfonate (**1**) for the synthesis of peptides, conditions were defined under which no racemization was observed in the Anderson test.[2] Since then,



1

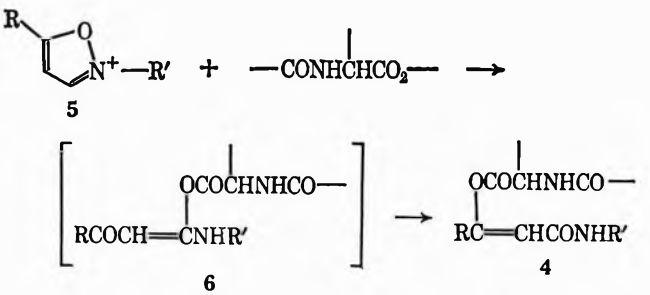
other workers have reported the detection of some degree of racemization in different tests with **1**.[3-5] Our further studies of the reaction of isoxazolium salts with N-acylamino acids have now provided clarification of the potential for racemization in this method of peptide synthesis.

The common mechanism established[6,7] for racemization during peptide synthesis involves fragmentation of an acylating agent (**2**) derived from a peptide acid to give an azlactone (**3**), which may then ionize with loss of chirality at the α carbon. Although with other acylat-



2 **3**

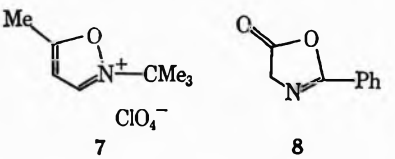
ing agents of the active ester type racemization *via* azlactones usually does not compete effectively with acylation of an amine group during the peptide bond formation reaction itself, preparation of the optically pure active esters of peptide acids by acyl transfer from a racemization-prone acylating agent of greater activity is a common problem.[8] However, it has been proposed that the enol ester acylating agents (**4**) from isoxazolium salts (**5**) are formed from more highly reactive, intermediate acylating agents (**6**) by an intramolecular acyl migration process.[9] On the basis of the initial favorable



5 **6** **4**

racemization results with **1**, it appeared likely that the decomposition of **6** to azlactone was not so rapid as the facile rearrangement of **6** to **4** and that the use of isoxazolium salts might, therefore, eliminate the problem of racemization during the formation of active esters of peptide acids.

Infrared spectral studies of the reaction of hippuric acid with a variety of isoxazolium salts have now revealed that, actually, enol ester preparation generally is complicated by azlactone formation.[10-12] The spectrum of the product mixture from hippuric acid, triethylamine, and the new reagent, N-*t*-butyl-5-methylisoxazolium perchlorate (**7**),[13] in acetonitrile contained a strong peak at 5.45 μ attributable to 2-phenylazlactone (**8**),[14] with only weak enol ester absorption at 5.65 μ. A



7 **8**

similar result was obtained with N-*t*-butyl-5-phenylisoxazolium perchlorate (**9**), while N,5-diphenylisoxazolium

(1) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Amer. Chem. Soc.*, **83**, 1010 (1961); *Tetrahedron Suppl.*, **8**, 321 (1966).

(2) G. W. Anderson and F. M. Callahan, *J. Amer. Chem. Soc.*, **80**, 2902 (1958).

(3) F. Weygand, A. Prox, L. Schmidhammer, and W. König, *Angew. Chem.*, **75**, 282 (1963).[4]

(4) The observation of racemization in this test was not unexpected since under comparable conditions racemization also was observed in the Anderson test.

(5) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963).

(6) M. Goodman and K. C. Stueben, *J. Org. Chem.*, **27**, 3409 (1962); M. Goodman and L. Levine, *J. Amer. Chem. Soc.*, **86**, 2918 (1964); M. Goodman and W. J. McGahren, *ibid.*, **87**, 3028 (1965).

(7) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 3701 (1964); I. Antonovics and G. T. Young, *Chem. Commun.*, 398 (1963).

(8) M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience Publishers, New York, N. Y., 1966, p 150.

(9) R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.*, **83**, 1007 (1961); *Tetrahedron Suppl.*, **7**, 415 (1966).

(10) The extent of racemization, since it depends on the relative rates of acylation and racemization for the azlactone, would be less than the amount of azlactone formed. Thus, in cases where the azlactone is stable, direct spectral assay of the actual amount of azlactone provides an especially sensitive measure of the potential hazard of racemization associated with the formation of enol esters.

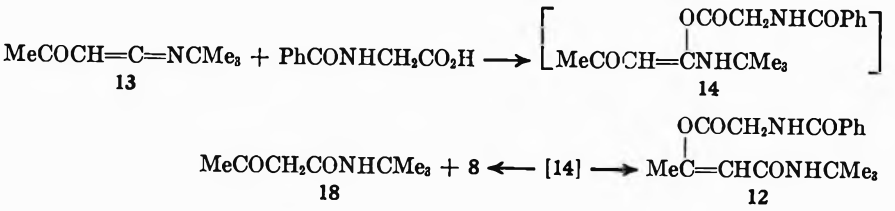
(11) Related results were previously obtained in a study of the N-ethylbenzisoxazolium cation.[12]

(12) D. S. Kemp, Ph.D. Thesis, Harvard University, 1964.

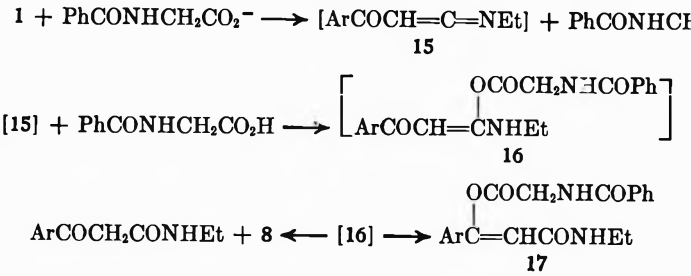
(13) R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **90**, 1371 (1968).

(14) Assignment confirmed by isolation of **8**.

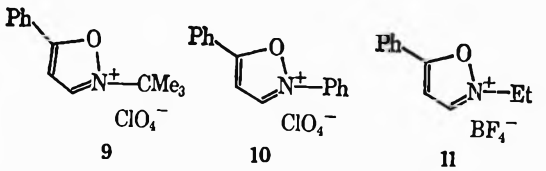
SCHEME I



SCHEME II



perchlorate (**10**) gave an azlactone band of lesser intensity than that of the enol ester. Azlactone absorption was negligible only with the original reagent **1**, and even the closely related compound, N-ethyl-5-phenylisoxazolium fluoroborate (**11**), gave an azlactone peak comparable in intensity with that of the enol ester.



9 **10** **11**

It was also found that the relative amounts of azlactone (**8**) and enol ester (**12**) from the reaction of hippuric acid and the ketoketenimine **13**, from **7**, varied with the basicity of the reaction mixture. In a series of spectral tests in acetonitrile containing progressively greater concentrations of pyridine, the proportion of ester in the product mixture increased steadily, but some azlactone was formed even when pyridine was used as the solvent. The effect of pyridine concentration on the product ratio cannot be attributed to an equilibrium between the enol ester and azlactone since control experiments established that there is no interconversion of **8** and **12** in the presence of pyridine. Therefore azlactone and enol ester must be formed by competing reactions.

The observation of azlactone formation under conditions where the product ester itself does not give **8** provides support for the proposal[9] that the reaction of carboxylic acids with isoxazolium salts proceeds *via* a highly reactive intermediate acylating agent such as **6**. Presumably, then, alternate modes of decomposition of the corresponding intermediate **14**, from hippuric acid and **13**, give either **8** or **12** (Scheme I), and increasing basicity favors the pathway to enol ester.[15]

A similar dependence of the reaction course upon basicity of the medium can be invoked to explain why in the spectral tests only the reagent **1** gave the enol ester of hippuric acid relatively free of azlactone. The crucial difference between **1** and the other isoxazolium salts tested is that **1** is a zwitterion which is relatively insoluble in acetonitrile. All the other isoxazolium salts dissolve immediately in the triethylammonium hippurate solution with rapid ring opening to give hippuric acid and ketoketenimine,[16] which then combine in the slow step of the reaction. In contrast **1** dissolves so slowly (45 min) that the rate of solution is rate determining, and the acid and ketoketenimine (**15**) do not build up to detectable concentrations. Thus, while the intermediates from the other isoxazolium salts decompose in a medium containing acid generated by the fast prior ring opening and give azlactone, the intermediate (**16**) from **1** is exposed to unconsumed base which favors the formation of enol ester (**17**) (Scheme II). That the avoidance of azlactone with **1** is the result of the rate of solution, rather than some other factor, was confirmed in a test in which the order of combination of the reactants was altered. By allowing **1** to react with a solution of triethylamine before combination with the hippuric acid, a reaction mixture similar in acidity to those with the other isoxazolium salts was obtained, and, as expected, the product spectrum contained an azlactone peak comparable in intensity with that of the enol ester.

In view of the potential advantages of the enol esters from the new reagent **7** for synthetic use,[13] it was of interest to determine if the basicity of the reaction medium could be maintained at such a level that azlactone-free enol ester could also be obtained from **7**. Attempts to preserve a basic environment by very slow addition of a solution of **7** to triethylammonium hippurate in acetonitrile resulted in some enrichment of the product mixture in enol ester, but, even when **7** was added at a constant rate over a period of 6 hr, the enol ester absorption was not so great as that of **8**. The failure of the slow addition approach with **7** and the fact that a greater proportion of azlactone is obtained from **7** and triethylammonium hippurate than from the reverse addition experiment with **1** suggest that azlactone formation is more favorable, relative to enol ester formation, from **14** than from **16**.

Although the use of more strongly basic conditions still offered the possibility of channeling the decomposition of **14** exclusively to **12**, such conditions also pre-

(15) This effect of basicity on the reaction course, which could be rationalized on the basis of preferential rearrangement of the anion of **14** to **12**, was originally proposed by D. S. Kemp as a result of his study of the N-ethylbenzisoxazolium cation.[10]

(16) Detected by the characteristic band in the cumulene region of the infrared spectrum.

sented the hazard of equilibration of enol ester with azlactone. Racemization of the closely related enol esters from peptide acids and benzisoxazolium salts in the presence of triethylamine has recently been explained on the basis of such an equilibrium.[17] In the present system the equilibrium actually favors azlactone as shown by spectral tests in acetonitrile containing a catalytic amount of triethylamine in which **12** slowly gave **8** but no reverse reaction was observed with a mixture of **8** and **18**. Complete avoidance of azlactone therefore required that conditions be found more basic than the tests with pyridine to prevent the formation of **8** from **14** yet not so basic that **8** would be formed from **12**. Since the equilibrium favors **8** relative to **12**, direct spectral assay could be used to detect azlactone from either source in further tests designed to find conditions of appropriate intermediate basicity.

Substantial reduction in the proportion of azlactone was achieved in a test of the reaction of **13** and hippuric acid with 10% excess triethylamine in dimethylformamide (DMF) under vacuum on a rotary evaporator. It was hoped that the excess strong base liberated during the reaction would be continually removed by evaporation along with the high boiling solvent. However, all of the azlactone could not be eliminated by this approach even when the more volatile trimethylamine or only an exact equivalent of triethylamine was employed. A more promising method for controlling the basicity was to use a tertiary base intermediate in strength between triethylamine (pK_a of the conjugate acid in water = 10.65[18]) and pyridine ($pK_A = 5.17$[19]). In a test with 10% excess N-methylmorpholine ($pK_A = 7.14$[18]) in acetonitrile, some azlactone absorption was observed in the initial product spectrum, and, later in the reaction, the azlactone peak began to increase as that of the ester diminished. It is likely that in this test the basicity at the outset was insufficient to prevent the formation of **8** from **14** and that increasing basicity as the reaction progressed with consumption of acid subsequently brought about conversion of **12** into **8**. Apparently, then, a base weaker than N-methylmorpholine was needed to avoid the latter problem while the base would have to be present in large excess so that decomposition of **14** would give only **12**. The range of base strength in question spans the picolines and lutidines, but with 3-picoline ($pK_A = 5.68$[17]) as the solvent the result was the same as with pyridine. Finally, tests with either 2-picoline ($pK_A = 5.97$[17]) or 2,6-lutidine ($pK_A = 6.75$[17]) as the solvent did give product spectra which contained no azlactone peak, establishing that in this range of basicity both pathways to azlactone are inoperative.[20]

The practical consequence of the spectral tests of azlactone formation with **7** is that special precautions would have to be taken for the preparation of enol esters with the new reagent and N-acylamino acids or peptide acids which are likely to form azlactones. Vacuum evaporation of a solution of equivalents of hippuric acid and the ketoketenimine **13** from **7** in dry 2-picoline after the reaction is largely complete (20 hr) forces the enol ester preparation to completion and azlactone can not be detected in the spectrum of the residue. However, azlactone is apparent with only minor variations on this technique, such as using the isoxazolium salt **7** instead of **13** or evaporating the solvent immediately. In both these modifications the basicity of the reaction medium is diminished slightly and some decomposition of **14** to **8** presumably occurs.[21]

Finally, while the rate of solution of the original peptide reagent **1** has been shown to favor enol ester formation under the optimum conditions previously described[1] for its use, it must be stressed that modifications of the procedure which might upset this accidental control mechanism can lead to competing azlactone formation and the attendant danger of racemization. For example increased azlactone absorption was detected in a spectral test in which 10% excess hippuric acid was present in acetonitrile and also when exact equivalents were used in the solvent nitromethane, in which the reagent **1** dissolves more rapidly. Therefore any changes in the conditions for enol ester preparation with **1** which might increase the rate of solution of the reagent and/or increase the acidity of the medium should be avoided.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope, calibrated with melting point standards from Arthur H. Thomas Co. The nmr spectra were run on a Varian A-60 spectrometer and chemical shifts are reported in τ values relative to tetramethylsilane as an internal standard (τ 10.00). The ir spectra were recorded with a Perkin-Elmer Infracord spectrophotometer, using fixed 0.2-mm path length cells. All amines were dried over type 5A molecular sieves. The analysis was performed by Scandinavian Microanalytical Laboratories.

Spectral Tests of Azlactone Formation.—A solution of 0.179 g (1 mmol) of hippuric acid and 0.101 g (1 mmol) of Et_3N in 10 ml of MeCN (spectral grade) was stirred vigorously while 0.240 g (1 mmol) of **7** was added rapidly. The ir spectrum of the resulting solution was scanned repeatedly from 4 to 7 μ until the ketenimine absorption near 4.85 μ disappeared in about 20 min (t), and the absorbance of the carbonyl peak of **8** at 5.45 μ in the product spectrum was 0.58 (A).[22]

The test was repeated with 1 mmol each of **9**[23] (t = 20 min, A = 0.63), **10**[23] (t = 5 min, A = 0.13), and **11**[1] (t = 7 min, A = 0.20). With 1 stirring was continued until all but traces of the reagent had dissolved (45 min), and no ketenimine absorption could be detected in the spectrum of the solution ($A < 0.02$).

2-Phenylazlactone (8).—A duplicate of the test reaction mixture with **7** was allowed to stand overnight, diluted with 20 ml of CH_2Cl_2, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was washed with three 5-ml portions of cold water to remove the bulk of the by-product **18**, and the remaining solid was dried under vacuum. Partial sublimation (80–90°, 0.1 mm) gave 0.034 g (21%) of **8**, mp 88–88.5° (lit.[12] mp 90.0–91.2°). Further sublimation gave **8** contaminated with **18**. The ir spectrum was identical with that of an authentic sample of **8**;[12] nmr ($CDCl_3$) showed τ 5.65 (s, 2) and 2.83–2.00 (m, 5).

Tests with Pyridine.—A mixture of 1 mmol of hippuric acid and 0.155 ml (1 mmol) of **13**[24] in 10 ml of MeCN was swirled

(17) D. S. Kemp and S. W. Chien, *J. Amer. Chem. Soc.*, **89**, 2745 (1967).

(18) H. K. Hall, Jr., *ibid.*, **79**, 5441 (1957).

(19) H. C. Brown, D. H. McDaniel, and O. Hafliger, in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, p 567.

(20) The possibility that the absence of the azlactone peak can be attributed to rapid, selective decomposition of **8** by reaction with traces of nucleophilic impurities in these solvents is ruled out by the detection of azlactone in 2-picoline in the modified procedures below.

(21) The yield of **12** with the successful technique could not be determined accurately because the ester failed to crystallize, but with carbobenzoxyglycine the crude enol ester (**19**) was obtained in 90% yield, albeit in a low state of purity. Since carbobenzoxyglycine is not subject to the azlactone problem and pure **19** can be recovered from the reaction conditions, additional side reactions must be responsible for the low purity of the product obtained from the reaction in 2-picoline.

(22) For 0.1 M **8** in MeCN, A = 1.0.

(23) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **31**, 2039 (1966).

(24) R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **88**, 3169 (1966).

until all the acid had dissolved. The ir spectrum of the solution was scanned from 4 to 7 μ until 13 had been consumed completely (t = 30 min, A = 0.77). The product spectrum was identical after 24 hr. No change was observed in the ratio of intensities of the azlactone and enol ester peaks after a duplicate of the test mixture was diluted with pyridine (final concentration 2.0 M).

The test was repeated with reaction mixtures 0.1 M (A = 0.50), 0.2 M (A = 0.39), 0.5 M (A = 0.33), and 2.0 M (A = 0.17) in pyridine. A final test was conducted in pyridine as the solvent (A = 0.05).

Reverse Addition with 1.—A mixture of 0.202 g (2 mmol) of Et_3N in 10 ml of MeCN and 0.507 g (2 mmol) of **1** was stirred until all but traces of the solid had dissolved. Then 5 ml of the resulting solution was added rapidly to a vigorously stirred suspension of 1 mmol of hippuric acid in 5 ml of MeCN. The acid dissolved within 2 min, and the product spectrum was recorded (A = 0.35).

Slow Addition with 7.—A solution of 1 mmol of **7** in 0.5 ml of MeCN was added during 75 min at a constant rate with a motor driven syringe control to a well-stirred solution of 0.102 g (1.01 mmol) and 0.181 g (1.01 mmol) of hippuric acid in 9.5 ml of the solvent. The product spectrum was recorded when the addition was complete (A = 0.35). The test was repeated with addition times of 150 min (A = 0.32) and 375 min (A = 0.29).

Interconversion of 12 and 8.—The ir spectrum of a 0.1 M solution of **12** (isolated below) in MeCN containing a catalytic amount (1 drop/100 ml) of Et_3N showed an azlactone band at 5.45 μ (A = 0.04) within 1 hr at room temperature. The spectrum of the solution the next day contained a diminished enol ester peak and increased azlactone absorption (A = 0.18). No ester absorption was detected on long standing of an MeCN solution 0.1 M in both **8** and **18** (from below) with a catalytic amount of Et_3N.

N-*t*-Butylacetoacetamide (18).—The isoxazolium salt **7** (2.40 g, 10 mmol) was dissolved in 50 ml of 8% $NaHCO_3$. After 24 hr the solution was extracted with three 25-ml portions of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and filtered. Removal of the solvent under reduced pressure left 1.2 g of crystalline solid, mp 45–47.5°. Two recrystallizations from ether gave pure **18**: mp 46.5–48° (lit.[25] mp 44–45°); nmr (CCl_4) τ 8.70 (s), 7.83 (s), 6.95 (s), and 2.97 (broad).

Tests with Other Bases.—A mixture of 1 mmol each of hippuric acid and **13** in 10 ml of DMF containing 0.154 ml (1.1 mmol) of Et_3N was swirled until all the acid had dissolved, and the solution was evaporated in the course of 3 hr at room temperature with a rotary evaporator attached to a mechanical vacuum pump. After 2 hr more on the evaporator, the residue was taken up in 10 ml of MeCN and the ir spectrum recorded (A = 0.15). The test was repeated with 1 mmol of Et_3N (A = 0.17) and with excess (<0.06 g) of Me_3N (A = 0.12).

The spectrum of a solution of 1 mmol each of hippuric acid and **13** in 10 ml MeCN containing 1.1 mmol of N-methylmorpholine recorded 2 min after combining the reactants contained enol ester absorption and a weaker azlactone peak (A = 0.03). After 10 hr both bands had increased in intensity (A = 0.07), and after 60 hr the ester peak had diminished while that of the azlactone had further increased (A = 0.13).

Spectra were scanned from 4 to 7 μ until all the ketenimine had been consumed in test reactions of 1 mmol each of **13** and hippuric acid in 3-picoline (t = 25 hr, A = 0.06), 2-picoline (t = 30 hr, A < 0.01), and 2,6-lutidine (t = 30 hr, A < 0.01).

N-*t*-Butyl-β-hippuryloxycrotonamide (12).—A duplicate of the spectral test solution of **13** and hippuric acid in 2-picoline was allowed to stand 20 hr and then evaporated under vacuum at room temperature. The residue was taken up in 10 ml of MeCN, and the ir spectrum showed enol ester absorption at 5.65 μ free of any azlactone peak. Attempts to crystallize the oil from a variety of solvents were unsuccessful. The procedure was repeated, evaporating the solution immediately (A = 0.02) and substituting 1 mmol of **7** for **13** (A = 0.04).

N-*t*-Butyl-β-carbobenzoxyglycyloxycrotonamide (19).—A solution of 1.05 g (5 mmol) of carbobenzoxyglycine in 40 ml of 2-picoline was combined with 0.696 g (5 mmol) of **13** in 10 ml of the solvent under dry nitrogen. The next day the solution was evaporated and the residue was taken up in CH_2Cl_2 and washed with water, 8% $NaHCO_3$, and water. Each aqueous extract was washed with two small portions of CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered, and evaporated. Precipitation of the residue from benzene with petroleum ether (bp 40–60°) gave 1.57 g (90%) of yellow crystals, mp 76–83°, contaminated with a small amount of tarry material. Recrystallization from benzene–petroleum ether gave pure, colorless **19**:[15] mp 84–85°; nmr ($CDCl_3$) τ 8.72 (s, 8.8), 8.10 (3), 5.92 (d, 1.9; J = 6 Hz), 4.91 (s, 2.1), 4.60 (1.1), 4.26 (broad, 1.9), 2.73 (s, 5.1).

Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.26; H, 7.06; N, 8.07.

When pure **19** was dissolved in 2-picoline and isolated by the above procedure, evaporation of the CH_2Cl_2 left material (93%) of mp 84–85°.

Modifications of the Procedure with 1.—The spectral test with **1** was repeated in the solvent $MeNO_2$ (solution in 15 min, A = 0.07) and with 1.1 mmol of hippuric acid in MeCN (solution in 30 min, A = 0.03).

Registry No.—Hippuric acid, 495-69-2; **7**, 10513-45-8; **12**, 20122-51-4; **19**, 19625-78-6.

Acknowledgment.—This work was generously supported in part by the National Institutes of Health.

(25) C. H. Eugster, L. Leichner, and E. Jenny, *Helv. Chim. Acta*, **46**, 543 (1963).

Formation of Pyrazoles from 3,3-Disubstituted 2,4-Pentanediones and 2-Hydroxyethyl Hydrazines. Coproduction of 3,3a,5,6-Tetrahydropyrazolo[3,2-*b*]oxazoles

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Received January 15, 1969

Condensation of various 3,3-disubstituted 2,4-pentanediones with 2-hydroxyethylhydrazines affords 3,3a,5,6-tetrahydropyrazolo[3,2-*b*]oxazoles resulting from an intramolecular alcohol–enamine reaction of the initially formed 5-methylene-2-pyrazolines. Nuclear magnetic resonance studies of these nonplanar heterobicycles which have been isolated indicate that phenyl, when attached to C-5, generally occupies a single preferred configuration. When one or both of the starting diketone substituents is allylic, a rearrangement, evidently of the Claisen–Cope type, occurs producing isomeric pyrazoles as coproducts. Tetrahydropyrazolo[3,2-*b*]oxazoles bearing one or more allyl groups at C-3 undergo isomerization to their pyrazole coproducts under thermal conditions (*ca.* 200°) or upon simple refluxing in ethanol solution. This latter transformation of 3-allyltetrahydropyrazolo-[3,2-*b*]oxazoles suggests that they are kinetically favored products which give rise to their thermodynamically stable pyrazole isomers during the course of the condensation reaction.

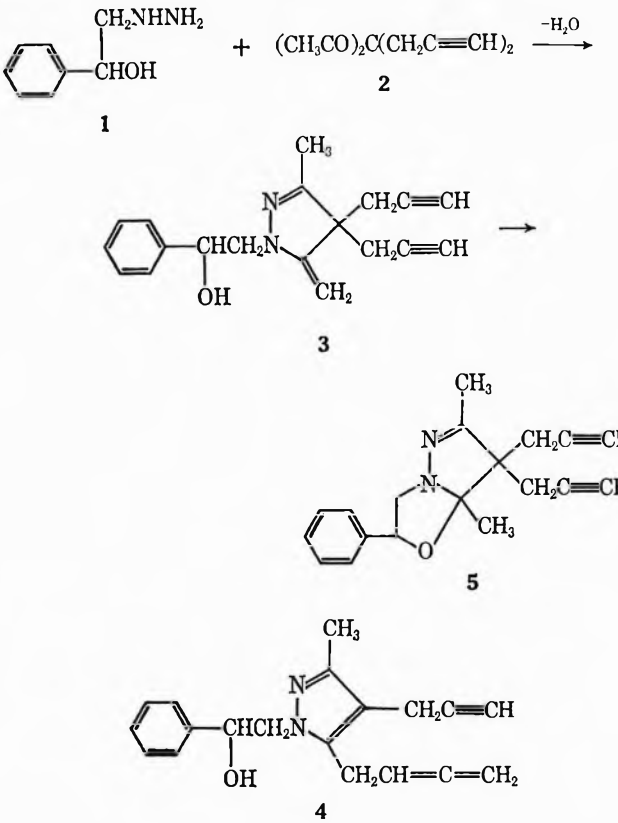
Earlier we noted that 3,3-disubstituted 2,4-pentanediones having allylic or propargylic groups at C-3 react with monosubstituted hydrazines forming rearranged pyrazoles *via* a Claisen–Cope type of rearrangement.[1] By means of an exceptionally facile propargylic rearrangement, the reaction enables preparation, in good yields, of pyrazoles having C-5 allenic substitution. The aim of obtaining such unsaturated pyrazoles with additional pharmacophoric β-phenylethyl substitution suggested α-(hydrazinomethyl)benzyl alcohol (1) as an appropriate carbonyl reactant.

Results and Discussion

Treatment of 3,3-di(2-propynyl)-2,4-pentanedione (**2**) with **1** was performed in refluxing ethanol under conditions typical[1] for formation of **4** by propargylic rearrangement (Scheme I). The product, obtained in 59% yield, displayed none of the expected spectroscopic features of **4**, however, but was a nonhydroxylic isomer with strong C–O–C (9.95 μ) absorption. The nmr spectrum showed two methyl groups and three AMX protons as pairs of doublets at δ 3.07, 3.99, and 4.65. These data, along with mass spectral studies, led to formulation of the new product as 3,3a,5,6-tetrahydro-2,3a-dimethyl-5-phenyl-3,3-di(2-propynyl)pyrazolo-[3,2-*b*]oxazole (**5**) representing a heterobicyclic system described only recently by Gillis and Weinkam.[2]

Formation of **5** may be viewed as an intramolecular nucleophilic interception of the Claisen–Cope precursor **3** by an alcohol–enamine addition related to the oxidative cyclization of 2-pyrrolidinoethanols reported by Leonard and Musker.[3] We had observed that allylic groups at the pyrazoline C-4 of intermediates such as **3** rearrange more rapidly than do propargylic groups.[1]

SCHEME I



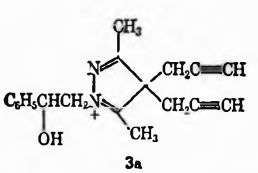
Thus it was not unexpected that in the reaction of 3,3-diallyl-2,4-pentanedione (**6**) with **1** rearrangement competed with enamine cyclization giving both the pyrazole **10** and the tetrahydropyrazolo[3,2-*b*]oxazole **9** in crude yields of 54 and 24%, respectively (Scheme II). The relatively nonpolar **9** was readily separated from **10** by column chromatography.

Condensation of **1** with **6** to give the carbinol **7** is a reasonable first step and the ability to form enamines such as **8** under these reaction conditions has been demonstrated.[1] Compound **9** may then arise *via* paths A or B. The ability of **9** to serve as the precursor of **10**

(1) D. T. Manning, H. A. Coleman, and R. A. Langdale-Smith [*J. Org. Chem.*, **33**, 4413 (1968)] describe the general background of and lead references pertinent to this new variant of the Claisen–Cope rearrangement.

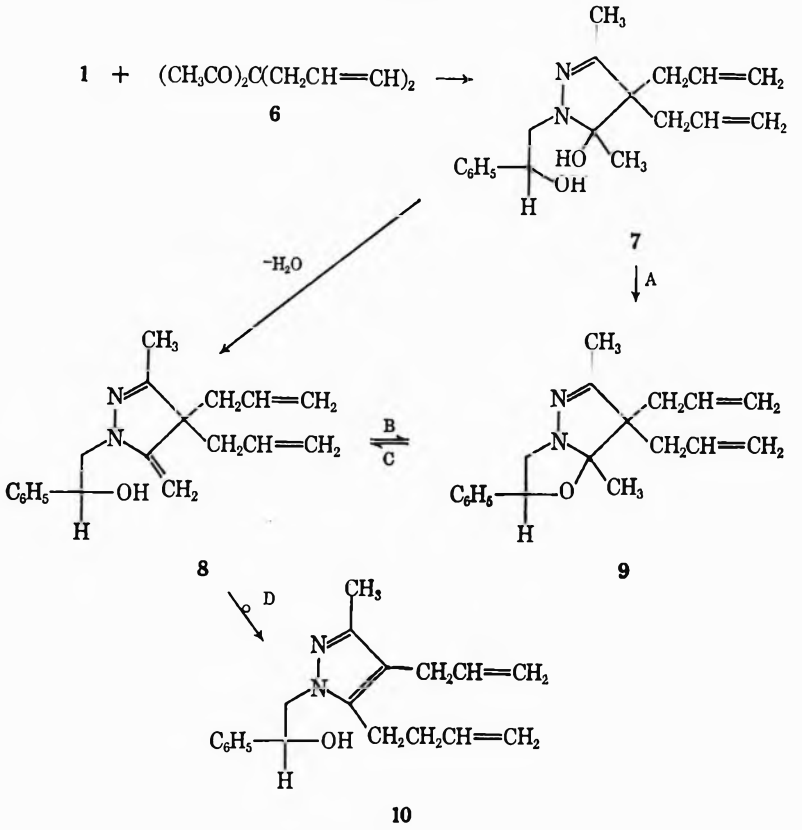
(2) B. T. Gillis and R. Weinkam, *ibid.*, **32**, 3321 (1967).

(3) N. J. Leonard and W. K. Musker, *J. Amer. Chem. Soc.*, **82**, 5148 (1960). By analogy with the oxidative cyclization of these authors the protonated iminium species **3a** may be considered to be the precursor of the bicyclic system.



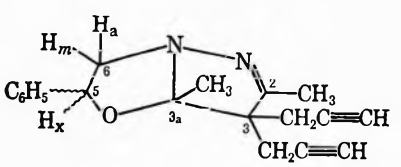
3a

Scheme II

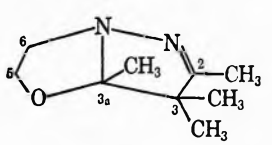


was shown by refluxing **9** with ethanol under simulated reaction conditions. An approximately 85% conversion of **9** into **10** occurred suggesting that 3-allylic tetrahydropyrazolo[3,2-*b*]oxazoles are kinetically controlled products which are converted into their thermodynamically stable pyrazole isomers during the reaction by paths C and D. Similarly, synthesis of the 3-allyl-3-propargyl derivative **11** resulted in coproduction of **12** along with a small amount of the product (**13**) of propargylic rearrangement (Scheme III). Attempted vacuum distillation of **11** also gave **12**, containing a trace of **13**, in high yield. Tetrahydropyrazolo[3,2-*b*]oxazoles were the only products observed upon reaction of hydroxyethylhydrazines with 3,3-dimethyl-2,4-pentanedione.

Inferences from Nmr Spectral Data.—The rigid tetrahydropyrazolo[3,2-*b*]oxazole system is butterfly shaped with magnetically nonequivalent "concave" and "convex" surfaces. This accounts for the δ 2.55–2.82 resonance range of the propargyl methylenes of **5** (at C-3) and for the appearance of two C-3 methyl singlets for the tetramethyl derivative **14**. With two

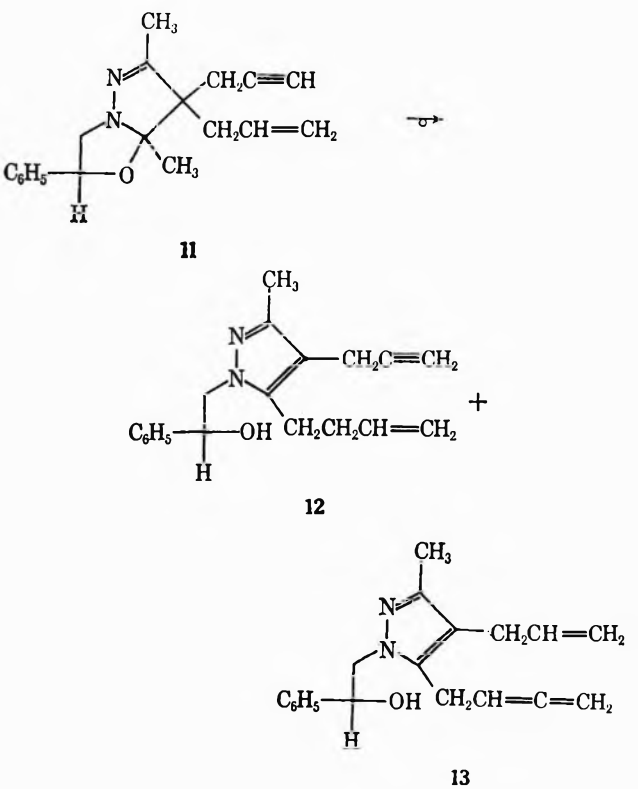


5



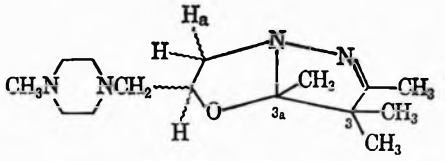
14

Scheme III



centers of asymmetry **5** can exist, theoretically, as two stereoisomers. The appearance of both the C-2 and C-3a methyl resonances of **5** as sharp singlets indicates that either (a) a mixture of *cis* and *trans* isomers exists but this variation in phenyl position is without effect on the chemical shift of the methyl protons, or (b) the C-5 phenyl group exists in a single preferred configuration.

Consideration of the above-mentioned AMX patterns of the 5-phenyltetrahydropyrazolo[3,2-*b*]oxazoles enables a choice between these alternatives. While we are not able to give configurational assignments to H_a, H_m, H_x, and phenyl, the appearance of three sharp pairs of doublets, with no second AMX sets apparent, indicates that the phenyl group occupies one preferred configuration and **5** is therefore a single stereoisomer. In the case of **11** the unlike allyl and propargyl groups at C-3 form a *ca.* 50:50 *cis–trans* mixture with the C-2 and C-3a methyls consequently showing pairs of singlets of approximately equal area. Unlike phenyl substitution, **15**, having an aminomethyl group at C-5, was isolated as an isomer mixture of *ca.* 2:1 as estimated from the integrals of the two C-3a methyl signals. Here, the usual AMX pattern was obscured by the apparent presence of isomers and by additional coupling with the methylene protons attached at C-5. Surprisingly, the apparent isomer mixture melted relatively sharply at 55.8–58°. Two additional recrystallizations changed the isomer ratio, indicated by the C-3a methyl integrals, to 3–5:1, but with only a small change in melting point. Despite the nmr evidence of stereoisomerism, both **11** and **15** behaved as single compounds upon thin layer chromatography (tlc). An nmr examination of **15** in a second solvent produced an identical spectrum following which the unchanged compound was recovered. This result seems to eliminate the possibility that a single isomer of **15** is converted into two isomers by ring opening–reclosing in the nmr solvent system.[4] In the tetramethyl derivative **14**, as expected, the AMX system was replaced by an ABCD multiplet representing the CH_2CH_2 groups at positions 5 and 6.



15

Experimental Section

All melting points are corrected. Nmr spectra were obtained with Varian A-60 and HA-100 instruments employing tetramethylsilane as the internal standard. An Aerograph Model 202B dual-column gas chromatograph was used for vpc analysis. 3,3-Di(2-propynyl)-2,4-pentanedione (**2**),[1,5] 3-allyl-3-(2-propynyl)-2,4-pentanedione,[1] 3,3-diallyl-2,4-pentanedione (**6**),[6] and 3,3-dimethyl-2,4-pentanedione[7] were prepared as previously described.[7,8]

α-(Hydrazinomethyl)benzyl Alcohol (1).—To a stirred solution of 186.9 g (5.84 mol) of hydrazine in 500 ml of butanol, held at 86–92° by a steam cone, was added 60 g (0.5 mol) of styrene oxide over a 45-min period. After continued heating and stirring for 17 hr, 150 ml of water was carefully added and volatiles removed under reduced pressure. Distillation gave 54.0 g (71.0%) of product, bp 162–165° (4 mm) [lit.[9] 165° (4 mm)].

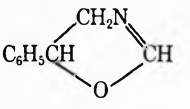
1-Glycidyl-4-methylpiperazine.—Was prepared from epichlorhydrin and 1-methylpiperazine by a method similar to that of Heywood and Phillips.[10] The dihydrochloride, mp 212–216° dec, was analyzed.

Anal. Calcd for $C_8H_{18}N_2OCl_2$: N, 10.50. Found: N, 10.32.

α-(Hydrazinomethyl)-4-methylpiperazine-1-ethanol.—1-Glycidyl-4-methylpiperazine (78.1 g, 0.5 mol) and anhydrous hydrazine (165.0 g, 5.0 mol) were allowed to react under conditions similar to those employed in the preparation of **1**. Distillation and redistillation gave 55.8 g of product, bp 132–135° (0.35 mm), whose nmr spectrum was confirmatory but showed the presence of some remaining butanol solvent.

Anal. Calcd for $C_8H_{20}N_4O$: N, 29.76. Found: N, 28.13.

3,3a,5,6-Tetrahydro-2,3a-dimethyl-5-phenyl-3,3-di(2-propynyl)pyrazolo[3,2-*b*]oxazole (5).—To a mixture of **1** (7.6 g, 0.05 mol) and **2** (8.8 g, 0.05 mol) in 200 ml of ethanol was added 15 ml of 5% acetic acid and the resulting mixture was then refluxed for a period of 3.5 hr. Evaporation of volatiles gave an oil which crystallized on standing. The crude product was dissolved in methanol and precipitated with water giving 7.05 g of cream-colored crystals, mp 99–101°. An impure fraction (1.55 g, mp 72–95°) brought the total yield to 58.9%: ir (KBr) 3.04 (C≡CH), 6.16 (C=N), 7.24 (CCH_3), 9.95 (COC), 13.25 and 14.32 μ (monosubstituted phenyl); mass spectrum [70 eV (49°)] *m/e* 292 (parent), 186 (loss of $C_6H_5CHCH_2$ ion), 147 (ion a), 104 ($C_6H_5CHCH_2$ ion), 91 (benzyl ion), 77 (phenyl ion),



a

43 (CH_3CO ion), 39 (propargyl ion); nmr (deuterioacetone) δ 1.63 (s, 3, CH_3CO), 2.0 (s, 3, CH_3C=N), 2.46 (t, 2, HC≡C), 3.07 (doublet pair, 1, J_{am} = 13 Hz, J_{ax} = 10 Hz, H_aCN), 3.99 (doublet pair, 1, J_{ma} = 13 Hz, J_{mx} = 5.5 Hz, H_mCN), 4.65 (doublet pair, 1, J_{xm} = 5.5 Hz, J_{xa} = 10 Hz, H_xCO), 7.32 (s, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.15; H, 6.95; N, 9.72.

3,3-Diallyl-3,3a,5,6-tetrahydro-2,3a-dimethyl-5-phenylpyrazolo[3,2-*b*]oxazole (9).—A mixture of **6** (14.9 g, 0.083 mol), **1** (12.6 g, 0.083 mol), 5% acetic acid (30 ml), and ethanol (400 ml) was refluxed for 4 hr and then stripped under reduced pressure to give 24.4 g of an oil. The latter was diluted with ether and the resulting solution was chromatographed (alumina) giving four fractions, obtained by anhydrous ethyl ether elution, having a combined composition (estimated by ir) of 5.9 g of **9** (24.1% crude yield) along with the isomeric rearranged pyrazole **10** and ketonic impurities. Rechromatographing (ether elution) fractions rich in **9** followed by recrystallization of the residue from isopropyl alcohol gave 1.5 g of **9** as white crystals: mp 71–72°; ir (KBr) 6.1 (C=C), 7.21 (CCH_3), 8.19 (CN), 9.71 (COC), 10.58, 10.91, and 11.84 μ ($CH=CH_2$); nmr ($CDCl_3$) δ 1.54 (s, 3, CH_3CO), 1.89 (s, 3, CH_3C=N), 2.10–2.80 (m, 4, 2 CH_2-C=C), 3.12 (doublet pair, 1, J_{am} = 12.5 Hz, J_{ax} = 10 Hz, H_aCN), 4.04 (doublet pair, 1, J_{ma} = 12.5 Hz, J_{mx} = 5 Hz, H_mCN), 4.71 (doublet pair, 1, J_{xa} = 10 Hz, J_{xm} = 5 Hz, H_x-CO), 5.14–6.25 (m, 6, 2 $CH=CH_2$), 7.34 (s, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.37; H, 8.14; N, 9.41.

4-Allyl-5-(3-butenyl)-3-methyl-α-phenylpyrazole-1-ethanol (10). A. As Coproduct of 9.—Infrared examination of the chromatographed fractions from the preparation (above) of **9** indicated an approximate content of 13.2 g (53.9% crude yield) of **10** showing OH at 3.0 μ (NaCl). An ether solution of the fractions was rechromatographed, eluting with ether to remove impurities. The alumina column was then washed with methanol releasing 7.6 g of moderately pure **10**. Recrystallization from petroleum ether gave 1.65 g of crystals: mp 47.5–50°; ir (KBr) 3.14 (OH), 6.1 (C=C), 9.38 μ (COH); nmr ($CDCl_3$) δ 2.05 (m, 2, CH_2CH_2CH=CH_2), 2.17 (s, 3, CH_3), 2.43 (t, J = 3.5 Hz, CH_2CH_2CH=CH_2), 3.08 (m, 2, allyl CH_2), 4.09 (m, 2, CH_2N), 5.0 (m, 5, 2C=CH_2 and C_6H_5CH), 5.27 (s, 1, OH), 5.45–6.20 (m, 2, CH=C<), 7.32 (s, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16, N, 9.45. Found: C, 76.71; H, 8.11; N, 9.46.

(4) A possible rationale of the melting point behavior suggested by a referee.

(5) E. K. Schulte, J. Reisch, and A. Mock, *Arch. Pharm.*, **295**, 627 (1962).

(6) R. B. Davis and P. Hurd, *J. Amer. Chem. Soc.*, **77**, 3284 (1955).

(7) J. J. Bloomfield, *J. Org. Chem.*, **26**, 4112 (1961).

(8) A. W. Johnson, E. Markham, and R. Price, *Org. Syn.*, **42**, 75 (1962).

(9) G. Benoit, *Bull. Soc. Chim. Fr.*, **6**, 708 (1939).

(10) D. L. Heywood and B. Phillips, *J. Amer. Chem. Soc.*, **80**, 1257 (1958).

B. By Isomerization of 9.—A solution of 0.15 g of **9** in 200 ml of ethanol containing 3 drops of water (pH ~6) was refluxed for 3.5 hr after which the solvent was removed under reduced pressure. Infrared analysis of the residual colorless syrup (0.15 g) produced a spectrum essentially identical with that of **10** obtained in part A (above). The nmr spectrum showed the product to be predominantly **10** (≥85%) containing some unconverted **9**.

3-Allyl-3,3a,5,6-tetrahydro-2,3a-dimethyl-5-phenyl-3-(2-propynyl)pyrazolo[3,2-*b*]oxazole (11).—A mixture of 3-allyl-3-(2-propynyl)-2,4-pentanedione (12.6 g, 0.0708 mol), **1** (10.75 g, 0.0708 mol), 5% aqueous acetic acid (20 ml), and ethanol (300 ml) was refluxed for an 8-hr period after which volatiles were evaporated leaving an oil. This was dissolved in ether, dried ($MgSO_4$), and chromatographed on alumina giving 8.7 g (41.7%) of crude **11**, recovered by ether elution. Two recrystallizations from hexane gave pure material: mp 66–68°; ir (KBr) 3.01 and 3.06 (C≡CH), 7.25 (CCH_3), 9.75–9.80 μ (COC); nmr ($CDCl_3$) δ 1.51 and 1.60 (two singlets, 3, CH_3CO, *cis* and *trans*), 1.90 and 2.01 (two singlets, 3, $CH_3C{=}N$, *cis* and *trans*), 2.10 (m, 1, HC≡C), 2.34–2.70 (m, 4, $CH_2CH{=}CH_2$, and $CH_2C{\equiv}CH$), 3.11 (doublet pair, 1, J_{am} = 12.6 Hz, J_{ax} = 10.5 Hz, H_aCN), 4.03 (doublet pair, 1, J_{ma} = 12.6 Hz, J_{mx} = 5.5 Hz, H_mCN), 4.68 (doublet pair, 1, J_{xm} = 5.5 Hz, J_{xa} = 10.5 Hz, H_xCO), 4.9–6.4 (m, 3, $CH{=}CH_2$), 7.32 (s, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.83; H, 7.67; N, 9.55.

Separation of the apparent allyl–propargyl *cis–trans* isomers was attempted by tlc but the various systems examined revealed only a single product spot.

5-(3-Butenyl)-3-methyl-α-phenyl-4-(2-propynyl)pyrazole-1-ethanol (12). A. As Coproduct of 11.—Following ether elution of **11** from the above-described chromatography the column was flushed with methanol to give, on evaporation, 10.8 g (51.8% crude yield) of syrupy **12**: ir (NaCl) 2.95–3.10 μ (OH and C≡CH). A weak allene band at 5.1 μ was due to the isomeric **13**, an impurity which could not be separated from the product.

B. By Thermolysis of 11.—A 10.76-g sample of **11** was distilled through a short-path system employing a pot temperature of 193–215° (0.25 mm). The distillate, bp 154–166° (8.93 g), crystallized in the receiver. Two recrystallizations of the solid from hexane gave 4.2 g of **12**, mp 80–82°. The infrared spectrum was essentially identical with that of the coproduct of **11** (part A, above) and showed, in addition to weak allene absorption, bands at 3.01 (C≡CH), 3.15 (OH), 4.7 (C≡C), 6.1 and 6.42 (C=C, C=N), 7.21 (CCH_3), 9.37 (COH), 10.05 and 10.95 (=CH, $=CH_2$), 13.0 and 14.25 μ (monosubstituted phenyl).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52 Found: C, 77.79; H, 7.66; N, 9.52.

3,3a,5,6-Tetrahydro-2,3,3,3a-tetramethylpyrazolo[3,2-*b*]oxazole (14).—A mixture of 3,3-dimethyl-2,4-pentanedione (12.9 g, 0.10 mol), 2-hydroxyethylhydrazine (8.37 g, 0.11 mol), 5% aqueous acetic acid (26 ml), and ethanol (200 ml) was refluxed for a 3.5-hr period and then evaporated free of volatiles under reduced pressure. The residual oil was dissolved in ethyl ether and the solution was chromatographed on alumina. Elution with ether gave fractions of crude product totaling 11.0 g. These were distilled giving 10.3 g (61.2%) of **14**: bp 50° (1.1 mm); 100% pure by vpc; ir (KBr) 3.4 and 3.5 (CH_3, CH_2), 6.15 (C=N), 7.24 and 7.32 (CCH_3), 8.55 (CN), 9.77 (COC); nmr ($CDCl_3$) δ 1.03 and 1.13 (two singlets, 6, CH_3CCH_3), 1.25 (s, 3, CH_3CO), 1.83 (s, 3, $CH_3C{=}N$), 3.17–3.94 (ABCD multiplet, 4, CH_2-CH_2).

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.71; H, 9.69; N, 16.69.

3,3a,5,6-Tetrahydro-5-(4′-methylpiperazin-1′-ylmethyl)-2,3,-3,3a-tetramethylpyrazolo[3,2-*b*]oxazole (15).—A solution of α-(hydrazinomethyl)-4-methylpiperazine-1-ethanol (20.6 g, 0.11 mol), 3,3-dimethyl-2,4-pentanedione (12.9 g, 0.1 mol), and 5% aqueous acetic acid (26 ml) in ethanol (300 ml) was refluxed for 4.5 hr after which volatiles were removed under reduced pressure. The residue was distilled through a short-path system giving 19.3 g (69.0%) of **15**, bp 116–118° (0.2 mm), which solidified on standing. Crystallization from petroleum ether at −80° gave white crystals: mp 55.5–58°; ir (KBr) 3.35 and 3.55 (CH_3, CH_2), 6.15 (C=N), 7.25 (CCH_3), 8.57 (CN), 9.83 (COC); nmr ($CDCl_3$) δ 1.02 and 1.12 (two singlets, 6, CH_3CCH_3), 1.26 (s, 0.33 × 3, CH_3CO of isomer "A"), 1.29 (s, 0.67 × 3, CH_3CO of isomer "B"), 1.82 (s, 3, $CH_3C{=}N$), 2.26 (s, 3, $CH_3N{<}$), 2.34–2.70 (m, 10, 5 CH_2), 3.01–4.30 (series of multiplets, 3, NCH_2CHO).

Anal. Calcd for $C_{15}H_{28}N_4O$: C, 64.25; H, 10.06; N, 19.98. Found: C, 64.27; H, 10.25; N, 19.72.

Two additional recrystallizations (pentane) of the product gave material, mp 54.5–55.5°, whose nmr spectrum showed the apparent isomer "A" (CH_3CO at δ 1.26) content reduced to 20–25%. A similar spectrum was obtained in deuterioacetonitrile and the sample, recovered from the solution, was unchanged **15** (melting point and mixture melting point). Various tlc systems were investigated in an attempt to separate the apparent isomers. The various product fractions, including those recovered from nmr determinations, behaved identically and in no case was separation of a second component evident. Best results were obtained by elution with methanol–diethylamine (3%) on silica gel which produced single, well-defined spots.

Registry No.—1-Glycidyl-4-methylpiperazine dihydrochloride, 20238-14-6; α-(hydrazinomethyl)-4-methylpiperazine-1-ethanol, 20238-15-7; **5**, 20238-16-8; **9**, 20238-17-9; **10**, 20238-18-0; **11**, 20238-19-1; **12**, 20238-20-4; **14**, 20238-21-5; **15**, 20238-22-6.

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Potential Naphthoquinone Antimalarials. 2-Acylhydrazino-1,4-naphthoquinones and Related Compounds[1]

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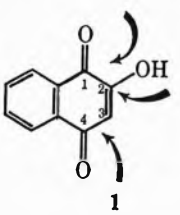
The course of condensation of a carboxylic acid hydrazide with 2-hydroxy-1,4-naphthoquinone (1) is dependent upon the solvent employed. In 80% acetic acid, condensation occurred at C_2 of the naphthoquinone nucleus; in weakly alkaline solution, condensation occurred at C_1. These reactions are discussed in context with earlier work regarding the condensations of phenylhydrazine and hydroxylamine with 1 in neutral and alkaline solution. Reaction of hydrazide with ammonium 1,2-naphthoquinone-4-sulfonate constituted a method for obtaining a condensation product at C_4 of the 2-hydroxy-1,4-naphthoquinone (1) nucleus. Ir, nmr, uv, and visible spectra favored assignment of naphthoquinone structures to the three classes of condensation products, rather than an assignment of potential tautomeric naphthalene structures.

This Article describes reactions of a carboxylic acid hydrazide with some naphthoquinones, reactions which permit preparation of the three possible, positional condensation products of the 2-hydroxy-1,4-naphthoquinone system (*e.g.*, as denoted by arrows in **1**). Attention was directed especially to an understanding of the physical properties of the 2-acylhydrazino-1,4-naphthoquinone system (**2**, R = alkyl), for this system showed an unusual acidic character and was amenable to distribution (between aqueous buffers and ether). A knowledge of certain physical parameters of **2** was of particular interest because of bearing to the *critical extraction value* (p*E*), a measurement which had been correlated with, and related to, the optimal antirespiratory (antimalarial) activities of certain 2-hydroxy-3-alkyl-1,4-naphthoquinones,[6] and which, thus could be determined as a guideline in the synthesis of analogs of **2** for biological evaluation (antimalarial activity). A more extensive list of 2-acylhydrazino-1,4-naphthoquinone (**2**, R = alkyl or aryl), their p*E* data, and their biological data, will be submitted elsewhere.



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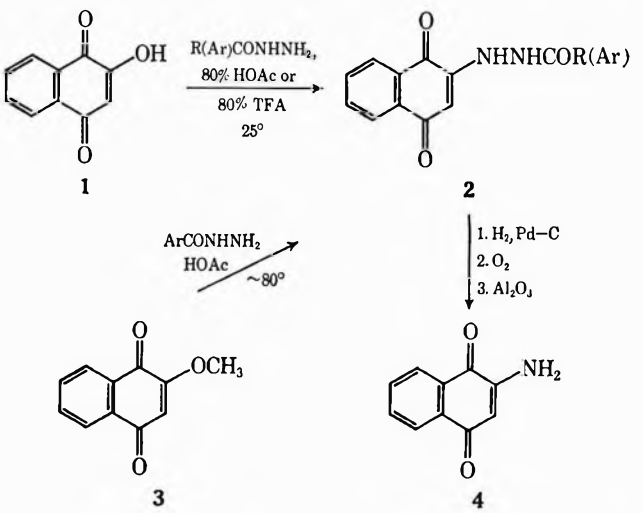
2-Acylhydrazino-1,4-naphthoquinones.—2-Acylhydrazino-1,4-naphthoquinones (**2**) were prepared by reaction of a carboxylic acid hydrazide with **1** in 80% acetic acid, this type of reaction having precedent in the classical preparation of 2-anilino-1,4-naphthoquinone.[7] A simple, unambiguous structure proof of **2** lay in the reaction of hydrazide with 2-methoxy-1,4-naphthoquinone (**3**) in glacial acetic acid. In addition, the point of condensation in **2** was identified by catalytic hydrogenolysis of the –NHNH– bond, which, when followed by aerobic oxidation, led to isolation of 2-amino-1,4-naphthoquinone (**4**).



Infrared (ir) and nuclear magnetic resonance (nmr) spectra of the condensation products (*e.g.*, **2**) were consistent with an assignment of a naphthoquinone structure. For example, the ir spectrum of 2-acetylhydrazino-1,4-naphthoquinone (**5**) contained two bands at 3330 and 3230 cm^{-1}, assignable to –NH– stretching frequencies of the acylhydrazino group (–CONHNH–), and two bands at 1675 and 1640 cm^{-1} (overlapping hydrazide carbonyl at 1675 cm^{-1}), typical of 1,4-naphthoquinone bands. The nmr spectrum of **5** (in dimethyl-d_6 sulfoxide, DMSO-d_6) contained a sharp one-proton singlet at δ 5.80, the positioning of which correlated with the assignment of the quinone-ring proton resonance (δ 5.96, DMSO-d_6) in the spectrum of **4**.

Ultraviolet and visible absorption spectra of the 2-acylhydrazino-1,4-naphthoquinones (**2**, R = alkyl, undissociated species) were similar to curves measured of 2-amino-1,4-naphthoquinone (**4**) (note Figure 1). However, a 2-acylhydrazino-1,4-naphthoquinone (**2**) proved uniquely different from **4**,[8] in that the acylhy-

(1) The Union Carbide Corp. is gratefully acknowledged for a fellowship which supported the preliminary work. The greater part of this investigation was carried out at the Research Triangle Institute under Contract No. DA-49-193-MD-2862 with the Department of Army and the U. S. Army Research and Development Command. This paper is contribution number 238 from the Army Research Program on Malaria.

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(6) (a) L. F. Fieser, "The Scientific Method," Reinhold Publishing Corp., New York, N. Y., 1964, pp 163–191; (b) L. F. Fieser, M. T. Leffler, and coworkers, *J. Amer. Chem. Soc.*, **70**, 3151 (1948); (c) L. F. Fieser, S. Archer, and coworkers, *J. Med. Chem.*, **10**, 513 (1967), and references therein; (d) L. F. Fieser, M. G. Ettlinger, and G. Fawaz, *J. Amer. Chem. Soc.*, **70**, 3228 (1948). See also C. M. Moser and M. Paulshock, *ibid.*, **72**, 5419 (1950).

(7) (a) C. Liebermann, *Ber.*, **14**, 1664 (1881); (b) C. Liebermann and P. Jacobson, *Ann.*, **211**, 82 (1881).

(8) L. F. and M. Fieser, *J. Amer. Chem. Soc.*, **56**, 1565 (1934).

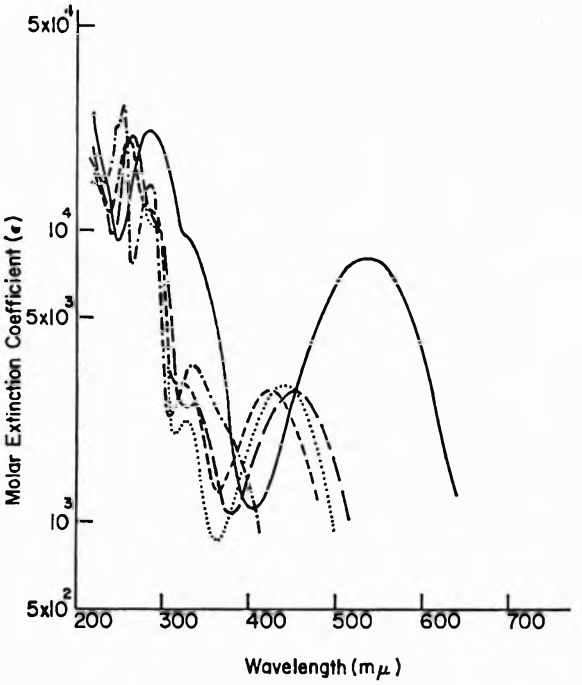
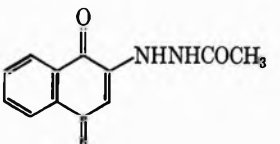


Figure 1.—The ultraviolet and visible light absorption curves of 2-acetylhydrazino-1,4-napthoquinone in methanol (------) and alkaline (———) solutions; 2-acetamido-1,4-naphthoquinone in methanol (·–·–·) and alkaline (— —) solutions; and 2-amino-1,4-naphthoquinone in methanol (·····) solution.

drazino moiety (–CONHNH–) exhibited an acidity comparable with a phenol. Proton release in **2** was marked by a striking, reversible color change. Acid solutions (pH 1–6) were bright yellow, while alkaline solutions (pH 8–13) were royal purple (alkyl series, *i.e.*, **2**, R = alkyl) or deep blue (aromatic series, *i.e.*, **2**, R = *para*-substituted C_6H_5). Such properties, say of **5**, were contrasted furthermore by the character of 2-acetamido-1,4-naphthoquinone (**6**). The acetamido derivative **6** may be regarded as a vinylog of an imide and, in analogy,[8] ought to be "imidelike". It was therefore surprising that **6** was cleaved readily by alkali to 2-amino-1,4-naphthoquinone (**4**) during spectral measurement (note Figure 1) and potentiometric titration (note Experimental Section).



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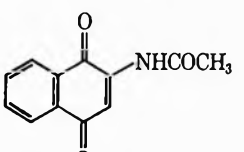

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Potentiometric titration of the 2-acylhydrazino-1,4-naphthoquinones (**2**, R = alkyl) showed curves typical of monobasic acids; the ionization exponents (pK_a') lay in the range 8–9 (note Table I).[9] The reversible yellow-to-purple color change exhibited by the 2-acylhydrazino-1,4-naphthoquinones (**2**, alkyl series) was shown by potentiometry and spectrophotometry to be associated with the one-proton release commensurate with the acidic and monobasic forms. The variation of the molar extinction coefficients (ϵ) of various light absorption with $-\log [H^+]$ is shown in Figure 2. The in-

(9) These exponents are 1.5–2.0 pK_a units above values reported for 2-hydroxy-3-alkyl-1,4-naphthoquinones (pK_a' 6.3–6.7) representative of the antimalarial drugs, *cf. ref 6b*.

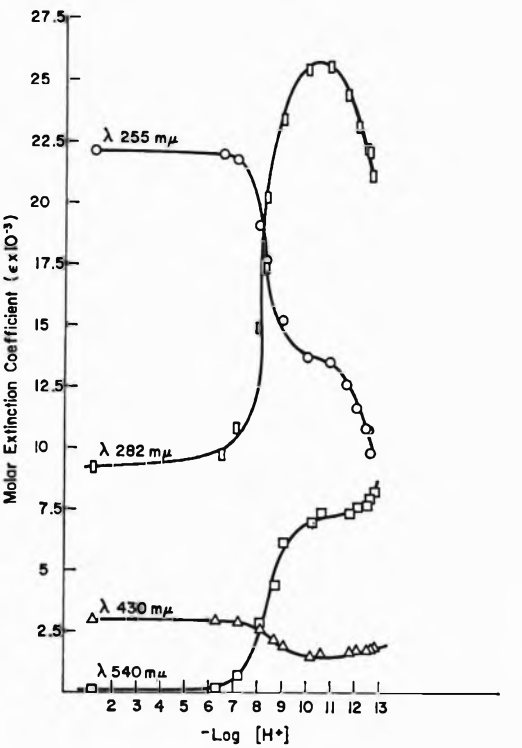


Figure 2.—The variation of the molar extinction coefficient of 2-hexanoylhydrazino-1,4-naphthoquinone [**2**, R = $-(CH_2)_4CH_3$] for various light absorption bands with $-\log [H^+]$. At pH $\lesssim$9, isosbestic points were indicated at 265 mμ (log ϵ 4.25) and at 447 (3.45). At pH $\gtrsim$12, isobestic points were indicated at 290 mμ (log ϵ 4.33) and 620 (3.49).

TABLE I

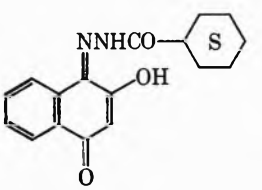
SOME IONIZATION EXPONENTS (pK_a') OF 2-ACYLHYDRAZINO-1,4-NAPHTHOQUINONES DETERMINED BY POTENTIOMETRIC TITRATION

Side chain	50% acetone	50% ethanol
$-CH_3$	8.23	8.16
$-CH_2CH_3$	8.42	
$-(CH_2)_4CH_3$	8.41	
$-CH_2$-c-C_6H_9	8.50	
-Cyclohexyl	8.83[a]	8.90[a]

[a] The cyclohexyl compound was titrated as a slight suspension.

flections, particularly those of the 430- and 540-mμ bands in the range pH 6–10, agreed with data obtained potentiometrically. In addition, there was evidence for a second ionization occurring at higher alkalinity (pH 10–13).

2-Hydroxy-1,4-naphthoquinone-1-acylhydrazones.[10] —In weakly alkaline solution, reaction of cyclohexane carboxylic acid hydrazide with **1** resulted in formation of the 2-hydroxy-1,4-naphthoquinone-1-acylhydrazone **7**. The yellow compound titrated as a monobasic acid, $pK_a' = 4.3$; its ir spectrum (KBr) had two bands in the carbonyl region at 1660 and 1618 cm^{-1}; and its nmr



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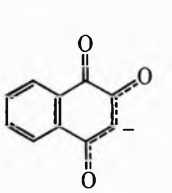

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(10) Observations regarding a similar variance observed in the condensation reactions of phenylhydrazine with **1** in 80% acetic acid and aquous ethanolic solutions are noted in the Experimental Section.

spectrum (DMSO-d_6) showed a one-proton singlet at δ 5.95 (quinone-ring hydrogen).

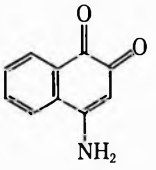
It would seem that the variance observed in the course of condensation of hydrazide with **1** upon changing from 80% acetic acid to alkaline solution would be related to the concentrations of the conjugate forms of **1** present under the specific conditions. 2-Hydroxy-1,4-naphthoquinone (**1**, pK_a[8] = 3.98) in weakly alkaline solution would be present largely as its conjugate base **8**, and the fact that condensation occurred largely at position C_1 would seem consistent with the electronic disposition of **8**. No significant condensation at position C_1 occurred in 80% acetic acid solution, and no significant condensation at position C_2 occurred in alkaline solution (as evidenced by tlc). It would thus seem that the formation of **2** in 80% acetic acid involved the acid form of **1**; the acid form (*i.e.*, **1**) would be required to exist only to the measure at which hydrazide "condensation" at position C_2 would be exclusively rate favored. Plausible mechanisms would include[11] (1) addition of hydrazide at position C_2 of **1** followed by loss of water, and/or (2) addition of hydrazide at position C_3 of **1** followed by loss of water.

2-Hydroxy-1,4-naphthoquinone-4-acylhydrazones.—The reaction of aniline with ammonium 1,2-naphthoquinone-4-sulfonate (**9**) is well established,[12] and an analogous displacement of bisulfite by hydrazide has been reported.[13] Reaction of either cyclohexanecarboxylic acid hydrazide or isobutyric acid hydrazide with **9** provided products which, after inspection of their spectral data, were assigned structures as 2-hydroxy-1,4-naphthoquinone-4-acylhydrazones (*e.g.*, **10**). This

9 **10**

structural assignment was based principally upon correlations of ultraviolet and visible light absorption data. That is, as spectra of **2** (R = alkyl, undissociated form) and **4** were nearly identical with respect to band positions and molar absorptivities (note Figure 1), it would thus seem that the displacement products obtained here, if actually possessing basic structures as 4-acylhydrazino-1,2-naphthoquinones (*e.g.*, **11**), ought to correlate spectrally with 4-amino-1,2-naphthoquinone (**12**). However, the displacement products (*i.e.*, **10**), like the 2-hydroxy-1,4-naphthoquinone-1-acylhydrazone **7**, were bright yellow in the crystalline state and bore no visual resemblance to the deeply colored, red-brown **12**. Spectrographically, the longer wavelength absorption maximum of **10** (R = isopropyl) was positioned at $\lambda_{max}^{pH\ 1.3}$ 394 mμ (log ϵ 4.22), which proved different in position and molar absorptivity from the principal visible band of **12**, $\lambda_{max}^{pH\ 2}$ 462 mμ (log ϵ 3.47).

11



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Infrared and nmr data were consistent with the naphthoquinone structure **10**. Infrared spectra of **10** contained a broad absorption in the 3600–2900-cm^{-1} region (ν_{max} 3260 cm^{-1}), typical of the hydroxyl stretching frequency shown by **1** itself; in the carbonyl region, maxima of equal intensity were positioned at 1670 and 1640 cm^{-1}. In the nmr spectra (DMSO-d_6), a one-proton singlet was observed at δ 7.50 for each of the two examples (*i.e.*, **10**, R = cyclohexyl or isopropyl) and was attributed to the quinone-ring hydrogen in **10**. Although the chemical shift of the quinone-ring hydrogen in **10** was displaced from the region (δ 5.5–6.5) where such resonances commonly occur, this chemical shift was paralleled in the spectrum (DMSO-d_6) of 2-acetamido-1,4-naphthoquinone (**6**) by the positioning of the quinone-ring hydrogen resonance at δ 7.70.

Experimental Section[14]

Carboxylic Acid Hydrazides.—Except for one compound employed here, the hydrazides are known compounds.

Cyclopentylacetic acid hydrazide was prepared as follows. Cyclopentylacetic acid (7.0 g)[15] was treated with an excess of etheral diazomethane (0–5°, 15–20 min), the excess diazomethane was destroyed by dropwise addition of glacial acetic acid, and the ethereal solution was washed with two 100-ml portions of saturated

(11) Either of these mechanisms could be applied to rationalize the formation of **2** from the reaction of hydrazide with **3** in glacial acetic acid. It is interesting to note that neither 2-hydroxy-3-methyl-1,4-naphthoquinone (phthicol) nor 2-hydroxy-3-bromo-1,4-naphthoquinone would react with a carboxylic acid in 80% acetic acid (25°), or even under more forcing conditions (refluxing glacial acetic acid). If these reactions were granted to be not wholly retarded by steric or electronic effects of the 3-methyl and 3-bromo groups, it would appear that the mechanism would actually involve an addition of hydrazide at position C_3 followed by loss of the hydroxyl group from position C_2. The "normal" (C_2 addition) and "abnormal" (C_3 addition) displacement mechanisms have been considered previously in connection with the nucleophilic displacement of halogen by thiol in 2-halogeno-1,4-naphthoquinones: F. G. Rothman, *J. Org. Chem.*, **23**, 1049 (1958), and J. W. McLeod and R. H. Thomson, *ibid.*, **25**, 36 (1960).

(12) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p 859.

(13) W. L. Mosby and M. L. Silva, *J. Chem. Soc.*, 3990 (1964).

(14) Thin layer plates were prepared by coating microscope slides with silica gel H. The following abbreviations represent the solvent systems employed for elution of chromatograms: (A) the organic phase of 1-butanol–pyridine–saturated sodium chloride (1:1:2); (B) the organic phase of benzene–acetic acid–water (2:2:1); (C) the organic phase of acetic acid–1-butanol–water (2:2:1); (D) the organic phase of 1-butanol–pyridine–water (3:2:1); (E) benzene–chloroform (2:1); (F) benzene–ethyl acetate–acetic acid (90:10:1); (G) benzene–ethyl acetate–acetic acid (9:1:1). Potentiometric titrations were carried out by dissolving an accurately weighed sample (0.800–0.850 mmol) in 50 ml of acetone, diluting a 20-ml aliquot with an equal volume of water, and titrating with 0.100 *N* sodium hydroxide. Values reported in Table I are averaged from at least two determinations (±0.06 accuracy). The set of curves used for construction of Figure 2 was measured from buffered solutions (pH 2.0–11.0) prepared with tablets of Coleman Instruments, Inc. (Maywood, Ill.), and sodium hydroxide solutions (pH 11.0–12.7) of known concentration. The pH's of final solutions were measured. To test a possible salt effect on the negative variation of absorbance (*A*) at 255 and 283 mμ, spectra were measured of **2** in 0.0125 *N* sodium hydroxide with added salt (so that final solutions were 0.00–0.10 *N* in sodium chloride). The 282-mμ band showed a positive 0.02 *A* unit change at NaCl = 0.10 *N*, and the 255-mμ band showed a positive 0.045 *A* unit change at NaCl 0.10 *N*. The stability of **2** in alkaline solution was indicated by the following spectral changes: the visible curves of **2** [R = $-(CH_2)_4CH_3$] at $\lambda^{0.1\ N\ HCl}$ 430 mμ and $\lambda^{0.1\ N\ NaOH}$ 535 mμ were measured at identical concentration; when the alkaline solution was acidified with 1 small drop of concentrated sulfuric acid, the resultant curve was identical with the standard curve and varied by 0.005 *A* unit. Melting points were taken in capillaries (copper block) and are uncorrected. Infrared spectra were measured on Perkin-Elmer Models 421 and 237 spectrophotometers; samples were prepared in the form of pressed KBr disks. Uv and visible spectra were measured on Cary Models 14 and 15 spectrophotometers. Nmr spectra were measured on a Varian A-60 instrument using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane (TMS) as an internal standard. Microanalyses were carried out by one of us (K. H. D), Mr. A. Bernhardt (Mülheim, Germany), and Micro-Tech Laboratories (Skokie, Ill.).

(15) Aldrich Chemical Co., Inc.

bicarbonate solution and dried (anhydrous Na_2SO_4). The crude methyl ester, obtained by removal of the ether, was treated with 95%+ anhydrous hydrazine (3.0 g), the mixture was heated (steam bath) for 16 hr, and volatiles were removed at reduced pressure (aspirator, 50°). The solid residue was recrystallized from benzene (15 ml) to give the product as a white cake; this material was suitable for preparation of **2** (R = $-CH_2$-c-C_5H_9) but was not pure. A small sample would not dissolve completely in water, even upon heating; the slight suspension of insoluble product was presumably a diacylhydrazine as judged by its insolubility in dilute acid.

For purification the sample (6.5 g) was added to water (100 ml) and the solution was filtered free of the slight suspension. The hydrazide solution was diluted with 50 ml of saturated sodium chloride solution and was extracted with six 50-ml portions of ether. Another portion (50 ml) of saturated salt solution was added and an ether extraction (three 100-ml portions) was repeated. The ether solution was dried (anhydrous Na_2SO_4) and stripped, and the residue was redissolved in benzene and further dried (anhydrous Na_2SO_4). Evaporation of the solvent provided a white crystalline residue which was recrystallized from *dry* ether to give cyclopentylacetic acid hydrazide (3.4 g), mp 89–91° (sharp), and characterized by formation of a sublimate (slender needles) at ~70°. Sublimation, 60–65° (0.05–0.10 mm), raised the melting point to 94–95°.

Anal. Calcd for $C_7H_{14}N_2O$ (142.2): C, 59.12; H, 9.92; N, 19.70. Found: C, 58.98; H, 10.08; N, 20.00.

Condensations of Hydrazide with 1 in 80% Acetic Acid. A. 2-Benzoylhydrazino-1,4-naphthoquinone (2, R = C_6H_5) and Related 2-Aroylhydrazino-1,4-naphthoquinones. 1—A suspension of equimolar quantities (0.056 mol) of finely pulverized 1[16] and benzhydrazide in 80% acetic acid (200 ml) was stirred at 25° for 24 hr, whereafter the original suspension of quinone had given place to a thick mass of crystalline product (suspension checked by microscopic examination prior to work-up). The product was filtered off and was washed successively with 80% acetic acid, ethanol, and ether. Recrystallization of the product from absolute ethanol gave **2** (R = C_6H_5) as a matt of long silky, orange threads (37%): mp 210–212° dec, gas; ir 3340, 3300, 1685, 1635, 1614, and 1578 cm^{-1}; visible spectrum $\lambda_{max}^{0.1\ N\ HCl}$ 435 mμ (ε 3030); $\lambda_{max}^{0.1\ N\ NaOH}$ 555 mμ (11,500).

Anal. Calcd for $C_{17}H_{12}N_2O_3$ (292.3): N, 9.59. Found: N, 9.73.

The above procedure was adequate for the preparation of six other *para*-substituted benzoylhydrazino-1,4-naphthoquinones, using a *para*-substituted benzhydrazide and 1; yields of recrystallized product ranged from 40 to 55%.

2.—A solution of 544 mg (2.9 mmol) of 2-methoxy-1,4-naphthoquinone (**3**)[16] and 390 mg (2.9 mmol) of benzhydrazide in glacial acetic acid (15 ml) was heated on the steam bath for 1 hr, allowed to stand at 25° for 30 hr, and the clear, deep red solution was seeded with a crystal of 2-benzoylhydrazino-1,4-naphthoquinone. After 20 hr, the product was filtered off and was recrystallized (absolute ethanol) to give **2** (R = C_6H_5) (100 mg, 12%), mp 210–212°.

Method 2 was applied to the preparation of three of the compounds prepared under method 1; the yields in all examples of **2** ranged from 10 to 15%.

B. 2-Acylhydrazino-1,4-naphthoquinones (2, R = Alkyl or Cycloalkyl).—Representatives of **2** (R = alkyl or cycloalkyl) are included in Table II. A suspension of 0.029 mol of 1[16] and 0.056 mol of hydrazide in 200 ml of 80% acetic acid was stirred at 25° for 12–24 hr. If product precipitated, the reaction period was extended at least 2 hr after microscopic examination indicated complete solution of **1**, whereafter the product was filtered off and was recrystallized. In cases where the product was soluble, the reaction was permitted to run for 24 hr, and the solution was freed by filtration from any small amount of insoluble material. The solvent was stripped *in vacuo* (temperature of bath did not exceed 50°), first at the aspirator and then at the vacuum pump. The orange-red residue was washed with an appropriate solvent to remove unreacted hydrazide, and the residual solid afforded a chromatographically pure (or nearly so) product upon one recrystallization.

Catalytic Hydrogenolysis of 2-Benzoylhydrazino-1,4-naphthoquinone.—A suspension of 630 mg of naphthoquinone and 100 mg of 10% palladium on charcoal in 100 ml of absolute ethanol was shaken for 24 hr in a Paar apparatus under hydrogen (initial pressure: 60 psi). The catalyst was filtered off, and a stream of air was drawn through the solution for several hours, after which the solvent was stripped (orange crystalline residue contained starting material, as evidenced by tlc and color imparted to an alkaline solution). The residue was extracted with 100 ml of 2% ethanol–chloroform, this extract then being filtered through a column of 25 g of Merck alumina (basic) and worked up to give 130 mg of crude **4**. The sample was chromatographed through 50 g of Merck alumina (basic) to give **4** (100 mg), mp 206–208°, identified by mixture melting point and comparison of ir spectra.

TABLE II

Side chain[a,b]	Mp,[c] °C	Calcd,[d] % C	H	N
$-CH_3$	225–227			12.35[e]
$-C_2H_5$	201–205	63.82	5.09	11.49
$-(CH_2)_4CH_3$	157–159.5	66.90	6.13	9.92
$-CH_2$-c-C_5H_9	187–190	68.69	6.18	9.68
-Cyclohexyl	202–205	68.41	6.11	9.49

[a] Compounds in Table II were recrystallized from acetone for purification and analysis. [b] Yields of recrystallized products ranged from 30 to 65%. [c] Fusion was accompanied by decomposition and gas evolution. [d] Elemental analyses (C, H, N) agreed with theoretical values within ±0.3%. [e] Analysis performed by K. H. D.

2-Acetamido-1,4-naphthoquinone (6).—A solution of 2.0 g of **4** in a mixture of 25 ml of acetic anhydride and 2 ml of pyridine was heated under reflux for 1.5 hr. The crude solid (1.95 g), obtained by hydrolysis of excess acetic anhydride, was washed with small portions of cold acetone, thus giving 1.35 g of deep yellow material. Chromatography of this product through alumina,[17] followed by recrystallization of the main band from acetone, gave **6** (0.86 g), mp 205–207°, as bright yellow plates (lit.[17] mp 206°).

During potentiometric titration (50% acetone) of **6**, in which a total of 1.67 molar equiv of base was added, the solution of **6** developed a red-orange color which quickly passed to olive green. The olive color was also unstable, passing after 30 min to a murky brown. The similarity of the uv and visible spectra measured from alkaline solutions of **6** to those of **4** suggested deacetylation of **6**. In a separate experiment, 1 mmol of **6** in 10 ml of acetone was diluted with 5 ml of 1% sodium hydroxide and the resultant solution was kept at 25° until a final decomposition color was obtained (~1 hr). Dilution of an aliquot with water and tlc (*e.g.*, solvent system G) of an ether extract confirmed the presence of **6** and **4**.

2-Hydroxy-1,4-naphthoquinone-1-cyclohexanecarbonylhydrazone (7).—A suspension of 4.0 g (23.0 mmol) of 1[16] in 320 ml of 50% aqueous ethanol containing 12.0 ml of freshly prepared 1% sodium hydroxide solution was warmed to 65° to effect solution and a very small amount of insoluble material was removed by filtration. Cyclohexane carboxylic acid hydrazide (3.4 g, 23.6 mmol) was added in one portion, and the resulting solution was stirred at room temperature for 2.5 days. The thick mass of microcrystalline needles was filtered off, washed with water, and most of the water was removed by pressing during suction filtration. The solid crystallized from absolute methanol (~350 ml) as soft, bright yellow needles (2.88 g), mp 205–208° dec, and was chromatographically (tlc) uniform in solvent system G: ir 1660 (s), 1610 (s), 1595 (s), and 1562 cm^{-1}; uv $\lambda_{max}^{pH\ 1.3}$ 370 mμ (ε 16,400), 304 (19,300), 269 (10,900), 262 (11,100); $\lambda_{max}^{pH\ 12.2}$ 355 mμ (16,400), 311 (16,700), 266 (12,600); nmr δ 5.95, s, one proton (quinone-ring H); pK_a' (50% acetone, potentiometrically) = 4.30.

Anal. Calcd for $C_{17}H_{18}N_2O_3$ (298.3): C, 68.44; H, 6.08; N, 9.39. Found: C, 68.72; H, 6.08; N, 9.52.

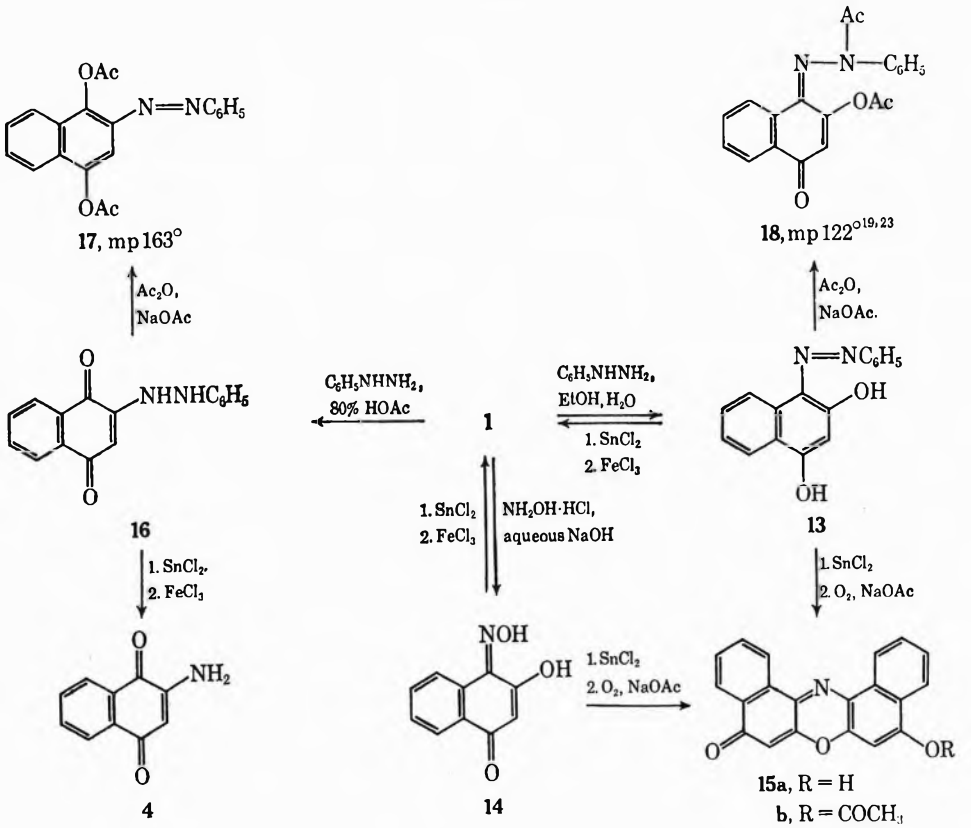
2-Hydroxy-1,4-naphthoquinone-4-acylhydrazone (10).—To a filtered solution of 2.0 g (7.8 mmol) of 9[16] in 40 ml of 50% aqueous ethanol was added a solution of 7.8 mmol of hydrazide in 30 ml of 50% aqueous ethanol. The yellow precipitate was collected after 24–48 hr and was recrystallized from boiling acetic acid.

2-Hydroxy-1,4-naphthoquinone-4-cyclohexanecarbonylhydrazone (10, R = cyclohexyl) had a 0.70-g yield: mp 272–278° dec; ir 3255, 1675, and 1643 cm^{-1}; uv (50% methanol) $\lambda_{max}^{pH\ 1.5}$

(16) L. F. Fieser and E. L. Martin, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons Inc., New York, N. Y., 1955, p 465.

(17) G. B. Barlin, K. G. Pausacker, and N. V. Riggs, *J. Chem. Soc.*, 3122 (1954).

SCHEME I



395 mμ (19,800); $\lambda_{max}^{pH\ 12.1}$ 450 mμ (12,600); pK_a' (50% MeOH) ~ 6.7; nmr δ 7.50, s, one proton (quinone-ring proton).

Anal. Calcd for $C_{17}H_{18}N_2O_3$ (298.3): C, 68.44; H, 6.08; N, 9.39. Found: C, 68.41; H, 5.99; N, 9.17.

2-Hydroxy-1,4-naphthoquinone-4-isobutyroylhydrazone [**10**, R = $CH(CH_3)_2$] had a 0.57 g yield: mp 279–284° dec; ir 3260, 1670, and 1638 cm^{-1}; uv (30% methanol) $\lambda_{max}^{pH\ 1.2}$ 394 mμ (16,800), 305 (10,800), 257 (7400), 224 (19,800), $\lambda_{max}^{pH\ 12.2}$ 450 mμ (11,000); 294 (9500); pK_a' (30% methanol) ~ 6.5; nmr δ 7.50, s, one proton (quinone ring proton).

Anal. Calcd for $C_{14}H_{14}N_2O_3$ (258.3): C, 65.10; H, 5.46; N, 10.85. Found: C, 65.13; H, 5.53; N, 11.11.

The pK_a' values for **10** (R = cyclohexyl or isopropyl) were determined spectrophotometrically (visible spectra), employing acid (0.1 *N*), base (0.1 *N*), and buffer solutions (pH 4–6). However, these values remain questionable even as a crude approximation, for the ultraviolet curves measured in each case from 0.1 *N* base solution did not pass through apparent isosbestic points seen at 309 and 229 mμ in the acid and buffer solutions spectra. It would thus seem that the values are an over-all pK_a' of two ionizations, the second of which has very little effect, if any, in altering the position of the visible bands; the isosbestic point seen at 415 mμ must then be fortuitous. The extreme insolubility of **10** (R = cyclohexyl and isopropyl) in aqueous ethanol or aqueous acetone prohibited potentiometric titration.

Reactions of Phenylhydrazine with 2-Hydroxy-1,4-naphthoquinone in Neutral and Acidic Media.—In 1884, Zincke and Thelen[18] described a reaction of phenylhydrazine with **1**. This reaction, which was conducted in aqueous ethanol, gave a condensation product regarded as 4-phenylazonaphthalene-1,3-diol (**13**). In 1889, Kostanecki[19] reported a related reaction, the derivation of **1** with hydroxylamine in alkaline solution, to give oxime **14**. The proposed structure of **14**, *i.e.*, the basic structure with respect to the point of condensation,[20] later accorded with conclusions drawn by Hooker,[21] but until Kehrman (1895) demonstrated conversion of **14** into "dinaphthoresorufin" (**15a**), no chemical evidence supported C_1 positioning of the oxime group.[22]

On the other hand, the final evidence[18,19,23] surrounding the phenylhydrazine **13**, though seemingly limiting the point of condensation to C_1 or C_4, was less convincing. The issue of structure **13** was regarded with additional reserve in view of Zincke and Thelen's comment[18] that phenylhydrazine underwent reaction with **1** in aqueous, or in alcoholic, or in acetic acid solution. It was not apparent in the original article,[18] nor was it clarified in the subsequent literature, whether the phenylhydrazine derivative of **1** formed in acetic acid solution was **13** as well or a positional counterpart. It was therefore of interest to relate derivatives **13** and **14**, *i.e.*, those prepared in neutral and weakly alkaline solution, and to clarify the reaction course of phenylhydrazine with **1** in acetic acid medium.

The basic structure of the phenylhydrazine derivative **13** was more firmly established by its conversion to Kehrman's dinaphthoresorufin (**15a**), a compound which was best converted into acetate **15b** for characterization purposes (Scheme I).[24] Dinaphthoresorufin (**15a**) was the principal product when the tin(II) reduction product[25] of either **13** or **14** was subjected to aerobic oxidation in acetate buffer. It is noteworthy here that iron(III) oxidation of this reduction product[25] led to **1** (note **13** → **1**, and **14** → **1**), for this set of reactions [*i.e.*, tin(II) reduction followed by iron(III) oxidation] was useful for characterizing the condensation product, presumably 2-phenylhydrazino-1,4-naphthoquinone (**16**, or a tautomer thereof), which we found to result from reaction of phenylhydrazine with **1** in 80% acetic acid. Unlike its counterpart **13**, compound **16** underwent extensive decomposition during attempted purification through its sodium salt and remained nonhomogeneous (contained a trace impurity) after several trials at purification. However, tin(II) reduction of **16** followed by iron(III) oxidation led to production of 2-amino-1,4-

(18) Th. Zincke and H. Thelen, *Ber.*, **17**, 1809 (1884).

(19) St. von Kostanecki, *ibid.*, **22**, 3163 (1889).

(20) Insofar as we are aware, the correct tautomeric representations of **13** and **14** have not been determined.

(21) S. C. Hooker and E. Wilson, *J. Chem. Soc.*, **65**, 717 (1894).

(22) (a) F. Kehrman, *Ber.*, **28**, 353 (1895). (b) In the preceding paper [*ibid.*, **28**, 345 (1895)], F. Kehrman and B. Masconi describe the use of tin(II) and iron(III) for the conversion of **14** into **1**.

(23) Th. Zincke and P. Wiegand, *Ann.*, **286**, 86 (1895).

(24) The reported melting point for **15b** is 200° (*cf.* ref 22a). This value is presumably a typographical error, for it markedly conflicts with our value of 275° for samples of **15b** prepared from either **13** or **14**. Our preparation of **15b** gave satisfactory analytical data, the reported color reactions, and was homogeneous by tlc.

(25) The reduction product, which may be isolated as its hydrochloride, is presumably 1-amino-2,4-dihydroxynaphthalene.

naphthoquinone (4) in 65% yield.[26] Mild acetylation of **16** with acetic anhydride–sodium acetate gave a homogeneous (by tlc) diacetate, assigned structure **17** on the basis of a single, intense 1760-cm^{-1} absorption contained in the carbonyl region of the ir spectrum.

4-Phenylazonaphthalene-1,3-diol (13).—Reaction of 5.0 g of phenylhydrazine and 8.0 g of **1** in aqueous ethanol by the procedure of Zincke and Thelen[18] gave crude **13** which, contrary to the opinion of Kostanecki,[19] required for purification the preparation[18] and recrystallization of the sodium salt. The yields of **13** ranged from 8.6 to 10.0 g, mp 231° dec, gas, but the samples still contained a trace impurity as evidenced by tlc in solvent systems A and B. Recrystallization of 8.6 g from absolute ethanol gave 7.1 g of chromatographically uniform, bright orange-red needles, mp 231° dec, gas.

Conversion of 13 into O-Acetyldinaphthoresorufin (15b).—A suspension of 3.0 g (11.4 mmol) of **13** in a mixture of 50 ml of water, 60 ml of ethanol, and 30 ml of concentrated hydrochloric acid containing 6.75 g (30.0 mmol) of tin(II) chloride 2-hydrate was heated under reflux for 5 hr and then concentrated by boiling to remove most of the alcohol. The hot solution was filtered by gravity and, after adding 30 ml of concentrated hydrochloric acid and cooling, the hydrochloride was isolated and recrystallized from 80 ml of 6 *N* hydrochloric acid (2.3 g of lavender needles). A solution of the hydrochloride (2.3 g) in 50 ml of water was added to a solution of 3.0 g of sodium acetate in 200 ml of water (immediate darkening), and air was drawn through the solution for 7 hr. After collection of the brown solid (1.15 g), trituration and washing with ether, the ether insoluble residue (1.07 g) appeared deep reddish purple in color. The infrared spectrum, color reactions,[22a] and thin layer chromatograms (two zones, solvent systems A, B, and D) were identical in all respects with those of **15a** prepared from **14**.[22a] O-Acetyldinaphthoresorufin (**15b**) was prepared by heating under reflux for 40 min a solution of 1.07 g of **15a** in 50 ml of acetic anhydride containing 0.5 g of sodium acetate. Recrystallization of the crude acetate (1.10 g) from toluene gave 0.88 g of orange-red needles, mp 274–276° dec (lit.[22a] mp 200°), which proved identical by ir and mixture melting point with a sample (mp 275–276°) prepared from **14**.[22a] The compound moved as one zone in solvent systems A, B, C, and D; chromatograms developed in A and D showed the hydrolysis of the orange acetyl derivative to a blue ion, ir 1760 and 1635 cm^{-1}.

Anal. Calcd for $C_{22}H_{13}NO_4$ (355.3): C, 74.37; H, 3.66; N, 3.94. Found: C, 74.33; H, 3.52; N, 4.32.

2-Phenylhydrazino-1,4-naphthoquinone (16).—A suspension of 5.0 g (28.7 mmol) of **1** (finely pulverized) in 80 ml of 80% acetic acid containing 3.4 g (31.5 mmol) of phenylhydrazine was stirred at 25° for 2 days; the deep purple precipitate was filtered and washed successively with two 10-ml portions of 80% acetic acid, two 10-ml portions of absolute ethanol, and ether: yield 4.09 g; mp 170° dec and vigorous gas. A chromatogram eluted in solvent system F contained a brilliant magenta zone (major product) and a bright yellow zone (trace product, retained near the origin). The product failed to crystallize satisfactorily from the common solvents, and attempted purification by preparation of a sodium salt (as described for **13**[18]) led to immediate, extensive decomposition. A sample (0.25 g, two zones on tlc), which had been crystallized repeatedly from toluene (with considerable loss and without any apparent improvement) was suspended in chloroform and filtered through a column of silicic acid (15.0 g). Eleven fractions [(1–8 (25 ml), 9 (200 ml), 10 (100 ml), 11 (200 ml)] were collected; all showed two zones on tlc.

Because of its intense color and poorly resolved ir spectrum, the compound was considered a quinhydrone, and purification was attempted by shaking a solution of 1.0 g of **16** in 100 ml of 1:3 ethanol–chloroform with an aqueous solution containing 2.2 g of iron(III) chloride 6-hydrate. The isolated organic layer showed no less than five zones on tlc.

The uv and visible spectrum of **16** was markedly different from that of **4**: λ_{max}^{MeOH} 227 mμ (18,000), 298 (13,000), 453 (10,200), and 525 (12,200). A sample was dried at 80° (0.05 mm) for analysis.

Anal. Calcd for $C_{16}H_{12}N_2O_2$ (264.3): C, 72.71; H, 4.58; N, 10.60. Found: C, 72.50; H, 4.57; N, 10.40.

Diacetyl Derivative 17.—The diacetyl derivative was prepared by heating under reflux for 15 min a solution of 1.0 g of **16** (dec pt 171°) and 0.1 g of sodium acetate in 20 ml of acetic anhydride. After hydrolysis of excess acetic anhydride by stirring with water (200 ml, 2 hr), collection, and drying of the crude product through its etheral solution (anhydrous Na_2SO_4), the product was isolated by cautious concentration of its ether–petroleum ether solution as an orange powder (0.8 g), mp 161–163°, to an orange oil. Tlc (solvent systems A, B, C, D, and E) indicated the derivative to be uniform. Chromatography of the above sample (0.8 g) through silicic acid (40 g) and several recrystallizations from petroleum ether (bp 90–100°) raised the melting point to 163–165°: ir a strong symmetrical band was seen at 1763 cm^{-1}; other bands appeared at 1602 (w), 1372 (s), 1205 (s), 1170 (s), 1064 (m), 1010 (m), 918 (w), 770 (m) and 750 cm^{-1} (m); uv λ_{max}^{MeOH} 285 mμ (ε 16,400), 295 (16,900), 331 (20,500); λ_{sh} 365 (9200).

Anal. Calcd for $C_{20}H_{16}N_2O_4$ (348.4): C, 68.94; H, 4.63; N, 8.04. Found: C, 68.87; H, 4.54; N, 8.61.

Conversion of 16 into 2-Amino-1,4-naphthoquinone (4).—A mixture of 3.15 g (12.0 mmol) of **16**, 50 ml of water, 60 ml of absolute ethanol, and 30 ml of concentrated hydrochloric acid containing 6.75 g (30.0 mmol) of tin(II) chloride 2-hydrate was heated under reflux and, after 4 hr (solution contained a black suspension), the solution was concentrated by boiling to about 70 ml and was filtered (activated charcoal). The yellow filtrate was diluted with 30 ml of concentrated hydrochloric acid and chilled to 0–5° (failed to yield a precipitate of hydrochloride). To this solution was added all at once a cold solution of 13.5 g (50.0 mmol) of iron(III) chloride 6-hydrate in a mixture of 50 ml of water and 10 ml of concentrated hydrochloric acid. After 5–10 min in the cold, a copious crop of small orange-red needles separated, which was collected and washed with water until a consistent bright orange color was obtained. The vacuum dried product (1.35 g, 65%) was chromatographically uniform (solvent system B) and crystallized from benzene in the form of slender orange needles, mp 204–206°. A mixture melting point with authentic **4**,[27] which was further purified by filtering its chloroform solution through Merck basic alumina and then recrystallization from benzene, was 204–206°.

Registry No.—**2**, R = C_6H_5, 20287-12-1; **2**, R = CH_3, 20287-13-2; **2**, R = C_2H_5, 20287-14-3; **2**, R = $(CH_2)_4CH_3$, 20287-15-4; **2**, R = CH_2-cyclopentyl, 20287-16-5; **2**, R = cyclohexyl, 20287-17-6; **4**, 2348-81-4; **6**, 2348-74-5; **7**, 20287-20-1; **10**, R = cyclohexyl, 20287-21-2; **10**, R = $CH(CH_3)_2$, 20287-22-3; **15b**, 20287-26-7; **16**, 20287-23-4; **17**, 20287-24-5; cyclopentylacetic acid hydrazide, 20287-25-6.

(26) The reduction of **16** to **4** is interesting in connection with the report [D. B. Bruce and R. H. Thomson, *J. Chem. Soc.*, 1428 (1954)] that tin(II) reduction of 2-anilino-1,4-naphthoquinone, followed by oxidation, gave 1,4-naphthoquinone.

(27) L. F. Fieser and J. L. Hartwell, *J. Amer. Chem. Soc.*, **57**, 1482 (1935).

Base-Catalyzed Hydrogen–Tritium Exchange Rates of ω-Tritium-Substituted Picolines and Methylquinolines[1]

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The sodium methoxide catalyzed exchange rates between methanol and ω-tritium-substituted picolines and methylquinolines were determined. The relative reactivities were 2-methylquinoline > 4-picoline > 2-picoline > 3-methylquinoline > 3-picoline. These results have been interpreted by use of the qualitative resonance theory and correlated by means of LCAO–MO calculations.

The weak acidity of alkylated pyridines, quinolines, and other similar heterocyclic systems has long been recognized and has been utilized in condensation reactions of these substances to effect the synthesis of desired carbon skeletons.[3] However, there seems to be no definite information regarding the relative reactivities of various substituted alkylpyridines or alkylquinolines. Knowledge of this sort should be of interest not only from a practical standpoint but also for theoretical reasons. With regard to the latter, a quantitative evaluation and interpretation of the effect of a ring nitrogen on reactivity of side chains should lead to a better understanding of the fundamental nature of such systems.

Previous studies of the reactivity of alkylated pyridines have not yielded results capable of quantitative comparison. In some instances they are confusing or conflicting. Thus, although 2,4-lutidine is preferentially metallated on the 2-methyl group with phenyllithium,[4] it has been shown that alkylation of the same compound with methyl iodide in the presence of sodamide gives mainly the 4-methyl-alkylated product.[5] The studies of Pines and coworkers[6] also support a higher alkylation reactivity for the 4-alkylated pyridines. Since it is very difficult to alkylate 3-picoline[7] and because 2,3-dimethylpyridine is alkylated on the 2-methyl,[5] the available information with regard to the base-catalyzed alkylation reactions leads to the reactivity order 4-picoline > 2-picoline ≫ 3-picoline. However, the results (except for those of Pines and his coworkers[6]) do not lend themselves to quantitative comparisons and there is no established relationship between the pyridine series and the quinoline series. Furthermore, the alkylation reaction is a two-step process (anion formation and alkylation) and either or both stages may be responsible for the over-all rate. The rate of alkylation is therefore not necessarily a true reflection of the acidity of the substrate.

The condensation of alkylpyridines and quinolines with aldehydes and ketones may also involve ionization of an α hydrogen on the alkyl group. Again the results are often conflicting. Thus, 2,4-lutidine reacts with formaldehyde to give the 4-ethanol derivative[8] but 2,4,6-collidine with formalin at 200° yields the 2-ethanol.[9]

There are quite a few other contradictory examples of reactivities of alkylpyridines and quinolines. In view of this it is desirable to have some unambiguous, quantitative relative reactivity data for reactions of these systems. In particular, hydrogen exchange rates which can be related to acidities should be especially valuable.

Results

ω-Tritiated 2-, 3-, and 4-picolines and 2- and 3-methylquinolines were prepared by decarboxylation of the corresponding pyridyl- or quinolylacetic acids in tritium water (eq 1). 2-Pyridylacetic acid, 4-pyridyl-

$$ArCH_2CO_2H \xrightarrow{T_2O} ArCH_2T + CO_2 \qquad (1)$$

acetic acid, and 2-quinolylacetic acid decarboxylated readily at 100° in neutral solution. Decarboxylation of 3-pyridylacetic acid and 3-quinolylacetic did not occur under these conditions and was carried out at 215–220°.

To determine the extent of nuclear tritiation during decarboxylation, quinoline was subjected to the decarboxylation conditions. Quinoline rather than picoline or methylquinoline was used to eliminate the possibility of methyl-group tritiation. Methylquinolines should undergo nuclear tritiation faster than quinoline, but picoline should react more slowly if the reaction is an electrophilic substitution. In an experiment at 220°, the relative activities of the recovered quinoline and of the tritium water used indicated that tritium in the nucleus of 3-picoline-ω-*t* and 3-methylquinoline-ω-*t* could account for no more than 1% of the total activity. At 100° nuclear tritiation of quinoline did not occur; thus the other compounds probably contain no nuclear tritium.

In all cases, the activity of the tritiated compound was approximately equal to that of the tritium water used (10^6 to 10^8 cpm/mmol).

The exchange rates were determined by heating samples of the tritiated compounds with methanolic sodium methoxide (ionic strength was maintained constant with sodium chloride) for varying lengths of time. The reaction mixture was acidified, the meth-

(1) Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964.

(2) To whom inquiries should be addressed: Department of Chemistry, University of Vermont, Burlington, Vt. 05401.

(3) E. Klingsberg, "The Chemistry of Heterocyclic Compounds—Pyridine and Its Derivatives, Part Two," Interscience Publishers, Inc., New York, N. Y., 1961.

(4) J. F. Arens, D. A. van Dorp, and G. M. van Dijk, *Rec. Trav. Chim.*, **69**, 287 (1950).

(5) A. L. Lochte and T. H. Cheavens, *J. Amer. Chem. Soc.*, **79**, 1667 (1957).

(6) H. Pines and B. Notari, *ibid.*, **82**, 2209, 2945 (1960); H. Pines and D. Wunderlich, *ibid.*, **81**, 2568 (1959).

(7) H. C. Brown and W. A. Murphey, *ibid.*, **73**, 3308 (1951).

(8) K. Winterfeld, *Arch. Pharm.*, **268**, 308 (1930); *Chem. Abstr.*, **24**, 3790 (1930).

(9) F. Melichan, *Chem. Ber.*, **88**, 1208 (1955).

anol was distilled off, and its tritium content was determined.

The exchange reaction was found to be first order in the tritiated compound and first order in the base concentration. For each of the compounds, the rates of exchange were determined at two temperatures and extrapolated to 135°. The results are summarized in Tables I and II.

TABLE I

TRITIUM EXCHANGE RATES IN METHANOLIC SODIUM METHOXIDE AT 135° (EXTRAPOLATED)

Compound	$k_2^a \times 10^6$
2-Methylquinoline-ω-t	2200
4-Picoline-ω-t	760
2-Picoline-ω-t	54
3-Methylquinoline-ω-t	2.9
3-Picoline-ω-t	0.42

[a] l. mol^{-1} sec^{-1}.

TABLE II

TRITIUM EXCHANGE RATES IN METHANOLIC SODIUM METHOXIDE

Compound	Temp, °C	M NaOMe	M NaCl	$k_1^a \times 10^6$	$k_2^b \times 10^6$
2-Picoline-ω-t	129.8	0.102	0.000	3.53 ± 0.01	3.50 ± 0.01
	149.5	0.100	0.000	17.4 ± 0.2	17.4 ± 0.2
	149.5	0.054	0.048	9.54	17.6
3-Picoline-ω-t	169.8	0.100	0.000	1.36 ± 0.04	1.36 ± 0.04
	184.2	0.098	0.000	4.93 ± 0.02	5.00 ± 0.02
	184.2	0.051	0.048	2.53 ± 0.05	4.97 ± 0.10
4-Picoline-ω-t	101.0	0.102	0.000	3.56 ± 0.02	3.49 ± 0.02
	119.7	0.098	0.000	20.1 ± 0.4	20.6 ± 0.5
	119.7	0.051	0.048	10.3 ± 0.1	20.2 ± 0.2
2-Methylquinoline-ω-t	85.8	0.102	0.000	3.33 ± 0.07	3.26 ± 0.06
	105.1	0.100	0.000	19.3 ± 0.8	19.3 ± 0.8
	105.1	0.061	0.040	10.9 ± 0.7	17.9 ± 1.2
3-Methylquinoline-ω-t	149.5	0.100	0.000	1.08 ± 0.01	1.08 ± 0.01
	169.8	0.099	0.000	5.98 ± 0.04	6.08 ± 0.06
	169.8	0.052	0.048	2.94 ± 0.08	5.70 ± 0.14

[a] sec^{-1}. [b] l. mol^{-1} sec^{-1}.

Discussion

Hydrogen exchange rates of very weak acids often parallel the acidities of this type of compound.[10] This parallelism would be expected from the Brønsted catalysis law[11] if k is the rate constant for the protonation of the strong base by the weak acid and k_a is the dissociation constant of the weak acid. This procedure for evaluating relative acidities of weak acids is not without some ambiguities. The mechanism of the exchange process must be the same for each of the weak acids and must be a true acid–base reaction. The results are least equivocal if the reaction is uncomplicated by ion-pair formation or recombination of the anion of the weak acid with its original proton before exchange with the bulk solvent can occur. Andreades has shown that these phenomena do not occur in sodium methoxide–methanol solutions.[12] In this medium, the transition state for the hydrogen-exchange reaction has considerable carbanionic character and the relative exchange rates can be interpreted by comparison of the factors stabilizing the anion and its conjugate acid.

$$\log k = \alpha \log k_a + \log G$$

Qualitative resonance theory[13] can be used to estimate the relative acidities of the heterocyclic "acids" if several features of the resonance structures of the acids and their anions are taken into account. The location of the negative charge in the anion and the relative number of important resonance structures of the acid and anion appear to be important. The possibility of positioning a portion of the anion's negative charge on the electronegative nitrogen atom appears to be the principal factor in determining the exchange rates of these compounds. Thus, 2- and 4-picolines are more reactive than 3-picoline, and 2-methylquinoline reacts faster than 3-methylquinoline. Superimposed upon this consideration is that of the number of resonance structures of the anion compared with the acid. There is a larger difference between the numbers of resonance contributors to the anion and the acid for the methylquinolines than for the picolines. For this reason, 2-methylquinoline undergoes exchange more rapidly than 2-picoline and 3-methylquinoline is more reactive than 3-picoline. The difference in reactivity between 2-picoline and 4-picoline may be the result of additional stabilization of the 4-picoline anion occasioned by the fact that there are two pairs of equivalent contributors to the 4-picoline anion and no equivalent resonance structures for the 2-picoline anion. Thus, the exchange rates of the picolines and methylquinolines can be interpreted qualitatively by application of the resonance theory.

A quantitative correlation of the exchange rates of the picolines and methylquinolines by means of molecular orbital calculations was also attempted. The exchange rate should be related to the π-electron energy change of the reaction, which is simply the difference between the π-electron energies of the heterocyclic anion and its conjugate acid.[14] These π-electron energies are readily calculated by the LCAO–MO method. In treating compounds that contain atoms other than carbon, it is necessary to take account of the perturbing influence of the electronegative heteroatom on the rest of the system[14] by assigning different parameters to the carbons bonded to the heteroatom since they will be inductively affected. The best correlation resulted when the coulomb and resonance integrals were defined as shown in Chart I. h was varied from 0.50 to 2.50, while $h_{\alpha C}$ was allowed to assume values from 0.100 to 0.417. The best fit of the experimental data resulted when $h = 1.00$ and $h_{\alpha C} = 0.125$ (see Figure 1) with $\beta_{eff} = 49.6$ kcal/mol.

CHART I

$$\alpha_C = \alpha_0$$
$$\alpha_N = \alpha_0 + h\beta_0$$
$$\alpha_{\alpha C} = \alpha_0 + h_{\alpha C}\beta_0$$
$$\beta_{CN} = \beta_{CC} = \beta_0$$

In conclusion, it appears that the rates of anion formation for picolines and methylquinolines is that

(10) (a) A. Streitwieser, Jr., J. I. Brauman, J. H. Hammons, and A. H. Pudjaatmaaka, *J. Amer. Chem. Soc.*, **87**, 384 (1965); (b) R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953); (c) A. I. Shatenshtein, *Advan. Phys. Org. Chem.*, I, 155 (1963); (d) S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, "Progress in Physical Organic Chemistry," Vol. 3, Interscience Publishers, New York, N. Y., 1965, pp 41–80.

(11) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley & Sons, Inc., New York, N. Y., 1953, pp 209–218.

(12) S. Andreades, *J. Amer. Chem. Soc.*, **86**, 2003 (1964).

(13) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1955.

(14) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961.

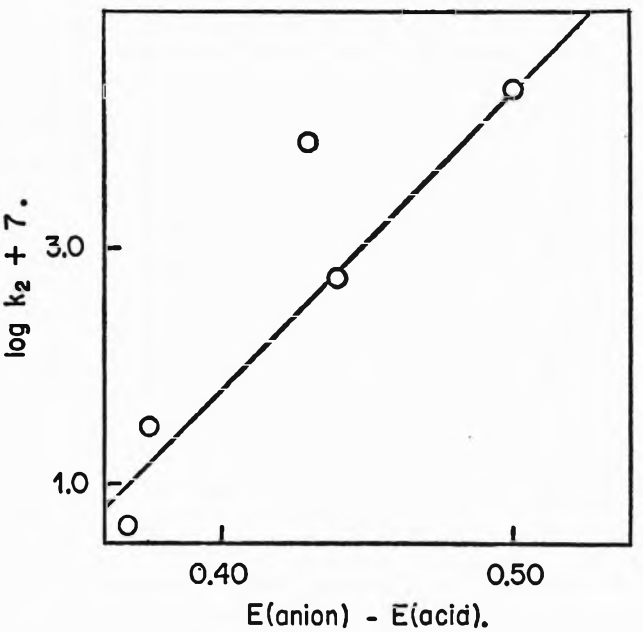

Figure 1.—Logarithms of the exchange rates of picolines and methylquinolines *vs.* the calculated π-electron energy changes (h = 1.0, $h_{\alpha C}$ = 0.125) for anion formation from these compounds.

suggested by the results of alkylation and condensation reactions of these compounds. The semiquantitative correlation of these rates by the molecular orbital approach is obviously not completely satisfactory. This may be due to deficiencies in the computational methods used or to complicating features in the exchange reaction. However, the fundamental validity of these procedures is indicated by the fact that they lead to the approximately correct ordering of reactivities. The exchange rates can be satisfactorily interpreted qualitatively by the resonance theory.

Experimental Section

Methyl 2-Pyridylacetate.—The ester was purified by conversion into the picrate which was crystallized from absolute methanol to give yellow crystals, mp 141.6–142.8° (lit.[15] mp 142–144°).

Methyl 4-Pyridylacetate.—Treatment of the ester with picric acid yielded a picrate which melted at 146.4–147.7° (lit.[16] mp 146.5–147.5°) after crystallization from methanol.

Methyl 2-Quinolylacetate.—A solution of 21.4 g (0.15 mol) of quinaldine in 50 cc of anhydrous ether was added during 15 min to 160 cc of 0.95 *M* phenyllithium in ether. The mixture was stirred for 3 hr at room temperature and then rapidly poured on Dry Ice. After completion of the reaction, the ether was allowed to evaporate at room temperature, and the residue was suspended in 250 cc of absolute methanol. The suspension was saturated with dry hydrogen chloride and the resulting solution was allowed to stand for 24 hr at 25°. At the end of this period the methanol was distilled off under reduced pressure, and to the residue was added 100 cc of water and sufficient sodium carbonate to make the solution basic. The basic solution was extracted three times with 100-cc portions of ether, and the combined ether extracts were dried over magnesium sulfate and evaporated. The residue was dissolved in a small volume of benzene and chromatographed on a 2.5 × 40 cm column of activity grade II Woelm alumina, using Skellysolve F as the eluent. The first fraction of the eluate, which corresponded to a light yellow band on the column, yielded 14 g (65%) of quinaldine. The residue obtained upon evaporation of the second fraction (corresponding to a dark yellow band) was chromatographed a second time. The ester so obtained was converted into the picrate, which was crystallized from absolute methanol. The yield of the ester picrate, mp 161.0–162.6° (lit.[17] mp 162°) was 10.5 g (15%).

3-Cyanoquinoline.—Heating of 3-bromoquinoline with cuprous cyanide[18] until the mixture liquefied followed by immediate distillation of the product and recrystallization from methanol yielded 62% of 3-cyanoquinoline, mp 106.8–107.4° (lit.[18] mp 106–108°).

Methyl 3-Quinolinecarboxylate.—Reaction of 3-cyanoquinoline with hydrogen chloride in methanol[19] followed by crystallization of the product from Skellysolve B at 0° yielded 58% methyl 3-quinolinecarboxylate as white crystals, mp 70–72° (lit.[19] mp 73–74°).

3-Acetylquinoline.—Methyl 3-quinolinecarboxylate was condensed with ethyl acetate in the presence of sodium methoxide,[20] and the crude keto ester was hydrolyzed and decarboxylated in 25% sulfuric acid at 100°. The crude product was crystallized from Skellysolve F to give 3-acetylquinoline in 37% yield as tan flakes, mp 98.4–99.2° (lit.[20] mp 97.5–98.5°).

3-Quinolylacetic Acid Hydrochloride.—3-Acetylquinoline was subjected to the Willgerodt reaction under the conditions described by Jones, Soper, Behrens, and Corse.[20] The procedure was modified as described below so that the acid hydrochloride rather than the methyl ester was isolated. The solution remaining after hydrolysis of the 3-quinolylthioacetamide was evaporated to 50 cc, made basic with solid potassium carbonate, and filtered. The filtrate was extracted five times with 150-cc portions of ether to remove nonacidic substances. The aqueous solution was then evaporated to dryness under reduced pressure, and the residue was extracted three times with 50-cc portions of absolute ethanol. The volume of the ethanol solution was reduced to 50 cc under vacuum, and the solid which precipitated was collected by filtration. To the filtrate was added 200 cc of ether, and the precipitate formed was filtered off. Both precipitates appeared to be mixtures of potassium chloride and the organic product; so they were combined. The 3-quinolylacetic acid hydrochloride was isolated by boiling the combined residues with 25 cc of absolute ethanol for a few minutes, filtering the hot suspension, and allowing the product to crystallize from the filtrate. This extraction was repeated three times with 10-cc portions of absolute ethanol. In this way there was obtained 2.35 g (15%) of 3-quinolylacetic acid hydrochloride, mp 194.8–197.4°.

Anal. Calcd for $C_{11}H_{10}O_2NCl$: C, 59.1; H, 4.5; N, 6.3; Cl, 15.9. Found: C, 59.4; H, 4.7; N, 6.6; Cl, 15.3.

2-Picoline-ω-t.—A suspension of 2.5 g of methyl 2-pyridylacetate picrate in 5 cc of concentrated hydrochloric acid was extracted with seven 20-cc portions of ether to remove the picric acid. The aqueous solution was then refluxed for 4 hr and evaporated to dryness under vacuum. The residual 2-pyridylacetic acid hydrochloride was dried by adding 5 cc of acetone and again evaporating to dryness. This was repeated three times. A methanol solution of a portion of the residue gave no precipitate with picric acid, indicating the absence of both the ester and 2-picoline. A solution of 0.9 g of the 2-pyridylacetic acid hydrochloride in 1 cc of tritium water was sealed in a tube and heated for 3 hr at 100°. The tube was then opened, the contents were made basic with solid potassium carbonate, and to the basic solution were added 5 cc of ether and 2 g of magnesium sulfate. The mixture was allowed to stand for several hours, and the ether was decanted. The residue was washed with 2-cc portions of ether until portions of the washings no longer gave a precipitate with picric acid. The combined ether solutions were distilled through a short column at atmospheric pressure until all of the ether appeared to have been removed. The residue was then distilled under vacuum to give 0.44 g (91%) of 2-picoline-ω-t with an approximate activity of 2.03 × 10^7 cpm/mmol. Gas phase chromatography indicated that this product was at least 98.5% pure 2-picoline. The picrate melted at 164.8–166.6° (lit.[21] mp 164°).

4-Picoline-ω-t.—This compound was prepared from methyl 4-pyridylacetate picrate in the way described above for 2-picoline-ω-t. One gram of 4-pyridylacetic acid hydrochloride yielded 0.48 g (89%) of 4-picoline-ω-t of approximate activity 2.03 × 10^7 cpm/

(15) W. Gruber and K. Schlögl, *Monatsh.*, **81**, 473 (1950).
(16) J. Thesing, H. Ramlock, and C. Willersinn, *Chem. Ber.*, **89**, 2896 (1956).
(17) W. Borsche and R. Manteuffel, *Ann.*, **526**, 22 (1936).
(18) H. Gilman and S. M. Spatz, *J. Amer. Chem. Soc.*, **63**, 1533 (1941).
(19) S. Chiavarelli and G. B. Marini-Betollo, *Gazz. Chim. Ital.*, **82**, 86 (1952).
(20) R. G. Jones, Q. F. Soper, O. K. Behrens, and J. W. Corse, *J. Amer. Chem. Soc.*, **70**, 2843 (1948).
(21) E. J. Constam and J. White, *Am. Chem. J.*, **29**, 38 (1903).

mmol. This material was shown to be pure by gas phase chromatography. Its picrate melted at 166.8–168.2° (lit.[22] mp 167°).

2-Methylquinoline-ω-*t*.—A suspension of 2 g of methyl 2-quinolylacetate picrate (mp 161.0–162.6°) in 5 cc of concentrated hydrochloric acid was extracted seven times with 100-cc portions of ether. The hydrochloric acid solution was then evaporated to dryness under vacuum at 25°. The residue was dissolved in 2 cc of tritiated 4 *N* hydrochloric acid solution, sealed in a tube, and heated for 7 hr at 100°. The resulting solution was treated in the same way as was the reaction mixture obtained in the preparation of 2-picoline-ω-*t*. Upon distillation there was obtained 0.44 g (65%) of 2-methylquinoline-ω-*t* having an activity of about 3.79 × 10^6 cpm/mmol. The product was shown to consist entirely of this compound by gas phase chromatography. The picrate melted at 194.8–196.4° (lit.[23] mp 195°).

3-Picoline-ω-*t*.—A suspension of 1.0 g of 3-pyridylacetic acid in 1 cc of tritium water was sealed in a tube and heated for 7 hr at 220°. At the end of this period, the tube was cooled and opened and 2.0 g of magnesium sulfate was added. The 3-picoline-ω-*t* was isolated according to the procedure given for the isolation of 2-picoline-ω-*t*. The yield of 3-picoline-ω-*t* with an activity of 1.83 × 10^6 cpm/mmol was 0.59 g (87%). Gas phase chromatography indicated that the product was at least 98.5% pure. The picrate had mp 150.4–150.8° (lit.[21] mp 149.5°).

3-Methylquinoline-ω-*t*.—A solution of 0.7 g of 3-quinolylacetic acid hydrochloride in 0.7 cc of tritium water was neutralized with 0.15 g of solid potassium carbonate and sealed in a tube. The tube was heated for 7 hr at 215–220°. To the resulting suspension were added 2.0 g magnesium sulfate and 5 cc of ether. The ether solution was decanted and the residual magnesium sulfate was then washed with ether until portions of the washings no longer gave precipitates with picric acid. The combined ether solutions were evaporated to 10 cc. and chromatographed on a 1 × 12 cm column of activity grade I Woelm alumina, using ether as the eluent. Evaporation of the ether from the eluate gave 0.17 g (38%) of 3-methylquinoline-ω-*t*. Its picrate melted at 190.4–191.6° (lit.[24] mp 187.5°). To the 3-methylquinoline-ω-*t* was then added 0.15 g of pure inactive 3-methylquinoline and the mixture was further purified by evaporative distillation. The approximate activity of the product was 1.07 × 10^8 cpm/mmol. The presence of only one component was demonstrated by gas phase chromatography.

Tritiation of Quinoline.—A solution of 0.52 g of quinoline and *ca.* 0.3 g of Dry Ice in 0.5 cc of tritium water (activity 4.4 × 10^5 cpm/mmol) was sealed in a tube and heated for 7 hr at 215–220°. The tube was opened and the contents were extracted five times with 2-cc portions of ether. The combined ether solutions were dried over sodium oxide and evaporated. The residue was distilled under vacuum. The activity of the product was 4.34 × 10^3 cpm/mmol.

(22) A. Landenburg, *Ann.*, **247**, 5 (1888).

(23) R. F. Manske, L. Marion, and F. Leger, *Can. J. Research*, **20B**, 133 (1942).

(24) W. P. Utermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943).

In another experiment a solution of 0.30 g of quinoline in 0.5 cc of 6 *N* tritiated hydrochloric acid solution (activity 5.28 × 10^5 cpm/mmol) was sealed in a tube and heated for 7 hr at 100°. The tube was opened and the contents were made basic with solid potassium carbonate and then extracted five times with 2-cc portions of ether. The combined ether solutions were dried over sodium oxide and evaporated, and the residue was distilled under vacuum. The quinoline treated in this manner exhibited no activity.

Kinetic Procedure.—The rates of tritium exchange were determined in 0.1 *N* and 0.05 *N* sodium methoxide solutions. The ionic strength was maintained at 0.1 by the addition of sodium chloride. The solutions were prepared immediately before using by dissolving sodium in degassed absolute methanol (Mallinckrodt, reagent grade) and were titrated with standard 0.0999 *N* hydrochloric acid, using phenolphthalein as the indicator.

Aliquots (2.5 cc) of a solution of 10–20 mg of the tritiated compound in 25 cc of sodium methoxide solution were sealed in tubes under nitrogen and heated in a constant-temperature bath for varying timed intervals. After removal from the constant-temperature bath, a tube was cooled and opened and a 2.00-cc aliquot of the contents was added to 1.00 cc of 0.5 *N* sulfuric acid in 95% methanol. The resulting mixture was distilled almost to dryness under vacuum at 25°. A 2.00-cc aliquot of the distillate was then added to 15 cc of the scintillator solution {0.4 g of diphenyloxazole and 5 mg of 1,4-bis[2-(5-phenyloxazolyl)]benzene in 1 l. of reagent grade toluene} and the activity was determined in a Tracerlab CE-1B liquid scintillation counter.

In the runs using solutions containing sodium chloride the distillate contained traces of hydrochloric acid. It was therefore made basic with a small quantity of sodium oxide and redistilled.

Infinity values were calculated from the count rate obtained with 1.00 cc of the original solution in a mixture of 1.00 cc of absolute methanol and 15 cc of the scintillator solution. The quenching effect of the tritiated compound was ascertained by noting whether the count rate for a mixture of the original amine solution and 1.00 cc of a standard methanol-*t* solution was equal to the sum of the count rates of the two solutions determined individually. Significant quenching was found only in the runs with 3-picoline-ω-*t* and with 2-methylquinoline-ω-*t* at 105°. In these runs larger quantities of the tritiated compound were used than in the others. Infinity values were corrected for any quenching effect.

The counting results were treated by means of a first-order rate expression. When log ($a_\infty - a_t$) was plotted against *t*, the points defined a straight line. The rate constant was determined from the slope of this line in the usual way.

Registry No.—2-Picoline-ω-*t*, 19656-78-1; 3-picoline-ω-*t*, 19656-79-2; 4-picoline-ω-*t*, 19656-80-5; 2-methylquinoline-ω-*t*, 19656-81-6; 3-methylquinoline-ω-*t*, 19656-82-7; 3-quinolylacetic acid hydrochloride, 19656-83-8.

Ring–Chain Isomerism of Tetrahydropyrimido[4,5-*d*]pyrimidines[1a]

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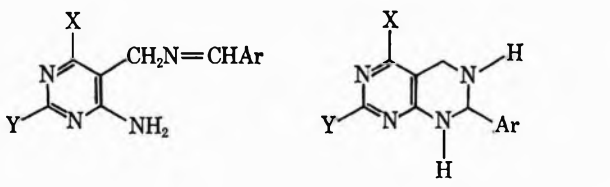
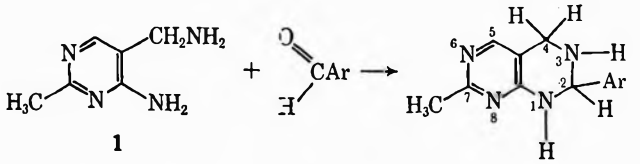
Recent work by McDonagh and Smith[2,3] and Dorman[4] has demonstrated the existence of ring–chain tautomerism involving hydroxyl and imine functions. This paper describes a new type of ring–chain isomerism involving the amine and imine functions of tetrahydropyrimido[4,5-*d*]pyrimidines.

In 1955, Suter and Habicht[5] reported that the reaction of 4-amino-5-(aminomethyl)-2,6-disubstituted pyrimidine with aromatic aldehydes gave two isomers, the Schiff base A or the tetrahydropyrimido[4,5-*d*]pyrimidine B. But they were unable to differentiate between these two isomers. On reinvestigating the reaction of 4-amino-5-(aminomethyl)-2-methylpyrimidine (**1**) with a number of substituted aromatic aldehydes by nmr and ir spectroscopy, we have obtained strong evidence for the existence of a ring–chain isomerism between the two forms A and B. Thus, the reaction of *p*-methoxy, *p*-nitro, 2,4-dichloro- and 3,4-dichlorobenzaldehydes with **1** afforded only the corresponding ring isomers, tetrahydropyrimido(4,5-*d*)pyrimidines **2**–**5** as outlined below. Their tlc indicated only one spot.



A

B, X = H, NH_2, OH, etc.
Y = CH_3, NH_2, OH, etc.

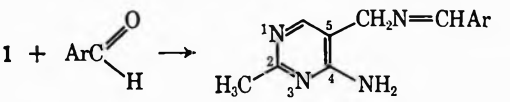


1

2, Ar = *p*-methoxyphenyl
3, Ar = *p*-nitrophenyl
4, Ar = 2,4-dichlorophenyl
5, Ar = 3,4-dichlorophenyl

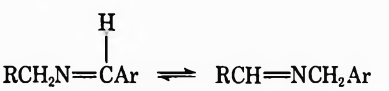
The ir spectra (Nujol) had only one absorption band in the region 3300–3200 cm^{-1}, characteristic of secondary amines. The nmr spectra of these compounds showed a singlet at δ 5.42–5.83, characteristic of the methine proton.[4] In confirmation of the proposed ring structure **2**, the protons on N-1 and N-3 could be exchanged with deuterium.

The reaction of **1** with *p*-chloro- and *p*-bromobenzaldehydes furnished the Schiff bases **6** and **7**, respectively, which were found to be homogenous by tlc.



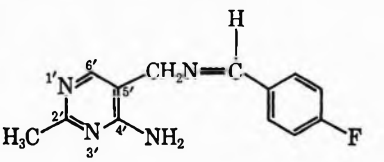
6, Ar = *p*-chlorophenyl
7, Ar = *p*-bromophenyl

Their ir spectra showed two bands at 3400 and 3300 cm^{-1} for the NH_2 group. The nmr spectra of the chain isomers **6** and **7** were considerably different than those of the ring isomers, **2**–**5**. The most significant difference was the peak for the azomethine proton at δ 8.44. This assignment was confirmed by the nmr spectra of authentic Schiff bases of aniline with *p*-chloro- and *p*-bromobenzaldehydes. As expected, the protons on the 4-NH_2 group in **6** could be exchanged with deuterium. To determine if **6** and **7** were involved in the following type of equilibrium, **6** was hydrolyzed with 1

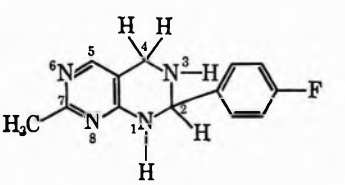


N hydrochloric acid at room temperature for 15 min. A quantitative yield of *p*-chlorobenzaldehyde appeared to rule out this possibility.[6]

The reaction of **1** with *p*-fluorobenzaldehyde afforded a mixture of the open-chain and the ring isomers, **8** and **9**, respectively, as shown by ir and nmr spectra and tlc of the reaction mixture. Tlc indicated two spots, and the ir spectrum (Nujol) showed three bands in the N–H region at 3400, 3300, and 3250 cm^{-1}. The nmr spectrum showed absorptions characteristic of both **8** and **9**. The



8



9

(1) (a) R. E. Harmon and J. L. Parsons, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., September 1967, S 138. (b) To whom correspondence should be sent. (c) J. L. Parsons, M. A. Thesis, Western Michigan University, Kalamazoo, Michigan, 1966.
(2) A. F. McDonagh and H. E. Smith, *Chem. Commun.*, **12**, 374 (1966).
(3) A. F. McDonagh and H. E. Smith, *J. Org. Chem.*, **33**, 8 (1968).
(4) L. C. Dorman, *ibid.*, **32**, 255 (1967).
(5) H. Suter and E. Habicht, U.S. Patent 2,707,185 (1955).
(6) B. Witkop and T. W. Beiler, *J. Amer. Chem. Soc.*, **76**, 5589 (1954).

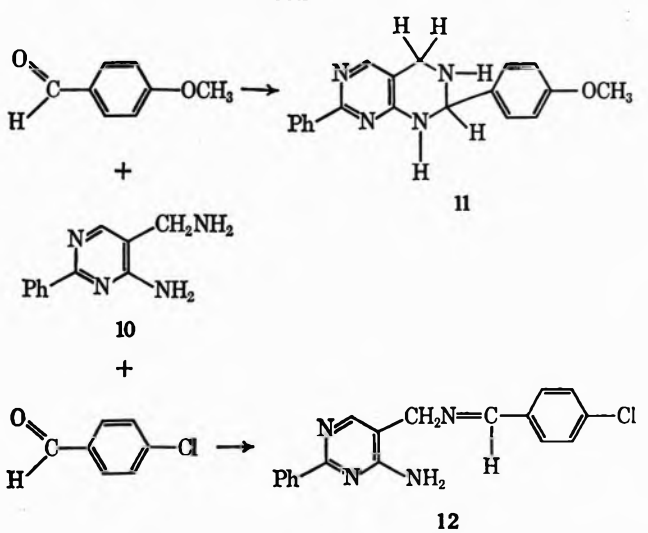
TABLE I

Compd	Mp, °C	Empirical formula	Analysis	Calcd, %	Found, %	Nmr data Solvent	δ
2	142–143	$C_{14}H_{16}N_4O$	C H N	65.60 6.29 21.89	65.40 6.17 22.12	$CHCl_3$-*d*	2.0 (m, 1, 3 H); 2.35 (s, 3, CH_3); 3.80 (s, 3, OCH_3); 3.87 (m, 2, 4 CH_2); 5.42 (s, 1, 2 H); 6.55 (s, 1, 1 H); 7.13 (m, 4, aromatics); 7.83 (s, 1, 5 H)
3	189–190	$C_{13}H_{13}N_5O_2$	C H N	57.56 4.83 25.82	57.80 5.02 25.58	DMSO-*d*	2.32 (s, 3, CH_3); 3.23 (m, 2, CH_2); 5.50 (s, 1, 2 H); 7.98 (m, 4, aromatics); 8.04 (m, 1, 5 H)
4	179–180	$C_{13}H_{12}Cl_2N_4$	C H N	52.90 4.10 18.98	52.89 4.19 18.74	$CHCl_3$-*d*	2.13 (m, 1, 3 H); 2.41 (s, 3, CH_3); 3.90 (d, 2, J = 3.0, CH_2); 5.83 (s, 1, 2 H); 6.21 (s, 1, 1 H); 7.38 (m, 4, aromatics); 7.93 (m, 1, 5 H)
5	163–165	$C_{13}H_{12}Cl_2N_2$	C H N	52.90 4.10 18.98	52.85 4.32 19.24	$CHCl_3$-*d*	2.48 (s, 3, CH_3); 3.86 (d, 2, J = 2.0, CH_2); 5.50 (s, 1, 2 H); 7.37 (m, 4, aromatics); 7.55 (m, 1, 5 H)
6	169–170	$C_{13}H_{13}N_4Cl$	C H N	59.88 5.02 21.49	59.73 5.10 21.27	$CHCl_3$-*d*	2.30 (s, 3, CH_3); 4.82 (s, 2, CH_2); 6.06 (s, 2, NH_2); 7.60 (m, 4, aromatics); 8.16 (s, 1, 6 H); 8.44 (s, 1, azomethine H)
7	170–172	$C_{13}H_{13}BrN_4$	C H N	51.16 4.29 18.36	51.27 4.39 18.64	$CHCl_3$-*d*	2.46 (s, 3, CH_3); 4.60 (s, 2, CH_2); 5.92 (s, 2, NH_2); 7.52 (m, 4, aromatics); 7.98 (2, 1, 6 H); 8.26 (s, 1, azomethine H)
8 and 9	163–170	$C_{18}H_{13}FN_4$	C H N	63.92 5.36 22.94	63.72 5.47 23.09	DMSO-*d*	2.34 (s, 3, CH_3); 3.60 (s, 0.7, 4 CH_2); 4.54 (s, 1.3, 5 CH2); 5.36 (m, 0.33, 2 CH); 6.60 (s, 1.2, 4 NH_2); 7.20 (m, 2.6, chain aromatics); 7.78 (m, 1.4, ring aromatics); 7.92 (m, 1, 5, and 6 CH); 8.44 (m, 0.66, azomethine H)
11	132.5–133	$C_{19}H_{18}N_4O$	C H N	71.78 5.70 17.60	71.77 5.74 17.68	DMSO-*d*	3.78 (s, 5, OCH_3 and CH_2); 5.42 (s, 1, 2 H); 7.44 (m, 8, aromatics)
12	182–182.5	$C_{18}H_{15}ClN_4$	C H N	66.97 4.68 17.36	67.21 4.81 17.51	DMSO-*d*	4.66 (s, 2, CH_2); 6.80 (s, 2, NH_2); 7.80 (m, 8, aromatics); 8.48 (s, 1, azomethine H)

peak at δ 8.44 (azomethine proton, structure **8**) integrated for 0.66 H, whereas the peak at δ 5.36 (methine proton, structure **9**) integrated for 0.33 H. This suggested the approximate composition of the mixture to be 33% **9** and 67% **8**.

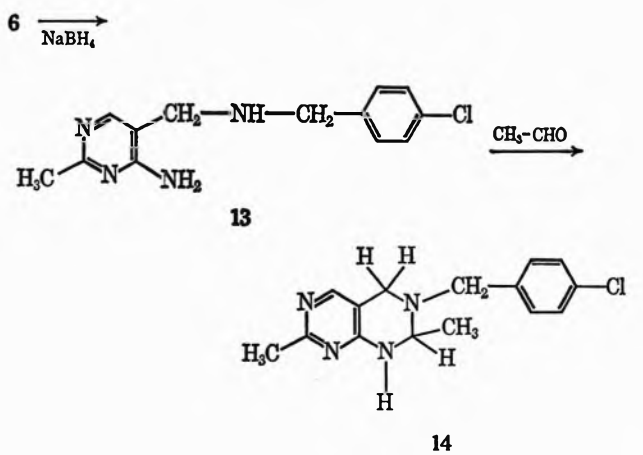
The reaction of 4-amino-5-(aminomethyl)-2-phenylpyrimidine (**10**) with *p*-chloro- and *p*-methoxybenzaldehydes furnished products (shown in Scheme I) similar to those obtained from **1**.

SCHEME I



Sodium borohydride reduction of the Schiff base **6** afforded 4-amino-5-(*p*-chlorobenzylaminomethyl)-2-methylpyrimidine (**13**). Reaction of **13** with acetaldehyde gave the ring isomer **14** as shown in Scheme II. The nmr and ir spectra of **14** were consistent with the structure.

SCHEME II



The conclusion is that the reaction of 4-amino-5-(aminomethyl)-2-methylpyrimidine with substituted aromatic aldehydes afforded Schiff bases, tetrahydropy-

rimido(4,5-*d*)pyrimidines, or a mixture of both, depending on the aldehyde substituent.

Experimental Section

The melting points were taken on a Thomas–Hoover melting point apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The nmr spectra were obtained with a Varian A-60 spectrometer. A Beckman IR-8 spectrophotometer was used to determine the ir spectra. Glass plates coated with silica gel G were used for tlc in ethanol–water.

General Procedure for the Reaction of 4-Amino-5-(aminomethyl)-2-methylpyrimidine (1)[7] and 4-Amino-5-(aminomethyl)-2-phenylpyrimidine (10) with Substituted Benzaldehydes.—To a solution of 0.075 mol of the benzaldehyde in 150 ml of benzene was added 0.075 mol of the pyrimidine with stirring. The mixture was heated under reflux for 8–12 hr in the presence of a Dean–Stark trap. The reaction mixture was filtered while hot to remove any unreacted pyrimidine. The product, the Schiff base or the tetrahydropyrimido(4,5-*d*)pyrimidine, was obtained in 70–90% yield by either cooling the filtrate or by evaporating it to dryness and triturating the residue with petroleum ether (bp 30–60°). The analytical samples were obtained by three or four recrystallizations from benzene or ethanol. The analyses as well as the nmr data are summarized in Table I.

Hydrolysis of 4-Amino-5-(*p*-chlorobenzylideneaminomethyl)-2-methylpyrimidine (6).—A solution of 2.06 g (0.008 mol) of **6** in 50 ml of 1 *N* hydrochloric acid was kept at room temperature for 15–20 min. Colorless crystals, mp 45–48°, of *p*-chlorobenzaldehyde were obtained by filtration of the reaction mixture. Extraction of the mother liquors with ether furnished an additional yield of *p*-chlorobenzaldehyde, mp 45–48°. The *p*-chlorobenzaldehyde thus obtained was dissolved in ether and treated with a solution of 2,4-dinitrophenylhydrazine in ether. Filtration afforded 2.3 g (93%) crystals of *p*-chlorobenzaldehyde-2,4-dinitrophenylhydrazone, mp 264–267° (lit.[8] mp 266°).

4-Amino-5-(*p*-chlorobenzylaminomethyl)-2-methylpyrimidine (13).—To a solution of 2.0 g (0.008 mol) of **2** in 40 ml of absolute MeOH at −5° was added slowly and with stirring 0.43 g (0.012 mol) of sodium borohydride. The reaction mixture was heated under reflux for 20 min and then made basic by the addition of 45 ml of 1.0 *N* sodium hydroxide with vigorous stirring. Extraction with six 25-ml portions of ether and evaporation of the ether extract to dryness afforded 1.7 g (84%) of crystals of **13**, mp 97–100°. Three recrystallizations from benzene furnished the analytical sample: mp 101.5–102.5°; nmr ($CHCl_3$-*d*) δ 1.50 (m, 1, NH), 2.43 (s, 3, CH_3), 3.64 (s, 2, 5 CH_2), 3.75 (m, 2, benzylic CH_2), 6.23 (s, 2, NH_2), 7.30 (m, 4, aromatics), and 7.92 (s, 1, 6 H); ir ν_{max}^{Nujol} 3400 and 3300 cm^{-1} (NH_2).

Anal. Calcd for $C_{13}H_{15}ClN_4$: C, 59.42; H, 5.75; N, 21.33. Found: C, 59.36; H, 5.82; N, 21.48.

3-(*p*-Chlorobenzyl)-2,7-dimethyl-1,2,3,4-tetrahydropyrimido(4,5-*d*)pyrimidine (14).—Two drops of concentrated HCl was added to a solution of 2.0 g (0.008 mol) of **13** and 2.5 g (0.06 mol) of acetaldehyde in 75 ml of benzene. The reaction mixture was heated under reflux for 6 hr. Evaporation to dryness afforded 1.6 g (73%) of crystals of **14**, mp 144–146°. Recrystallization from benzene gave the analytical sample: mp 146–147°; nmr ($CHCl_3$-*d*) δ 1.40 (d, 3, J = 7.0, 2 CH_3), 2.47 (s, 3, 7 CH_3), 3.57 (d, 2, J = 2.0, 3 CH_2), 3.73 (d, 2, J = 7.0, 4 CH_2), 5.71 (m, 1, 1 NH), 7.31 (m, 4, aromatics), and 7.85 (s, 1, 5 H); ir ν_{max}^{Nujol} 3230 cm^{-1} (NH).

Anal. Calcd for $C_{15}H_{17}ClN_4$: C, 62.92; H, 5.88; N, 19.40. Found: C, 63.25; H, 6.10; N, 19.23.

Registry No.—**2**, 20352-37-8; **3**, 20352-38-9; **4**, 20352-39-0; **5**, 20352-40-3; **6**, 20352-46-9; **7**, 20352-47-0; **8**, 20352-48-1; **9**, 20352-41-4; **11**, 20352-42-5; **12**, 20352-43-6; **13**, 20352-44-7; **14**, 20352-45-8.

Acknowledgment.—This work was supported by a grant from the Michigan Cancer Foundation.

(7) W. H. Huber, *J. Amer. Chem. Soc.*, **66**, 876 (1944).
(8) G. Harris, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1966, p 599.

Preparation of Substituted 5,6-Dihydro-1,4-dithiins

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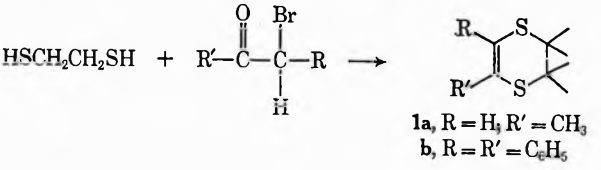
Received January 29, 1969

There is a great deal of interest in the chemistry of 1,4-dithiins and 1,4 dithianes.[1] Unsubstituted dithiins and dithianes can be prepared by relatively straightforward procedures.[2,3] There are, however, few good methods for the preparation of simple alkyl or aryl dithianes or dithiins. Of the existing methods, the usual procedures give 2,5-disubstituted or 2,3,5,6-tetrasubstituted derivatives.[4-9] The reported methods for the preparation of monoalkyl and aryl substituted dithiins usually involve multistep syntheses and proceed with poor yields.[10,11] There are no reports in the literature of simple procedures for the preparation of 2,3-disubstituted dithianes or dithiins except for benz-1,4-dithianes.[12]

We report here a novel synthesis of 2- and 2,3-mono- and disubstituted 5,6-dihydro-1,4-dithiins (**1**). These compounds can readily be prepared by treating ethanedithiol with an α-bromo ketone.



1a, R = H, R′ = CH_3
b, R = R′ = C_6H_5

When α-bromoacetone is treated with ethanedithiol, the resulting 2-methyl-5,6-dihydro-1,4-dithiin (**1a**) is obtained in 60% yield. This compound has previously been reported in a multistep synthesis which resulted in 10% yields[10] of **1a**. As an example of the formation of 2,3-disubstituted dithiins, 2-bromo-2-phenylacetophenone gives the corresponding 2,3-diphenyl-5,6-dihydro-1,4-dithiin (**1b**) in 50% yield.

The dihydrodithiins resulting from these reactions may be reduced to the dithianes[12] or oxidized to the dithiins[13] by established procedures.

Experimental Section

Micro analyses were carried out by Werby Laboratories, Boston, Massachusetts. Melting points are corrected. Nuclear

(1) W. E. Parham in "The Chemistry of Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press Ltd., London, 1966, p 248.
(2) R. G. Gillis and A. B. Lacey in "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley & Sons, New York, N. Y., 1963, p 396.
(3) W. Schroth and J. Peschel, *Z. Chem.*, **4** (7), 27 (1964).
(4) W. Draher, *Chem. Ber.*, **100** (5), 1559 (1967).
(5) Y. Hiroyoshi, *Chem. Pharm. Bull.* (Tokyo), **16** (3), 148 (1968); *Chem. Abstr.*, **69**, 20399 (1968).
(6) K. D. Gundermann and C. Burba, *Chem. Ber.*, **94**, 2157 (1961).
(7) B. Hirsch and H. Fink, *Angew. Chem.*, **74**, 28 (1962).
(8) R. H. Baker and C. Barkenbus, *J. Amer. Chem. Soc.*, **58**, 262 (1936).
(9) H. Szmant and L. M. Alfonso, *ibid.*, **79**, 205 (1957).
(10) A. Bottini and E. F. Böttner, *J. Org. Chem.*, **31**, 586 (1966).
(11) W. Schroth, B. Strekenbach, and B. Werner, *Z. Chem.*, **7** (4), 152 (1967).
(12) W. E. Parham, T. M. Roder, and W. R. Hasek, *J. Amer. Chem. Soc.*, **75**, 1647 (1953).
(13) S. Landa and A. Mrnkova, *Collection Czech. Chem. Commun.*, **31** (5), 2202 (1966); *Chem. Abstr.*, **65**, 545*h* (1966).

magnetic resonance spectra were determined on a Varian Model A-60 nmr spectrometer using tetramethylsilane as a standard.

Preparation of 5-Methyl-2,3-dihydro-1,4-dithiin (1a).—A 250-ml single neck flask fitted with a Dean–Stark trap and a magnetic stirrer was charged with 120 ml of benzene (sodium dried), 26.6 g (0.196 mol) of α-bromoacetone,[14] 18.3 g (0.195 mol) of 1,2-ethanedithiol and 0.044 g of purified *p*-toluenesulfonic acid. The resulting solution was stirred and refluxed for 3 hr, and 4.22 ml of water was collected in the trap. The reaction mixture was cooled and washed twice with 100 ml of 2 *N* sodium hydroxide and twice with 100 ml of water. The organic layer was concentrated and distilled, giving 13.7 g, bp 44–52° (0.5–0.7 mm), and 2.6 g, bp 70–94° (0.7–0.9 mm). The purity of these fractions was checked by glpc using a 6 ft Carbowax column; the first fraction was 98% 1a and the second fraction 72% 1a. A total yield of 60% 1a was obtained in this reaction (by glpc assay); this product showed the correct microanalysis, nmr, and infrared spectra for 1a as previously reported.[10]

Preparation of 4,5-Diphenyl-2,3-dihydro-1,4-dithiin (1b).—The above described apparatus was charged with 5.31 g (0.0194 mol) of 2-bromo-2-phenylacetophenone (Eastman), 2.48 g (0.0265 mol) of 1,2-ethanedithiol, 0.02 g of *p*-toluenesulfonic acid, and 120 ml of benzene (sodium dried). The resulting solution was refluxed for 54 hr, and 0.4 ml of water was collected. The reaction mixture was washed and concentrated as above, leaving a solid residue. This was recrystallized three times from methanol, giving a white solid: 2.66 g (50.6%), mp 101.9–102.2°. Examination of the nmr spectrum (CCl_4) showed a singlet at δ 7.05 (aromatic) and a singlet at δ 3.31 (aliphatic); the ratio of aliphatic to aromatic protons was 2:5.

Anal. Calcd for $C_{16}H_{14}S_2$: C, 71.1; H, 5.18; S, 23.7. Found: C, 71.30; H, 5.22; S, 23.73.

Registry No.—1a, 5769-49-3; 1b, 20273-71-6.

(14) P. A. Levene in "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley & Sons, New York, N. Y., 1963, p 88.

Synthesis of 2,5-Dihydrothiophenonium 2,4,6-Trinitrobenzenesulfonates from Butadienes and Methanesulfenyl 2,4,6-Trinitrobenzenesulfonates[1]

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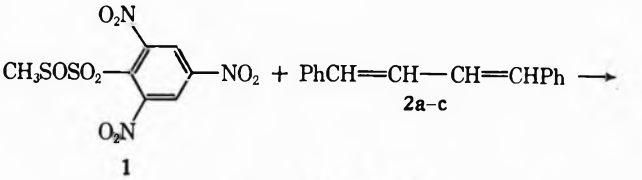
Received January 24, 1969

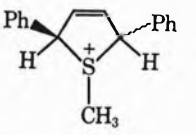
The reaction of a very limited variety of sulfenyl compounds with conjugated dienes has received recent attention, but the process has the potential of providing interesting results related to the problem of concerted cycloaddition. Mueller and Butler[4,5] studied the reaction of methanesulfenyl or benzenesulfenyl chloride with a number of conjugated dienes. Their findings showed that the additions occurred predominantly in a 1,2 manner. This was in contrast to the report of earlier workers[6] in which 1,4 addition was tentatively proposed to occur in the reaction of sulfenyl chlorides with cyclopentadiene or cyclooctatetraene.

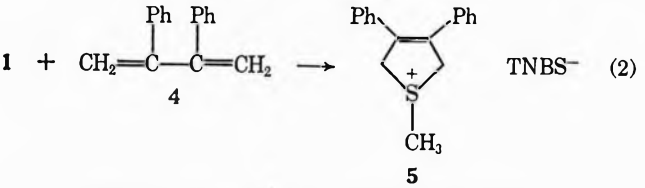
An alkanesulfenium ion (RS^+, or its alkanesulfenyl 2,4,6-trinitrobenzenesulfonate progenitor) can be compared to nitrenes and carbenes with regard to formation of three-membered rings from alkenes. With one exception, all of the reported examples of the reaction of conjugated dienes with carbenes[7] and nitrenes[8] proceed by formation of 1,2 adducts as primary reaction products. In that exceptional case[9] a concerted 1,4 cycloaddition of cyanonitrene to cyclooctatetraene was proposed on the basis of a time- and temperature-dependency study of the stability of the 1,2 adduct in the system.

As part of our continuing studies on the synthetic utility of methanesulfenyl 2,4,6-trinitrobenzenesulfonate[10,11] (**1**), some of the isomeric diphenylbutadienes have been used as substrates for this reagent. It was of interest to determine whether the products isolated from these reactions arose from a 1,4 cycloaddition in a concerted manner, a 1,2 addition, or a 1,2 addition followed by rearrangement to the 1,4 product.

The reaction of **1** with *trans,trans*- (**2a**), *cis,trans*- (**2b**), or *cis,cis*-1,4-diphenylbutadiene (**2c**) was found to yield the same product, namely 2,5-dihydro-2,5-diphenyl-S-methylthiophenonium 2,4,6-trinitrobenzenesulfonate (**3**) as shown in eq 1. The structure of **3** was assigned on the basis of its nmr spectrum and molecular weight (data are provided in the Experimental Section). The structural equivalence of **3** originating from the three different dienes was based on comparison of infrared and nmr spectra, on mixture melting points, and on constancy of these physical characteristics on repeated purification procedures.







TNBS⁻ = 2,4,6-trinitrobenzenesulfonate anion

The reaction of the same reagent (**1**) with 2,3-diphenylbutadiene (**4**, eq 2) yielded 2,5-dihydro-3,4-diphenyl-S-methylthiophenonium 2,4,6-trinitrobenzenesulfonate (**5**).

The stereochemistry of **3** has not been established unequivocally, although nmr data suggest that the

(1) This investigation was supported by the National Science Foundation under Grant No. GP-8594.

(2) Environmental Sciences Trainee, United States Public Health Service, 1967–1969.

(3) NSF–URP Summer Fellow, 1968 (Grant No. GY-3041).

(4) W. H. Mueller and P. E. Butler, *Chem. Commun.*, 646 (1966).

(5) W. H. Mueller and P. E. Butler, *J. Org. Chem.*, **33**, 2642 (1968).

(6) H. Brintzinger and H. Eilwanger, *Chem. Ber.*, **87**, 300 (1954).

(7) See, for example, W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964.

(8) For example of isolable, stable 1,2-adducts see: S. Massmune and N. T. Castellucci, *Angew. Chem.*, **76**, 569 (1964); K. Hafner, W. Kaiser, and R. Puttner, *Tetrahedron Lett.*, 3953 (1964).

(9) A. G. Anastassiou, *J. Amer. Chem. Soc.*, **90**, 1527 (1968).

(10) D. J. Pettitt and G. K. Helmkamp, *J. Org. Chem.*, **29**, 2702 (1964).

(11) G. K. Helmkamp, D. C. Owsley, W. M. Barnes, and H. N. Cassey, *J. Amer. Chem. Soc.*, **90**, 1635 (1968).

phenyl groups are *cis*, and the observation of constancy of product suggests thermodynamic control. If compound **3** contained *trans*-phenyl groups, the nmr spectrum might be expected to show nonequivalence of the hydrogen atoms at the 2 and 5 positions. Since the methynyl hydrogens appear as only one singlet[12] (at δ 6.07), it seems most likely that they are *cis*, for the S-methyl group would provide a different chemical environment for a *trans* pair. An unfavorable interaction between the S-methyl group and an adjacent phenyl group also leads to the tentative conclusion that a *cis*-diphenyl array is thermodynamically favored over the opposite configuration.

The production of the same product from each of the isomeric compounds **2a**, **2b**, and **2c** is inconsistent with a concerted 1,4 addition[13] of the methanesulfenyl group, CH_3S^+, to the diene. In such a reaction, **2b** should yield a product that is stereoisomeric with that obtained from either **2a** or **2c**. A concerted, stereospecific addition has been observed, for example, in the reaction of sulfur dioxide with 1,3-dienes.[14,15] Thus, the reaction of **1** with **2a**, **2b**, or **2c** probably proceeds *via* 1,2 addition followed by rearrangement, even though it has been impossible to detect any primary product under a variety of reaction conditions and with different isolation techniques. Our results show direct agreement with the conclusions of Mueller and Butler[4,5] that addition of sulfenyl compounds to conjugated dienes occurs in a 1,2 manner.

Experimental Section

Micoanalyses on the dihydrothiophene products were carried out by Elek Microanalytical Laboratories, Torrance, Calif., and Galbraith Laboratories, Knoxville, Tenn. All solvents were reagent grade and were dried over Linde 4A Molecular Sieves before use. **2a** was prepared by the method described by Fieser;[16] **2b** was prepared from the Wittig reaction of triphenylcinnamylphosphonium bromide with benzaldehyde;[17] and **2c** was prepared by catalytic hydrogenation of 1,4-diphenylbutadiyne as described by Lindlar.[18] The 2,3-diphenylbutadiene was prepared from acetophenone pinacol by the prodedure of Alder and Hayden.[19] All melting points are uncorrected.

2,5-Dihydro-2,5-diphenyl-S-methylthiophenonium 2,4,6-Trinitrobenzenesulfonate.—On the fritted disk of a modified Schlenk tube apparatus as previously described[11] was placed a solution of 5.23 g (0.01 mol) of silver 2,4,6-trinitrobenzenesulfonate (acetonitrile complex)[10] in 20 ml of dry nitromethane. Dry nitrogen was passed upward through the fritted disk to keep the reaction mixture blanketed with an inert atmosphere. A solution of 0.01 mol of methanesulfenyl bromide in 35 ml of dichloromethane (solution prepared *in situ* from bromine and dimethyl disulfide) was added to the silver salt solution, with immediate formation of a silver bromide precipitate. The solution was stirred for 30 min, then filtered free of silver bromide by forcing the mixture through the fritted disk with positive nitrogen pressure above and a partial vacuum below. The solution of methanesulfenyl 2,4,6-trinitrobenzenesulfonate was mixed with 2.06 g (0.01 mol) of one of the isomeric 1,4-diphenylbutadienes in 35 ml of dichloromethane. The color of the reaction mixture immediately turned a deep purple. The product was isolated by the addition of about 650 ml of anhydrous ether to the stirred solution. The precipitate was dissolved in acetone and crystallized from warm acetone–ether to yield crystals of the thiophenonium salt, mp 132–135.5° dec. The yields from the three isomers of 1,4-diphenylbutadiene were as follows: *trans,trans*, 49%; *cis,trans*, 15%; *cis,cis*, 29%.

Anal. Calcd for $C_{23}H_{19}N_3O_9S_2$: C, 50.64; H, 3.51; N, 7.70; S, 11.75; mol wt, 546. Found: C, 50.90; H, 3.72; N, 7.08; S, 11.37; mol wt, 565 (by vapor pressure osmometry).

The nmr spectrum of the product in perdeuteronitromethane showed peaks at δ 3.40 (singlet, three protons assigned to S-methyl); 6.07 (singlet, two methynyl protons); 6.59 (singlet, two vinyl protons); 7.45 (broad singlet, ten phenyl protons); and 8.50 (singlet, two protons from the anion).

2,5-Dihydro-3,4-diphenyl-S-methylthiophenonium 2,4,6-Trinitrobenzenesulfonate.—In a manner exactly analogous to that described above, 0.01 mol of methanesulfenyl 2,4,6-trinitrobenzenesulfonate and 0.01 mol of 2,3-diphenylbutadiene yielded 3.40 g of an amorphous solid that melted with decomposition at about 110°. The desired product could be isolated only with great difficulty from this mixture. After many recrystallizations from acetone–ether, 30 mg of an analytically consistent sample of 2,5-dihydro-3,4-diphenyl-S-methylthiophenonium 2,4,6-trinitrobenzenesulfonate was isolated: mp 230.5–231.5°.

Anal. Calcd for $C_{23}H_{19}N_3O_9S_2$: C, 50.64; H, 3.51; N, 7.70; S, 11.75. Found: C, 50.75; H, 3.48; N, 7.75; S, 11.81.

Registry No.—**3**, 20178-09-0; **5**, 20178-10-3.

(12) The absence of splitting between the methynyl protons and the adjacent vinyl protons can be accounted for by a dihedral angle that may be as large as 80° owing to ring distortion from phenyl–phenyl interaction.

(13) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

(14) W. L. Mock, *J. Amer. Chem. Soc.*, **88**, 2857 (1966).

(15) S. D. McGregor and D. M. Lemal, *ibid.*, **88**, 2858 (1966).

(16) L. F. Fieser, "Organic Experiments," 2nd ed, Raytheon Education Co., Lexington, Mass., 1968, pp 121–123.

(17) H. Misumi and M. Nakagawa, *Bull. Chem. Soc. Jap.*, **36**, 399 (1963).

(18) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(19) K. Alder and J. Hayden, *Ann.*, **570**, 201 (1950).

Concerning the Postulated Rearrangement of 4-Acyloxy- and 4-Aroyloxycoumarins to 5-Acyl- and 5-Aroyl-4-hydroxycoumarins

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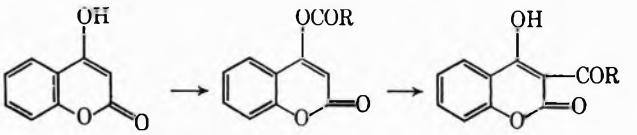
Received January 13, 1969

There have been a number of reports on the acylation of 4-hydroxycoumarin (**1**) with aliphatic and aromatic acid chlorides.[1–3] Eisenhauer and Link[2] studied the mechanism of the reaction of **1** with aliphatic acid chlorides in pyridine leading to 3-acyl-4-hydroxycoumarins (**3**), using acetyl chloride as representative of this class, and found that the initial product formed was 4-acetoxycoumarin (**2a**), which then rearranged to 3-acetyl-4-hydroxycoumarin (**3a**). These authors also investigated the reaction of **1** with various aromatic acid chlorides in pyridine and observed that the initially formed esters **4** did not rearrange to the corresponding 3-aroyl-4-hydroxycoumarins (**5**) as in the aliphatic series.[3] The ester **4a**, however, can be rearranged to 3-benzoyl-4-hydroxycoumarin (**5a**) with aluminum chloride.[4]



1 **2**, R = alkyl; **2a**, R = CH_3; **4**, R = aryl; **4a**, R = C_6H_5 **3**, R = alkyl; **3a**, R = CH_3; **5**, R = aryl; **5a**, R = C_6H_5

(1) T. Ukita, S. Nojima, and M. Matsumoto, *J. Amer. Chem. Soc.*, **72**, 5143 (1950).

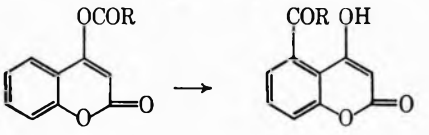
(2) H. R. Eisenhauer and K. P. Link, *ibid.*, **75**, 2044 (1953).

(3) H. R. Eisenhauer and K. P. Link, *ibid.*, **75**, 2046 (1953).

(4) K. Veres and V. Horak, *Coll. Czech. Chem. Commun.*, **20**, 371 (1955).

In view of these observations, the recent report of Woods[5] concerning the rearrangement of 4-acetoxycoumarin (**2a**) and various 4-aroyloxycoumarins (**4**) to 5-acetyl-4-hydroxycoumarin (**6a**) and the corresponding 5-aroyl-4-hydroxycoumarins (**7**) (Scheme I) was noted

SCHEME I

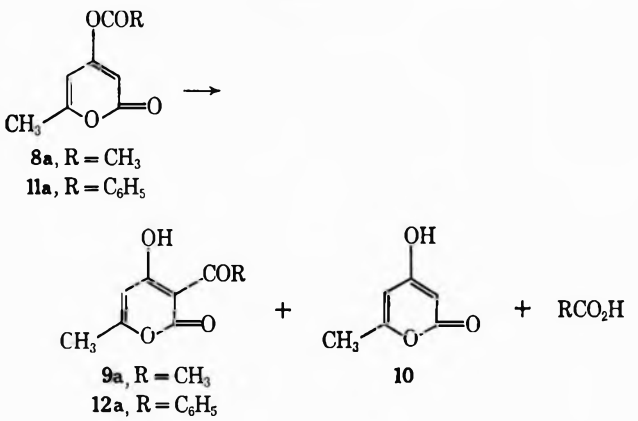


2a, R = CH_3
4, R = aryl

6a, R = CH_3
7, R = aryl

with considerable interest. However, these results were surprising, not only because of the unprecedented course of the rearrangements involved, but also because recent studies[6] in these laboratories have shown that the related 4-acetoxy-6-methyl-2-pyrone (**8a**) rearranges to dehydroacetic acid (**9a**) with some degradation to triacetic acid lactone (**10**) in refluxing trifluoroacetic acid (Scheme II). 4-Benzoyloxy-6-methyl-2-pyrone (**11a**), on the other hand, is rearranged only with difficulty[6] to 3-benzoyl-4-hydroxy-6-methyl-2-pyrone (**12a**) and suffers considerable degradation to **10** and benzoic acid, under similar conditions. It would be supposed *a*

SCHEME II



8a, R = CH_3
11a, R = C_6H_5

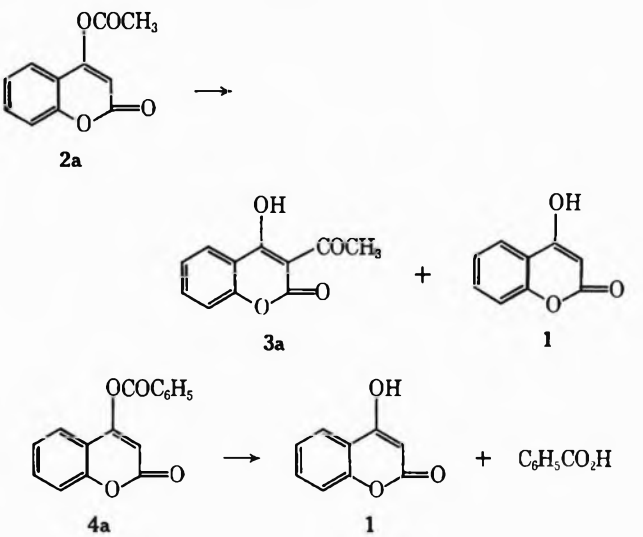
9a, R = CH_3
12a, R = C_6H_5

10

priori that analogous rearrangements would occur with 4-acetoxycoumarin (**2a**) and 4-benzoyloxycoumarin (**4a**) in trifluoroacetic acid. We wish to report at this time our observations concerning the fate of **2a** and **4a** upon treatment with trifluoroacetic acid.

4-Acetoxycoumarin (**2a**) was treated with trifluoroacetic acid under reflux for 15.5 hr. Thin layer chromatography of the product mixture showed the presence of 4-hydroxycoumarin (**1**), 3-acetyl-4-hydroxycoumarin (**3a**), as well as unchanged **2a** (Scheme III). Nmr analysis (DMF-d_6) indicated that the mixture contained about 46 mol % of **1**, 43 mol % of **3a**, and 11 mol % of **2a**. Compounds **1** and **3a** were separated from unchanged **2a** by extraction into aqueous sodium carbonate. 3-Acetyl-4-hydroxycoumarin (**3a**) was isolated in 29% yield by acidification of the carbonate extract followed by fractional crystallization of the resulting solid from ethanol. 4-Hydroxycoumarin (**1**) was obtained in 40% yield[7] by evaporation of the ethanol mother liquor from the above crystallization, followed by recrystallization from water. The structures of **3a** and **1** were confirmed by comparison of their ir and nmr spectra and mixture melting point determinations with authentic **3a** and **1**, respectively. Structure **3a** was further substantiated when **3a** was converted into 2-methylchromone (**13**) upon refluxing with concentrated hydrochloric acid in ethanol solution.[8] No formation of 5-acetyl-4-hydroxycoumarin (**6a**) was observed in this reaction.

SCHEME III



Treatment of 4-benzoyloxycoumarin (**4a**) with trifluoroacetic acid under reflux for 15 2/3 hr gave a mixture, thin layer chromatography of which indicated the presence of **1**, benzoic acid, and unchanged **4a**. Nmr analysis (DMF-d_6) showed that the mixture contained about 45 mol % of **1**, 31 mol % of benzoic acid, and 24 mol % of **4a**. The product mixture was easily separated from **4a** by extraction into aqueous sodium bicarbonate followed by acidification. 4-Hydroxycoumarin (**1**) and benzoic acid were then isolated in 48 and 26% yields, respectively, by fractional crystallization from water. The identity of these products was established by comparison of their respective ir and nmr spectra and mixture melting point determinations with authentic samples of **1** and benzoic acid. No rearrangement product, **5a** or **7a**, was detected in this reaction.

As mentioned above, in neither the reaction of 4-acetoxycoumarin (**2a**) nor the reaction of 4-benzoyloxycoumarin (**4a**) with trifluoroacetic acid did we detect the previously reported[5] rearrangement products, **6a** and **7a**, respectively. The reason for these differing results is not apparent to us.

(5) L. L. Woods and M. Fooladi, *J. Org. Chem.*, **33**, 2966 (1968).

(6) E. Marcus, J. F. Stephen, and J. K. Chan, *J. Heterocycl. Chem.*, **6**, 13 (1969).

(7) Such a high yield of 4-hydroxycoumarin (**1**) cannot be accounted for by hydrolysis of ester **2a** by traces of water in the solvent. The mechanism for the formation of **1** is uncertain. 4-Hydroxycoumarin could conceivably be formed by direct hydrolysis of **2a** with trifluoroacetic acid or by acidolysis and subsequent hydrolysis of the formed trifluoroacetic acid ester during work-up.

(8) C. Mentzer, J. Chopin, and M. Mercier, *C. R. Acad. Sci.*, (*Paris*), **242**, 1034 (1956).

Experimental Section[9]

4-Acetoxycoumarin (2a) was prepared from 1 and acetic anhydride in 10% aqueous sodium hydroxide as outlined by Eisenhauer and Link.[2] 4-Benzoyloxycoumarin (4a) was obtained from 1 and benzoyl chloride in pyridine.[3]

Treatment of 4-Acetoxycoumarin (2a) with Trifluoroacetic Acid.—A solution of 2a (20 g, 0.098 mol) in 60 ml of trifluoroacetic acid was refluxed for 15.5 hr and then poured into 400 ml of water. The mixture was chilled in ice for several hours, and the precipitated solid of 17.5 g, mp 76–184°, was collected by filtration. Tlc of this material with benzene–ethanol (3:2) indicated the presence of 1, 3a, and some unchanged starting material. The solid was extracted with three 100-ml portions of 5% aqueous Na_2CO_3; the insoluble portion was crystallized from ethanol to give 1.33 g of 2a, whose melting point and mixture melting point with authentic 2a was 111–112°. The carbonate extract was acidified with concentrated hydrochloric acid, and the solid of 14.0 g, mp 130–185°, which precipitated was filtered off. Recrystallization from *ca.* 75 ml of ethanol afforded 5.18 g of 3a, mp 137–138°. The ethanol mother liquor was chilled in ice to give a second crop of material, which upon recrystallization from ethanol furnished an additional 0.53 g of 3a, mp 137–138°. The combined yield of 3a (5.71 g) was 28.6%; ir (KBr) 3.25 (aromatic CH), 3.4 (CH_3), 4.0 (broad, weak, chelated OH), 5.8 (lactone C=O), 6.23 (chelated acetyl C=O and C=C), 6.5 and 6.68 (aromatic C=C), 7.34 (CH_3CO), 8.55 (lactone C—O), 9.66, 10.24, 11.14, and 13.1 μ (4 adjacent aromatic hydrogens); nmr ($CDCl_3$) δ 2.73 (s, 3, $COCH_3$), 7.51 (complex m, 2, H-6 and H-8), 7.64 (t split into d, 1, H-7), 7.96 (d split into d, 1, H-5), and 17.60 (broad s, 1, intramolecularly chelated OH).

Anal. Calcd for $C_{11}H_8O_4$: C, 64.70; H, 3.95. Found: C, 64.71; H, 4.00.

The ethanol mother liquors from the above crystallizations were combined and the ethanol was evaporated under reduced pressure. Recrystallization of the residue thus obtained from water furnished 6.31 g (39.7%) of 1, mp 210–212°. The mixture melting point with authentic 1 was not depressed.

Conversion of 3-Acetyl-4-hydroxycoumarin (3a) into 2-Methylchromone (13).—A mixture of 3-acetyl-4-hydroxycoumarin (3a) (3 g, 0.0245 mol), 150 ml of concentrated hydrochloric acid, and 90 ml of ethanol was heated under reflux for 67 hr. The ethanol and most of the hydrochloric acid were removed under reduced pressure. The pH of the solution was adjusted to 7 by adding 30% sodium hydroxide solution, and the oil which separated was extracted with ether. The ether extract was washed with 5% sodium bicarbonate solution; the ether layer was dried ($MgSO_4$), and after evaporation *in vacuo*, a solid residue was obtained. Recrystallization from hexane gave 1.1 g (47%) of 2-methylchromone, mp 70–71°. This material was identical with authentic 2-methylchromone prepared from *o*-hydroxybenzoylacetone as described by Badcock, *et al.*[10]

Treatment of 4-Benzoyloxycoumarin (4a) with Trifluoroacetic acid.—A solution of 4a (10 g, 0.038 mol) in 30 ml of trifluoroacetic acid was heated under reflux for 15 $^2/_3$ hr and then poured into 200 ml of water. After chilling in ice for several hours, the mixture was filtered to give 10.0 g of a solid, mp 74–184°, which according to tlc (with benzene–ethanol 3:2) contained 1, benzoic acid, and unchanged 4a. This solid was extracted with two 100-ml portions of 5% aqueous sodium bicarbonate; the insoluble solid was recrystallized from ethanol to afford 3.07 g of 4a, whose melting point and mixture melting point with authentic 4a was 125–127°. The bicarbonate solution was acidified with concentrated hydrochloric acid, and the precipitated solid was filtered off and recrystallized from water to give 2.93 g (48.1%) of 1, mp 210–213°. A mixture melting point with authentic 1 was not depressed. Evaporation of the aqueous mother liquor to small volume under reduced pressure furnished 1.2 g (26.2%) of benzoic acid, mp 118–120°. Recrystallization from water followed by sublimation *in vacuo* raised the melting point to 121–122°. No depression in melting point was observed on admixture with authentic benzoic acid. The materials were spectrally identical.

Registry No.—2a, 15059-36-6; 3a, 2555-37-5; 4a, 16709-58-3; trifluoroacetic acid, 76-05-1.

(9) Melting points are uncorrected. Ir spectra were determined with a Baird-Atomic 4-55 spectrometer using potassium bromide pellets of the compounds. Nmr spectra were obtained with a Varian HA-100 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed by Union Carbide Corporation, Analytical Department, South Charleston, West Virginia. Fluorescent silica gel (Eastman Chromatogram Sheet type K 301 R) was used for tlc. Visualization of spots was accomplished with uv light.

(10) G. G. Badcock, F. M. Dean, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 903 (1950).

Silicon Tetrachloride as a Coupling Reagent for Amide Formation

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Received January 22, 1969

Even though silicon tetrachloride is known to react vigorously with water[3] and the silicon–oxygen–silicon bond is extremely stable thermodynamically as exemplified by silica and the silicones,[4] the use of halosilanes as dehydrating agents for organic synthesis has not been fully explored.[5,6]

We report the use of silicon tetrachloride in pyridine as a coupling reagent for the formation of an amide from a carboxylic acid and an amine.[7] Thus, to a solution of 2.5 g (0.04 mole) of acetic acid and 3.8 g (0.04 mol) of aniline in 50 ml of pyridine, 4.0 g (0.023 mol) of silicon tetrachloride was added. A white precipitate was formed instantaneously. The mixture was stirred at room temperature for 10 hr, and was poured onto crushed ice. The acetanilide was obtained in 60% yield after recrystallization from water. Under these conditions, aromatic amines reacted with both aliphatic and aromatic acids to give good to moderate yields of amides. Aliphatic amines, however, gave only poor yields of amides at room temperature. The yield could be substantially improved by raising the reaction temperature to reflux (Table I).

This method of effecting the formation of a carbon–nitrogen bond appears to be simple and efficient. It offers the advantage that the other product of this

(1) To whom inquiries should be addressed.

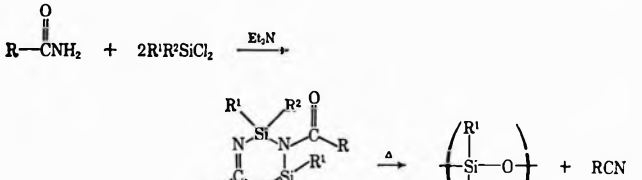
(2) Holder of National Research Council Studentship, 1968–1969.

(3) See for example, R. J. H. Voorhoeve, "Organohalosilanes," Elsevier Publishing Co., Amsterdam, 1967.

(4) See for example, E. G. Rochow, "An Introduction to the Chemistry of the Silicones," John Wiley & Sons, New York, N. Y., 1946; and also, G. Fritz, *Angew. Chem. Intern. Ed. Engl.*, **7**, 1 (1968).

(5) The use of silanes for organic reactions has been reviewed by R. Calas, *Pure Appl. Chem.*, **18**, 61 (1966).

(6) J. F. Klebe [*J. Amer. Chem. Soc.*, **90**, 5346 (1968)] reported the reaction of acetamide or benzamide with dichlorosilanes and found that nitrile was eliminated on heating



(7) For a summary of reagents for amide formation, see J. P. Greenstein and M. Winitz, "The Chemistry of the Amino Acids," Vol. 2, John Wiley & Sons, New York, 1961.

TABLE I
AMIDE FORMATION FROM CARBOXYLIC ACID AND AMINE WITH SILICON TETRACHLORIDE–PYRIDINE AS COUPLING REAGENT

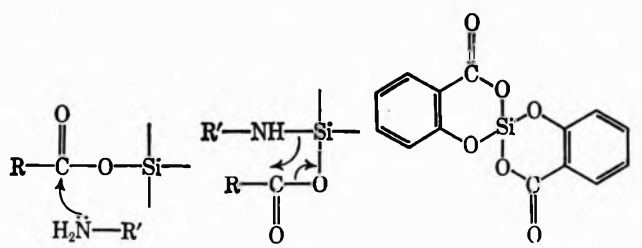
Acid	Amine	Conditions	Product (yield,[a] %)
Acetic	Aniline	R.t., 10 hr	Acetanilide (60)
Stearic	Aniline	R.t., 10 hr	Stearanilide (70)
Benzoic	Aniline	Reflux, 1 hr	Benzanilide (70)
p-Toluic	Aniline	R.t., 10 hr	*p*-Toluanilide (40)
p-Toluic	Aniline	Reflux, 1 hr	*p*-Toluanilide (70)
p-Hydroxybenzoic	Aniline	Reflux, 1 hr	*p*-Hydroxybenzanilide (50)
Salicylic	Aniline	Reflux, 1 hr	<1%[b]
Benzoic	Cyclohexylamine	R.t., 10 hr	N-Cyclohexylbenzamide, (25)
Benzoic	Cyclohexylamine	Reflux, 1 hr	N-Cyclohexylbenzamide (90)
Benzoic	*t*-Butylamine	Reflux, 1 hr	N-*t*-Butylbenzamide (65)
Benzoic	2,4,6-Mesidine	Reflux, 1 hr	N-2,4,6-Trimethylphenylbenzamide (80)
Acetic	N-Methylaniline	Reflux, 1 hr, N_2	N-Methylacetanilide (75)

[a] Isolated yield. [b] Salicylic acid was recovered quantitatively.

reaction is silica, which is insoluble in all common solvents, and thereby avoids the problem of contamination by side product.[8]

$$2RCO_2H + 2R'NH_2 + SiCl_4 \longrightarrow 2RCONHR' + (SiO_2)_n + HCl$$

Some comments can be made about the mechanism of this reaction. Both carboxylic acids[9] and amines[10] are known to displace chlorine from chlorosilanes to form the acyloxy- or aminosilanes. Two modes of condensation can be postulated to take place. One involves a nucleophilic attack by amine on what may be considered as a mixed anhydride (A). The other involves an intramolecular four-centered reaction (B). At present, we favor the latter mode of reaction. This is based on the observation that *p*-hydroxybenzoic acid reacted with aniline to give the anilide, whereas under identical conditions, salicyclic acid was recovered after hydrolysis.[11] Salicyclic acid forms a stable chelate with silicon (C)[12] and thus prevents the formation of B.



A B C

Experimental Section

Example A. Acetanilide.—To a solution of acetic acid (2.5 g) and aniline (3.8 g) in anhydrous pyridine (50 ml), silicon tetrachloride (4.0 g) was introduced. The mixture was stirred at room temperature for ten hours and was poured onto crushed ice. The precipitate was filtered and the filtrate was concentrated to yield 3.3 g of crystalline acetanilide, mp 113°.

Example B. N-*t*-Butylbenzamide.—To a solution of benzoic acid (1.0 g) and *t*-butylamine (0.60 g) in anhydrous pyridine (30 ml), silicon tetrachloride (1.0 g) was introduced. The mixture was refluxed for one hour, and was poured onto crushed ice. The precipitate was filtered and triturated with hot ethanol. The ethanol solution was concentrated to yield 0.90 g of N-*t*-butylbenzamide, mp 134–136°.

Registry No.—Silicon tetrachloride, 10026-04-7.

Acknowledgment.—We gratefully acknowledge financial support from the National Research Council of Canada.

(8) For example, the well-known coupling reagent dicyclochexylcarbodiimide sometimes gives acylurea as a side product which is difficult to separate.

(9) R. C. Mehrotra, *Pure Appl. Chem.*, **13**, 111 (1966).

(10) R. O. Sauer and R. H. Hasek, *J. Amer. Chem. Soc.*, **68**, 241 (1946).

(11) This differs from phosphonitrilic chloride, which activated salicyclic acid to form amide: L. Caglioti, M. Poloni and G. Rosini, *J. Org. Chem.*, **33**, 2979 (1968).

(12) R. C. Mehrotra and B. C. Pant, *J. Indian Chem. Soc.*, **40**, 623 (1963).

Perchloric Acid Catalyzed Acylations. Occurrence of Carbon Acylation in Enol Lactones[1]

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We have published earlier a versatile procedure for preparing the enol lactones and enol acetates using a reagent composed of acetic anhydride and perchloric acid in ethyl acetate.[3,4] After detailed experimentation with reaction times and reagent composition, we have established that a 5-min reaction at room temperature with a reagent composed of 1 *M* acetic anhydride and 10^{-3} *M* perchloric acid in ethyl acetate converts a δ-keto acid such as 17β-hydroxy-4-nor-5-oxo-3,5-seco-3-andro-

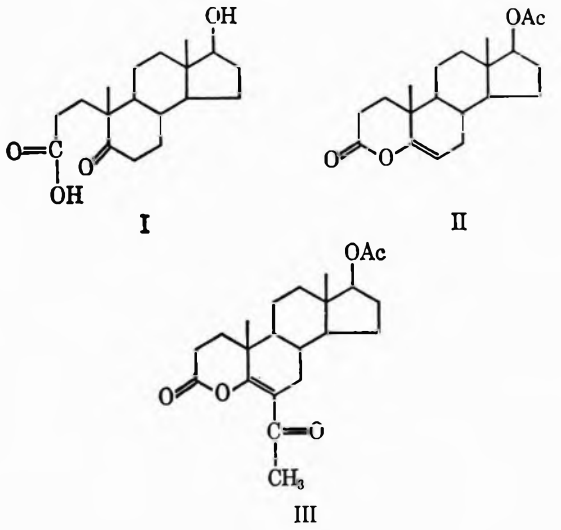
(1) This work was supported by Grant No. AM-03270, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

(2) (a) To whom all correspondence should be addressed. (b) Taken from the M.S. Thesis submitted by J. E. B. to St. Mary's University, San Antonio, Tex., May 1968.

(3) (a) P. Narasimha Rao and L. R. Axelrod, *Chem. Ind.* (London), 1838, (1963); (b) P. Narasimha Rao and L. R. Axelrod, *J. Chem. Soc.*, 1356 (1965).

(4) B. E. Edwards and P. Narasimha Rao, *J. Org. Chem.*, **31**, 324 (1966).

stanoic acid (I) to the corresponding 17β-acetoxy-3,5-enol lactone (II) in essentially quantitative yield with-



out formation of other side products.[4] However, with increase in reaction time or concentration of perchloric acid, or both, a second reaction product was obtained as the major product in addition to the enol lactone II. Accordingly, when the keto acid (I) was treated with a reagent consisting of 2 *M* acetic anhydride and 0.15 *M* perchloric acid in ethyl acetate for one hour at room temperature, a second product of mp 190.5–191.5° was obtained. This reaction product was identified as 17β-acetoxy-6-acetyl-5-hydroxy-3,5-seco-4-norandrost-5-en-3-oic acid 3,5-lactone (III) on the basis of analytical and other spectral data. Compound III analyzed for $C_{22}H_{30}O_5$ and had a molecular weight of 374 as determined by mass spectrum[5] (molecular ion peak at *m/e* 374). The infrared spectrum demonstrated enol lactone (1755 cm^{-1}), 17β-acetate (1725 and 1265 cm^{-1}) and conjugated carbonyl (1677 cm^{-1}) bands. The ultraviolet absorption spectrum showed an absorption maximum at 252 mμ (ε 9874) and is in good agreement with the calculated value[6] of 254 mμ. The nmr spectrum of compound III ($CDCl_3$, TMS) showed peaks at δ 0.85 (C-18 methyl), 1.22 (C-19 methyl), 2.06 (17β-acetate), and 2.51 (conjugated C-6 acetyl) ppm.

The possibility of the acetyl group being in the A ring was ruled out by mass spectral data. The major fragmentation pattern of both III and the enol lactone II showed the loss of C_3H_4O (56 mass units) as the first fragmentation product. If the acetyl group had been located in ring A, the fragmentation pattern would have been different since the C_3H_4O fragment was due to the loss of carbons 1, 2, and 3 of the lactone.

That the lactone II was the intermediate in the formation of III was shown by treatment of the lactone II with the perchloric acid reagent and isolation of the 6-acetyl product III in excellent yield.

Recently, Liston and Toft[7] have also observed a similar carbon acylation of enol acetates with perchloric acid and acetic anhydride.

(5) The mass spectrum was recorded on Model MS9 instrument of Associated Electrical Industries, Manchester, England.

(6) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 19.

(7) A. J. Liston and P. Toft, *J. Org. Chem.*, **33**, 3109 (1968).

Experimental Section[8]

Perchloric Acid Reagent.—To absolute ethyl acetate (30 ml) was added 72% perchloric acid (0.75 ml) and acetic anhydride (9.6 ml), and the solution was made up to 50 ml with ethyl acetate.

17β-Acetoxy-6-acetyl-5-hydroxy-3,5-seco-4-norandrost-5-en-3-oic acid 3,5-Lactone (III).—A sample of the keto acid (I, 200 mg) was treated with perchloric acid reagent (20 ml) for 1 hr at room temperature. The reaction mixture was then washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated to dryness. The total crude material was then chromatographed on silica gel to give compound III (114 mg). The analytical sample was crystallized from acetone–hexane: mp 190.5–191.5°, ν_{max}^{KBr} 1755, 1725, 1677 and 1265 cm^{-1}, $\delta_{TMS}^{CDCl_3}$ 0.85, 1.22, 2.06 and 2.51 ppm, λ_{max}^{MeOH} 252 mμ (ε 9,874).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.47; H, 8.08.

17β-Acetoxy-6-acetyl-5-hydroxy-3,5-seco-4-norandrost-5-en-3-oic acid 3,5-Lactone (III) from II.—A sample of the lactone II (31 mg) was treated with perchloric acid reagent (3 ml) for 40 min at room temperature. The crude product obtained after the usual work-up was chromatographed on silica gel to give compound III (27 mg), mp 190.5–191.5°, which was found to be identical in all respects with the authentic sample obtained earlier.

Registry No.—Perchloric acid, 7601-90-3; III, 20104-38-5.

Acknowledgment.—We wish to thank Dr. Walter J. McMurray of Yale University, School of Medicine, for determining the mass spectrum, and Dr. David Buss of our department for stimulating discussions.

(8) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60A spectrometer using TMS as internal standard. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer. Ultraviolet absorption spectra were determined with a Cary recording spectrophotometer (Model 11 MS). Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

The Acetolyses of Certain 3,5-Disubstituted 6-Oxo-5β-cholestanes[1a]

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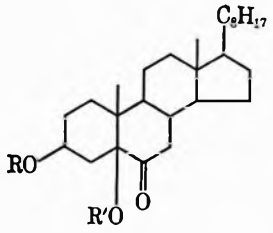
When 3β-tosyloxy-5-hydroxy-5β-cholestan-6-one (**1d**) was solvolyzed in anhydrous ethanol, methanol, or dimethyl sulfoxide, the major product was 3β,5-epoxy-5β-cholestan-6-one (**3**).[2] The formation of the oxetane ring from *cis* functional groups is unusual. Furthermore, we have found that the C-3 epimer (**2d**) of **1d** is recovered unchanged when heated under reflux for 19.5 hr in ethanol.[3] The usual stereochemical considerations lead to the conclusion that **2d** and *not* **1d** would be more likely to undergo oxetane ring formation. We have attempted to determine if some type of participation by hydroxyl occurs in the conversion **1d** → **3** by

(1) (a) This work was supported by National Science Foundation Undergraduate Research Participation Grants GE-2760 and GE-9534; (b) NSF-URP, 1964-1965; (c) NSF-URP, Summer, 1965.

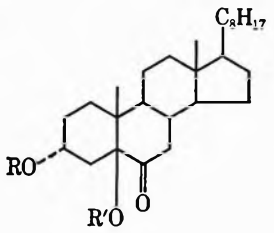
(2) A. T. Rowland, *Steroids*, **7**, 527 (1966).

(3) Unpublished observation in this laboratory.

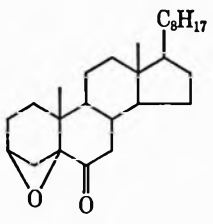
studying the kinetics and product compositions of the acetolyses of **1d**, **2d**, and their C-5 acetates **1e** and **2e**.



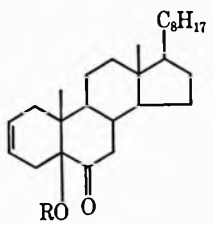
1a, R = R′ = H
b, R = Ac; R′ = H
c, R = R′ = Ac
d, R = Ts; R′ = H
e, R = Ts; R′ = Ac



2a, R = R′ = H
b, R = Ac; R′ = H
c, R = R′ = Ac
d, R = Ts; R′ = H
e, R = Ts; R′ = Ac

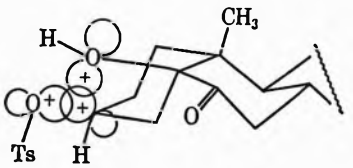


3



4a, R = H
b, R = Ac

The first-order rate constants for the acetolyses are listed in Table I. Since neighboring group participation reactions are often reflected in rate enhancements,[4] the rate ratio of 19:1 of **1d**:**2d** in buffered solution at 70° is instructive. Since the ratios for epimeric axial and equatorial tosylates are normally 2–6:1 in saturated cyclohexanes,[5] the larger ratio found here is probably due in part to the size of the C-5 axial hydroxy group, which provides some steric acceleration in the solvolysis of **1d**. Nishida has shown that an axial tosylate subjected to 1,3 diaxial interactions with a hydrogen atom and a methyl group undergoes acetolysis ten times faster than its equatorial isomer.[6] On the basis of the comparative sizes of the methyl and hydroxy groups, the rate ratio for **1d**:**2d** is probably due to a modest amount of steric acceleration in **1d** by the C-5 hydroxyl accompanied by partial bond formation in the transition state by the free p electrons on the oxygen atom



Partial bonding from the oxygen to C-3 before significant carbonium ion character at C-3 is developed is necessary to explain the facile formation of **3** in lieu of products of inversion in unbuffered acetic acid (see Table II). In solutions containing acetate ion or water the amount of **3** decreases while products of inversion and elimination increase. These results are in accord with partial bonding to C-3 of the C-5 oxygen during ionization of **1d**. Acetolysis of **2d** in buffered solution yielded products typical of those from equatorial steroid tosylates, and therefore shows no participation by the *trans* C-5 hydroxy group. In unbuffered acetic acid, **2d** gave the 3,5-diacetates **1c** and **2c** in poor yield (see Table II). In this case, **2c** (a product of retention) was probably produced by acetolysis of **2e** which was formed *in situ* from the acetylation of **2d** under *p*-toluenesulfonic acid catalysis.

TABLE I
RATE DATA FROM ACETOLYSES OF THE TOSYLATES

Tosylate	Temp, °C[a]	Equiv of added solute	$k_1 \times 10^4$, min^{-1}
1d	60	...	0.73 ± 0.02
	70	...	2.40 ± 0.08
	70	1 NaOAc	2.70 ± 0.04
	70	2 NaOAc	2.80 ± 0.13
	70	1 *p*-TsOH	2.49 ± 0.03
	70	1 $LiClO_4$	*b*
	70	1 Ac_2O	2.52
	70	3 Ac_2O	2.52
	70	1 $HClO_4$	*b*
	80	...	7.10 ± 0.03
1e	70	1 NaOAc	6.06 ± 0.19
	80	...	*b*
	80	1 NaOAc	18.1 ± 0.5
	80	2 NaOAc	18.8
2d	70	1 NaOAc	0.14 ± 0.01
	80	...	*b*
	80	1 NaOAc	0.48 ± 0.03
	80	2 NaOAc	0.49 ± 0.02
2e	60	...	5.43 ± 0.07
	70	...	16.9 ± 0.3
	70	1 NaOAc	17.5 ± 0.3
	70	2 NaOAc	17.3 ± 0.3
	80	...	48.8 ± 0.6

[a] ±0.05°. [b] Darkening of reaction mixture precluded accurate rate measurement.

The activation parameters for the acetolyses of **1d**, **2d**, and the corresponding acetates (**1e** and **2e**) are given in Table III. The values obtained are typical of saturated steroid tosylate acetolyses[6] and are consistent with rate-determining ionization reactions.

In contrast to the rates found for the acetolyses of the hydroxy tosylates **1d** and **2d**, the acetate derivative (**2e**) of the equatorial tosylate **2d** undergoes acetolysis 125 times faster than **2d** and *ca.* 3 times faster than its axial epimer **1e** at 70°. Tosylate **2e** therefore undergoes solvolysis with participation of the C-5 acetoxy group, probably through an acetoxonium ion.[7] As seen in Table II, the major product produced from the acetolysis of **1e** is 3β,5-diacetoxy-5β-cholestan-6-one (**1c**) resulting from retention of configuration at C-3 while the equatorial tosylate **2e** gives a significant amount of diacetate **1c** (product of inversion) along with the diacetate **2c** (product of retention of configuration at C-3). The difference in product composition from the acetoxy tosylate **1e** and **2e** rules out the possibility of a common intermediate and renders a firm explanation for the observed behaviors difficult. A possible rationale may lie in the formation of an acetoxonium ion during the solvolysis of **2e** followed by reaction with acetic acid by a pathway similar to that proposed for the acetolysis of *cis*-2-tosyloxymethylcyclohexyl acetate.[7] In the latter case, a mixture of *cis* and *trans* diacetates was formed with 80% retention. On the other hand, the acetoxy

(4) H. W. Heine, A. D. Miller, W. H. Barton, and R. W. Greiner, *J. Amer. Chem. Soc.*, **75**, 4778 (1953).
(5) C. W. Shoppee and G. A. R. Johnston, *J. Chem. Soc.*, 3261 (1961).
(6) S. Nishida, *J. Amer. Chem. Soc.*, **82**, 4290 (1960).
(7) Ö. K. J. Kovács, Gy. Schneider, L. K. Láng, and J. Apjok, *Tetrahedron Lett.*, **23**, 4181 (1967).

TABLE II

PRODUCT DISTRIBUTION FROM ACETOLYSES OF THE TOSYLATES[a]

Tosylate	Solvent	Added NaOAc, equiv	Reaction time, hr	% product 3	4a	2b	1b	2a	2c	1c
1d	HOAc	...	7	54	7	...	...	...	16	11
	HOAc	1.06	7	40	13	28	...	...	...	...
	HOAc	11.3	7	37.5	15	18	...	16	...	...
	HOAc–H_2O (5/1, v/v)	...	6	2.7	14	48	...	26	...	...
1e	HOAc[b]	...	4	...	10[c]	...	...	...	~4	~64
	HOAc	1.03	15	3.8	2.6[c]	...	...	...	7.3	70.5
2d	HOAc[b]	...	6.2	...	...	...	...	...	16.5	13.5
	HOAc	1.06	42.5	...	40	...	44.5	...	...	...
2e	HOAc[b]	...	2.1	...	18.5[c]	...	...	...	48	19.5
	HOAc	1.02	2.25	...	3.8[c]	...	...	...	51	34

[a] Acetolyses carried out at 92 ± 4° for indicated times. [b] All yields from the unbuffered reaction low because of side reactions of products. [c] As its acetate 4b.

TABLE III

ACTIVATION PARAMETERS OF THE TOSYLATE ACETOLYSES

Tosylate	E_a, kcal/mole	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, eu
1d	26.8	26.1	−2.9
1e	26.3	25.6	−2.6
2d	29.6	28.9	−0.3
2e	25.6	24.9	−2.5

group in tosylate 1e may serve only to hold the configuration of the incipient carbonium ion at C-3 without formation of a true acetoxonium ion, thus permitting attack from the β side of the molecule by a molecule of acetic acid, resulting in the production of mainly the *cis* diacetate 1c.

Experimental Section[8]

Kinetic Procedures.—Reaction rates in anhydrous acetic acid were determined titrimetrically according to a reported procedure.[9]

Steroids.—With the exception of the three compounds discussed below, all steroids have been previously reported from this laboratory.[10]

3α,5-Diacetoxy-5β-cholestan-6-one (2c).—A solution of 562 mg (1.34 mmol) of the 3α,5β-diol-6-one 2a and 129 mg of *p*-toluenesulfonic acid monohydrate in 5 ml of glacial acetic acid and 5 ml of acetic anhydride was allowed to remain at room temperature for 21.5 hr. The customary work-up[11] gave a crystalline precipitate which was dissolved in methanol and filtered. Partial removal of the solvent by an air steam caused the deposition of needles, one of which was used to seed the further concentrated solution (crystallization did not occur without seeding), resulting in the precipitation of 555 mg (82%) of diacetate 2c as white needles with mp 108–110°; $[\alpha]_D$ −41° (*c* 1.095); ir (CCl_4) 1748 (s, with strong shoulders at higher frequency and at 1730), 1229 (s, br absorption with strong shoulder at higher frequency) cm^{-1}; uv max (absolute EtOH) 292 mμ (ε 53).

Anal. Calcd for $C_{31}H_{50}O_5$ (502.71): C, 74.06; H, 10.02. Found: C, 74.05, 74.10; H, 9.80, 10.00.

5-Hydroxy-5β-cholest-2-en-6-one (4a).—This material was tentatively, but incorrectly, identified previously as the isomeric 3-ene.[2] Nmr analysis (60 MHz, CCl_4) of 4a exhibited vinyl hydrogens absorptions at C-2 and C-3 as a two-proton doublet centered at 337.5 Hz ($W_{1/2}$ = 4.5 Hz). Under increased amplification, two small satellite peaks were observed at 325 and 351 Hz. The nature and frequency of the vinyl hydrogen absorptions are strikingly similar to those of 5α-cholest-2-ene but much different from those in 5α-cholest-3-ene.[12] Also, the spectrum of 5-hydroxy-5β-cholest-3-ene[13] showed a two-proton absorption of the C-3 and C-4 hydrogens as four small peaks at 314.5, 325, 334, and 344.5 Hz in marked contrast to the vinyl hydrogens in 4a. On the basis of these nmr data, compound 4a must be the 2-ene.

The acetate 4b was prepared as follows. A suspension of 471 mg (1.18 mmol) of 4a and 44 mg of *p*-toluenesulfonic acid monohydrate in 15 ml of acetic anhydride was heated on the steam bath for 35 min. The resulting solution was cooled and diluted with ice and a little 2 *N* hydrochloric acid. The white needles that separated were collected and recrystallized from aqueous methanol, yielding 400 mg (77%) of 5-acetoxy-5β-cholest-2-en-6-one (4b) with mp 116–118.5°. A further recrystallization from methanol gave mp 119.5–121°; $[\alpha]_D$ −18° (c 1.01), −20° (c 1.00); ir (CCl_4) 1754 (s), 1730 (s), 1233 (s, with strong shoulder at lower frequency) cm^{-1}.

Anal. Calcd for $C_{29}H_{46}O_3$ (442.66): C, 78.68; H, 10.47. Found: C, 78.95; H, 10.31.

Solvolyses.—Acetolysis reactions were conducted with *ca.* 2×10^{-2} *M* tosylate solutions at 92 ± 4°. Standard isolation techniques were employed. Separation of products was accomplished by column chromatography and identification was made by tlc and/or ir analysis and by comparison of the crystallized materials with authentic samples. In those cases where similar adsorptivity on the column precluded separation, the entire mixture was subjected to a derivative forming reaction. Two representative solvolyses are as follows.

Acetolysis of 3β-Tosyloxy-5-hydroxy-5β-cholestan-6-one (1d) in Buffered Solution.—A solution of 660 mg (1.15 mmol) of 1d in 59 ml of 0.0208 *N* sodium acetate–acetic acid was heated at 90–92° for 7 hr. The colorless solution was cooled, diluted with water, saturated with sodium chloride, and extracted three times with ether. The ether extracts were washed twice with water and dried. The colorless oil thus obtained was chromatographed on 24 g of alumina. Elution with 40% benzene in petroleum ether gave 184 mg (40%) of the oxide 3. Recrystallization from acetone–methanol yielded 172 mg of 3 with mp 112–115°.[2]

The material (229 mg, a mixture of 4a and 2b) eluted from the column with ether–benzene mixtures was subjected to hydrogenation with a palladium-on-carbon catalyst in ethyl acetate solution. The product was chromatographed on 7 g of alumina. Elution with 50–80% benzene in petroleum ether yielded 61 mg (13%) of 5-hydroxy-5β-cholestan-6-one (reduction product of 4a). Recrystallization from acetone–methanol gave 46 mg of the hydroxy ketone with mp 101–103°. Elution with 20% ether–benzene produced 149 mg (28%) of the 3α-acetate 2b. Recrystallization from methanol gave, in two crops, a total of 130 mg of 2b, mp 126–128°.

Acetolysis of 3α-Tosyloxy-5-hydroxy-5β-cholestan-6-one (2d) in Buffered Solution.—A solution of 588 mg (1.03 mmol) of

(8) Experimental details have been reported elsewhere: A. T. Rowland, P. J. Bennett, and T. S. Shoupe, *J. Org. Chem.*, **33**, 2426 (1968).

(9) S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, **70**, 821 (1948).

(10) See ref 8 and references cited therein.

(11) A. T. Rowland, *J. Org. Chem.*, **29**, 222 (1964).

(12) G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meakins, E. E. Richards, and T. L. Whateley, *J. Chem. Soc., C*, 1266 (1966).

(13) (a) E. Glotter, S. Greenfield, and D. Lavie, *Tetrahedron Lett.*, 5261 (1967); (b) We thank Professor Peter S. Wharton, Wesleyan University, for the sample used in the nmr analysis.

2d in 55 ml of 0.0198 *N* sodium acetate–acetic acid was heated at 90–95° for 42.5 hr. The colorless solution was worked up as in the preceding example. A preliminary attempt to separate the products by chromatography was unsuccessful, hence the entire mixture (indicated by ir to be **4a** and **1b**) was subjected to catalytic hydrogenation. The resulting oil was chromatographed on 20 g of alumina. Elution with 80% benzene–petroleum ether gave 165 mg (40%) of 5-hydroxy-5β-cholestan-6-one which had mp 103–105° after crystallization from methanol. Elution with 15% ether–benzene yielded 210 mg (44.5%) of **1b** which melted at 141–143° when crystallized from methanol.

Registry No.—**1b**, 14956-13-9; **1d**, 6770-44-1; **1e**, 20352-32-3; **2b**, 6580-09-2; **2c**, 20352-49-2; **2d**, 20352-33-4; **2e**, 20398-53-2; **4a**, 20352-34-5; **4b**, 20352-50-5; 5-Hydroxy-5β-cholestan-6-one, 16526-09-3.

The Acid-Catalyzed Rearrangements of *endo,endo*-6,7-Dihydroxy- and *endo,endo*-6,7-Diacetoxycineole

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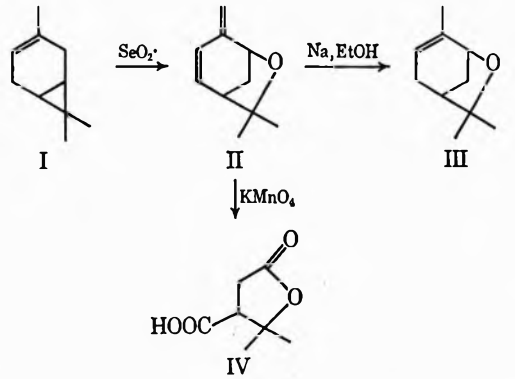
Received December 30, 1968

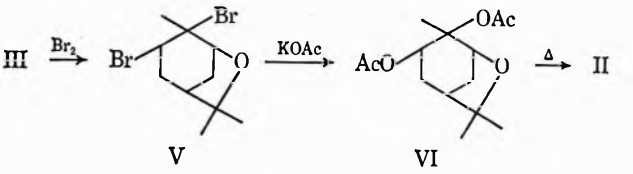
Recently, Arbuzov, Isaeva, and Ratner[2] reported the isolation of the interesting oxabicyclic diene II as one of the products arising from the oxidation of Δ^3-carene (I) with selenium dioxide. The structure assignment was substantiated by the infrared and ultraviolet spectra, the formation of pinol (III) upon reduction with sodium in ethanol, and the production of terebic acid (IV) by permanganate oxidation. Further evidence offered in support of structure II included an independent synthesis from pinol (III) using the steps outlined



in Scheme I based upon the early work of Wallach[3,4] in which "pinol dibromide" and "pinol diacetate" were assigned structures V and VI, respectively. Normal acetate pyrolysis of VI would be expected to afford II. Indeed, one of the pyrolysis products of VI, isolated by column chromatography, had an infrared spectrum "identical" with II (although the ir sample contained a carbonyl impurity) and gave IV upon oxidation with permanganate. Noteworthy was the finding that the pyrolysis was successful only in the presence of a small

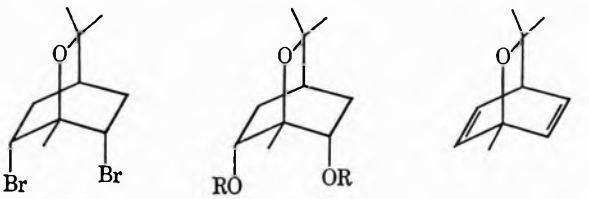
(1) Undergraduate research participant, 1968–1969.
(2) B. A. Arbuzov, Z. G. Isaeva, and V. V. Ratner, *Zh. Org. Khim.*, **2**, 1401 (1966); *J. Org. Chem. USSR*, 1391 (1966).
(3) O. Wallach and A. Otto, *Ann.*, **253**, 249 (1889).
(4) O. Wallach, *ibid.*, **259**, 309 (1890).

SCHEME I



amount of acid; attempts to pyrolyze VI alone gave only tar. The Russian workers also reported the presence of a ketone and a hydrocarbon in the reaction mixture, but these were not identified.

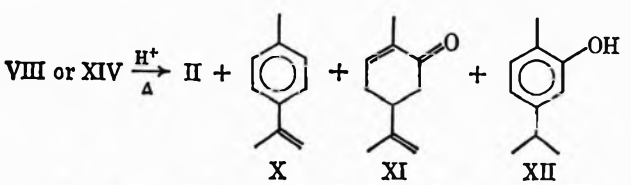
Our interest in the above series of reactions stemmed from the recently reported findings[5,6] that, contrary to the early literature,[3,4] pinol reacts with bromine to afford the rearranged dibromide VII (*endo,endo*-6,7-dibromocineole) instead of the reported structure V and that "pinol diacetate" is actually VIII (*endo,endo*-6,7-diacetoxycineole). In view of these revised assignments, regular acetate elimination reactions would be expected to give diene IX, while the conversion of VIII to II, if correct, represents a rather unusual and inter-



esting rearrangement, certainly not proceeding by a normal acetate pyrolysis mechanism. In order to clear up the above anomalies and to determine the composition of the unidentified hydrocarbon and ketone, we have reinvestigated the acid-pyrolysis reaction of VIII.

Under the same conditions employed by Arbuzov and coworkers, an oily mixture was obtained which was successfully separated by gas–liquid partition chromatography and the four major components (>90% of mixture) identified as the diene II (42.2%), *p*-isopropenyltoluene (X, 36%), carvone (XI, 13.9%), and carvacrol (XII, 7.9%). The data are tabulated in Table I.

TABLE I
ACID PYROLYSIS OF *endo,endo*-6,7-DIACETOXY- AND DIHYDROXYCINEOLE



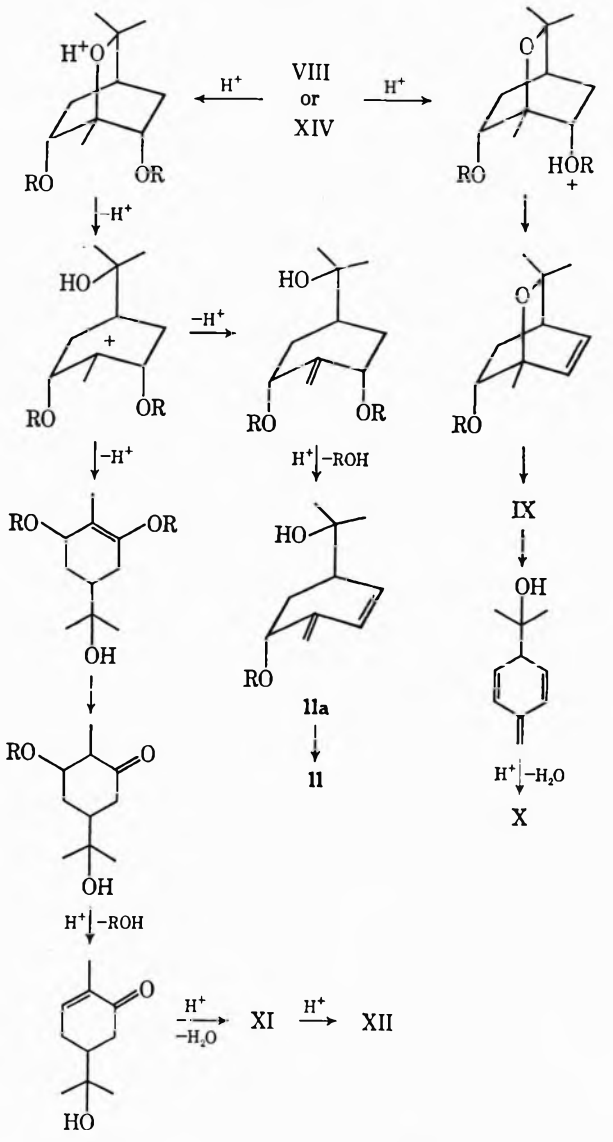
Compd	% II[a]	% X	% XI	% XII
VIII	42.2	36.0	13.9	7.9
XIV	8.2	8.5	65.0	18.3

[a] The percentages reflect only the relative amounts of the four major products (*ca.* 90% of the total volatile material) and are approximate, since differences in glpc detector responses were not measured.

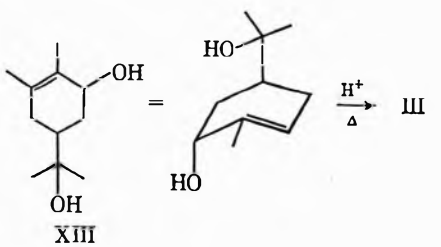
(5) R. O. Hutchins, Ph.D. Thesis, Purdue University, Jan 1967.
(6) J. Wolinsky and R. O. Hutchins, presented at the 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967.

Identification of X, XI and XII was accomplished by glpc and spectral comparisons with authentic samples or literature values. The data obtained for the diene II agreed well with that reported[2] and, furthermore, the nmr spectrum was in complete accord with II and inconsistent with structure IX (see Experimental Section). The mechanistic pathways for the observed transformations must be complex, but probably involve a series of acid-catalyzed elimination and isomerization reactions similar to those depicted in Scheme II.

SCHEME II



The formation of the rearranged diene II most likely occurs by initial ring opening followed by an acid-catalyzed ring closure of a labile allylic intermediate as IIa. Such a closure is similar to that observed in the acid-catalyzed formation of III from pinol hydrate



(XIII);[4,5] this suggested that the corresponding diol (XIV, *endo,endo*-6,7-dihydroxycineole) should also afford similar products upon heating with acid and, indeed, treatment of XIV under the same reaction conditions produced the same four products although the relative amounts of each were different (Table I). No evidence for the isomeric cineole diene IX was obtained from either reaction, but trace amounts of several other products were detected by glpc in both cases (<10% total) so that presumably one of these might be IX. Even if IX were initially formed in substantial quantity, it probably would not survive the acidic reaction conditions, since the compound is a diallylic ether. In fact, the expected product from ring opening of IX, *p*-isopropenyltoluene (X), may arise, at least in part, from this source. Carvacrol (XII) most probably arises from the well known acid catalyzed isomerization of XI.[5,7]

The conversion of VIII and XIV into the rearranged diene II somewhat parallels the corresponding transformation of *endo,endo*-6,7-dibromocineole (VII) to pinol (III) upon reaction with sodium in refluxing toluene or with hot alcoholic potassium hydroxide.[4,5] Finally, it is noteworthy that the successful conversion of III to diene II by Arbuzov and coworkers involved a combination of two skeletal rearrangements, unknown to them, which fortuitously cancelled and generated the desired product.

Experimental Section[8]

endo,endo-6,7-Dibromocineole (VII).—Bromination of pinol[4,5] in methylene chloride as previously described[3,5] afforded colorless prisms (from cyclohexane), mp 92–94° (lit. mp 92–94°, 94°).[3]

endo,endo-6,7-Diacetoxycineole (VIII).—Treatment of VII with silver acetate in glacial acetic acid in the reported manner[4,5] gave diacetate VIII in 78% yield. Recrystallization from *n*-pentane and sublimation gave white needles, mp 94–96° (lit. mp 97°,[4] 95.5–96.5°,[2] 92°[5]).

endo,endo-6,7-Dihydroxycineole (XIV).—Reaction of III with aqueous performic acid followed by hydrolysis of the resulting formate ester with sodium hydroxide[5] gave XIV. Recrystallization from *n*-hexane–ethyl acetate and sublimation afforded colorless needles, mp 121–124° (lit.[4,5,9] mp 122–124°).

Acid-Pyrolysis Reactions. A. VIII.—Following the procedure of Arbuzov,[2] a mixture of 5.01 g of VIII, 0.10 g of β-naphthalenesulfonic acid, and 20 ml of di-*n*-butyl phthalate was slowly heated with a Wood's metal bath to *ca.* 280° under a 90-mm nitrogen atmosphere. The distillate (bp *ca.* 60–173°) was diluted with 5 ml of ether, washed with 10 ml of water and twice with 10-ml portions of 5% sodium bicarbonate, and dried ($MgSO_4$). Distillation in a short-path apparatus at 11 mm afforded 0.74 g of yellow oil. Analysis by glpc[10] demonstrated the presence of four major constituents which were isolated by preparative glpc.[10] In order of increasing retention times, the following components were identified. (1) Diene II: $n^{25}D$ 1.5004 (lit.[2] $n^{20}D$ 1.5020, 1.5030); ir (neat) 1630, 1587, 1374, 1359, 1271, 1046, 993, and 880 cm^{-1} (lit.[2] 1636, 1592, 1378,

(7) H. Rupe and P. Schlochoff, *Ber.*, **38**, 1719 (1905).

(8) All boiling points and melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrometer or a Perkin-Elmer Model 621 spectrometer. Nmr spectra were measured with a Varian Associates A-60 spectrometer; chemical shifts are given in parts per million downfield from tetramethylsilane as internal standard. Ultraviolet spectra were obtained with a Perkin-Elmer ultraviolet–visible spectrometer, Model 202. Gas–liquid partition chromatography was performed with a Perkin-Elmer Model 900 gas chromatograph or an Aerograph A-700 preparative chromatograph, both equipped with thermal conductivity detectors.

(9) G. Wagner and K. Slawinski, *Ber.*, **32**, 2064 (1899).

(10) Analysis was accomplished using a 10 ft × 1/8 in. 20% Apiazon L on Chromosorb W column at 160°. Preparative isolations were performed using a 20 ft × 3/8 in. 15% Bentone, 5% SE-52 on Chromosorb W column at 160°. A 20 ft × 3/8 in. 20% DEGS on Chromosorb W column also separated the components, but in this case the elution order of II and X was reversed.

1362, 1278, 1052, 1000, and 887 cm^{-1}); uv λ_{max} (cyclohexane) 232 mμ (log ϵ 4.17) [lit.[2] λ_{max} 233 (log ϵ 4.2)]; (C_2DCl_3) δ 1.27 [s, 6 H; $(CH_3)_2CO$], 1.7–2.6 (m, 3 H), 4.52 (broad d, 1 H, C=CCHCO, bridge H), *ca.* 4.81 (m, 2 H; C=CH_2), *ca.* 6.10 (m, 2 H; conj CH=CH). (2) *p*-Isopropenyltoluene (X): $n^{25}D$ 1.5325 (lit. $n^{25}D$ 1.5290,[11] $n^{20}D$ 1.5350[12]); uv λ_{max} (cyclohexane) 245 mμ (log ϵ 4.08) [lit.[13] λ_{max} 245 mμ (log ϵ 4.13)]; nmr ($CDCl_3$) δ 2.14 (d, 3 H, J = *ca.* 1 cps; CH_3C=C), 2.34 (s, 3 H; CH_3Ar), 5.10 and 5.34 (two m, 2 H; CCH_2), *ca.* 7.26 (m, 4 H; ArH); ir spectrum identical with that reproduced in the literature.[13] (3) Carvone (XI) was identified by glpc retention time and ir and nmr spectral comparisons with an authentic sample. (4) Carvacrol (XII) was identified by ir and nmr spectral comparisons with an authentic sample. In a second experiment, 5.0 g of VIII gave 1.22 g of the product mixture.

B. XIV.—In the same manner described for VIII, a mixture of 2.68 g of XIV and 0.06 g of β-naphthalenesulfonic acid in 20 ml of di-*n*-butyl phthalate was heated at 100-mm pressure under nitrogen. Work-up and distillation gave 0.58 g of yellow oil. Analysis by glpc indicated the oil to be primarily XI (65%) with lesser amounts of II (8.2%), X (8.5%), and XII (18.3%).

Registry No.—VIII, 20178-11-4; XIV, 20178-12-5.

(11) G. B. Bachman and H. M. Hellman, *J. Amer. Chem. Soc.*, **70**, 1772 (1948).
(12) V. N. Ipatieff, H. Pines, and R. C. Olberg, *ibid.*, **70**, 2123 (1948).
(13) M. J. Murray and W. S. Gallaway, *ibid.*, **70**, 3867 (1948).

A Novel Procedure for the Removal of o-Nitrophenoxyacetyl Amino-Protecting Groups[1]

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Received January 20, 1969

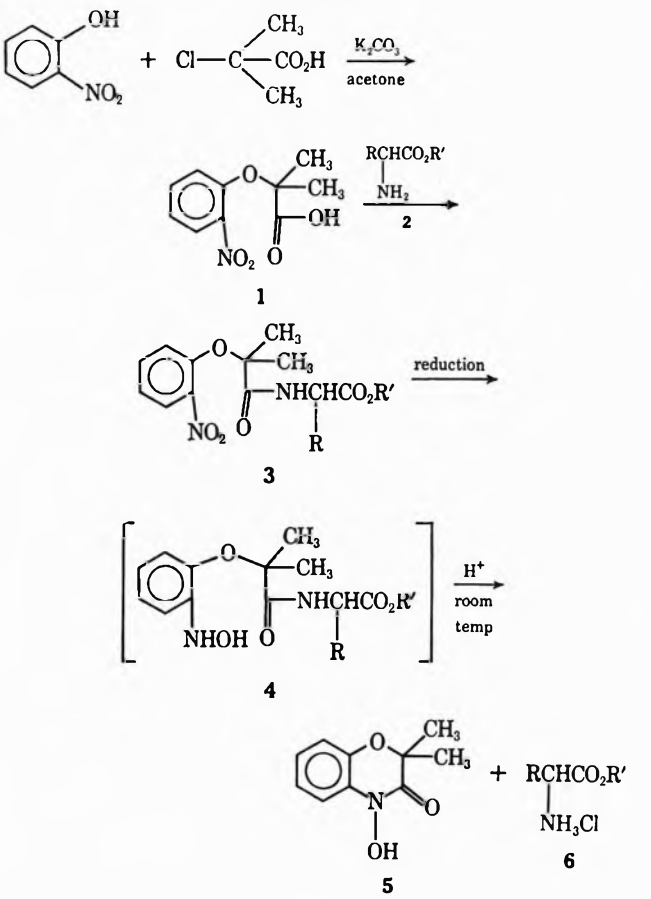
Several years ago, Holley and Holley[2] introduced the *o*-nitrophenoxyacetyl moiety as an amino-protecting group during the synthesis of peptides. They reported that this type of blocking group is removed by thermal cyclization of the corresponding *o*-aminophenoxyacetyl derivative which is obtained by catalytic reduction. Formation of the lactam of *o*-aminophenoxyacetic acid occurs with concomitant liberation of the amino group on the peptide.

We have found that the removal of the *o*-nitrophenoxyacetyl protecting group is facilitated by partial reduction of the nitro group to a hydroxylamino moiety. The deblocking is accomplished at room temperature, does not require a noble metal catalyst, and is unaffected by sulfur-containing amino acids. The procedure is illustrated in Scheme I.

The specific blocking group used in this work was derived from α-methyl-α-(*o*-nitrophenoxy)propionic acid (**1**).[3] It is easily coupled to an amino acid ester (**2**) *via* either the acid chloride or carbodiimide procedure. The amino-protected derivative (**3**) was named an MNP-amino acid ester. It has an infrared spectrum which contains a very characteristic peak at 1600 cm^{-1} (apparently an aromatic stretching band) among the other expected absorptions.

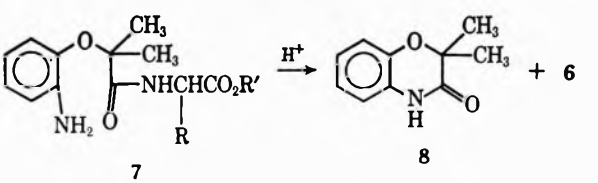
(1) Presented at the 20th Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 4, 1968.
(2) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **74**, 3069 (1952).
(3) D. A. Johnson, C. A. Panetta, and R. R. Smith, *J. Org. Chem.*, **31**, 2560 (1966).

SCHEME I



The reduction of the MNP-amino acid ester **3** to the *o*-hydroxylamino derivative (**4**) is accomplished using either aluminum amalgam or zinc and ammonium chloride in aqueous tetrahydrofuran. The former method was the less preferred one because it appeared, by tlc, to give a much larger amount of the *o*-aminophenoxyacetyl derivative (**7**) than did the latter. α-Methyl-α-(*o*-aminophenoxy)propionyl glycine ethyl ester (**7**, R = H, R′ = Et) was prepared by using a 10:1 molar ratio of aluminum amalgam to **3** (R = H, R′ = Et) and was characterized. According to tlc, **7** (R = H, R′ = Et) was found to deblock (Scheme II) much

SCHEME II



more slowly than did the ferric chloride positive[4] reduction product which is apparently the corresponding hydroxylamino derivative **4**, (R = H, R′ = Et). A proportionately smaller amount of aluminum amalgam afforded a larger yield of **4** (R = H, R′ = Et) from **3** (R = H, R′ = Et).

Compound **4** was not isolated, but a solution of it was acidified with alcoholic hydrogen chloride solution and stored at room temperature. The hydrochloride of the amino acid ester (**6**) crystallized and was separated

(4) R. L. Shriner, R. C. Tuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y., 1964, p 135.

TABLE I

THE RESULTS OF ZINC AND AMMONIUM CHLORIDE DEBLOCKING EXPERIMENTS ON SEVERAL MNP-AMINO ACID ESTERS 3

MNP-amino acid ester 3			% yield of deblocked		
R	Optical isomer	R′	amino acid ester HCl	Mp (lit.[a] value), °C	[α] of product ([α] of starting material)
H-(glycine)		Et	72.8	142.5–143.0 (144)	
$(CH_3)_2CHCH_2$-(leucine)	L	Et	41.6	120.5–126.0 (134)	
CH_3-(alanine)	L	Et	57.0		
CH_3-(alanine)	L	Me	44.6	101.0–104.0 (109)	
$C_6H_5CH_2$-(phenylalanine)	L	Me	46.7	158.0–159.0 (159)	+1.83° (*c* 0.5, MeOH) (+1.84°)
$(CH_3)_2CH$-(valine)	L	Me	78.1	164.0–167.0 (168)	+2.42° (*c* 0.5, MeOH) (+2.31°)

[a] See ref 7, pp 929–932.

from the reaction mixture by filtration. The by-product N-hydroxylactam (**5**) was isolated, in some cases, by evaporation of the filtrate.

Several MNP-amino acid esters were prepared and subsequently deblocked by the zinc and ammonium chloride procedure. The results of these experiments are summarized in Table I. Except in the case of glycine ethyl ester (**2**, R = H, R′ = Et) all of the MNP-protected derivatives **3** were made from the L-isomer of the corresponding amino acid ester hydrochloride. A check of the specific rotations of the methyl esters of valine and phenylalanine before and after blocking and deblocking experiments were completed showed essentially no change, indicating that racemization probably does not occur during these processes. The homogeneity of the amino acid ester hydrochloride products was established by tlc and the melting point and R_f of each product was compared with known values in order to prove identity.

Experimental Section[5]

The thin layer chromatograms of the amino acid ester hydrochlorides **6** were run on microscope slides coated with a 250-μ layer of Camag D-5 silica gel. Spotting was performed using 0.5–1.0 μl of a 1% solution and the solvent system was benzene–EtOH–NH_4OH (60:39:1). The thin layer chromatograms of the MNP-amino acid esters **3** and the reduction products **4**, **5**, **7**, and **8** were run on slides coated with neutral aluminum oxide G (E. Merck). The solvent system was benzene–EtOAc (70:30). The zones were detected as yellow areas on a purple background after spraying with a 0.5% aqueous $KMnO_4$ solution sometimes followed with heating. Cited R_f values are approximate figures.

General Procedure for the Preparation of MNP-Amino Acid Esters 3.—The general procedure is illustrated by the preparation of MNP-Gly-OEt[6] *via* the acid chloride method and by the preparation of MNP-Phe-OMe[6] *via* the carbodiimide process.

MNP-Gly-OEt (3, R = H, R′ = Et).—The acid chloride of **1** was prepared from 5.0 g (22.2 mmol) of **1**, 25 ml (0.344 mol) of $SOCl_2$, and 0.3 ml of DMF according to a published procedure.[3] A solution of the acid chloride in 20 ml of CH_2Cl_2 was added during a 10-min period to a cooled and stirred mixture of 3.10 g (22.2 mmol) of H-Gly-OEt·HCl,[5] 10 ml (7.25 g, 71.6 mmol) of triethylamine, and about 200 ml of CH_2Cl_2. The resultant mixture was stirred at room temperature for 16 hr and was then diluted with 100 ml of water. The phases were thoroughly mixed, after which the organic layer was washed with water at pH 1.5 and then with neutral water. The rich CH_2Cl_2 solution was dried ($MgSO_4$) and concentrated under reduced pressure to an amber oil which easily crystallized. One recrystallization from a warm mixture of benzene and petroleum ether (bp 30–60°) afforded 3.81 g (55.3%) of **3** (R = H, R′ = Et) from which an analytical sample was obtained after a second recrystallization: mp 102.5–104.0°; ir (CH_2Cl_2) 1730 (ester C=O), 1670 (amide I), 1520 (amide II), 1535 and 1360 (NO_2), and 1600 (aromatic stretching); nmr ($CDCl_3$) consistent with kind and number of protons present in **3** (R = H, R′ = Et); tlc showed the product to be homogeneous.

Anal. Calcd for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.91; H, 5.83; N, 9.10.

MNP-Phe-OMe (3, R = $C_6H_5CH_2$, R′ = Me).—To a solution of 2.16 g (10 mmol) of H-L-Phe-OMe·HCl,[6] 40 ml of acetonitrile, and 1.4 ml (1.01 g, 10.0 mmol) of triethylamine was added in succession, 2.25 g (10 mmol) of **1** and 4.24 g (10 mmol) of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (Aldrich Chemical Co.). A solution was the immediate result, but a solid separated slowly while the mixture was stirred at room temperature for 2 days. The solvent was removed under reduced pressure and the residue was distributed between 1.2 *N* aqueous HCl and ether (about 50 ml and 100 ml, respectively). The ether layer was washed consecutively with water, 1 *N* aqueous Na_2CO_3, and water and was dried ($MgSO_4$). Removal of the ether left a yellow oil **3** (R = $C_6H_5CH_2$, R′ = Me) which weighed 0.972 g (25.2%): ir (CH_2Cl_2) 1735 (ester C=O), 1665 (amide I), 1510 (amide II), 1537 and 1348 (NO_2), and 1600 (aromatic stretching); tlc showed the product to be essentially homogeneous.

General Procedure for the Deblocking of MNP-Amino Acid Esters 3.—The general procedure is illustrated by the removal of the MNP-protecting group from MNP-Gly-OEt.[6]

The Deblocking of MNP-Gly-OEt (3, R = H, R′ = Et).—A mixture of 0.31 g (1.0 mmol) of **3** (R = H, R′ = Et), 0.082 g (1.53 mmol) of NH_4Cl, 9 ml of THF, and 3 ml of water was vigorously stirred at room temperature while 0.654 g (10 mmol) of zinc dust was added in one portion. After 35 min a thin layer chromatogram was run on the reaction mixture. The zone for the starting material (MNP-Gly-OEt, $R_f \sim 0.9$) was completely missing, but two new and slower zones were visible. The spot at $R_f \sim 0.6$ was faint and small and was later shown to be **7** (R = H, R′ = Et). The spot at $R_f \sim 0.3$ was quite large and intense and was assumed to be **4** (R = H, R′ = Et). Vigorous agitation was continued for a total of 48 min, whereupon the mixture was filtered and the filtrate was distilled under reduced pressure until all of the THF was removed. The aqueous residue was extracted thrice with ether and the resultant ethereal solution was dried ($MgSO_4$) and diluted with 1.5 ml of EtOH. The rich solution was then acidified (to pH ~0) with alcoholic HCl solution. Crystals of **6** (R = H, R′ = Et) began to separate almost immediately. The mixture was stored at ambient temperature for 2 1/6 hr (other amino acid ester hydrochlorides completely precipitated in up to 24 hr) and was then filtered in order to separate 0.1014 g (72.8%) of gray-white crystals: mp 142.5–143.0° (lit.[7] mp 144°); tlc showed the product to be homogeneous and to have an R_f value identical with that of authentic H-Gly-OEt·HCl.[6]

(5) Melting points are corrected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

(6) Nomenclature according to E. Schröder and K. Lübke, "The Peptides," Vol. 1, Academic Press, New York, N. Y., 1965, p xiii.

(7) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley & Sons, Inc., New York, N. Y., 1961, p 932.

The ethereal filtrate from above gave a deep purple color when a sample of it in EtOH was treated with a few drops of 5% aqueous $FeCl_3$ solution. This test is indicative of the presence of a hydroxamic acid (such as **5**).[4] The solution was distilled at reduced pressure in order to remove the ether solvent, and the dark oily residue was crystallized from hot aqueous EtOH. The colored solid thus obtained, **5**, gave a positive test with $FeCl_3$ solution and was identical with an authentic sample of **5**[3] when these samples were compared by tlc. The yield of **5** was 84 mg (43.5%).

α-Methyl-α-(*o*-aminophenoxy)propionylglycine Ethyl Ester (7, R = H, R′ = Et).—A solution of 0.7868 g (2.54 mmol) of **3** (R = H, R′ = Et) in 25 ml of THF and 15 ml of water was treated with Al(Hg)[8] made from 0.685 g (0.0254 g-atom) of Al. The resultant mixture was stirred at room temperature and a tlc was run after 90 min. The only zone visible had an R_f of ~0.6, which was smaller than that of the starting material. After being stirred for 105 min, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure in order to remove the THF. The aqueous residue contained a relatively large amount of crystals which gave a negative test with $FeCl_3$ in aqueous alcohol.[7] These were collected, washed with water, and dried. The yield of **7** (R = H, R′ = Et) was 0.5763 g (81%): mp 100.0–101.5°; ir (CH_2Cl_2) 3457 (NH), 1745 (ester C=O), 1681 (amide I), 1502 (amide II), and 1617 (aromatic stretching); nmr ($CDCl_3$) consistent with kind and number of protons present in **7** (R = H, R′ = Et). One recrystallization from benzene and petroleum ether (bp 30–60°) (1:5) afforded an antlytically pure sample: mp 101.0–101.5°.

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 10.00. Found: C, 60.34, 60.54; H, 7.43, 7.28; N, 10.32, 10.13.

Compound **7** (R = H, R′ = Et) was converted into H-Gly-OEt·HCl by a procedure similar to that used on **4** (R = H, R′ = Et) above. The time required for cyclization and fragmentation to **8** and **6** (R = H, R′ = Et), however, was 18 hr, and the yield of the second product was 62%. Comparable figures *via* the hydroxylamino derivative **4** (R = H, R′ = Et) were 2¹/₆ hr and 72.8%.

Registry No.—**3** (R = H, R′ = Et), 20178-13-6; **3** (R = i-Bu, R′ = Et), 20178-14-7; **3** (R = CH_3, R′ = Et), 20178-15-8; **3** (R = CH_3, R′ = Me), 20178-16-9; **3** (R = $C_6H_5CH_2$, R′ = Me), 20178-17-0; **3** (R = i-Pr, R′ = Me), 20178-18-1; **7** (R = H, R′ = Et), 20178-19-2; zinc chloride, 7646-85-7; ammonium chloride, 12125-02-9.

Acknowledgment.—Support of this work in part by a Frederick Gardner Cottrell Grant in Aid of the Research Corporation, New York, N. Y., is gratefully acknowledged.

(8) I. Vogel, *J. Chem. Soc.*, 597 (1927).

Resin Acids. XVI. Some Transformations of Methyl 12α-Hydroxy-13β-abiet-8(9)-en-18-oate[1,2]

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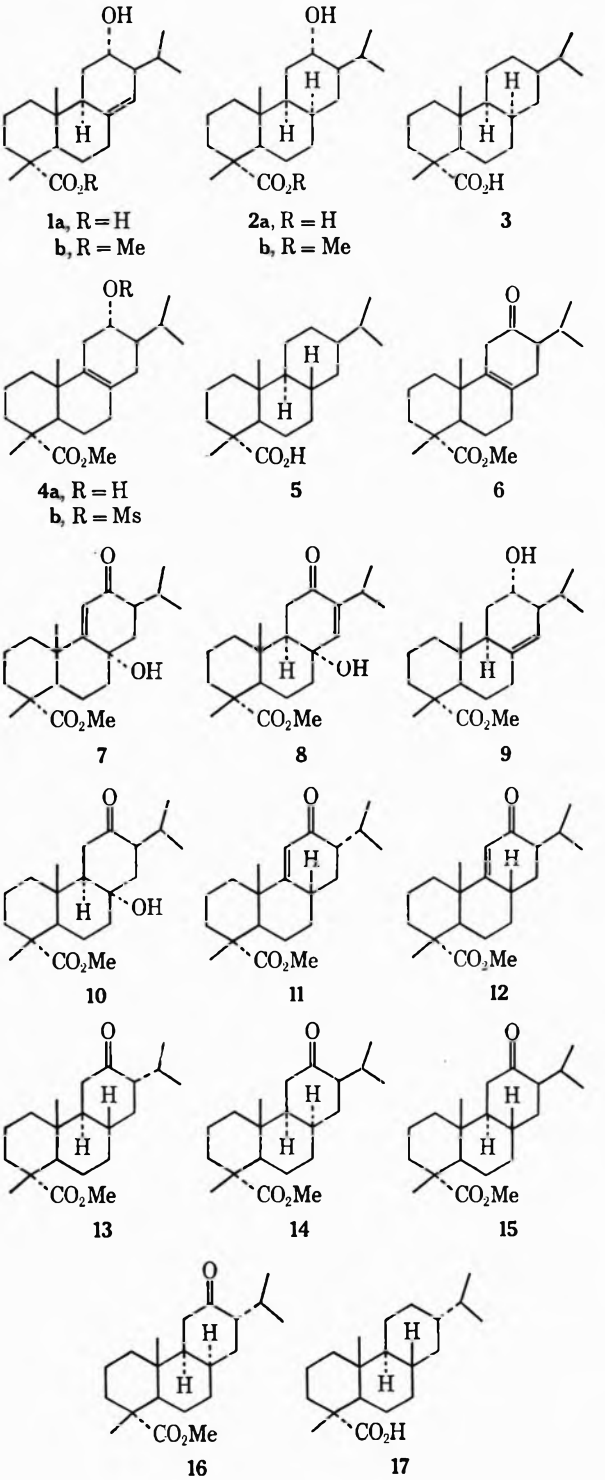
Received January 14, 1968

In an earlier[4] paper we reported the hydrogenation of **1a** to **2a** in acetic acid solution. The corresponding methyl ester **2b** was utilized[5] for our synthesis of authentic 8α,13β-abietan-18-oic acid (**3**),[6] and was generally prepared by hydrogenation of **1b**[8] in ethanol.



In an effort to improve the yield, the reduction was carried out in acetic acid, with the result that partial

(1) Previous paper, W. Herz and R. C. Blackstone, *J. Org. Chem.*, **34**, 1257 (1969).

(2) Supported in part by a grant from the National Science Foundation (GP-6362).

(3) National Science Foundation Fellow 1967–1968.

(4) W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *J. Org. Chem.*, **30**, 3190 (1965).

(5) J. M. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *ibid.*, **31**, 4128 (1966).

(6) Numbering and nomenclature used in this paper are based on a recent proposal (third revision, October 1968) by J. W. Rowe, "The Common and Systematic Nomenclature of Cyclic Diterpenes," subscribed to by most workers in the area. The parent abietane skeleton possesses the *trans-anti-trans* configuration with a 13α-isopropyl group.[7] Inverted configurations are designated by the position number and the correct stereochemistry just before the skeletal name.

(7) E. Fujita, T. Fumita, and H. Katayama, *Chem. Commun.*, 968 (1967).

(8) W. G. Dauben and R. Coates, *J. Org. Chem.*, **28**, 1698 (1963).

isomerization (20%) to a new hydroxy ester took place.[9] The new compound was identified as **4a** because of the nmr spectra which had no signals characteristic of vinyl protons. It exhibited the resonance of an axial (H-12) proton as a broad multiplet ($W_{1/2}$ = 19 Hz) and the C-10 methyl signal at 0.97 ppm, 6 Hz downfield relative to **5** in accordance with the postulated structure.[10] Some transformations of this compound which cast additional light on stability relationships in the abietane series are reported in this note.

Oxidation of **4a** with Jones reagent[12] gave two products (9:1) readily separable by chromatography. The major product appeared to be **6** (ir bands at 1720 and 1712 cm^{-1}). The nmr spectrum possessed a somewhat broadened ($W_{1/2}$ = 7 Hz) two proton signal at 2.73 ppm which was ascribed to the 11-methylene group. The minor product, $C_{21}H_{34}O_4$, was a hydroxylic α,β-unsaturated keto ester (ir bands at 3600, 1658, and 1605 cm^{-1}, λ_{max} 236, ϵ 19,800), whose nmr displayed a very sharp singlet at 5.83 ppm ascribable to a vinyl proton α to the carbonyl groups. The absence of other low-field signals required that the hydroxyl group be tertiary and attached to C-8, since a proton at C-8 would have been expected to couple allylically to H-11 (*vide infra*). Moreover the observed chemical shift of the C-10 methyl group (1.26 ppm) corresponded approximately to the expected deshielding effect of the $\Delta^{9(11)}$-12-oxo function (16 Hz);[11] hence the hydroxyl group was assigned the 8α configuration as in **7**.

The formation of an analogous α,β-unsaturated γ-hydroxy ketone (**8**) as a minor product in the oxidation of **9** has been reported previously. Hydrogenation of **8** gave **10**.[4] Hydrogenation of **7** also afforded **10**, thus confirming the postulated structure.

It was expected that isomerization of **6** would result in predominant formation of one of the two possible 8β-H isomers **11** or **12**. However base treatment of **6** or exposure to acid-washed alumina produced a 1:1 mixture of *two* α,β-unsaturated keto esters (A and B) which were separated by preparative tlc. The less polar keto ester A (ir bands at 1722, 1658, and 1605 cm^{-1}; λ_{max} 238 nm, ϵ 12,500, vinyl proton signal at 5.78 ppm, $J_{H\text{-}11,H\text{-}8}$ = 2 Hz) could be hydrogenated to the known[4,8] keto ester **13**. Hence hydrogenation of A took place exclusively from the α face and ketone A had to be **11**.

Hydrogenation of the more polar keto ester B (ir bands at 1719, 1660, and 1609 cm^{-1}, λ_{max} 241 nm, ϵ 15,000, vinyl proton signal at 5.70 ppm, $J_{H\text{-}11\ H\text{-}8}$ = 1.8 Hz) in a similar fashion gave a new saturated keto ester C (ir bands at 1716 and 1700 cm^{-1}) different from **13** and the previously reported **14**.[4] On the assumption that hydrogenation of B, like that of A, had taken place from the α face, keto ester C had to be formulated as either **15** or **16**.

The octant rule predicts a fairly strong positive Cotton effect for **15**, almost all of the contributing atoms of ring B and C being located in the upper left rear octant, whereas **16** might be expected to exhibit a negative Cotton effect even if ring C were somewhat distorted.[4] Since the observed Cotton effect was positive and of moderately strong amplitude, formula **15**, in which the isopropyl group is axial and should be epimerizable, was strongly favored. Indeed, base-catalyzed equilibration of C resulted in quantitative conversion to **13**. Hence C was **15** and B was **12**.[13]

(9) Treatment of a chloroform solution of **2a** with gaseous hydrogen chloride was somewhat more efficient for producing the new isomer (40% of **4a**, 20% of starting material and 40% of a mixture of unidentified substances).

(10) In the steroid series, $\Delta\delta$ $\Delta^{8,9}$ = 7 and $\Delta\delta$ 12α-OH = −0.5 Hz.[11]

(11) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

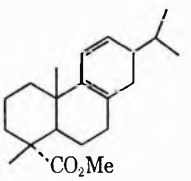
(12) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, New York, N. Y., 1967, p 142.

Experimental Section[14]

Methyl 12α-Hydroxy-13β-abiet-8(9)-en-18-oate (4a).—Gaseous hydrogen chloride was bubbled through a chloroform solution of 4.0 g of **2a** for 3 hr. The solution was washed thoroughly with water, dried, and evaporated. The residue, 3.8 g, was chromatographed over alumina. Elution with hexane–benzene (1:1) gave nonhydroxylic material. Elution with benzene gave **4a** (40%) followed by **2a** (20%). Elution with ether gave small amounts of unidentified products. Recrystallization of **4a** from cold ether gave crystals which had mp 95–98°, $[\alpha]^{25}D$ ($CHCl_3$, *c* 0.92), ir 3600 (hydroxyl) and 1720, 1240 cm^{-1} (ester); nmr 3.62 (methoxyl), 3.56 m ($W_{1/2}$ 19, βH-12), 2.42 (hydroxyl), 1.18 (C-4 methyl), 0.97 (C-10 methyl), 0.91 d and 0.82 d (J = 7, isopropyl). The reaction was capricious, the 40% yield of **4a** being difficulty to reproduce.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25; O, 14.35. Found: C, 75.33; H, 10.26; O, 14.36.

Treatment of 80 mg of **4a** with methanesulfonyl chloride–pyridine at 0° for 15 hr, dilution with water, extraction with ether, washing and drying the ether extract, and evaporation at reduced pressure gave the mesylate **4b** as a gum (85 mg) which solidified on standing but could not be recrystallized satisfactorily: ir 1715, 1250 (ester) and 1340, 1170 cm^{-1} (mesylate); nmr 4.78 m ($W_{1/2}$ = 19, βH-12), 3.62 (methoxyl), 2.99 (mesylate), 1.17 (C-4 methyl), 0.97 (C-10 methyl), 0.93 and 0.87 d (J = 6.8, isopropyl). In an attempt to prepare the unknown resin acid ester **18** the mesylate was placed on a column of alumina, but was recovered unchanged after 18 hr. Attempts to eliminate the mesylate function by refluxing with collidine or sodium acetate–acetic acid resulted in complex mixtures.



18

Oxidation of 4a.—Jones reagent[12] was added to a solution of 0.5 g of **4a** in acetone at room temperature until the brown color persisted. Work-up in the usual manner[1] gave a gum, tlc analysis of which showed the presence of two components. Preparative tlc afforded 0.37 g of **6** and 0.050 g of **7**. The major product (**6**) was a gum, $[\alpha]^{25}D$ +32° ($CHCl_3$, *c* 3.76); ir 1720, 1220 (ester), and 1712 cm^{-1} (ketone), nmr 3.61 (methoxyl), 2.73 br (2 protons, $W_{1/2}$ = 7, 11-methylene), 1.19 (C-4 methyl), 0.99 (C-10 methyl), 0.91 d and 0.88 d (J = 6.5, isopropyl).

The minor product **7** was recrystallized from methanol and had mp 196–198°; $[\alpha]^{25}D$ +6° ($CHCl_3$, *c* 635); uv λ_{max} 236 nm (ϵ 19,800); ir 3600 (hydroxyl), 1720, 1250 (ester), and 1658, 1615 cm^{-1} (conjugated enone); nmr 5.83 (H-11), 3.62 (methoxyl),

(13) The observed chemical shifts of the C-10 methyl resonances of **11** and **12** were in excellent agreement with the predicted values ($\Delta\delta$ $\Delta^{9(11)}$-12-oxo function 16 Hz,[11] observed for **11** 17 Hz relative to **17**, observed for **12** 17 Hz relative to **5**.

(14) Melting points are uncorrected. Analyses were by Dr. F. Pascher, Bonn, Germany. Nmr spectra were run on a Varian A-60 instrument in deuteriochloroform with tetramethylsilane as internal standard. Line positions are expressed in ppm from tetramethylsilane. Signals are characterized in the usual way: d doublet, br somewhat broadened singlet, m multiplet. Coupling constants are expressed in Hz. Infrared spectra were run on Perkin-Elmer Infracord or Model 257 spectrophotometers in chloroform solution. Ultraviolet spectra were run on a Cary 14 recording spectrometer in 95% ethanol solution. Ord curves were obtained with a Jasco ORD/UV-5 recording spectrophotometer in methanol solution. Column chromatograms were performed on Alcoa F-20 alumina. Silica gel G was used for analytical tlc, silica gel $PF_{254+366}$ (Merck) for preparative tlc.

1.26 (C-10 methyl), 1.17 (C-4 methyl), 0.93 d and 0.87 d (J = 7, isopropyl).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.37. Found: C, 72.15; H, 9.25; O, 18.48.

Catalytic hydrogenation of 60 mg of **7** in 10 ml of absolute ethanol (15 psi, 10% Pd–C) for 10 hr gave 60 mg of **10**, mp 161–164°, mmp with authentic material[4] 162–164°, ir and nmr spectra superimposable.

Isomerization of 6.—Treatment of **6** with sodium methoxide–methanol in the usual fashion[4] or chromatography over alumina gave a 1:1 mixture of **11** and **12** which was separated by preparative tlc. The less polar substance **11** was recrystallized from methanol–water and had mp 99–100°; $[\alpha]^{25}D$ +47° ($CHCl_3$, c 0.256); ir 1722, 1225 (ester), and 1658, 1605 cm^{-1} (conjugated enone); uv λ_{max} 238 nm (ϵ 12,500); nmr 5.87 d (J = 2, H-11), 3.60 (methoxyl), 1.22 (C-4 methyl), 1.13 (C-10 methyl), 0.92 and 0.79 d (J = 7.1, isopropyl).

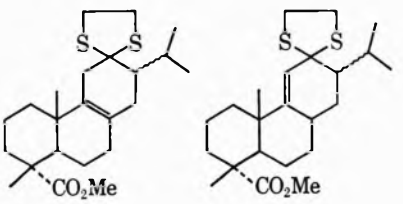
Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.64; H, 9.69; O, 14.62.

Hydrogenation of 50 mg of **11** in absolute ethanol (10 psi, 5% Pd–C) for 1 hr gave 50 mg of **13**,[4,8] mp 96–97°, mmp 96–97°, ir and nmr spectra superimposable.

The more polar ketone **12** was recrystallized from methanol–water and had mp 103–104°; $[\alpha]^{25}D$ +163° ($CHCl_3$, c 0.33); ir 1719, 1225 (ester), and 1660, 1609 cm^{-1} (conjugated enone); uv λ_{max} 241 nm (ϵ 15,000); nmr 5.70 d (J = 1.8, H-11), 3.60 (methoxyl), 1.22 (C-4 methyl), 1.14 (C-10 methyl), 0.91 d and 0.83 d (J = 6, isopropyl).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.90; H, 9.71; O, 14.50.

In an attempt to form the thioketal of **11** for the purpose of eventually removing the ketone group, a solution of 130 mg of **11** in 1.5 ml of ethanedithiol was allowed to stand with 0.75 ml of boron trifluoride for 4 hr, poured into water, and extracted with ether. The washed and dried ether extracts were evaporated at reduced pressure. The residue could not be induced to solidify. Preparative tlc afforded separation of the two major components as gums. The major product, *ca.* 70%, appeared to be **19** since the nmr spectrum did not display signals characteristic of vinyl protons, but had signals at 3.63 (methoxyl), 3.22 m (4 protons, $-CH_2S-$), 2.53 (2 protons, 11-methylene group), 1.17 (C-4 methyl), 1.01 (C-10 methyl), and 0.92 d (J = 6.7, isopropyl). The minor product, less than 20%, appeared to be **20**, nmr 5.55 br ($W_{1/2}$ = 2.2, H-11), 3.62 (methoxyl), 3.20 m (4 protons, $-CH_2S-$), 1.19 (C-4 methyl) and 0.92 d (J = 7.5, isopropyl). The nmr spectrum of the crude product also indicated that a small amount, *ca.* 10%, of a third product was present, possibly a C-13 epimer.



19 **20**

Methyl 12-Oxo-13β-abietan-18-oate (15).—A solution of 70 mg of **12** in absolute ethanol was hydrogenated (9 psi, 5% Pd–C) for 4 hr, filtered, and evaporated. Recrystallization of the residue from methanol–water afforded 60 mg of **15** which had mp 123–125°; ir 1716, 1230 (ester), and 1710 cm^{-1} (ketone); nmr 3.62 (methoxyl), 1.10 (C-4 methyl), 0.92 (C-10 methyl), 0.97 d and 0.88 d (J = 7, isopropyl); ord curve (c 0.048), $[\alpha]_{400}$ +274°, $[\alpha]_{304}$ +1880°, $[\alpha]_{255}$ −1580°.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25; O, 14.35. Found: C, 75.45; H, 9.95; O, 14.34.

A solution of 55 mg of **15** in 20 ml of aqueous methanol containing 250 mg of potassium hydroxide was allowed to stand for 2 hr, acidified, diluted with water, and extracted with ether. The washed and dried ether extracts on evaporation furnished 50 mg of **13** identical in all respects with authentic material.

Registry No.—**4a**, 20104-28-3; **4b**, 20104-29-4; **6**, 20144-61-0; **7**, 20104-30-7; **11**, 20104-31-8; **12**, 20104-32-9; **15**, 20104-33-0; **19**, 20104-34-1; **20**, 20104-35-2.

The Rates of Hydrolysis of Two Thiol Esters in Water[1]

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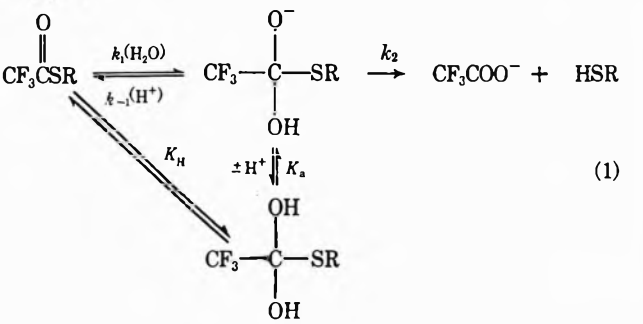
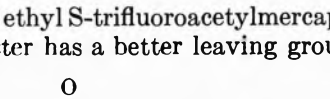
The purpose of this note is to point out that limiting values of the rate constants for decomposition of the tetrahedral addition intermediate in thiol ester hydrolysis to starting materials and products may be calculated from the observed rate constants at a pH value near that at which a change in rate-determining step occurs. In the case of a thiol ester of trifluoroacetic acid the value of these rate constants approach those expected for a diffusion-controlled reaction, reflecting the low stability of the tetrahedral intermediate.

Kinetic evidence for a change in rate-determining step with changing pH, the absolute values of the rate constants required for alternative mechanisms, and a dependence on pH of the exchange of ^{18}O from labeled ester into the solvent that agrees with the behavior predicted from the kinetic data provide convincing evidence that the hydrolysis of ethyl trifluorothiolacetate proceeds with the formation of a kinetically significant intermediate according to the mechanism of eq 1.[2,3] At high and intermediate pH values the



(1)

rate-determining step is the attack of hydroxide ion or the general base catalyzed attack of water on the ester, whereas below pH 2 the breakdown of the anionic tetrahedral addition intermediate becomes rate determining. Calculations of limiting values for the rate constants of eq 1, based upon estimates of the equilibrium constants for formation and ionization of the neutral tetrahedral intermediate, suggested that these rate constants approach the magnitude expected for diffusion-controlled reactions[4] and led us to examine the hydrolysis of ethyl S-trifluoroacetylmercaptoacetate I. This thiol ester has a better leaving group (pK =



I

(1) Contribution No. 653 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Mass. 02154. Supported by grants from the National Science Foundation (GB-5648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD-1247). R. B. was a National Science Foundation Predoctoral Fellow, 1965–1968.

(2) L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.*, **86**, 5697 (1964); **87**, 4138 (1965).

(3) M. L. Bender and H. d'A. Heck, *ibid.*, **89**, 1211 (1967).

(4) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill Book Co., New York, N. Y., 1969, p 521.

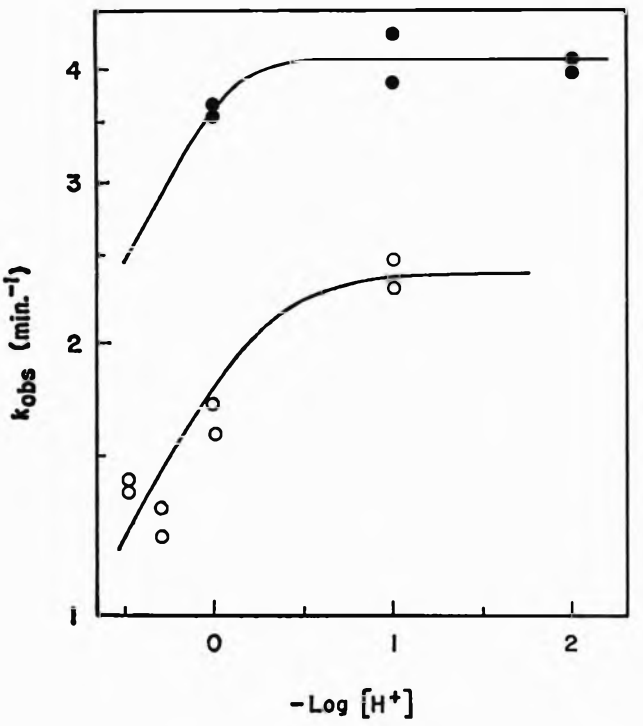


Figure 1.—Hydrolysis of ethyl S-trifluoroacetylmercaptoacetate (I) in hydrochloric acid solutions at 25°, followed at 244 mμ: upper curve, ionic strength maintained at 1.0 *M* with potassium chloride; lower curve, ionic strength maintained at 3.0 *M* with lithium chloride.

7.8) than that of ethyl trifluorothiolacetate (pK = 10.3) and might be expected to exhibit even larger absolute rate constants.

The pH–rate profiles for the hydrolysis of the thiol ester bond of I are shown in Figure 1. At an ionic strength of 1.0 *M*, maintained with potassium chloride (upper curve), there is an indication of a decrease in rate in the most acidic solution. This small rate decrease is probably not an activity coefficient effect, because it is observed even more clearly in solutions maintained at an ionic strength of 3.0 *M* with lithium chloride (lower curve). In contrast, the pseudo-first-order rate constants for the hydrolysis of phenyl thioformate increase with increasing acidity and follow the rate law of eq 2, with values of k_w and k_a of 3.3 ×

$$\text{rate} = k_w[\text{ester}] + k_a a_{H^+}[\text{ester}] \quad (2)$$

10^{-3} min^{-1} and 9.2 × 10^{-2} M^{-1} min^{-1}, respectively (Table I).

The rate constant for the pH-independent hydrolysis of I is 4.1 min^{-1}, compared with a value of 0.42 min^{-1} for the corresponding reaction of ethyl trifluorothiolacetate.[2] This corresponds to a Brønsted β value of 0.4 for the sensitivity of water-catalyzed thiol ester hydrolysis to the pK_a of the leaving group.

The acid inhibition of the hydrolysis of I is similar to that observed with ethyl trifluorothiolacetate[2] and suggests that the hydrolysis of I also proceeds according to the mechanism of eq 1, with a change from rate-determining attack of water to rate-determining breakdown of the anionic addition intermediate as the pH is decreased. The alternative mechanism of rate-determining hydroxide ion attack at low pH would require a rate constant of 4 × 10^{13} M^{-1} sec^{-1}. This value is above the rate of diffusion-controlled encounter of the

TABLE I

HYDROLYSIS OF PHENYL THIOFORMATE AT 25° IONIC STRENGTH 1.0 *M*[a]

pH	k_{obsd}, min^{-1}
0.09	0.072
0.10	0.076
0.49	0.027
0.50	0.027
1.07	0.012
1.07	0.012
1.46	0.0072
1.46	0.0066
2.06	0.0058
2.06	0.0057
3.10[b]	0.0039[c]
4.99[d]	0.0033[c]

[a] Maintained with potassium chloride. [b] Methoxyacetate buffer, 0.017–0.100 *M*, 30% base. [c] Extrapolated to zero buffer concentration. [d] Acetate buffer, 0.017–0.100 *M*, 70% base.

reactants and serves to rule out this mechanism, as shown previously for ethyl trifluorothiolacetate.[2] In the case of phenyl thioformate, there is no indication of a change in rate-determining step and acid catalysis of the rate-determining attack of water becomes apparent with increasing acidity. The change in rate-determining step for I occurs approximately one pH unit below that for ethyl trifluoroacetate, as might be expected in view of the better leaving group of the former compound; it must occur at a still lower pH with phenyl thioformate.

The rate constant for breakdown of the anionic tetrahedral addition intermediate of eq 1 is given by eq 3, in which k_{obsd} is the observed pseudo-first-order rate

$$k_2 \geq \frac{k_{obsd} a_{H^+}}{K_H K_a} \quad (3)$$

constant for hydrolysis at a given acidity, K_H is the equilibrium constant for formation of the uncharged tetrahedral intermediate from the ester, and K_a is the acid dissociation constant of this intermediate. No evidence for accumulation of an addition compound was obtained by comparison of the ultraviolet (uv) absorbance of I (or phenyl thioformate) in hexane and water. The value of the pK_a of the addition intermediate was estimated to be approximately 9 from a plot of pK_a against $\Sigma\sigma_I$ for a series of alcohols.[5] The pK_a of trifluoroacetaldehyde hydrate, $CF_3CH(OH)_2$, is 10.2.[6] If the value of K_H is assumed to be $\leq$0.1 and K_a is taken as 10^{-9}, the value of k_2 for the anionic addition intermediate formed from I is $\geq 4 \times 10^9$ sec^{-1}.[7] The magnitude of this first-order rate constant suggests that as the pH is increased the rate of diffusion-controlled protonation of the anionic intermediate will become slower than its rate of breakdown to products; *i.e.*, it will not be in equilibrium with its conjugate acid.

A change in rate-determining step occurs with increasing acidity when the addition intermediate undergoes acid-catalyzed breakdown to starting materials faster than it decomposes to products, *i.e.*,

(5) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **81**, 5343 (1959); P. R. Wells, *Chem. Rev.*, **63**, 171 (1963); M. Charton, *J. Org. Chem.*, **29**, 1222 (1964); R. Barnett, Ph.D. Thesis, Brandeis University, 1968.

(6) R. Stewart and M. M. Mocek, *Can. J. Chem.*, **41**, 1160 (1963).

(7) This rate constant may be calculated more exactly from the steady-state rate equation, $k_{obsd} = K_A K_H k_2 (1 + k_2/k_{-1})$ and the data of Figure 1. Note that a low value for the experimental rate constant in acid solution will give too low a value for k_2.

$k_{-1}[H^+] > k_2$. Thus, the value of k_{-1} must also be large; from the pH at which the change in rate-determining step occurs this rate constant may be estimated to be on the order of $10^9\ M^{-1}\ sec^{-1}$. These rate constants are of the magnitude expected for diffusion-controlled reactions[8] and raise the possibility that the $k_{-1} - k_1$ step might represent a diffusion-controlled proton transfer. A rate-determining proton-transfer step of this kind should exhibit general acid–base catalysis with Bronsted β values of 0 or 1.0 when the acidities of the proton donors and acceptors are sufficiently different.[8,9] The value of β for the hydrolysis of ethyl trifluorothiolacetate[2] is approximately 0.3, which means either that this hypothesis does not hold for this ester or that the observed catalytic constants represent a curved portion of the Bronsted plot. In any case, the calculations serve to emphasize the high reactivity, low stability, and short lifetime of the addition intermediate even for the hydrolysis of thiol esters of trifluoroacetate; the line between the usual type of intermediate and a series of incompletely defined way stations along the reaction coordinate at which proton transfer may occur becomes increasingly hard to draw for these reactions.

Experimental Section

Ethyl S-trifluoroacetylmercaptoacetate [bp 106–107° (60–65 mm); ir 1709, 1739 cm^{-1} in acetonitrile, λ_{max} 242 mμ in water] was synthesized[2] from ethyl mercaptoacetate and trifluoroacetic anhydride at 0°. Phenyl thioformate[10] [bp 73–75° (1.5 mm); ir 1682, 782, 728 cm^{-1} in acetonitrile; λ_{max} 230 mμ in water, 236 mμ in hexane] was prepared from benzenethiol and the mixed anhydride formed from formic acid and ethyl chloroformate.[11] Pseudo-first-order rate constants for the hydrolysis of these esters were determined spectrophotometrically as described previously.[12] Good first-order kinetics were observed for at least two half times and the total change in absorbance was approximately the same at all pH values.

Registry No.—I, 20104-50-1; phenyl thioformate, 20104-51-2.

(8) M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).
(9) R. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 4199 (1968); **91**, 2358 (1969).
(10) G. A. Olah and S. J. Kuhn, *ibid.*, **82**, 2380 (1960).
(11) T. Wieland and H. Köppe, *Ann. Chem.*, **581**, 1 (1953).
(12) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 675 (1960).

Ionic and Radical Reactions in the Bromination of Butadiene

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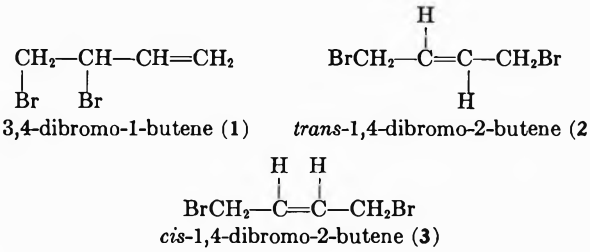
Received December 10, 1968

While continuing our studies on the bromination of dienes,[1] we became concerned that previous reports[1,2] which proposed ionic mechanisms in the bromination of dienes may have overlooked a possible radical component to these reactions. This concern was intensified by a report by Poutsma[3] confirming a radical route in the chlorination of butadiene at high diene concentrations. Therefore, we decided to reinvestigate the bromination of butadiene. The structures of the three possible dibromide products in this reaction are shown.



Results and Discussion

Treatment of butadiene at various concentrations in carbon tetrachloride with bromine gave **1**, **2**, and **3** in the quantities indicated in Table I. The formation of **3** was not previously reported in the bromination of butadiene. The percentages of the dibromides were determined by vpc analysis. The material balances were obtained by the internal standard method using *p*-dichlorobenzene.

TABLE I
ADDITION OF BROMINE TO BUTADIENE UNDER VARIOUS CONDITIONS

Mole fraction of butadiene	% of 1	Yield, %
Nitrogen, Safelight, − 15°		
0.020	60	
0.032	60	
0.045	56	100
0.067	51	100
0.11	45[a]	
0.39	21	100
1.0	21	
Nitrogen, Illuminated, −15°		
0.020	58	
0.045	52	80
0.067	45[a]	
0.10	34	
0.14	21	85
1.0	23	
Nitrogen, Safelight, 25°		
0.045	56	
0.10	45[a]	
0.18	37	
0.30	24	
Nitrogen, Illuminated, 25°		
0.032	41[a]	
0.045	31	
0.10	21	85

[a] Dibromide **3** first appears here in trace amounts and increases with increasing concentration of butadiene until it becomes approximately 4% at complete radical conditions.

The results in Table I show that at −15° the percentages of **1** vary from approximately 60% at low concentrations of butadiene to approximately 20% at

(1) For previous paper, see. V. L. Heasley, C. L. Frye, R. T. Gore, Jr., and P. S. Wilday, *J. Org. Chem.*, **33**, 2342 (1968).
(2) L. F. Hatch, P. D. Gardner, and R. E. Gilbert, *J. Amer. Chem. Soc.*, **81**, 5943 (1956).
(3) M. L. Poutsma, *J. Org. Chem.*, **31**, 4167 (1966).

high concentrations of butadiene, both under safelight and illumination. The percentages of **1** and **2** (under safelight) are remarkably similar to the percentages of 3,4-dichloro-1-butene and *trans*-1,4-dichloro-2-butene reported by Poutsma[3] for the chlorination of butadiene. Poutsma[3] also observed that when the percentage of 3,4-dichloro-1-butene is high (*ca.* 60%), the reaction is following an ionic pathway. Conversely, when the percentage of 3,4-dichloro-1-butene is low (*ca.* 20%), a radical mechanism is operative.

These relationships also seem to apply to the bromination of butadiene under safelight at −15°, where we have determined that bromination of butadiene at low concentrations leads to **1** and **2** by an ionic pathway, whereas **1**, **2**, and small amounts of **3** are formed by a radical mechanism at high concentrations of butadiene. These conclusions are based on the following observations: (1) significant quantities of α-bromoethylbenzene are formed from ethylbenzene[4] and butadiene where the concentration of the latter is high, and the amount of α-bromoethylbenzene decreases with decreasing concentration of butadiene to become a mere trace (see Table II); and, (2) where the percentage of **1** is low, suggesting a radical reaction, it can be significantly increased by the addition of the radical inhibitor, 2,6-di-*t*-butyl-4-methylphenol (see Table III).

TABLE II

RELATIVE REACTIVITIES AT −15°

Mole fraction of butadiene and ethylbenzene[a]	Relative Reactivities	
	Safelight	Illumination
0.50	100	60
0.40	155	42
0.25	500	64
0.10	2000	5
0.032	[b]	161

[a] Where necessary, carbon tetrachloride was added to give a mole fraction of 1. [b] No α-bromoethylbenzene was detected at these conditions. When the mole fraction of ethylbenzene was increased to 0.968 (for butadiene, n = 0.032) a trace of α-bromoethylbenzene was detected.

TABLE III

EFFECT OF THE INHIBITOR AT −15°

Mole fraction of butadiene	Concentration, M, of the inhibitor	Percentage of 1	
		Safelight	Illumination
0.18	0.16		38
0.18	0.91		40
0.39	0.18	34	
0.39	0.46	39	

The results of bromination under illumination (−15°) are more difficult to understand. Assuming that a high percentage of **1** indicates an ionic reaction, then the results in Table I would suggest that an ionic reaction occurs at low concentrations of butadiene, even under illumination, and that the mechanism becomes completely radical at a mole fraction of approximately 0.13. However, the relative reactivities in Table II indicate that under illumination the reaction is following a radical course under all concentrations of butadiene. We are unable to explain this apparent anomaly, except to say that we have more confidence in the validity of the results indicating an ionic mechanism than in the relative reactivity results from ethylbenzene.[5]

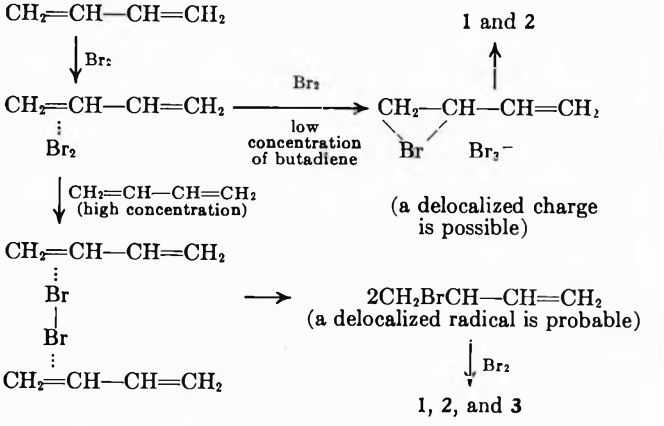
The results from the bromination of butadiene at room temperature under safelight and illumination are similar to those at −15° (Table I) with the exception that the reaction assumes a radical pathway at a lower concentration of butadiene.

The formation of *cis*-1,4-dibromo-2-butene (**3**) should be noted. As reported in Table I, **3** was observed only under radical conditions.

Table I shows that the earlier study of the bromination of butadiene by Hatch, *et al.*,[2] was carried out under essentially ionic conditions (*ca.* n = 0.1). Our investigation of isoprene[1] was undoubtedly in the ionic range since the concentration of isoprene was low (*ca.* n = 0.1).

A possible explanation for the change in mechanisms with a change in concentration of butadiene is suggested in Scheme I. These equations would seem to be general for the bromination of any linear[6] diene.

SCHEME I



Experimental Section

Materials.—Unless otherwise indicated, the solvents and reagents were obtained commercially in high purity. The butadiene was Matheson's instrument grade, 99.5%. α-Bromoethylbenzene was prepared by bromination of ethylbenzene in the presence of sunlamp illumination. The product had the following physical constants: bp 88° (15 mm), n^{20}D 1.5615. The reported values[7] are bp 86–88° (15–16 mm), n^{20}D 1.5612.

Bromination. General Procedure.—Butadiene was dissolved in carbon tetrachloride to give a solution of approximately 10 ml. To this solution, under the selected conditions, bromine was added until 10–20% of the butadiene had reacted. The resulting solution was then analyzed immediately by vpc.

The concentration of butadiene was determined by adding liquefied butadiene to the determined quantity of solvent, on a balance, until the appropriate weight was obtained. At 25°, and at high mole fractions of butadiene, some evaporation oc-

(4) Ethylbenzene was used rather than cyclohexane because the selective bromine atom preferred addition to butadiene exclusively over abstraction of a hydrogen atom from cyclohexane. It was confirmed that under the reactions conditions of safelight (−15°), ethylbenzene did not react directly with bromine. Toluene was not employed in the study because its bromination product, benzyl bromide, had the same retention time as **2**.

(5) Ethylbenzene (illumination, −15°) seemed to have an erratic effect on the percentages of **1** and **2**. For example, in the presence of ethylbenzene the percentage of **1** remained at approximately 20% (beginning at n = 0.5 for butadiene until *ca.* n = 0.02 where it suddenly jumped to 58%. As indicated, in the absence of ethylbenzene the results are considerably different. Under safelight (−15°) the percentages of **1** and **2** were uneffected by the presence of ethylbenzene.

(6) For a discussion on the effect of branching on the addition of chlorine to olefins, see M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 4285 (1965).

(7) "Dictionary of Organic Compounds," Vol. I, I. Heilbron and H. M. Bunbury, Editors, Oxford University Press, New York, N. Y., 1953, p 327.

curred. However, since the time required for bromination was very short, the effect of evaporation was negligible.

All brominations requiring the absence of light were carried out in a dark room with a photographic safelight.

Procedure for Analyses of Products.—The vpc analysis of the dibromides was accomplished with an Aerograph 90 P-3 chromatograph under the following conditions: flow rate (He) 300 cc/min; column length and diameter, 6 ft × 0.25 in.; column temperature, 50°; column composition, 2.5% SE-30 on 60–80 mesh DMCS Chromosorb W. Under these conditions the retention times of **1**, **2**, and **3** are, respectively, 108, 297, and 247 sec. The retention time of α-bromoethylbenzene was 372 sec.

None of the dibromides rearranged under the conditions of analysis. This was determined by collecting the dibromide mixture after it had passed through the chromatograph and observing that no change in composition had occurred on reinjection.

The percentages of the dibromides were based on their adjusted areas in the chromatograms. The adjustments were based on the following determination: the ratio of A_1/A_2 divided by W_1/W_2 is equal to 0.85. The area/weight ratio for dibromides **2** and **3** was assumed to be unity on the basis of their similar molecular structures.

The relative reactivities of butadiene and ethylbenzene were determined from the following expression where C_8H_9Br refers

$$\left[\frac{2(1 + 2 + 3)}{(C_8H_9Br)}\right]\left[\frac{(C_8H_{10})_0}{(C_4H_6)_0}\right]$$

to the quantity of α-bromoethylbenzene formed in the reaction, and $(C_8H_{10})_0$ and $(C_4H_6)_0$ refer to the initial concentrations of ethylbenzene and butadiene, respectively.

The Authentic Dibromide Isomers.—Dibromides **1** and **2** were prepared according to the methods described by Hatch, *et al.*[2] Dibromide **3** was prepared as described by Valette.[8] The peaks assigned to dibromides **1** and **2** were confirmed by comparison of their retention times with those of authentic samples, and by collecting the compounds as they emerged from the vpc and comparing the absorption bands in their infrared spectra with the reported absorption bands.[2] The peak assigned to dibromide **3** was done so on the basis of a comparison of its retention with that of authentic **3**.

Registry No.—Butadiene, 106-99-0; **1**, 10463-48-6; **2**, 821-06-7; **3**, 18866-73-4.

Acknowledgment.—Acknowledgment is made to the Petroleum Research Fund, administered by the American Chemical Society, and to Union Oil Co., Bea, Calif., for the support of this research.

(8) A. Valette, *Ann. Chim.*, **3**, 644 (1948).

Solvent Effects in the Oxymercuration of 2-Cyclohexenol and Related Allylic Derivatives

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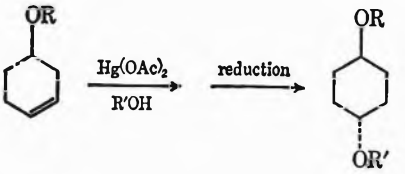
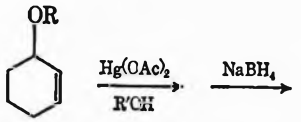
Received December 3, 1968

Stereoselective reactions are of great importance in the design of synthetic procedures. A number of simple olefin addition reactions exhibit this feature, which increases by a large factor the degree of synthetic utility. A related phenomenon, stereoselective addition controlled by a substituent in the vicinity of the double bond, has been explored in several reactions. Examples for which high selectivity has been reported include the epoxidation of 2-cyclohexeneol[3] (*cis*), the Simmons–Smith reaction of both allylic and homoallylic alcohols (*cis*),[4] and the hydroxymercuration of 3-cyclohexenol[5] (eq 1).

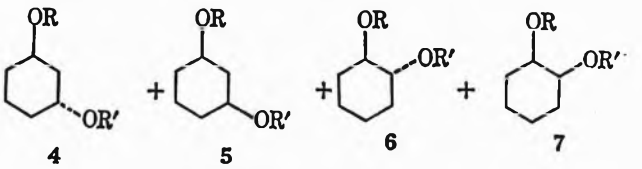


(1)

We have recently reported preliminary results on the hydroxymercuration of 2-cyclohexenol (**1**), its methyl ether (**2**), and acetate (**3**) derivatives.[6] The reaction proved to be only moderately stereoselective as normally carried out (THF–water), but appeared, in the limited range examined, to be somewhat solvent dependent. We report here the results of an expanded study of solvent effects with these systems. The products in each case were reduced by borohydride to the corresponding diols (or derivatives), which in turn were analyzed by vpc. The results are shown in Table I.



1, R = H
2, R = CH_3
3, R = $COCH_3$



R' = H, CH_3, or $COCH_3$ (2)

The most significant aspect to be noted is the high selectivity associated with the use of acetonitrile (5% water) as solvent. Thus all three substrates (**1**–**3**) give nearly pure (>94%) *trans*-3-hydroxy product in this medium. This feature should prove of synthetic utility.

All three starting materials show approximately the same responses to solvent changes, suggesting that nearly identical directive influences are exerted by the different substituents. The observed product distributions do not vary in any easily predictable manner with solvent change; the formation of 1,2 product appears to be associated with the less *trans*-3-selective reaction of **1**, but similar behavior is not found with the allylic acetate **3**.[7] In general, the preferred for-

(1) NDEA Title IV Predoctoral Fellow.

(2) Alfred P. Sloan Fellow, 1967–1969.

(3) (a) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957). (b) For a recent example of solvent effect on epoxidation of a homoallylic alcohol, see R. Zurflüh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *J. Amer. Chem. Soc.*, **90**, 6224 (1968).

(4) J. H. Chan and B. Rickborn, *ibid.*, **90**, 6406 (1968); references to earlier work are given here.

(5) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 227 (1959).

(6) M. R. Johnson and B. Rickborn, *Chem. Commun.*, 1073 (1968).

(7) Two early runs with **3** in aqueous THF gave only product **4** in moderate yield;[6] numerous subsequent attempts to repeat this observation have all resulted in the distribution shown in Table I.

TABLE I
PRODUCT DISTRIBUTION FROM OXYMERCURATION–REDUCTION (eq 2)

Solvent	R	R′	Yield, %	% 4	% 5	% 6	% 7
8% H_2O in THF	H	H	37[a]	73.5	24.6	0.9	1.0
50% H_2O in THF	H	H	86	78.2	19.6	0.9	0.8
H_2O	H	H	84	83.6	15.1	0.7	0.6
20% H_2O in glyme	H	H	78	86.4	12.6	0.6	0.4
5% H_2O in DMSO	H	H	[b]	90.5	1.6	3.3	4.6
20% H_2O in CH_3CN	H	H	78	94.0	6.0	0	0
5% H_2O in CH_3CN	H	H	83	96.3	3.7	0	0
CH_3OH	H	CH_3	92	84.4	15.6	0	0
AcOH	H	Ac	95	82.0	6.8	4.4	6.8
40% H_2O in THF	CH_3	H	85	86.8	13.2	0	0
50% H_2O in THF	CH_3	H	92	89.0	11.0	0	0
5% H_2O in DMSO	CH_3	H	[b]	88.8	11.2	0	0
5% H_2O in CH_3CN	CH_3	H	93	94.0	6.0	0	0
AcOH	CH_3	Ac	87	93.6	6.4	0	0
25% H_2O in THF	Ac	H	95	70.0	30.0	0	0
75% H_2O in THF	Ac	H	95	70.5	29.5	0	0
5% H_2O in DMSO	Ac	H	[b]	85.6	3.3	8.6	2.5
5% H_2O in CH_3CN	Ac	H	95	96.0	4.0	0	0
CH_3OH	Ac	CH_3	90	74.5	25.5	0	0
AcOH	Ac	Ac	95	92	8	0	0

[a] The reaction is quite slow under these conditions; 58% of starting material recovered after 33 hr. [b] Yields were not determined owing to difficulty in separating solvent from products.

mation of 1,3 derivative can be ascribed to the inductive effect of the ring substituent. Halpern and Tinker[8] have demonstrated that oxymercuration of **1** occurs at about one-tenth the rate for cyclohexene, and there is thus no kinetic basis for anticipating stereospecific reaction of this system.[4]

Experimental Section

Oxymercuration and Reduction.—The olefin was added in one portion to a stirred solution of solvent and mercuric acetate. The reactions were run at 25°, and in general for 0.5 hr after the disappearance of the colloidal yellow mercuric oxide (not formed in nonaqueous solvents or pure water). The reactions for the most part were rapid, requiring only a few minutes to become colorless. The reactions in acetonitrile (5% H_2O) were fast (4 min to decolorize). DMSO, glyme, and THF containing small amounts of water required longer times for reaction.

Reduction was accomplished by using the sodium borohydride procedure of Brown and Geoghegan.[9] The aqueous base used in this method causes rapid hydrolysis of the acetate esters; this can be avoided by omitting the base and using excess borohydride.

The mercury was removed by filtration through Celite, the aqueous solution saturated with salt and extracted several times with ether. The combined ether extracts were dried with magnesium sulfate and evaporated. The diols thus obtained were taken up in pyridine and treated with excess acetic anhydride. The diacetates were analyzed using a 9 m × 3.2 mm 15% Carbowax 20M column at 152°. Retention times (RT) in minutes for these derivatives follow: **4**, 86; **5**, 100; **6**, 66; **7**, 62. The methoxy alcohols formed by hydroxymercuration of **2** or methoxymercuration of **1** were analyzed directly using the same column at 132°: **4**, 50.5; **5**, 45.6; **6**, 25; **7**, 19. The starting materials 2-cyclohexenol (**1**),[4,10] 3-methoxycyclohexene (**2**),[4] and 2-cyclohexenyl acetate (**3**)[11] have been described previously.

Product Assignments.—Commercial samples of *cis,trans*-1,2-cyclohexanediol and *cis,trans*-1,3-cyclohexanediol were converted into the diacetate derivatives. Literature procedures were used to prepare *trans*-1,2-diol,[12] *trans*-1,3-diol,[13] and *trans*-2-methoxycyclohexanol.[14] Jones oxidation of the latter gave 2-methoxycyclohexanone (96%), which in turn was reduced by $LiAlH_4$ in ether to give a mixture (nearly equal amounts) of the *cis* and *trans* alcohols. *trans*-3-Methoxycyclohexanol was obtained by the procedure of Eliel and Brett.[15] All compounds exhibited the anticipated nmr and ir spectral properties.

(8) J. Halpern and H. B. Tinker, *J. Amer. Chem. Soc.*, **89**, 6427 (1967).
(9) H. C. Brown and P. Geoghegan, Jr., *ibid.*, **89**, 1522 (1967).
(10) R. Willstätter and E. Sonnenfeld, *Chem. Ber.*, **46**, 2952 (1913).
(11) H. J. Shine and J. R. Slagle, *J. Amer. Chem. Soc.*, **81**, 6309 (1959).
(12) A. C. Cope, H. E. Johnson, and J. S. Stephenson, *ibid.*, **78**, 5599 (1956).
(13) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 2103 (1959).
(14) S. Winstein and R. B. Henderson, *J. Amer. Chem. Soc.*, **65**, 2196 (1943).
(15) E. L. Eliel and T. J. Brett, *J. Org. Chem.*, **28**, 1923 (1963).

Registry No.—2-Cyclohexenol, 822-67-3.

Acknowledgment.—This work was supported in part by a grant from the National Science Foundation (GP 6043).

Convenient Synthesis of 2,2-Dimethylcyclobutanone

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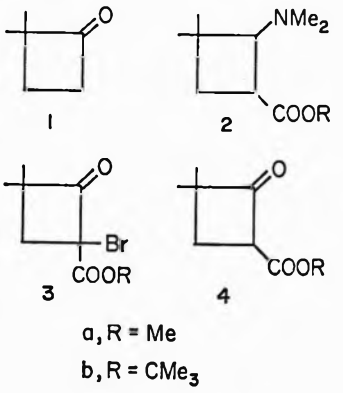
Received February 13, 1969

In connection with another investigation we required a convenient source of 2,2-dimethylcyclobutanone (**1**). There are two previously recorded preparations of this substance, the first[1] being the reaction of dimethylketene with ethylene at 200 atm pressure, and the second[2] involving addition of 2 equiv of diazomethane to dimethylketene. Neither of these seemed suitable for our purposes; the first requires pressure equipment not conveniently available, while the second gives largely the isomeric 3,3-dimethylcyclobutanone, from which the desired minor product **1** is difficultly separable. We describe below a useful preparative route to **1** from *t*-butyl acrylate and the dimethylenamine of isobutyraldehyde. Although four steps are involved from commercially available

(1) H. Bestian and D. Guenter, *Angew. Chem.*, **75**, 841 (1963).
(2) J.-M. Conia and J. Salaün, *Bull. Soc. Chim. Fr.*, 1957 (1964).

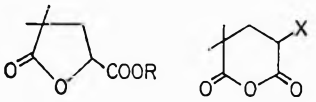
materials, the reactions proceed in high yield (50% over-all) and may be carried out quickly with little intermediate purification.



a, R = Me
b, R = CMe_3

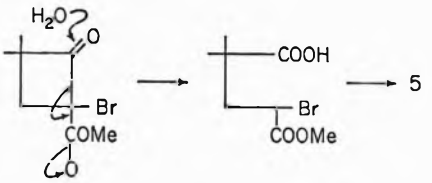
The cycloaddition of acrylic esters to isobutyraldehyde enamine leads readily to amino esters 2.[3] We have used both the previously known[3] methyl ester (**2a**) and the corresponding *t*-butyl ester (**2b**), finally converting the latter to **1**. The synthetic problem is then simply conversion of a dimethylamino group to carbonyl oxygen and complete elimination of an ester function. The first of these operations was smoothly effected by oxidation with bromine.[4] An aqueous solution of the amino ester buffered at pH 6 readily absorbed bromine to give the bromoketo ester (**3**). A second product accompanying **3a** is discussed later; this side reaction was absent in the *t*-butyl series, and **3b** could be obtained in good yield. The structure of **3** is clear from subsequent transformations, as well as completely appropriate spectroscopic properties. The extraneous bromine atom in bromoketo ester **3** was next removed by reduction with zinc dust in glacial acetic acid to furnish keto ester **4**. A second side product obtained in small amount in this reduction is also treated below; once again the side reaction occurred only in the methyl ester series.

We were unable to define acidic conditions which favored ester hydrolysis in **4a** rather than ring opening. While this result is in agreement with recent experience elsewhere,[5] it contrasts with an early description of the successful hydrolysis and decarboxylation in acid of a 2-carbethoxycyclobutanone.[6,7] Similarly, mildly basic hydrolysis of **4a** gave only open-chain products; exposure of **4a** to 1.1 equiv of bicarbonate in methanol at room temperature, for example, led to a mixture of monomethyl and dimethyl 2,2-dimethylglutarate in 87% yield. On the other hand, acid-catalyzed pyrolysis[8] of the *t*-butyl ester **4b** proceeded most satisfactorily. At 138° **4b** lost isobutylene and carbon dioxide to give 2,2-dimethylcyclobutanone (**1**), which was characterized both by its ir and nmr spectra[2] and by preparation of its known 2,4-dinitrophenylhydrazone.[1]



5, R = Me
8, R = H
6, X = H
7, X = Br

We now describe two side products encountered in the methyl ester series. The first arose in variable yield (up to 18%) in the bromine oxidation of **2a** and appeared to be favored at the expense of **3a** if the reaction mixture, which became heterogeneous as oily **3a** separated, was stirred vigorously. The two products were readily separated by fractional distillation, and spectroscopic and analytical data for the side product suggested that it was lactone ester **5**. There was some uncertainty in this conclusion, however, for the nmr spectrum of this substance showed a six-proton singlet for the geminal methyl groups, and the ir spectrum (carbon tetrachloride) had three carbonyl absorption bands, at 1800, 1775, and 1750 cm^{-1}. The problem was settled by independent synthesis of **5**. Direct bromination of 2,2-dimethylglutaric anhydride (**6**)[9] gave α-bromo anhydride **7**, treatment of which first with hot aqueous sodium hydroxide and then with hydrochloric acid furnished lactone carboxylic acid **8**. Diazomethane converted **8** into its methyl ester **5** without difficulty, and this substance proved to be identical with the observed side product. Apparently **5** arises in the bromination reaction by slow hydrolytic cleavage of **3a** followed by intramolecular displacement of bromide ion.



Occurrence of the second side product is rather more interesting, although its origin has not been clearly traced. If **3a** was not rigorously purified before reaction with zinc in acetic acid, **4a** was accompanied by 5–15% of an isomeric methyl ester. This isomer was easily purified by vpc, after which it showed spectroscopic properties indicative of a conjugated enol ether [ir 1710 (s), 1625 (s) cm^{-1}; nmr δ 6.98 (t, J = 1.5 Hz, 1 H); and uv λ_{max} 253.5 mμ (ϵ 11,000)]. The data point to the carbomethoxydihydrofuran **10**, a conclusion substantiated by direct comparison of the side product with an authentic sample of **10**.[10] While we have been unable to isolate the precursor of **10**, which must accompany **3a** and **5** in the bromine oxidation, we suggest that the required transformations can be explained starting with an intermediate such as alcohol **11**. We emphasize that **11** has not been isolated and that other precursors, also plausibly present in the reaction mixture, could be advanced in its stead. Ring contraction in **11** would lead to the cyclopropylaldehyde **12**, a reasonable rearrangement in light of

(3) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 625 (1961); **29**, 801 (1964).

(4) The conditions used were based on the general study of N. C. Deno and R. E. Fruit, Jr., *J. Amer. Chem. Soc.*, **90**, 3502 (1968).

(5) K. C. Brannock, R. D. Burpitt, and J. G. Thweatt, *J. Org. Chem.*, **29**, 940 (1964).

(6) A. Michael, *Ber.*, **33**, 3731 (1900).

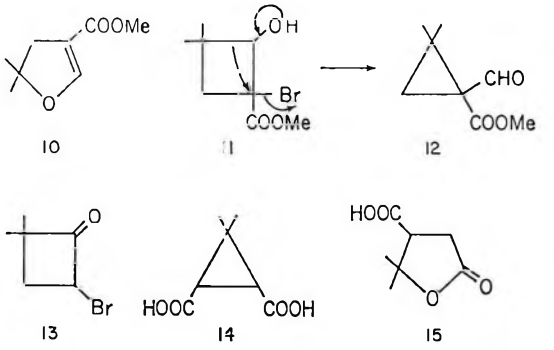
(7) We find, however, that from its nmr spectrum (see Experimental Section) the 2,4-dinitrophenylhydrazone of **4a**, formed under the usual acidic conditions, is indeed a cyclobutanone derivative rather than a glutaric acid hydrazide. The compound is identical with the hydrazone previously obtained[6] from the dimethylenamine of **4a**.

(8) D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1286 (1944); R. S. Yost and C. R. Hauser, *ibid.*, **69**, 2325 (1947); W. B. Renfrow and G. B. Walker, *ibid.*, **70**, 3957 (1948).

(9) E. Rothstein and W. G. Schofield, *J. Chem. Soc.*, 4566 (1965).

(10) F. Korte, K.-H. Büchel, D. Scharf, and A. Zschocke, *Chem. Ber.*, **92**, 884 (1959). We thank Professor Friedhelm Korte and Dr. Heinrich Wamhoff, University of Bonn, for generous samples of both **10** and the corresponding carboxylic acid.

the facility with which the parent bromo ketone (**13**) undergoes Favorskii rearrangement.[11] Acid-catalyzed transformation of **12** to **10** is mechanistically reasonable and has venerable analogy in the rearrangement of *cis*- or *trans*-caronic acid (**14**) to terebic acid (**15**).[12]



Experimental Section

Materials and Equipment.—Isobutyraldehyde dimethylenamine (N,N-dimethylisobutenylamine, K and K Laboratories), methyl acrylate (practical, Matheson Coleman and Bell), and *t*-butyl acrylate (Borden Chemical Co., Monomer–Polymer Laboratories) were used without further purification. Vpc was carried out using a Varian Aerograph Model 700 Autoprep with a 20 ft × 0.25 in. stainless steel column packed with 30% FFAP on Chromosorb W, and operated at 180° with a helium carrier gas flow rate of 100 ml/min. Unless otherwise noted, both ir and nmr spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer 237B spectrophotometer and the latter on a Varian A-60 spectrometer. Distillations were carried out under nitrogen.

***t*-Butyl 2-(Dimethylamino)-3,3-dimethylcyclobutanecarboxylate (2b).**—*t*-Butyl acrylate (16.25 g), isobutyraldehyde dimethylenamine (34.10 g), and 40 ml of acetonitrile were heated at reflux under nitrogen for 54 hr. Acetonitrile and excess enamine were removed by distillation at atmospheric pressure and the remainder was distilled at reduced pressure to give 18.06 g (63%) of product: bp 45–47° (0.08 mm); ir 2855, 2805, 2760, 1725 (s), 1365, 1145 cm^{-1}; nmr δ 2.72–2.18 (m, 3 H), 2.02 (s, 6 H), 1.70 (m, 1 H), 1.41 (s, 9 H), 1.12, 1.06 (two s, 6 H).

Anal. Calcd for $C_{13}H_{25}O_2N$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.54; H, 11.37; N, 6.05.

Methyl 1-Bromo-2-oxo-3,3-dimethylcyclobutanecarboxylate (3a).—Amino ester **2a**[3] (21.7 g) was dissolved in 600 ml of 2 *M* acetate buffer (pH 6). Bromine (43 g) was added dropwise with mechanical stirring and cooling below room temperature. Excess bromine was destroyed with solid $NaHSO_3$ about 15 min after bromine addition was complete, and the reaction mixture was extracted with ether. The ether extracts were washed with 0.5 *M* HCl, 0.6 *M* $NaHCO_3$, water, and brine, and dried over Na_2SO_4. Evaporation of ether gave 17.3 g (63%) crude product, which was distilled: bp 46–48° (0.1 mm); mp 31–33°; ir 1801 (s), 1730 (s), 1430, 1250 (s), 1120, 1000 cm^{-1}; nmr δ 3.80 (s, 3 H), 3.00 (d, J = 13 Hz, 1 H), 2.28 (d, J = 13 Hz, 1 H), 1.44 (s, 3 H), 1.26 (s, 3 H).

Anal. Calcd for $C_8H_{11}O_3Br$: C, 40.87; H, 4.72. Found: C, 41.13; H, 4.78.

***t*-Butyl 1-Bromo-2-oxo-3,3-dimethylcyclobutanecarboxylate (3b).**—*t*-Butyl amino ester **2b** (32.9 g) was oxidized as described above for **2a** to give 35.13 g (88%) crude product, which from nmr analysis contained very little impurity (no absorption below 3.1 ppm). Distillation gave an analytical sample: bp 71–73° (0.5 mm); ir 1798 (s), 1775 (m), 1725 (s), 1370 (s), 1255 (s), 1160 (s); nmr δ 2.92 (d, J = 13.5 Hz, 1 H), 2.22 (d, J = 13.5 Hz, 1 H), 1.48, 1.42 (two s, 12 H), 1.25 (s, 3 H).

Anal. Calcd for $C_{11}H_{17}O_3Br$: C, 47.66; H, 6.18. Found: C, 47.76; H, 6.24.

Methyl 3,3-Dimethyl-2-oxocyclobutanecarboxylate (4a).—A solution of slightly impure bromoketo ester **3a** [(671 mg, bp 72–87° (2.0 mm)] in 25 ml of glacial acetic acid was chilled in an ice bath. Zinc dust (1.0 g) was added with vigorous stirring and the mixture was allowed to come to room temperature as the stirring continued for 30 min. The mixture was filtered and the excess zinc washed with ether and water. The resulting solution was extracted with ether, and the ether extracts were washed with water, 0.6 *M* $NaHCO_3$, water, and brine and were dried over Na_2SO_4. Evaporation of ether gave 340 mg (76%) of crude keto ester contaminated with about 5% of dihydrofuran **10**: ir 1795 (s), 1735 (s), 1315, 1205, 1170 cm^{-1}; nmr (parts per million downfield from external tetramethylsilane in CCl_4) 4.12 (dd, J_1 = 10 Hz, J_2 = 6.5 Hz, 1 H), 3.68 (s, 3 H), 2.30–1.75 (m, 2 H), 1.20 (s, 6 H). When analytically pure bromoketo ester was reduced, no **10** was formed.

A 2,4-dinitrophenylhydrazone was prepared for analysis: mp 132–133° from methanol (lit.[6] mp 128.5–130°); nmr ($CDCl_3$; parts per million downfield from external tetramethylsilane in $CHCl_3$) 11.4 (broad s, 1 H), 8.95 (d, J = 2 Hz, 1 H), 8.20 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1 H), 7.80 (d, J = 9 Hz, 1 H), 4.23 (dd, J_1 = 10 Hz, J_2 = 6 Hz, 1 H), 3.84 (s, 3 H), 2.24–1.93 (m, 2 H), 1.33 (s, 6 H).

Anal. Calcd for $C_{14}H_{16}O_6N_4$: C, 49.99; H, 4.80; N, 16.66. Found: C, 49.80; H, 4.97; N, 16.91.

Methyl 4,5-Dihydro-5,5-dimethyl-3-furoate (10).—Reduction of crude bromoketo ester **3a** with zinc dust always gave 5–15% of dihydrofuran **10**. Preparative vpc destroyed the keto ester but gave pure **10** (retention time 24 min); ir 1710 (s), 1625 (s), 1175, 1090 cm^{-1}; nmr (parts per million downfield from external tetramethylsilane in CCl_4) 6.98 (t, J = 1.5 Hz, 1 H), 3.56 (s, 3 H), 2.53 (d, J = 1.5 Hz, 2 H), 1.32 (s, 6 H); uv (CH_3OH) λ_{max} 253.5 mμ (ϵ 11,000).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: 61.61; H, 7.56.

The vpc retention time and ir, uv, and nmr spectra of this material were identical with those of an authentic sample.[10]

Hydrolysis of Methyl 3,3-Dimethyl-2-oxocyclobutanecarboxylate (4a). A. Basic Hydrolysis.—Keto ester **4a** (4.74 g) was stirred at room temperature under nitrogen for 23 hr with 20 ml of methanol, 60 ml of water, and 2.90 g (1.1 equiv) of $NaHCO_3$. The reaction mixture was diluted with water and extracted with ether. The ether extracts were washed with water, dried over Na_2SO_4, and evaporated to give 2.04 g of colorless oil, ir and nmr spectra identical with those of authentic dimethyl 2,2-dimethylglutarate. Acidification of the reaction mixture followed by ether extraction gave 2.70 g of colorless oil: ir 3300–2700 (broad), 1740 (s), 1701 (s); nmr (parts per million downfield from external tetramethylsilane in CCl_4) 10.4 (s, 1 H), 3.57 (s, 3 H), 2.47–1.67 (m, 4 H), 1.17 (s, 6 H). Esterification of this material with diazomethane gave dimethyl 2,2-dimethylglutarate.

B. Acidic Hydrolysis.—The keto ester **4a** (820 mg) was heated at reflux with 1.6 ml of 6 *M* HCl for 1.5 hr and the reaction mixture was extracted with ether. The ether extracts were washed with water and brine and dried over Na_2SO_4. Evaporation of ether gave 746 mg of crude brown oil: ir 3400–2400 (broad), 1735 (w), 1710 (s). There was no cyclobutane carbonyl absorption.

***t*-Butyl 3,3-Dimethyl-2-oxocyclobutanecarboxylate (4b).**—*t*-Butyl bromoketo ester **3b** (5.93 g) was reduced as described above for **3a** to give 4.31 g (100%) of crude product which showed no impurities in its nmr spectrum. Distillation gave analytically pure material: bp 80.2° (2.8 mm); ir 1780 (s), 1724 (s), 1365 (m), 1150 (s); nmr δ 4.05 (dd, J_1 = 10 Hz, J_2 = 7 Hz, 1 H), 2.40–1.75 (m, 2 H), 1.41 (s, 9 H), 1.22 (s, 6 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.63; H, 9.15. Found: C, 66.81; H, 9.33.

2,2-Dimethylcyclobutanone (1).—*t*-Butyl keto ester **4b** (9.86 g) and *p*-toluenesulfonic acid monohydrate (40 mg) were heated with an oil bath in a distillation apparatus under nitrogen. Smooth gas evolution began at a bath temperature of 138°, and product began to distil. The reaction was complete in 15 min, during which time bath temperature increased to 152° and 4.31 g (91%) very slightly impure product distilled. Redistillation through a short Vigreux column gave pure material, bp 113.5–114° (760 mm). The spectroscopic properties of this material were in complete agreement with literature values.[2]

A 2,4-dinitrophenylhydrazone was prepared: mp 140.5–141.5° from methanol (lit.[1] mp 140–141°).

2,2-Dimethyl-4-bromoglutaric Anhydride (7).—A mixture of 2,2-dimethylglutaric anhydride (**6**)[9] (1.29 g) and red phosphorus

(11) Treatment of **13** with hot water or liquid ammonia or aqueous carbonate at 50° brings about quantitative Favorskii rearrangement.[2]

(12) A. Baeyer and W. Ipatiew, *Ber.*, **29**, 2796 (1896).

(about 10 mg) was heated to 85–90° and treated over 5 min with bromine (1.31 g). Direct crystallization of the product from benzene gave 610 mg. Several recrystallizations from benzene–cyclohexane followed by sublimation gave an analytical sample: mp 79–81°; ir 1823 (m), 1780 (s), 1024 (s) cm^{-1}; nmr δ 4.72 (t, J = 8 Hz, 1 H), 2.38 (d, J = 8 Hz, 2 H), 1.47 (s, 3 H), 1.43 (s, 3 H).

Anal. Calcd for $C_7H_9O_3Br$: C, 38.03; H, 4.10; Br, 36.15. Found: C, 37.97; H, 4.12; Br, 35.89.

2,2-Dimethyl-4-hydroxyglutaric Acid Lactone (8). A. Authentic Sample.—A mixture of bromo anhydride **7** (150 mg) and 10 ml of 5% aqueous sodium hydroxide was heated at reflux under nitrogen for 3 hr. The resulting clear solution was taken to dryness *in vacuo;* the residue was taken up in hydrochloric acid, and the solution was again taken to dryness. Extraction of the residue with several portions of hot benzene gave 89 mg (90%) of crude product. Several recrystallizations from benzene–cyclohexane gave an analytical sample: mp 82–84°; ir (KBr disk) 3600–2800 (broad), 1780 (s), 1750 (s), 1178 (s), 1165 (s), 1060 (s) cm^{-1}; nmr ($CDCl_3$) δ 10.71 (s, 1 H), 4.95 (t, J = 8 Hz, 1 H), 2.42 (dd, J_1 = 6 Hz, J_2 = 8 Hz, 2 H), 1.31 (s, 6 H).

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.16; H, 6.35.

B. By Saponification of 5.—A solution of lactone methyl ester **5** (300 mg) in 40 ml of methanol containing 6.9 ml of 0.5 *M* sodium hydroxide was kept overnight at room temperature under nitrogen and was then taken to dryness. The residue was taken up in water, acidified with concentrated HCl to pH 2, taken again to dryness, and then worked up as in A above. There was recovered 260 mg (94%) of crude crystalline product. Two recrystallizations gave a sample with melting point, mixture melting point, ir, and nmr spectra identical with those of an authentic sample.

2,2-Dimethyl-4-hydroxyglutaric Acid Lactone Methyl Ester (5). A. Authentic Sample.—A solution of lactone carboxylic acid **8** (50 mg) in 10 ml of ether was treated with excess ethereal diazomethane and allowed to remain at room temperature for 2 hr. The solution was taken to dryness and the product twice crystallized from benzene–cyclohexane: mp 49.5–50°; ir (KBr disk) 2950 (m), 1775 (s), 1760 (s), 1220 (ms), 1195 (ms), 1065 (s) cm^{-1}; (CCl_4) 2950 (m), 1800 (s), 1775 (ms), 1750 (ms), 1200 (ms), 1110 (m), 1070 (m) cm^{-1}; nmr δ 4.80 (t, J = 7.5 Hz, 1 H), 3.80 (s, 3 H), 2.29 (dd, J_1 = 7.5 Hz, J_2 = 6.5 Hz, 2 H), 1.25 (s, 6 H).

B. From Bromination of Amino Ester 2a.—Distillation of the crude bromination product described above gave a fraction of variable amount, bp 85–88° (0.3 mm), which spontaneously crystallized in the cold. Recrystallization of this material first from CCl_4 and then from benzene–cyclohexane gave stout needles, melting point, mixture melting point, and ir and nmr spectra identical with those of an authentic sample.

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.97; H, 7.25.

Registry No.—**1**, 1192-14-9; **2b**, 20104-44-3; **3a**, 20104-45-4; **3b**, 20104-46-5; **4b**, 20104-47-6; **5**, 20104-48-7; **7**, 20104-49-8; **8**, 20104-52-3; **10**, 20104-53-4.

Acknowledgment.—It is a pleasure to acknowledge the aid of the National Science Foundation through Grant GB-137 and a graduate fellowship to D. K. H.

Condensation of *p*-Nitrotoluene with Aldehydes

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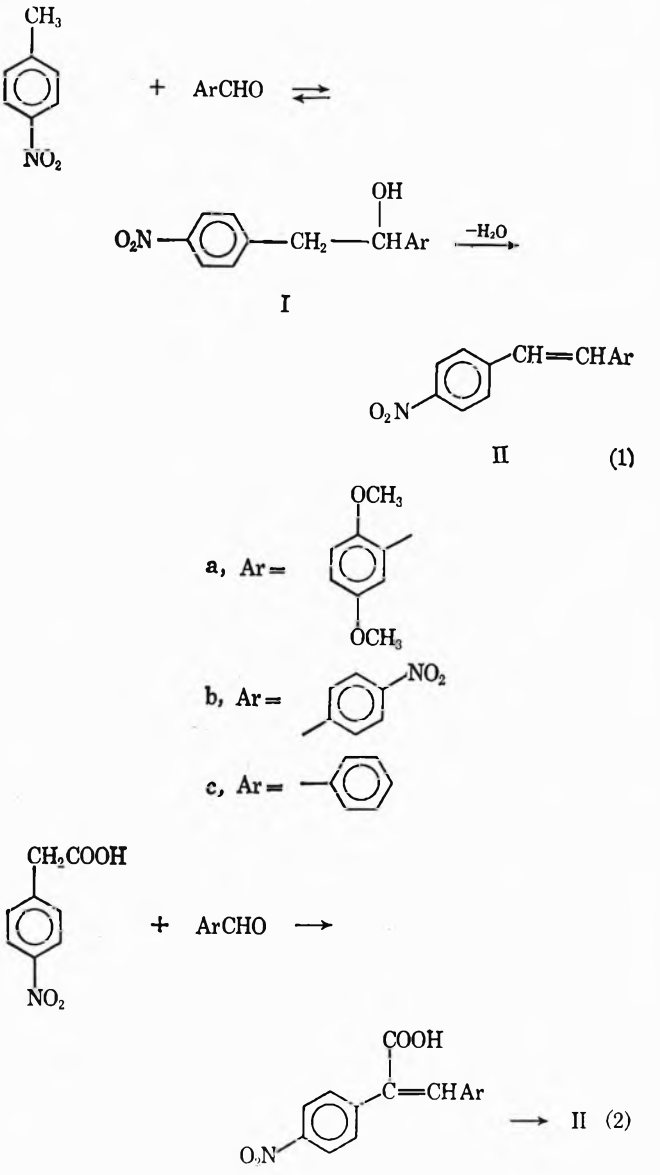
Base-catalyzed condensation reactions of *p*-nitrotoluene are complicated by the facile oxidation[1,2] and dimerization[2,3] of the *p*-nitrotoluene carbanion. Condensation with aldehydes has resulted in very poor yields of the desired stilbenes[4] (eq 1), and has led to the use of the condensation–decarboxylation sequence employing *p*-nitrophenylacetic acid[5] (eq 2).



Despite the unpromising past performance of the *p*-nitrotoluene carbanion in condensation reactions,[3,4] it was expected that the proper choice of solvent might improve the situation. That highly polar aprotic solvents can greatly assist a variety of anionic processes has been abundantly demonstrated in recent years.[2,6] Therefore, the condensation of *p*-nitrotoluene with aromatic aldehydes in dipolar aprotic solvent systems was investigated.

(1) T. Tsuruta, *et al.*, *Bull. Inst. Chem. Res., Kyoto Univ.*, **30**, 46, 47 (1952); *Chem. Abstr.*, **48**, 11369, 13376 (1954).

(2) G. A. Russell, A. J. Moye, E. G. Janzen, S. Mak, and E. R. Ralaty, *J. Org. Chem.*, **32**, 137 (1967).

(3) E. Borello and M. E. G. Locchi, *Ann. Chim.* (Rome), **43**, 25 (1953); *Chem. Abstr.*, **48**, 2015 (1954); F. W. Bergstrom, I. M. Granara, and V. Erickson, *J. Org. Chem.*, **7**, 98 (1942).

(4) L. Chardonnens and P. Heinrich, *Helv. Chim. Acta*, **22**, 1471 (1939); J. F. J. Dippy, L. T. Hogarth, H. B. Watson, and F. R. Williams, *J. Soc. Chem. Ind.*, **56**, 396 (1937).

(5) H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.*, **31**, 4146 (1966); A. A. R. Sayigh and H. Ulrich, U. S. Patent 3,363,004 (1968); R. Ketcham and D. Jambotkar, *J. Org. Chem.*, **28**, 1034 (1963), and references cited therein.

(6) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962); A. Schreischeim, *et al.*, Belgian Patent 617,842; *Chem. Abstr.*, **59**, 3772 (1963).

Results and Discussion

The reaction of *p*-nitrotoluene with 2,5-dimethoxybenzaldehyde was examined in a number of solvents, with several bases as catalysts and under a variety of conditions. Certain limitations were apparent at the outset. Dimethyl sulfoxide (DMSO), for example, added to the aldehyde under the reaction conditions,[6,7] to the exclusion of the desired condensation. Bases such as potassium *t*-butoxide promoted formation of 2,5-dimethoxybenzoic acid, rather than the condensation products. Of the bases (morpholine, piperidine, alkali metal hydroxides and alkoxides, tetra-*n*-butylammonium hydroxide) and solvents [DMSO, dimethylformamide (DMF), hexamethylphosphoramide] employed, a DMF–lithium hydroxide system offered the first spectral and tlc evidence of the desired stilbene reaction product, and showed that the condensation could compete favorably with the dimerization–oxidation reactions.

We sought, in subsequent experiments, to improve the yield of stilbene by increasing the severity of the reaction conditions (80–100°, 4–18 hr), by using benzene to aid in water removal, and by increasing the catalyst concentration (0.5–1.2 moles). Despite these efforts, starting material persisted at the termination of the reaction, and the products were accompanied by the usual tarry intractable matter. We were able, however, to isolate from these reaction mixtures a solid product which was shown to be the diarylethanol, Ia. Nearly quantitative yields of Ia could be obtained in 2 hr at 20–28° with a threefold excess of *p*-nitrotoluene.

Although the equilibrium nature of the reaction seemed probable from the experimental results, we sought spectral verification of this and the proposed *p*-nitrotoluene carbanion intermediate. Miller and Pobiner[8] have examined the ultraviolet and visible spectra of *p*-nitrotoluene in potassium *t*-butoxide–*t*-butyl alcohol solution and have observed bands at 362 mμ (*p*-nitrotoluene carbanion) and 557 mμ (charge-transfer complex). Neither is associated with free-radical formation. In sodium hydroxide–DMF we find an absorption at 580 mμ for *p*-nitrotoluene alone, and for the reaction mixture with dimethoxybenzaldehyde present. Most convincingly, a solution of Ia in DMF which is essentially transparent in the visible, develops a strong blue-green color and an absorption at 580 mμ on treatment with sodium hydroxide. On acidification, this solution yields recovered Ia plus *p*-nitrotoluene and dimethoxybenzaldehyde.[9]

To complete the stilbene synthesis, it remained to demonstrate that Ia was readily dehydrated to IIa. This could be accomplished with phosphoric acid, or, most conveniently, by refluxing a solution of Ia in dimethyl sulfoxide.[10] In 3 hr, there was obtained a 96.5% yield of exclusively *trans*-2,5-dimethoxy-4′-nitrostilbene (IIa).[11]

The product was of exceptional purity as evidenced by its infrared, ultraviolet, and nmr spectral data, melting point, and thin layer chromatography and was free of the minor impurities encountered in the mineral acid catalyzed dehydration. The over-all yield of 90% based on starting aldehyde represents a considerable improvement over the *p*-nitrophenylacetic acid method.[5]

p-Nitrobenzaldehyde and benzaldehyde have been condensed with *p*-nitrotoluene and the corresponding diarylethanols (Ib and Ic) prepared. This method provides a simple procedure for the synthesis of 4-nitrostilbenes and their derivatives. Of course, the equilibrium concentration, and hence the yield, of I will vary with the substrate, but the reaction appears suitable enough for general applicability.

Experimental Section[12]

***p*-Nitrotoluene Condensation. Synthesis of 1-(2,5-Dimethoxyphenyl-2-(4′-nitrophenyl)ethanol (Ia).**—To a well-stirred solution of 6.85 g (0.05 mole) of *p*-nitrotoluene and 8.3 g (0.05 mole) of 2,5-dimethoxybenzaldehyde in 100 ml of dimethylformamide was added, under nitrogen, 0.2 g (0.005 mole) of freshly ground sodium hydroxide. The reaction mixture turned bright green in 25 min at room temperature. After 2 hr, the reaction mixture was acidified with 60 ml of 5% hydrochloric acid and extracted with benzene. The benzene solution was dried and the benzene evaporated to an orange oil. Crystallization from benzene–cyclohexane (1:3) gave 8.34 g (0.027 mole, 55%) of a yellow solid, Ia, mp 99–101°. Repeated recrystallization from ethyl acetate–petroleum ether raised the melting point to 102.5–104.5°: nmr (DMSO-d_6), δ 8.09 (d, 2, Ar-H), 7.48 (d, 2, Ar-H), 6.9 (m, 3, Ar-H), 5.18 (m, 2, ArCHOH), 3.78–3.72 (2 s, 6, OCH_3), 3.0 (m, 2, CH_2).

Anal. Calcd for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.46; H, 5.82; N, 4.67.

Excess *p*-Nitrotoluene.—In a similar manner were reacted 61.6 g (0.45 mole) of *p*-nitrotoluene and 19.1 g (0.15 mole) of 2,5-dimethoxybenzaldehyde in 100 ml of dimethylformamide with 0.2 g (0.005 mole) of sodium hydroxide. The mixture turned dark green in 7 min. After 2 hr the reaction mixture was acidified with 1 ml of concentratedhydrochloric acid, filtered, and vacuum distilled. The solvent was removed at 45–52° (10 mm) and excess *p*-nitrotoluene at 90° (0.25 mm) to yield 45.15 g (0.149 mole, 99%) of a red oil which solidified on standing to a yellow solid, mp 99–101°.

The yield and quality of the product were not affected by introducing the catalyst as a 50% aqueous solution. However, as little as 3% water in the solvent gave a slower reaction rate and lower yield (75%) of inferior quality product.

In similar fashion 1,2-di(4-nitrophenyl)ethanol was prepared (Ib), mp 183–185°, in 16% yield, and 1-(4-nitrophenyl)-2-phenylethanol (Ic), mp 90–91°, in 33% yield.

Anal. Calcd for $C_{14}H_{13}NO_3$ (Ic): C, 69.12; H, 5.39; N, 5.76. Found: C, 68.93; H, 5.17; N, 5.92.

2,5-Dimethoxy-4′-nitrostilbene (IIa).—A solution of 1-(2,5-dimethoxyphenyl)-2-(4′-nitrophenyl)ethanol (Ia) (6.07 g, 0.02 mole) in dimethyl sulfoxide (40 ml) was refluxed with stirring for 3 hr. The reaction mixture was evaporated to a red oil (5.46 g) which began to crystallize at room temperature. After washing with petroleum ether, bright yellow 2,5-dimethoxy-4′-nitrostilbene (IIa) (5.50 g, 96.5%), mp 116.5–118°, was obtained. On recrystallization from cyclohexane, it had mp 119–119.5°,[13] λ_{max}^{380} (ε 19,150);[5] thin layer chromatography on a phosphor plate showed a single spot both under visible and ultraviolet light.

Registry No.—*p*-Nitrotoluene, 99-99-0; Ia, 20273-72-7; Ib, 20273-73-8; Ic, 20273-74-9.

(7) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962).
(8) J. M. Miller and H. Pobiner, *Anal. Chem.*, **36** (1), 238 (1964).
(9) G. A. Russell and E. G. Janzen, *J. Amer. Chem. Soc.*, **84**, 4153 (1962); **89**, 300 (1967); E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev.* (London), **22**, 128 (1968).
(10) V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti *J. Org. Chem.*, **29**, 123 (1964).
(11) . H. Wheeler and H. N. Battle de Pabon, *J. Org. Chem.*, **30**, 1473 (1965).
(12) Melting points are uncorrected. Infrared spectra were obtained on a Beckman IR-8; ultraviolet spectra on a Beckman DU and a Cary Model 14; nmr spectra on a Varian A-60.
(13) H. Kaufmann, *Ber.*, **54**, 795 (1921), reports mp 118°.

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The Steric Course of a Ketimine Reduction

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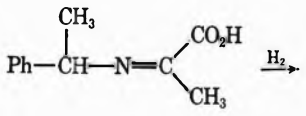
Asymmetric induction occurs when a new chiral center is formed by a reaction in which its symmetry is influenced by a second chiral center, already present in the reacting molecule. The phenomenon is most readily observed with optically active materials when the extent of asymmetric induction is evident from the optical activity of the products. For example, $R(-)$-alanine is formed in excess over the $S(+)$ enantiomer when pyruvic acid is reductively aminated with $R(+)$-α-methylbenzylamine.[2] More recently, an explanation of the stereochemistry involved has been proposed.[3] One problem, however, was the difficulty in specifying the amounts of the two geometrical isomers possible for ketimine **1**.



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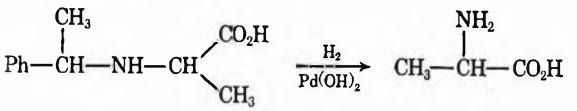
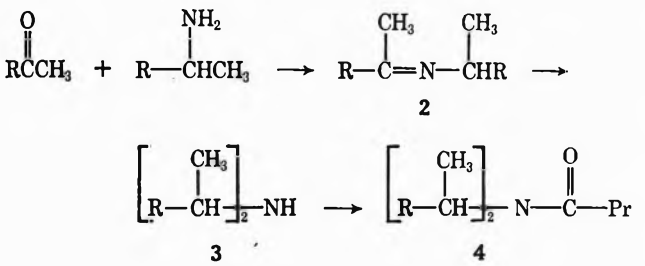


During the course of a synthesis of the amide **4**, we have observed a related case of asymmetric induction during the reduction of a ketimine with lithium aluminum hydride. In this case, the phenomenon was observed with optically inactive materials and the extent of the asymmetric induction was evident by glpc analysis of the two diastereoisomers present in the product. An explanation for the steric course of the reduction is presented which is based on the geometry of the ketimine **2**.



2 **3** **4**

The ketimine **2**, resulting from condensation of 2-octanone and 2-aminooctane, was reduced with lithium aluminum hydride to give the amine **3** in 69% yield. When analyzed by glpc, the amine product showed two barely resolved peaks in a roughly 2:1 ratio on a 6 ft × 1/4 in. Apiezon column. Acylation of the amine with butyryl chloride gave the amide **4**, which showed two peaks in a similar ratio. In the case of the amide, however, the two peaks were sufficiently well resolved to permit their separation by preparative glp, and in this way it was shown that the two peaks were due to diastereoisomers.

The two chiral centers in the amide **4** are probably closer to one another than are the chiral centers in the amine **3**. The greater interaction of symmetries in **4** presumably explains the ease of resolution of the diastereoisomers of **4** on a short-packed glpc column. The two isomers collected from preparative glpc were indistinguishable by ir, nmr, and tlc, while their mass spectra did show slight differences.

Before attempting to explain why the two diastereoisomers were produced in unequal amounts, it was first necessary to determine whether the major product from reduction of the ketimine **2** was the *meso* or the racemic form of the amine **3**. The racemic form should be resolvable on a glpc column containing an optically active liquid phase, and in fact Gil-Av[4] has reported the resolution of racemic amines as their trifluoroacetyl (TFA) derivatives on columns containing amino acid derivatives. Consequently, a 200 ft × 0.010 in. column was coated with the ureide of L-valine isopropyl ester. On this column, for example, the TFA derivative of 1-methylheptylamine gave two equal peaks due to the two enantiomers. However, all attempts to analyze the TFA derivative of bis(1-methylheptyl)amine (**2**) by this method were unsuccessful owing to excessive bleeding of the column above the recommended maximum temperature of 120°.

As an alternative method for distinguishing between the diastereoisomers, the amine **3** was acylated with an optically active acid chloride, N-trifluoroacetyl-L-prolyl chloride (TPC).[5] The product was analyzed on an 8 ft × 1/4 in. column containing diethylene glycol succinate and showed three peaks. Two of these were equal in size and clearly resulted from the racemic diastereoisomer of the amine.

As further confirmation of the above peak assignment, the amine **3** was converted to its hydrochloride salt, which was recrystallized several times. When the amine was regenerated from the purified salt, the ratio of the two diastereoisomers was found to be significantly altered. The TPC derivative of this refined amine was analyzed as described above, and the size of the two equal peaks had changed relative to the third peak, confirming the earlier peak assignment.

Having thus distinguished between the two isomers, it was now evident that the racemate of **3** was the major product from reduction of the ketimine **2**, and in fact the racemate made up 62% of the isomeric mixture. Any explanation of this difference in the quantity of the diastereoisomers is complicated by the existence in the ketimine itself of two geometrical isomers, which is evident from its nmr spectrum. The olefinic methyl group of **2** appears as two distinct singlets at 8.30 and 8.16 ppm. The peak at 8.30 is much larger and is probably

(1) Present address: Imperial Chemical Industries, Ltd., Petrochemical and Polymer Laboratory, P. O. Box No. 11, The Heath, Runcorn, Cheshire, England.

(2) R. G. Hiskey and R. C. Northrop, *J. Amer. Chem. Soc.*, **83**, 4798 (1961).

(3) K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1794 (1967).

(4) B. Feibush and E. Gil-Av, *J. Gas Chromatog.*, 257 (1967).

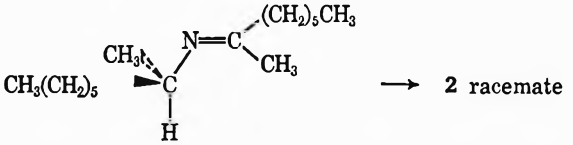
(5) B. Halpern and J. W. Westley, *Biochem. Biophys. Res. Commun.*, **19**, 361 (1965); *Tetrahedron Lett.*, 2283 (1966); *Chem. Comm.*, 34 (1966).

due to the more stable isomer **2A** which seems to make up 87% of the mixture.

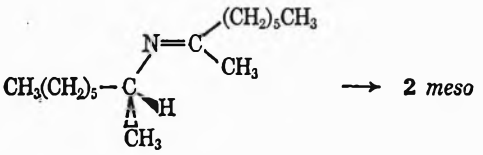
2A **2B**

R = n-hexyl
R′ = 2-octyl

Of the various conformations which can result from rotation about the single CN bond in **2A**, the two most likely to be present in the transition state leading to reduction are shown in the diagrams below. When the tertiary hydrogen lies in the plane of the paper, the attacking hydride ion is more likely to approach the olefinic carbon from below the plane of the paper for the particular enantiomer shown. In this case, the incoming ion encounters the methyl group rather than the bulkier six-carbon chain and the amine is produced as the racemic diastereoisomer.



A second likely conformation for this enantiomer would occur when the tertiary hydrogen and the methyl group are both staggered on either side of the plane of the paper. Then the attacking hydride ion would prefer to approach from above the plane of the paper and so encounter the hydrogen atom rather than the bulkier methyl group. Consequently, the amine would be produced in the *meso* form when the ketimine is reduced in this conformation.



The observation that **3** is formed as an isomeric mixture containing 62% of the racemate indicates that the first conformation is more favored than the second. Other factors, however, in addition to those described above may well be involved.

Experimental Section

N-(2-Octyl)methylhexylketimine (2).—A solution of 2-octanone (157.5 g, 1.24 mol) and 2-aminooctane (158.9 g, 1.24 mol) in toluene (1.5 l.) was refluxed overnight with a Dean–Stark trap in which water (20.2 g, 1.13 mol) was collected. The solvent was evaporated and the residue distilled under nitrogen to give a small forerun of starting materials, bp 45–95° (1 mm), followed by the ketimine (190 g, 62%): bp 96–97° (52 μ); n^{27}D 1.4414; uv max (isooctane) 245 mμ (ε 112); ir (liquid film) 1658 cm^{-1} (C=N); nmr (neat) τ 6.62 (m, 1, CH—N=C), 7.87 (t, 2, J = 6 Hz, CH_2—C=N), 8.16 and 8.30 (S, 3, CH_3=N) ppm. Analysis by glpc on several different columns showed one peak.

Anal. Calcd for $C_{16}H_{33}N$: N, 5.85. Found: N, 5.70.

Bis(1-methylheptyl)amine (3).—N-(2-Octyl)methylhexylketimine (150.0 g, 0.772 mol) was added to a stirred solution of lithium aluminum hydride (29.3 g, 0.772 mol) in tetrahydrofuran (1 l.) at room temperature under a nitrogen atmosphere. After refluxing for 24 hr, the metal complex was decomposed by treatment with aqueous base in the usual manner,[6] the resulting suspension was filtered, and the organic layer of the filtrate was dried ($MgSO_4$) and evaporated. The residue was distilled to give bis(1-methylheptyl)amine (105.4 g, 69%), bp 102–105° (60 μ), n^{26}D 1.4363–1.4372; nmr (neat) τ 7.36 (broad, 2, CH-N) ppm.

Anal. Calcd for $C_{16}H_{35}N$: C, 79.59; H, 14.61; N, 5.80. Found: C, 80.08; H, 14.85; N, 5.79.

Treatment of a sample of the amine in hexane with aqueous hydrochloric acid gave the amine hydrochloride salt, mp 104–107°, after two recrystallizations from heptane.

Anal. Calcd for $C_{16}H_{36}NCl$: C, 69.01; H, 13.05; N, 5.04. Found: C, 68.92; 13.51; N, 4.96.

A second sample of the amine was converted to the trifluoroacetyl derivative by treatment of a 10% solution of the amine in hexane (1 ml) with trifluoroacetic anhydride (100 μl). The solution was analyzed at 200° on a 6 ft × 1/4 in. glpc column containing 15% Apiezon L and shown to contain two isomers in a 62:38 ratio.

A third sample of the amine (50 mg, 0.21 μmol) in chloroform (2 ml) was treated with a 0.1 *M* solution of N-trifluoroacetyl-L-prolyl chloride in chloroform (2.3 ml), as obtained from Regis Chemical Co. After stirring for 1 min, triethylamine (40 μl, 0.23 μmol) was added and the solution stirred for 15 min at room temperature when 6 *N* hydrochloric acid (3 ml) was added. The organic layer was washed with water, dried ($MgSO_4$), and most of the solvent evaporated in a stream of nitrogen. The remaining derivative of **3** was analyzed directly at 225° on an 8 ft × 1/4 in. column containing 10% of diethylene glycol succinate.

Bis(1-methylheptyl)butyramide (4).—Bis(1-methylheptyl)amine (85.6 g, 0.356 mol) was refluxed overnight in toluene (600 ml) containing butyryl chloride (20.6 g, 0.193 mol). The toluene was evaporated and hexane (600 ml) was added when the amine hydrochloride was removed by filtration and the filtrate washed with aqueous base and water before drying ($MgSO_4$). The hexane was evaporated and the residue distilled, giving a small forerun of bis(1-methylheptyl)amine, bp 80–83° (8 μ), followed by bis(1-methylheptyl)butyramide (38.6 g, 64%) bp, 127–130° (8 μ), n^{26}D 1.4550, ir (liquid film) 1640 cm^{-1} (C=O).

It had two broad absorptions at τ 6.09 and 6.84 ppm in the nmr. These two peaks, which are due to the tertiary hydrogens in two distinct conformations, coalesced to one broad peak on warming above room temperature. The nmr also showed a peak at τ 7.71 ppm (t, 2 CH_2CO), while the glpc analysis gave two well-resolved peaks on Apiezon L at 250°.

Anal. Calcd for $C_{20}H_{41}NO$: C, 77.10; H, 13.27; N, 4.50. Found: C, 77.21; H, 13.26; N, 4.54.

Registry No.—**2A**, 20273-75-0; **2B**, 20273-76-1; (±)-**3**, 20221-59-4; (±)-**3** HCl, 20273-77-2; *meso*-**3**, 20273-78-3; *meso*-**3** HCl, 20273-79-4; (±)-**4**, 20273-80-7; *meso*-**4**, 20273-81-8.

Acknowledgment.—The author wishes to express his gratitude to Dr. J. J. Conradi and Dr. H. A. Harris for helpful discussions.

(6) N. G. Gaylord, "Reduction with the Complex Metal Hydrides," Interscience Publishers, Inc., New York and London, 1956, p 1011.

Alkoxyl Exchange Reactions of Naphthalene Ethers

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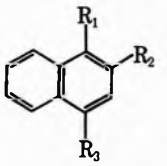
During the course of our work on the photooxidation of aromatic systems[2] we had occasion to prepare 1,2,4-trimethoxynaphthalene. In order to do this we hydrolyzed 1,4-diacetoxy-2-methoxynaphthalene[3] (**1**) with

(1) To whom all communications should be addressed.

(2) J. E. Baldwin, H. H. Basson, and H. C. Krauss, *Chem. Commun.*, 984 (1968).

(3) L. F. Fieser, *J. Amer. Chem. Soc.*, **48**, 2933 (1926).

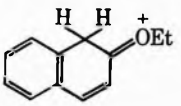
methanolic hydrogen chloride. Surprisingly the product isolated in quantitative yield after 1 min at 60°



1, $R_1 = R_3 = OAc$; $R_2 = OCH_3$
2, $R_1 = OH$; $R_2 = R_3 = OCH_3$
3, $R_1 = OH$; $R_2 = R_3 = OCH_2CH_3$
5, $R_1 = R_3 = OH$; $R_2 = OCH_3$
8, $R_1 = OH$; $R_2 = Cl$; $R_3 = OCH_3$
11, $R_1 = OAc$; $R_2 = R_3 = OCH_3$
12, $R_1 = OAc$; $R_2 = R_3 = OCH_2CH_3$
13, $R_1 = OAc$; $R_2 = Cl$; $R_3 = OCH_3$
14, $R_1 = OCH_3$; $R_2 = H$; $R_3 = OAc$

was 2,4-dimethoxy-1-naphthol (2). Hydrolysis of 1 with ethanolic hydrogen chloride yielded, under the same conditions, 2,4-diethoxy-1-naphthol (3) and, furthermore, the products 2 and 3 were found to be interconvertible under the same conditions of reaction and time.

There are in the literature a number of studies of acid-catalyzed conversions of phenols to phenol ethers.[4,5] These and related deuterium exchange studies[6] have demonstrated that the carbon-protonated species, *e.g.*, 4, is the reactive exchanging intermediate. However



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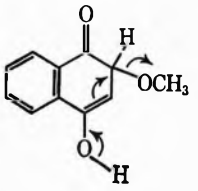
the generally vigorous conditions required,[7] completely different from those we used, suggested the possibility of an alternate mechanism for the conversion of 1 into 2. Acid-catalyzed ketonization of 5 would produce 6 which



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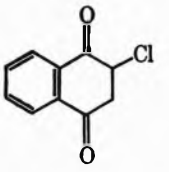
could readily lose the elements of methanol to give 1,4-naphthoquinone. Michael addition of solvent ethanol to the quinone would give 7. Enolization of 7 followed by acid-catalyzed ether exchange[4,5] of 7 at the less hindered 4 position would then provide the product 3 To test this possibility we subjected 1,4-naphthoquinone to methanolic hydrogen chloride under the same conditions as before and obtained in quantitative yield a chlorine-containing compound. This substance was shown to be the phenolic ether 8 by hydrogenolysis to 4-methoxy-1-naphthol.[8] The position of the chlorine atom in 8 was confirmed by the observation that the phenol 8 did not exchange with deuterium under conditions in which 4-methoxy-1-naphthol rapidly exchanged its 2-hydrogen atom. 1,4-Naphthoquinone can therefore not mediate in the ether exchange reaction of 1 and the conversion to 8 is best understood in terms of a simple addition of hydrogen chloride to the



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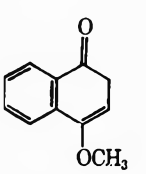
double bond[9] yielding the diketone 9. Exchange of the less hindered carbonyl followed by aromatization would provide the observed product.

We conclude from these observations that the exchange proceeds by the protonation process already described[4-6] with three additional qualifications: first, that an increased number of electron-releasing groups causes a large increase in the rate of protonation and hence in the rate of exchange; second, that β-alkoxyl exchange occurs more rapidly[6] and a *meta* orientation of two alkoxyls is particularly favorable. Thus whereas 1,4-dimethoxynaphthalene[10] did not exchange under our usual conditions, 1,3-dimethoxynaphthalene[11] proceeded to a 1,3-substituted monomethoxylmonoethoxylnaphthalene which was not further characterized. However the ethoxyl function could readily be replaced by a methoxyl function again in methanolic hydrogen chloride to give the original 1,3-dimethoxynaphthalene. Finally, that a *para*-hydroxyl group strongly assists the exchange of an alkoxyl function, as was noted when 1-acetoxy-4-methoxynaphthalene[12] 14 was treated under usual conditions with ethanolic hydrogen chloride to give 4-ethoxy-1-naphthol[8] while α-naphthyl methyl ether showed no exchange under the same conditions.

We believe that the origin of this last effect is to be found in the facile tautomerism to the keto form 10, in



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(4) K. B. Wiberg and K. A. Saegebarth, *J. Org. Chem.*, **25**, 832 (1960).
(5) S. Oae and R. Kiritani, *Bull. Chem. Soc. Jap.*, **39**, 611 (1966).
(6) P. F. Tryon, W. G. Brown, and M. S. Kharasch, *J. Amer. Chem. Soc.*, **70**, 2003 (1948).
(7) For example Kharasch[6] observed that the deuterium exchange of 4 required 112 hr at 120° in ethanolic sulfuric acid.
(8) A. Inoue, N. Kuroki, and K. Konishi, *Yuki Gosei Kagaku Kyokai Shi*, **17**, 773 (1959).
(9) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1963, p 860.
(10) P. P. T. Sah, *Rec. Trav. Chim. Pays-Bas*, **59**, 1021 (1940).
(11) Ng. Ph. Buu-Hoï and D. Lavit, *J. Org. Chem.*, **21**, 1022 (1956).
(12) F. Wessely, J. Kotlan, and W. Metlesics, *Monatsh. Chem.*, **85**, 69 (1954).

keeping with the generally faster deuteration of the free phenol relative to the ether,[5] followed by acid-catalyzed exchange of the free enol ether function, which has many precedents.[4,13] In summary we have observed rapid exchange reactions of various naphthols and their ethers which may be of use for the preparation of polyalkoxynaphthalenes by a process of aryl oxygen fission.

Experimental Section[14]

Melting points were measured on a Kofler hot stage and are uncorrected. Ultraviolet spectra were recorded in MeOH on a Coleman-Hitachi 124 double-beam spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Nmr spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane as internal reference. Mass spectra were measured on an AEI MS 9 mass spectrometer.

Alcoholic hydrogen chloride solutions were prepared by absorbing dry HCl gas (1.0 g) in 9.0 g of the respective alcohol. The three naphthols **2**, **3**, and **8** were characterized as the colorless crystalline acetate derivatives **11**, **12**, and **13**, respectively. The acetates **11**, **12**, **13**, and **14** were readily formed by heating the parent naphthol in Ac_2O in the presence of 2 equiv of NaOAc for 10 min at 80°.

2,4-Dimethoxy-1-naphthol (**2**).—**1** (0.5 g) was dissolved in 10 ml of methanolic HCl. The solution was heated to 60° for 1 min and then evaporated to yield pinkish crystals. This product was then redissolved in 10 ml of MeOH and evaporated down again in order to remove any remaining HCl gas. Another aliquot of MeOH was added to the product and then again evaporated off to yield a colorless crystalline compound **2**: mp 77–82°; uv max 242 mμ (ε 27,400), 313 (4080); ir ($CHCl_3$) 3560 (OH), 2940, 2840 (OMe), 1640, 1600, 1590 cm^{-1}; nmr ($CDCl_3$) δ 3.85 (s, 3), 3.90 (s, 3), 5.10 (bs, 1), 6.60 (s, 1), 7.40 (m, 2), 8.15 (m, 2); mass spectrum (70 eV) *m/e* (relative intensity) 204 (25), 189 (17), 174 (2), 161 (5).

2,4-Dimethoxy-1-naphthol acetate (**11**) had mp 90.5–91.5°; uv max 253 mμ (ε 40,200), 301 (4680); ir ($CHCl_3$) 2940, 2840 (OMe), 1760 (ester C=O), 1640, 1600, 1560 cm^{-1}; nmr ($CDCl_3$) δ 2.34 (s, 3), 3.76 (s, 3), 3.80 (s, 3), 6.47 (s, 1), 7.35 (m, 2), 7.56 (m, 1), 8.08 (m, 1); mass spectrum (70 eV) *m/e* (relative intensity) 246 (5), 204 (22), 189 (12).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.36; H, 5.85.

2,4-Diethoxy-1-naphthol (**3**).—Ethanolic HCl was substituted for methanolic HCl and the preparation proceeded as that for **2**: nmr ($CDCl_3$) δ 1.40 (t, 3), 1.46 (t, 3), 4.10 (q, 2), 4.12 (q, 2), 5.20 (bs, 1), 6.64 (s, 1), 7.35 (m, 2), 8.12 (m, 2).

2,4-Diethoxy-1-naphthol acetate (**12**) had mp 110.5–111.5°; uv max 236 mμ (ε 35,400), 301 (4130); ir ($CHCl_3$) 2980–2900 (m), 1760 (ester C=O), 1640, 1600, 1570 cm^{-1}; nmr ($CDCl_3$) δ 1.37 (t, 3), 1.48 (t, 3), 2.40 (s, 3), 4.14 (q, 4), 6.64 (s, 1), 7.36 (m, 2), 7.66 (m, 1), 8.20 (m, 1); mass spectrum (70 eV), *m/e* (relative intensity) 274 (3), 231 (11), 175 (16).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.96; H, 6.84.

2-Chloro-4-methoxy-1-naphthol (**8**).—1,4-Naphthoquinone (0.5 g) was substituted for **1** and the preparation proceeded as that for **2**: nmr ($CDCl_3$) δ 3.90 (s, 3), 5.55 (bs, 1), 6.67 (s, 1), 7.50 (m, 2), 8.16 (m, 2).

2-Chloro-4-methoxy-1-naphthol acetate (**13**) had mp 74–75.5°; uv max 235 mμ (ε 43,000), 295 (9200); ir (CCl_4) 3180–2950 (m), 2850 (OMe), 1790 (ester C=O), 1630, 1590; nmr ($CDCl_3$) δ 2.36 (s, 3), 3.82 (s, 3), 6.67 (s, 1), 7.40 (m, 2), 7.58 (m, 1), 8.14 (m, 1); mass spectrum (70 eV) *m/e* (relative intensity) 252 (3), 250 (10), 210 (30), 208 (50), 195 (20), 193 (55), 157 (10).

Anal. Calcd for $C_{13}H_{11}ClO_3$: C, 62.28; H, 4.42; Cl, 14.14. Found: C, 62.57; H, 4.37; Cl, 14.00.

Registry No.—**2**, 20352-27-6; **3**, 20352-28-7; **8**, 20352-29-8; **11**, 20352-30-1; **12**, 20352-35-6; **13**, 20352-36-7.

Acknowledgment.—We would like to thank Eli Lilly and Co. for generous financial support.

(13) W. F. Gannon and H. O. House, *Org. Syn.*, **40**, 41 (1960).

(14) Elemental analyses were performed by the Midwest Microlab Inc., Indianapolis, Ind. 46226.

The Stereochemistry of the Hydroformylation of Norbornene

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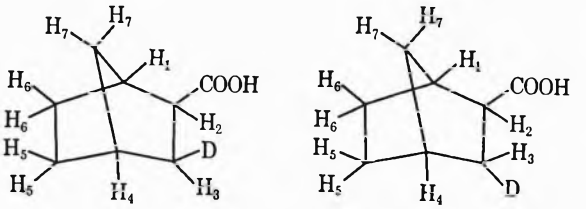
Received September 4, 1968

We recently reported that the hydrogenation of 1,2-diphenylcyclobutene with cobalt hydrocarbonyl, $HCo(CO)_4$, is primarily a *cis* process.[1] The stereochemistry of the stoichiometric hydroformylation of olefins has never been established, although two previous studies of the high-pressure catalytic oxo reaction indicated a cleanly *cis* hydroformylation of unsaturated carbohydrates possessing a vinyl ether structure.[2,3] We now wish to report that the stoichiometric hydroformylation of an olefin, norbornene, is largely, if not entirely, a *cis* process.

When a hexane solution of $DCo(CO)_4$ was added to norbornene under an atmosphere of carbon monoxide at room temperature, slow absorption of carbon monoxide occurred and deuterated norbornane-2-carboxaldehyde[4] was isolated in about 20% yield. The product was oxidized with potassium permanganate to give *exo*-norbornane-2-carboxylic acid which, were the hydroformylation *cis*, would have structure **1**, and were it *trans*, would have structure **2**. The nmr of the acid from the



hydroformylated product was essentially identical with that of an authentic sample[5] of **1** (Figure 1). We consider it quite unlikely that **2** would give a spectrum identical with **1**, since the coupling constant $J_{H_2\text{-}H_3}$ between two *endo* hydrogens in norbornyl systems is about 8 cps and that between an *endo,exo* pair is about 2 cps.[6]

Experimental Section

Melting points were taken on a Fisher–Johns block and are uncorrected. Nmr spectra were obtained with a Varian A-60 spectrometer and infrared spectra were determined with a Perkin-Elmer Infracord 337. Norbornene was purchased from Aldrich Chemicals.

(1) W. Fichteman and M. Orchin, *J. Org. Chem.*, **33**, 1281 (1968). Although a small amount of *trans* product was observed, it can be accounted for by olefin isomerization, followed by *cis* addition.

(2) A. Rosenthal and D. Abson, *Can. J. Chem.*, **42**, 1811 (1964).

(3) A. Rosenthal and H. J. Koch, *ibid.*, **43**, 1375 (1965).

(4) Y. Colleuille and P. Perras, French Patent 1,352,841, *Chem. Abstr.*, **61**, 593*a* (1964), reports that when norbornene is treated with dicobaltoctacarbonyl in cyclohexane solvent under high carbon monoxide pressure, a low yield of norbornane-2-carboxaldehyde is obtained along with other products. We found that under catalytic oxo conditions using dicobaltoctacarbonyl as catalyst, norbornene hydroformylates quite readily to give a good yield of norbornane-2-carboxaldehyde.

(5) Supplied by Dr. John Hudec; see C. W. Bird, R. C. Cookson, J. Hudec, and R. O. Williams, *J. Chem. Soc.*, 410 (1963), who report here the *cis* hydrocarboxylation of norbornene by $Ni(CO)_4$ and H_2O.

(6) A. Factor and T. G. Traylor, *J. Org. Chem.*, **33**, 2607 (1968).

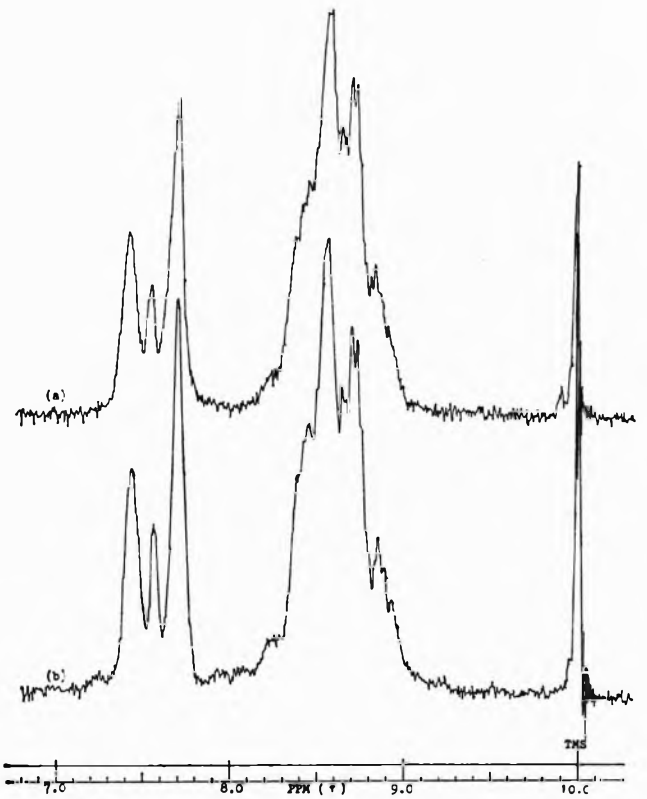


Figure 1.—(a) 60-Mc nmr spectrum of *exo*-norbornane-2-carboxylic acid from deuterioformylated norbornene. (b) 60-Mc nmr spectrum of authentic sample of 1, 30% by weight in $DCCl_3$; TMS reference.

Stoichiometric Reaction of $DCo(CO)_4$ with Norbornene.—Norbornene (2.42 g, 24.8 mmol) was dissolved in 50 ml of hexane and a small amount of some insoluble impurity was removed by filtration. About 75 ml of a hexane solution[7] of $DCo(CO)_4$ was injected in 10-ml portions over a period of 6 hr into the hexane solution of norbornene. The reaction was carried out in a serum stoppered flask connected to a gas buret, under an atmosphere of carbon monoxide and at room temperature. A total of 57.1 mmol of $DCo(CO)_4$ was used, and about 13 mmol of carbon monoxide was absorbed slowly. The reaction mixture was stirred for 24 hr, and 25 ml of dimethylformamide was added to destroy the dicobaltooctacarbonyl. About 50 ml of water was then added and the mixture was extracted with ether. The ether solution was dried with magnesium sulfate and evaporated to dryness on a rotary evaporator. The light pink viscous oil was vacuum distilled at 3 mm to give 0.65 g of clear distillate: bp 42–52°, 20% yield. The infrared spectrum of the distillate showed C-D stretching bands at 2163 and 2048 cm^{-1} and the C=O stretching band at 1713 cm^{-1}. The nmr ($DCCl_3$ solution, TMS reference) showed a multiplet from τ 7.23–7.83 (2.9 H) assigned to protons at positions 1, 2, and 4 and a multiplet from 8.08–8.97 (7.1 H) assigned to the protons at positions 3, 5, 6, and 7. An unsymmetrical doublet (J = 1 cps) at τ 0.36 due to the aldehydic proton indicated that about 7% of the product had no deuterium on the carbonyl carbon.

The aldehyde was oxidized with potassium permanganate to yield 0.13 g of the acid 1 (mp 52.0–53.5°, mmp with authentic sample, 53–54°). The nmr spectrum of the acid was taken in $DCCl_3$ (~30% by weight) and is shown in Figure 1. The carboxyl proton absorbed at τ −1.5; the carboxyl to norbornyl proton ratio was 1.0:10.0.

Registry No.—Norbornene, 498-66-8; deuterated *exo*-norbornane-2-carboxaldehyde, 20238-57-7.

Acknowledgment.—The authors are grateful to the donors of the Petroleum Research Fund administered by the American Chemical Society for partial support of this work. The authors are especially grateful to Drs. C. W. Bird and John Hudec for supplying us with an authentic sample of the deuterated *exo*-2-norbornanecarboxylic acid.

(7) L. Roos and M. Orchin, *J. Amer. Chem. Soc.*, **87**, 5502 (1965).

Use of N,N-Dimethylvinylamine in an Improved Synthesis of Derivatives of Thietane and Thiete[1]

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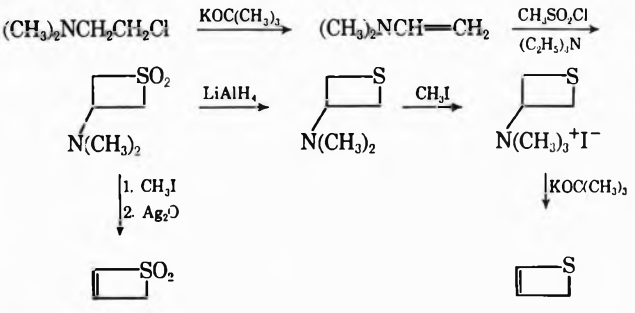
The original synthesis of thiete (thiacyclobutene) involved a long, multistep sequence starting with epichlorohydrin, and the over-all yield was relatively low.[2] Because large quantities of thiete were desired in order to study its chemical and physical properties, a new synthesis was devised utilizing the addition of "sulfene" to N,N-dimethylvinylamine, which was obtained conveniently and in high yield by dehydrohalogenation of N,N-dimethyl-N-β-chloroethylamine.[3] The addition of sulfenes to enamines is an efficient method of preparation of β-aminothietane sulfones.[4]

Both N,N-dimethyl- and N,N-diethylvinylamines were obtained by the dehydrohalogenation procedure in 84–87% yields as colorless liquids, stable below −20°. They are sensitive to air and become brown and resinous at room temperature. The nmr spectrum shows clearly the vinyl protons at τ 6.35–6.65 (CH_2=) and 3.95–4.10 (>C=C—H). The infrared spectrum shows absorption at 1630–1640 cm^{-1} attributed to the carbon–carbon double bond.

A chemical proof of the structure of N,N-dimethylvinylamine consists of its addition to sulfene to give 3-(N,N-dimethylamino)thietane 1,1-dioxide in 86% yield. The adduct can be converted either to thiete by



(1) This work was supported by National Science Foundation Grants GP5513 and GP8086.

(2) D. C. Dittmer, K. Takahashi, and F. A. Davis, *Tetrahedron Letters*, 4061 (1967).

(3) The preparation of N,N-dimethylvinylamine by other methods has been reported previously: K. H. Meyer and H. Hopff, *Ber.*, **54**, 2277 (1921); British Patent 832,078; *Chem. Abstr.*, **54**, 20877 (1960). Our attempts to prepare the vinylamine by published procedures were not successful. The preparation of N,N-diethylvinylamine from acetaldehyde and diethylamine has been reported: G. Laban and R. Mayer, *Z. Chem.*, **7**, 12 (1967); G. Opitz and H. Mildenberger, *Ann.*, **649**, 26 (1961).

(4) G. Stork and I. J. Borowitz, *J. Amer. Chem. Soc.*, **84**, 313 (1962); G. Opitz and H. Adolph, *Angew. Chem.*, **74**, 77 (1962); I. J. Borowitz, *J. Amer. Chem. Soc.*, **86**, 1146 (1964). The reaction is reviewed in L. L. Müller and J. Hamer, "1,2-Cycloaddition Reactions," Interscience Publishers, New York, N. Y., 1967.

procedures previously published[2,5] or to thiete 1,1-dioxide.

Experimental Section

N,N-Dimethylvinylamine.—N,N-Dimethyl-N-β-chloroethylamine hydrochloride (70.0 g, 0.485 mol) was converted to the free amine in crude form (45 g, 0.42 mol, 87%) by treatment with aqueous potassium hydroxide.[6] Pure amine can be obtained in 62% yield after distillation. The crude amine was added to a stirred solution of potassium *t*-butoxide (70.0 g, 0.625 mol) in 500 ml of purified N,N-dimethylformamide in a nitrogen atmosphere at −20°. After 15 min, the mixture was distilled (room temperature, 2 mm) until *ca.* 100 ml of liquid was collected in a receiver cooled in a bath at −78°. Fractional distillation of this liquid at 20 mm into a receiver in a bath at −78° gave N,N-dimethylvinylamine (25.0 g, 0.352 mol, 72.6% over-all).

The amine had the following properties: nmr (N,N-dimethylformamide, 60 MHz, TMS) τ 3.95 (m, =CH), 6.35–6.65 (m, $=CH_2$), and 7.45 ppm (s, 6 H, CH_3); ir (CCl_4) 3100 (w), 2900 (m), 1730 (w), 1690 (w), 1640 (s), 1550 (w), 1430 (m), 1335 (m), 1240 (w), 1090 (m), 1050 (w), 1000 (w), 965 (m), 940 (w), 910 (w) cm^{-1}; mass spectrum (20 eV) *m/e* 71 (parent ion), 58, 56 (parent − CH_3), 45 (parent − CH≡CH), 44, 43 (parent − $H_2C=CH_2$).

N,N-Diethylvinylamine.—By the above procedure, N,N-diethyl-N-β-chloroethylamine hydrochloride (17.2 g, 0.1 mol) was neutralized to the crude amine (11.0 g, 0.08 mol, 81%), which in turn was converted to N,N-diethylvinylamine (7.05 g, 0.071 mol, 71% overall).

This compound had the following properties: nmr (cyclohexane, 60 MHz, TMS) τ 4.10 (m, =CH), 6.30–7.60 (m 6 H, $=CH_2$, $—CH_2—$), and 8.75–9.15 ppm (2 t, 6 H, CH_3); ir (CCl_4) 2900 (s), 1720 (m), 1690 (s), 1630 (s), 1440 (s), 1370 (s), 1240 (w), 1200 (w), 1120 (s), 965 (w), 940 (w) cm^{-1}; mass spectrum (20 eV) *m/e* 99 (parent ion), 84 (parent − CH_3), 74, 73 (parent − HC≡CH), 71 (parent − $H_2C=CH_2$), 59, 58, 56, 45, 44, 31, 30.

3-(N,N-Dimethylamino)thietane 1,1-Dioxide.—Methanesulfonyl chloride (40.0 g, 0.352 mol) in 100 ml of dry ether was added dropwise to a stirred solution of pure N,N-dimethylvinylamine (25.0 g, 0.352 mol) and purified triethylamine (50.5 g, 0.500 mol) in 700 ml of dry ether at −20°. After 5 hr at −20°, triethylamine hydrochloride was removed by filtration and washed with dry ether. Ether and excess triethylamine were removed on a rotary evaporator at about 40°. The light yellow syrup obtained was recrystallized from dry ether to yield white crystals, mp 23–25° (45.5 g, 0.306 mol, 86.7%).

The adduct had the following properties: nmr (benzene, 60 MHz, TMS) τ 3.88 (2 H), 3.77 (2 H), 2.85 (1 H), and 1.95 ppm (s, 6 H, CH_3); ir (KBr) 3000 (m), 2860 (m), 2800 (m), 1460 (m), 1395 (m), 1315 (s), 1220 (s), 1175 (m), 1140 (s), 1050 (s), 975 (w), 915 (m), 850 (w), 785 (m), 765 (m), 705 (w) cm^{-1}. These spectra are identical with those of an authentic sample of 3-(N,N-dimethylamino)thietane 1,1-dioxide prepared from 3-chlorothietane 1,1-dioxide.[5a]

N,N,N-Trimethyl-N-(1,1-dioxo-3-thietanyl)ammonium Iodide.—Methyl iodide (1.5 g, 11 mmol) was added to a solution of 3-(N,N-dimethylamino)thietane 1,1-dioxide (1.49 g, 10.0 mmol) in 25 ml of methyl ethyl ketone. After 5 hr at room temperature, the white flakes of product were removed by filtration and recrystallized from 95% ethanol to yield N,N,N-trimethyl-N-(1,1-dioxo-3-thietanyl)ammonium iodide, mp 188–190° dec (lit.[5a] mp 188–190°) (2.60 g, 8.93 mmol, 89.3%) which had the following ir spectrum (KBr): 2970 (m), 2890 (m), 1460 (s), 1418 (w), 1320 (w), 1215 (s), 1140 (s), 1008 (w), 985 (w), 940 (m), 870 (w), 780 (m), 751 (w) cm^{-1}. The melting point and the infared spectrum are identical with that of the methiodide prepared from an authentic sample of 3-(N,N-dimethylamino)thietane 1,1-dioxide.[5a]

Thiete 1,1-Dioxide.—Silver oxide (1.59 g, 6.88 mmol) was mixed with N,N,N-trimethyl-N-(1,1-dioxo-3-thietanyl)ammonium iodide (1.0 g, 3.4 mmol) in 25 ml of water. The suspension was stirred for 5 min and the precipitate was removed by filtration. The aqueous filtrate was extracted three times with 25-ml portions of methylene chloride. The combined extract was dried with Drierite and evaporated to dryness on a rotary evaporator. The solids obtained were recrystallized from ether–ethanol to give thiete 1,1-dioxide (0.42 g, 2.73 mmol, 79.3%), mp 49.5–50.0° (lit.[7] mp 52–54°). When this compound was compared with an authentic sample,[7] no depression was observed in the mixture melting point, and their infrared spectra were identical.

Registry No.—N,N-Dimethylvinylamine, 5763-87-1; N,N-diethylvinylamine, 6053-97-0; 3-(N,N-dimethylamino)thietane 1,1-dioxide, 20440-18-0; N,N,N-trimethyl-N-(1,1-dioxo-3-thietanyl)ammonium iodide, 20440-19-1.

(5) (a) D. C. Dittmer and M. E. Christy, *J. Amer. Chem. Soc.*, **84**, 399 (1962); (b) D. C. Dittmer and F. A. Davis, *ibid.*, **87**, 2064 (1965).

(6) E. Baer and S. K. Pavanaram, *J. Biol. Chem.*, **236**, 2410 (1961).

(7) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961).

Synthesis and Reactions of *cis*-2,2-Dichloro-1,2,2a,7a-tetrahydro-7H-cyclobut[*a*]inden-1-one[1a]

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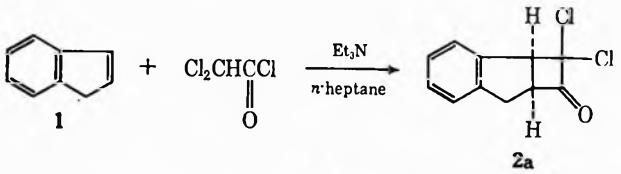
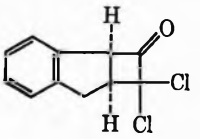
Received February 7, 1969

Recently, Turner and Sedan[2] reported the reaction of dichloroketene with indene to give small amounts (12%) of a compound, tentatively designated as *cis*-2,2-dichloro-1,2,2a,7a-tetrahydro-7H-cyclobut[*a*]inden-1-one, mainly on the basis of its nmr spectrum. This paper describes the synthesis and proof of structure of this compound.

The reaction of indene (**1**) with dichloroketene[3,4] furnished 48% yield of *cis*-2,2-dichloro-1,2,2a,7a-tetrahydro-7H-cyclobut[*a*]inden-1-one, which could have the structure **2a** or **2b**, assuming that the initial cycloaddition occurs *cis*.



1 + Cl_2CHCCl (=O) → **2a**



2b

The compound was found to be homogeneous by thin-layer and vapor-phase chromatographic analyses, and its physical constants were in agreement with those reported by the previous workers.[2] The study of nuclear magnetic resonance, infrared, and ultraviolet spectra did not prove to be of much help in distinguishing be-

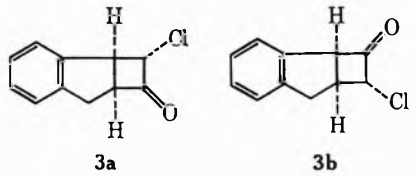
(1) (a) Robert E. Harmon and T. R. Potts, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p 159. (b) To whom inquiries should be directed.

(2) R. W. Turner and T. Sedan, *Chem. Commun.*, **13**, 399 (1966).

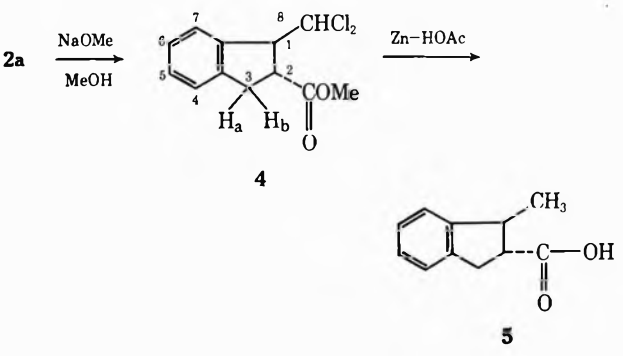
(3) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaugham, *J. Amer. Chem. Soc.*, **87**, 5257 (1965).

(4) L. Gosez, R. Montaigne, and P. Mollet, *Tetrahedron Lett.*, **1**, 135 (1966).

tween structures **2a** and **2b**. Catalytic hydrogenation of 2a (or **2b**) furnished a 93% yield of 2-chloro-7H-cyclobut[*a*]inden-1-one **3a** or **3b**. Again the nuclear magnetic resonance, infrared, and ultraviolet spectra were not helpful in distinguishing between the structures **3a** and **3b**. The reaction of *cis*-2,2-dichloro-1,2,2a,7a-tetrahydro-7H-cyclobut[*a*]inden-1-one with sodium methoxide in methanol gave a 79% yield of **4** which was found to be homogenous by thin layer and vapor phase chromatographic analyses. Its ir spectrum (Nujol) showed strong absorption at 1739 cm^{-1} ($-CO_2CH_3$), and the nmr spectrum (CCl_4), determined on a Varian A-60 spectrometer, gave signals at τ 2.5 (m, 4, aromatics), 3.85 (d, 1, $J_{1,8}$ = 6, $CHCl_2$), 5.50 (m, 1, 1 H), 6.17 (s, 3, CO_2CH_3), and 6.53 ppm (m, 3, 2 H, 3a H and 3b H). When **4** was treated with zinc dust in acetic acid, it afforded **5** in 41% yield. Compound **5** was found to be identical with an authentic sample of *trans*-1-methyl-2-indancarboxylic acid[5] by undepressed mixture melting point and superimposable infrared spectra. The conversion of *cis*-2,2-dichloro-1,2,2a,7a-tetrahydro-7H-cyclobut[*a*]inden-1-one to *trans*-1-methyl-2-indancarboxylic acid (**5**) unequivocally proves its structure to be **2a** and not **2b**.



3a **3b**



4 **5**

Experimental Section

The melting points were determined on a Thomas–Hoover melting point apparatus and are corrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Thin layer chromatography was done on 20 × 5 cm glass plates coated with a 0.1-mm thickness of silica gel G (Darmstadt). Vapor phase chromatographic analyses were carried out on an F & M (Model 720) instrument by using silicon gum rubber SE-30 on chromosorb P column. The infrared spectra were recorded on a Beckman IR-8 spectrophotometer. A Cary 14 spectrophotometer was used to measure the ultraviolet spectra. The nuclear magnetic resonance spectra were determined in carbon tetrachloride and deuterated chloroform as solvents and tetramethylsilane as an internal standard and were recorded on Varian A-60 and Varian HA-100 spectrometers.

cis-**2,2-Dichloro-1,2,2a,7a-tetrahydro-7H-cyclobut[a]inden-1-one** (**2a**).—A solution of 116.0 g (1.0 mol) of indene (1) and 74.0 g (0.74 mol) of triethylamine in 200 ml of anhydrous *n*-heptane was added dropwise with stirring to a solution of 100 g (0.68 mol) of dichloroacetyl chloride in 1 l. of anhydrous *n*-heptane. After the addition was over (*ca.* 30 min), the reaction mixture was refluxed for 15 hr. On letting it cool to 10°, triethylamine hydrochloride was precipitated. The precipitate was filtered and washed with five 200-ml portions of water. The filtrate was evaporated to dryness under reduced pressure and the resulting black oil was flash-distilled (0.1 mm). This furnished a viscous liquid which crystallized on standing to yield 64.0 g (42%) of yellowish white crystals of **2a**, mp 78–80°. It gave one spot on tlc (benzene or *p*-dioxane) and one peak on vpc. The analytical sample was obtained by one more recrystallization from petroleum ether (bp 30–60°); mp 80–81° (lit.[2] mp 78–79°); uv λ_{max}^{EtOH} 213 (ϵ 8600) and 205 (ϵ 16,400) mμ; ir ν_{max}^{Nujol} 1821 (C=O) and 741 cm^{-1} (C—Cl).

Anal. Calcd for $C_{11}H_8Cl_2O$: C, 58.18; H, 3.55. Found: C, 58.23; H, 3.59.

2-Chloro-7H-cyclobut[a]inden-1-one (**3a**).—A solution of 4.0 g (0.017 mol) of **2a** in 250 ml of anhydrous *p*-dioxane was hydrogenated for 3.5 hr at room temperature and 60 psi pressure in the presence of 2.0 g of 10% palladium on carbon and 2.0 g of anhydrous calcium carbonate. The catalyst was filtered off and the filtrate was evaporated to dryness to give a white solid, which on recrystallization from petroleum ether (bp 30–60°) yielded 3.1 g (93%) of colorless crystals of **3a**, mp 111.5–112°. It gave one spot on tlc (benzene or cyclohexane) and one peak on vpc. One more recrystallization from petroleum ether furnished the analytical sample: mp 111.5–112°; uv λ_{max}^{EtOH} 216 (ϵ 7600) and 207 mμ (ϵ 14,000); ir ν_{max}^{Nujol} 1786 (C=O) and 735 cm^{-1} (C—Cl).

Anal. Calcd for $C_{11}H_9ClO$: C, 68.58; H, 4.70; Cl, 18.41. Found: C, 68.62; H, 4.68; Cl, 18.49.

Methyl *trans*-**1-(Dichloromethyl)-2-indancarboxylate** (**4**).—To a solution of 3.0 g of sodium in 120 ml of absolute methanol at −5° was added with stirring 3.0 g (0.013 mol) of **2a**. The mixture was stirred at −5° for 30 min and then allowed to warm up to room temperature. It was neutralized with glacial acetic acid and then evaporated to dryness under reduced pressure. The resulting solid was dissolved in 50 ml of distilled water and extracted with five 150-ml portions of ether. The ether extract was dried (Na_2SO_4) and concentrated to give a yellow oil. Crystallization from petroleum ether (bp 30–60°)–ether furnished 2.7 g (79%) of colorless crystals of **4**, mp 45–46°. It gave one spot on tlc (benzene or chloroform–methanol, 20:1) and one peak on vpc; uv λ_{max}^{EtOH} 280 (ϵ 10,400), 267 (ϵ 20,000), 236 (ϵ 19,500), and 232 mμ (ϵ 21,000); ir ν_{max}^{Nujol} 1739 (CO_2CH_3) and 741 cm^{-1} (C—Cl).

Anal. Calcd for $C_{12}H_{12}Cl_2O_2$: C, 55.61; H, 4.66; Cl, 27.36. Found: C, 55.40; H, 4.77; Cl, 27.61.

trans-**1-Methylinden-2-carboxylic Acid** (**5**).—A solution containing 50 mg (0.193 mmol) of **4** and 12.3 mg (0.193 g-atom) of powdered zinc in 25 ml of glacial acetic acid was heated under reflux for 2 hr. The reaction mixture was then cooled to room temperature and the precipitated zinc chloride was removed by filtration. The filtrate was evaporated to dryness *in vacuo*, and the resulting oil was dissolved in 10 ml of ether. The ether solution was washed with five 5-ml portions of 10% sodium bicarbonate solution, dried (Na_2SO_4), and concentrated *in vacuo* to yield 31 mg (97%) of a crude yellow oil. The oil was chromatographed over a column containing 75 g of silica gel G. Elution with 150 ml of benzene and removal of the solvent *in vacuo* gave 23 mg of a light yellow oil which was treated with 10% sodium hydroxide solution and poured into ice–water containing concentrated hydrochloric acid. On letting it stand for sometime, 13 mg (41%) of colorless crystals of **5**, mp 78–79° (lit.[5] mp 79°), was obtained; ir ν_{max}^{Nujol} 2857 (OH) and 1724 cm^{-1} (C=O). A mixture melting point with an authentic sample was undepressed.

Registry No.—2a, 20429-38-3; **3a**, 20429-39-4; **4**, 20429-40-7.

Acknowledgment.—This work was supported by a grant from the Michigan Cancer Foundation. The authors wish to thank Professor Don C. Iffland for help in interpreting the nmr spectra and Mr. Michael McAneny for determining the uv spectra.

(5) S. C. Lahiri and B. Pathak, *J. Med. Chem.*, **8**, 131 (1965).

Cleavage, Reduction, and Decarboxylation of 1-Carboxybicyclo[4.3.1]decan-10-one

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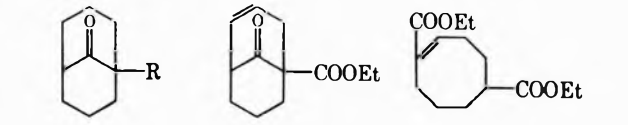
Received January 10, 1969

While 1-carboxybicyclo[3.3.1]nonan-9-one (Ia) has resisted decarboxylation,[1] and its ester, Ib, does not seem to have been cleaved, 1-carbethoxybicyclo[3.3.1]-non-3-en-9-one (II), which differs from Ib only by the double bond at C-3, has been smoothly converted into III with ethoxide.[2]

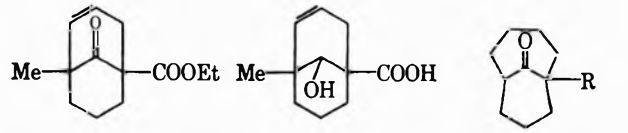
Suggestion has been made that the cleavage of II depends on the migration of the olefinic bond. That mechanism was supported when attempts to cleave IV under the same conditions resulted in formation of the alcohol V, because cleavage was blocked when the methyl group prevented the migration of the double bond.[3]



Ia, R = COOH
b, R = COOEt

II

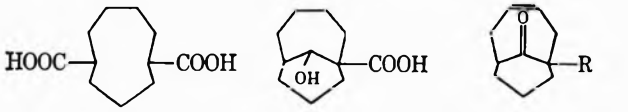
III



IV

V

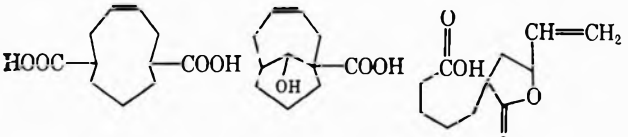
VIa, R = COOH
b, R = COOEt
c, R = H



VII

VIII

IXa, R = COOH
b, R = COOEt
c, R = H



X

XI

XII

In the present investigation, 1-carboxybicyclo[4.3.1]-decan-10-one (VIa), containing a six- and a seven-membered ring instead of the two six-membered rings of Ia, has been decarboxylated to VIc and has been cleaved upon heating with sodamide. The cleavage not only provides a convenient route to cyclononane-1,5-dicarboxylic acid (VII) but also demonstrates that the size of the ring as well as the double bond can help determine the course of the reaction. The reduction of the keto group of the ester, VIb, to the hydroxy acid, VIII, however, shows that the cleavage reaction still is not particularly easy.

Results similar to those obtained with VIa and VIb were obtained with IXa. The acid was cleaved to X with sodamide, it was decarboxylated to IXc by heat alone,[4] and the keto group of its ester, IXb, was reduced to an alcohol, XI, when the ester was heated with sodium hydroxide in methyl alcohol.

In addition to these reactions in common with VIa and VIb, however, IXb gave an unexpected cleavage of both rings. Upon standing in dilute ethoxide, IXb was partially converted to α-(δ-valeric acid)-γ-vinyl-γ-butyrolactone[5] (XII).

In an earlier investigation, 2-carbethoxycycloalkanones with five- and six-membered rings were cleaved during attempted alkylation while the seven-membered homolog was not.[5] It would now appear that a β-keto ester in a seven-membered ring is relatively easier to cleave when it is part of a bicyclic, instead of a monocyclic, molecule. The opposite apparently is true of a β-keto ester in a six-membered ring. It is concluded that the size of the rings involved is important in determining the occurrence of some of these cleavage, reduction, and decarboxylation reactions.

Experimental Section

Bicyclo[4.3.1]decan-10-one (VIc).—1-Carboxybicyclo[4.3.1]-decan-10-one[4] (8.75 g) was kept at its boiling point for 15 min and then distilled at 240° to give 5.0 g (72.7%) of solid with a camphor odor. Sublimation gave a pure white solid, mp 92–94°, whose infrared spectrum showed no carboxyl group and whose 2,4-dinitrophenylhydrazone derivative melted at 190°; ir ($CHCl_3$) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.95; H, 10.53. Found: C, 78.80; H, 10.45. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.83; H, 6.01. Found: C, 57.69; H, 5.95.

1-Carbethoxybicyclo[4.3.1]decan-10-one (VIb).—IXb (30 g) and 3.0 g of 5% Pd–$BaSO_4$ were placed in 300 ml of 95% alcohol and agitated overnight in a Parr low-pressure hydrogenator at 3 atm. Removal of the catalyst and the solvent was followed by distillation to give 19.3 g (63.6%) of light yellow liquid, bp 110–130° (2 mm). Redistillation gave a sample of pure material: bp 114° (1 mm), $n^{25}D$ 1.4752, ir (neat) 1712 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.91. Found: C, 69.65; H, 8.99.

1-Carboxybicyclo[4.3.1]dec-3-en-10-ol (XI).[6]—IXb (20 g, 0.06 mol) was added dropwise with stirring to a solution of 15.2 g of sodium hydroxide in 45.6 ml of anhydrous methyl alcohol maintained at 100–120° in an oil bath. The resulting mixture was stirred overnight at 120°, cooled, and diluted with 200 ml of water, and then the alcohol was distilled off. The residue was acidified, heated with decolorizing carbon, and filtered. The filtrate was extracted with ether, and the ether was in turn washed with $NaHCO_3$ solution.

Acidification of the $NaHCO_3$ solution produced an oil which was taken up in ether and dried (Na_2SO_4). Evaporation of the ether produced 3.5 g of an impure solid which was heated with 60–110° ligroin, treated with decolorizing carbon, filtered, and allowed to evaporate partially. Filtration gave 1.0 g of hard white crystals, mp 108–110°, ir ($CHCl_3$) 1695 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 66.98; H, 8.44.

1-Carboxybicyclo[4.3.1]decan-10-ol (VIII).[6]—1-Carbethoxybicyclo[4.3.1]decan-10-one (VIb) (15 g) was added over 30 min to a solution of 11.4 g of NaOH in 34.1 ml of methanol maintained at 125° in an oil bath. The resulting mixture was kept at 125° overnight, cooled, treated with 150 ml of water, and then distilled until the temperature of the residue reached 98°. Ex-

(1) A. C. Cope and M. E. Synerholm, *J. Amer. Chem. Soc.*, **72**, 5228 (1950).

(2) A. C. Cope, E. S. Graham, and D. J. Marshall, *ibid.*, **76**, 6159 (1954).

(3) G. L. Buchanan, A. McKillop, and R. A. Raphael, *J. Chem. Soc.*, 833 (1965).

(4) R. D. Sands, *J. Org. Chem.*, **29**, 2488 (1964).

(5) R. D. Sands, *ibid.*, **32**, 3681 (1967).

(6) The epimeric structure shown was assigned to V.[5] Similar considerations would lead to similar assignments for VIII and XI.

actly 74 ml of concentrated HCl was added over 1.5 hr, producing an orange–brown precipitate. The solid was taken up in ether, which was washed with $NaHCO_3$ solution. Acidification of the $NaHCO_3$ solution produced 11.4 g of crude solid, which yielded 8 g (60.3%) of white solid upon recrystallization from methylcyclohexane: mp 130–132°, neut equiv 198, ir ($CHCl_3$) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.08. Found: C, 66.60; H, 9.09.

Ethyl ester had bp 115° (2 mm); $n^{22}D$ 1.4982; nmr ($CDCl_3$) 1.1–2.2 (m, 18 H), 3.8 (1 H), 3.9–4.3 (m, 3 H); ir (neat) 1700 (C=O), 3530 cm^{-1} (O–H); mass spectrum, *m/e* (rel intensity) 226 (5), 208 (25), 135 (100), 134 (44), 123 (31), 93 (43), 91 (25), 81 (51), 73 (28), (72).

Cyclononane-1,5-dicarboxylic Acid (VII).—1-Carboxybicyclo[4.3.1]decan-10-one (VIa) (1.0 g) was refluxed with 2 g of sodium amide in 50 ml of xylene for 1 week. The xylene was distilled off, the residue was treated with water, and the mixture was then extracted with ether. Next the water suspension was acidified and again extracted with ether. The ether extract was washed with water and dried (Na_2SO_4). Evaporation gave a small amount of white solid and 0.4 g of crude, sticky solid. Recrystallization from ethyl acetate gave 0.3 g of a clear white solid: mp 138–140°.

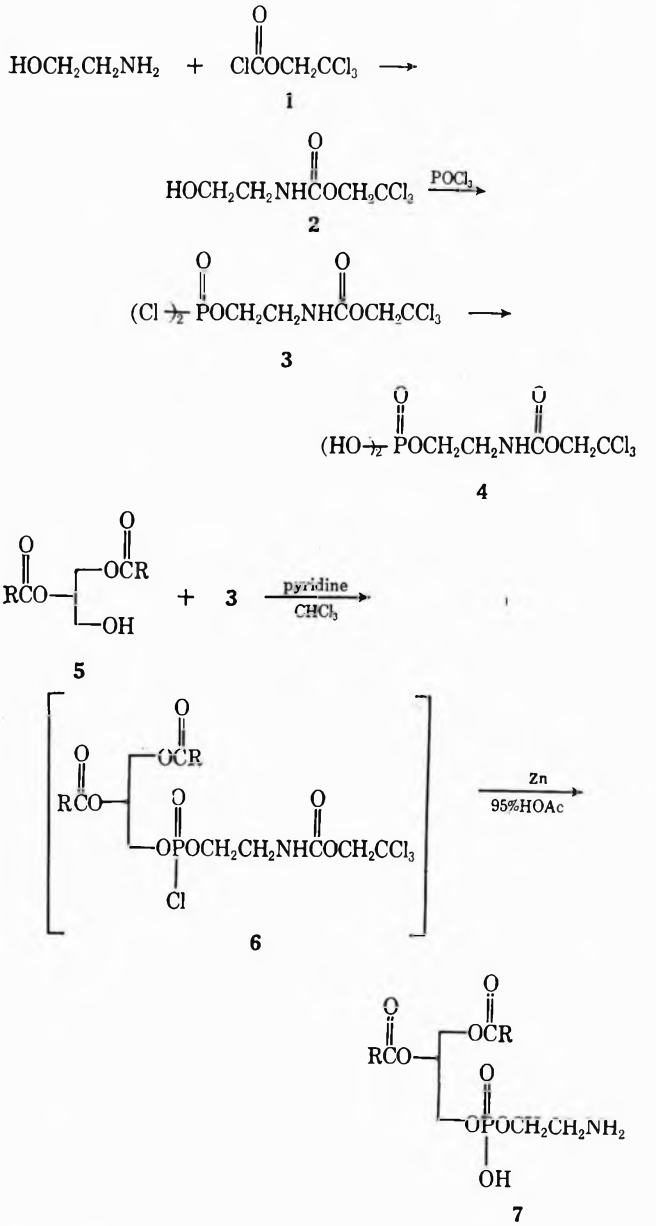
Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found: C, 61.36; H, 8.39.

1-Cyclononene-4,8-dicarboxylic Acid (X).—1-Carboxybicyclo[4.3.1]dec-3-en-10-one[4] (IXa) (6.0 g) was refluxed for 1 week with 5 g of sodium amide in 200 ml of xylene. The above work-up, followed by recrystallization from ethyl acetate, produced 0.70 g of a white solid: mp 183–185°.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.56. Found: C, 61.89; H, 7.56.

α-(δ-Valeric acid)-γ-vinyl-γ-butyrolactone (XII).—1-Carbethoxybicyclo[4.3.1]dec-3-en-10-one (IXb) (20 g) in a solution of 0.92 g of sodium in 58.3 ml of absolute ethyl alcohol was left at room temperature for 3 days. Treatment with $NaHCO_3$ solution was followed by extraction with ether. From the ether extract, 9.5 g of starting material was recovered. Acidification of the bicarbonate layer, followed by extraction with ether, drying, and evaporation of the ether produced a crude solid. Upon recrystallization from toluene, only about 1 g of pure white solid was recovered. Its infrared spectrum identified it as XII.[5]

Registry No.—VIa, 13348-05-5; VIb, 13348-03-3; VIc, 20440-21-5; VIc (2,4-dinitrophenylhydrazone), 20440-22-6; VII, 20440-24-8; VIII, 20440-23-7; VIII (ethyl ester), 20440-25-9; X, 20440-26-0; XI, 20440-27-1.



Glycerolipids. II.[1] Use of the β,β,β-Trichloroethoxycarbonyl Protecting Group in Phosphatidylethanolamine Synthesis

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Phosphorylation of 1,2-diacylglycerols with phosphorus oxychloride or with a phosphorylated, protected amine is an approach to phosphatidylethanolamines. This method was limited by (1) the availability of appropriate optically active 1,2-diglycerides and (2) the current use of the carbobenzoxy[2,3] and phthaloyl[2–6] protecting groups, which suffer from complications, including the difficulty of purifying the final products. Our recent facile and direct synthesis of either optical modification of 1,2-diacylglycerols[1] and the use of a new amine protecting group described below, which is removed under reductive, nonhydrolytic conditions, provides renewed impetus for use of this general sequence to phosphatidylethanolamines.

The new protecting group, β,β,β-trichloroethoxycarbonyl, was originally introduced in the total synthesis of cephalosporin C;[7] recently, further demonstrations of its utility,[8] as well as that of the closely related β,β,β-tribromoethoxycarbonyl group,[9] have been reported. Removal of the β,β,β-trichloroethoxycarbonyl group is accomplished with zinc in 90% acetic acid[7] or in refluxing methanol.[8] Under these conditions, phosphatidylethanolamine variants containing mono- or poly-

(1) Part I: F. R. Pfeiffer, S. R. Cohen, K. R. Williams, and J. A. Weisbach, *Tetrahedron Lett.*, 3549 (1968).
(2) W. G. Rose, *J. Amer. Chem. Soc.*, **69**, 1384 (1947).
(3) E. Baer, *J. Amer. Oil Chemists Soc.*, **42**, 257 (1965).
(4) R. Hirt and R. Berchtold, *Helv. Chim. Acta*, **40**, 1928 (1957).
(5) I. R. Hunter, R. L. Roberts, and E. B. Kester, *J. Amer. Chem. Soc.*, **70**, 3244 (1948).
(6) E. Baer and D. Buchnea, *Can. J. Biochem.*, **39**, 1471 (1961).
(7) R. B. Woodward, J. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *J. Amer. Chem. Soc.*, **88**, 852 (1966).
(8) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).
(9) A. F. Cook, *J. Org. Chem.*, **33**, 3589 (1968).

unsaturated acyl residues can be expected to be stable. β,β,β-trichloroethylchloroformate (**1**)[10] was allowed to react with ethanolamine in a suspension of dioxane containing magnesium oxide to give the syrupy N-(β,β,β-trichloroethoxycarbonyl)ethanolamine (**2**) in 90–95% yield. Treatment of **2** with excess phosphorus oxychloride in benzene afforded the dichloride **3**. Hydrolysis of **3** gave N-β,β,β-trichloroethoxycarbonyl-2-aminoethylphosphoric acid (**4**), which was isolated as the dicyclohexylamine salt. The purified dicyclohexylamine salt of **4** was converted into the free acid by stirring a solution of the salt with Amberlite IR-120 (H^+) ion-exchange resin.

The synthesis of O-(1,2-dilinoleoyl-*sn*-glycero-3-phosphoryl)ethanolamine (**7**), *i.e.*, 1,2-dilinoleoyl-3-*sn*-phosphatidylethanolamine,[11] is an example of the use of the intermediate **3**. *sn*-Glycerol 1,2-dilinoleate (**5**)[12] was allowed to react in chloroform with a benzene solution of **3** with pyridine as the acid acceptor. The derived diacylglycerophosphate ester chloride **6** was treated without further purification with zinc in 95% acetic acid. Thin layer chromatography of the crude phosphatidylethanolamine **7** showed one ninhydrin positive material and some trace phosphate-containing impurities.[12] Filtration of the crude product through DEAE-cellulose in the acetate form[13] provided 1,2-dilinoleoyl-3-*sn*-phosphatidylethanolamine. The phosphatide was hydrolyzed with boron trifluoride–methanol, and glpc analysis of the derived methyl esters indicated about 98% methyl linoleate.

Experimental Section[14]

N-(β,β,β-Trichloroethoxycarbonyl)ethanolamine (2).—A solution of 100 g (0.47 mol) of β,β,β-trichloroethylchloroformate[10] in 50 ml of dioxane was added at 0° to a mixture of 36.7 g (0.6 mol) of ethanolamine, 40 g of MgO, 125 ml of dioxane, and 125 ml of H_2O. The suspension was warmed to room temperature and stirred for an additional 16 hr. Ether (500 ml) was added, the inorganics were filtered, and the filtrate was washed with dilute HCl, brine, 5% $NaHCO_3$, and brine again. After being dried (Na_2SO_4), the solvent was evaporated to yield 112 g of the colorless syrup **2**. An analytical specimen was prepared by chromatography over Florisil, using 1:1 Et_2O–petroleum ether as the eluent: infrared absorption at 3.04, 5.83 and 8.01 μ.

Anal. Calcd for $C_5H_8Cl_3NO_3$: C, 25.39; H, 3.41; Cl, 44.98. Found: C, 25.56; H, 3.55; Cl, 44.48.

The 3,5-dinitrobenzoate derivative of **2** had mp 86–87° after crystallization from acetone–H_2O.

Anal. Calcd for $C_{12}H_{10}Cl_3N_3O_8$: C, 33.47; H, 2.34; N, 9.76. Found: C, 33.37; H, 2.20; N, 9.54.

Dichloro(N-β,β,β-trichloroethoxycarbonyl-2-aminoethyl)phosphate (3).—A solution of 41 g (0.174 mol) of **2** in 100 ml of dry C_6H_6 was added dropwise under N_2 over 4 hr to a cooled, stirred solution of 60 ml (0.64 mol) of freshly distilled $POCl_3$ in 250 ml of dry C_6H_6. After being stirred for 16 hr at room temperature, the reaction mixture was concentrated at H_2O aspirator pressure at 40°. Then the residue was azeotroped with dry C_6H_6 several times and finally concentrated at 1 mm to give about 55 g of crude **3**. The product was dissolved in dry C_6H_6, diluted to volume in a 100-ml volumetric flask, and stored at 0° under N_2. Under these conditions, the compound is stable for several months. Attempted molecular distillation at high vacuum did not give an analytically pure sample of **3**; the material readily polymerized in the distilling flask.

Dicyclohexylammonium Salt of N-β,β,β-Trichloroethoxycarbonyl-2-aminoethylphosphoric Acid (4).—A solution of 5 g of crude **3**, 50 ml of 50% aqueous dioxane, and 100 ml of 0.1 *N* KCl was stirred at room temperature for 2 hr. Solid NaCl was added, and the mixture was extracted several times with EtOAc. The EtOAc extracts were washed with H_2O, dried (Na_2SO_4), and concentrated to a colorless oil. Acetone (150 ml) was added, and the solution was treated with cyclohexylamine until basic. After being cooled, the white solid was filtered to give 5.8 g (80%) of the dicyclohexylammonium salt of **4**, mp 201–203°. Several recrystallizations from a mixture of EtOH–cyclohexylamine–H_2O (90:10:1) gave an analytical sample, mp 204–205°.

Anal. Calcd for $C_{17}H_{35}Cl_3N_3O_6P \cdot 0.5H_2O$: C, 38.98; H, 6.93; N, 8.02; H_2O, 1.72. Found: C, 38.58; H, 6.97; N, 7.69; H_2O, 1.60.[15]

N-β,β,β-Trichloroethoxycarbonyl-2-aminoethylphosphoric Acid (4).—The cyclohexylammonium salt of **4** (1 g) was dissolved in Me_2CO (100 ml) and H_2O and stirred with 10 ml of Amberlite IR-120 (H^+) for 1 hr. The resin was filtered and washed with $CHCl_3$, and the filtrate was concentrated to a viscous syrup. Chromatography on silicic acid with 9:2 $CHCl_3$–MeOH gave pure **4**, a colorless, viscous syrup.

Anal. Calcd for $C_5H_9Cl_3NO_6P$: C, 19.13; H, 2.87; N, 4.43; Cl, 33.61; P, 9.79. Found: C, 19.38; H, 3.11; N, 4.23; Cl, 33.45; P, 9.52.

1,2-Dilinoleoyl-3-*sn*-phosphatidylethanolamine (7).—A solution of 4.0 g (0.00644 mol) of **5**[1] in 35 ml of dry $CHCl_3$ and 3 ml of dry pyridine was added to an ice-cold solution of 4.1 g (0.0116 mol) of **3** in 10 ml of C_6H_6. The addition took about 70 min and, after being stirred 1 hr at 0°, the solution was stirred at room temperature under N_2 for 18 hr longer. Ether (700 ml) was added, and the mixture was washed with H_2O, dilute HCl, brine, 5% $NaHCO_3$, and brine again. The Et_2O layer was evaporated without drying to give the creamy **6**. Tlc showed one major spot which was phosphate positive. This material was dissolved in HOAc (50 ml) and Et_2O (25 ml) and 20 g of activated zinc[16] were added. Then the suspension was stirred at 25° for 16 hr. After being diluted with Et_2O (600 ml), the zinc and inorganics were filtered, and the filtrate was washed with four 200-ml portions of H_2O, then with 5% $NaHCO_3$ (the addition of brine retards emulsification), and finally with brine. Evaporation of the dried (Na_2SO_4) solvent gave 5.8 g of a yellow oil which contained one ninhydrin-positive material and some lesser amounts of phosphate-positive products. Chromatography on 400 g of DEAE-cellulose in the acetate form[13] gave 1.2 g of homogeneous **7** and an additional 0.8 g containing trace impurities (42% yield over-all): $[\alpha]^{25}D$ +6.2° (*c* 1, $CHCl_3$) {lit.[11] $[\alpha]D$ +5.8° (*c* 5, $CHCl_3$)}; R_f 0.67, using the solvent system 65:25:4, $CHCl_3$–MeOH–H_2O, on 0.25-mm silica gel G plates.

Anal. Calcd for $C_{41}H_{74}NO_8P$: C, 66.55; H, 10.08; N, 1.89. Found: C, 66.51; H, 9.94; N, 1.75.

Registry No.—**2**, 20708-12-7; **2** (3,5-dinitrobenzoate derivative), 20708-13-8; **4**, 20728-37-4; **4** (dicyclohexylammonium salt), 20708-11-6; **7**, 20707-71-5.

(10) Aldrich Chemical Co.

(11) E. Baer and J. Blackwell [*Biochemistry*, **3**, 975 (1964)] prepared this compound by acylation of the barium salt of L-α-glycerylphosphoryl-2′-hydroxyethylphthalimide followed by hydrazinolysis.

(12) J. C. Dittmer and R. L. Lester, *J. Lipid Res.*, **5**, 126 (1964).

(13) G. Rouser, G. Kritchevsky, D. Heller, and E. Lieber, *J. Amer. Oil Chemists Soc.*, **40**, 425 (1963).

(14) Elemental analyses and optical rotations were obtained by Miss Margaret Carroll and Mr. Walter Hamill with their staffs, respectively, of the Smith Kline and French Physical and Analytical Chemistry Section.

(15) Thermal gravitational analysis performed on a Du Pont 950 thermogravimetric analyzer.

(16) E. Baer and D. Buchnea, *J Biol. Chem.*, **230**, 447 (1958).

The Reaction of β-Keto Esters with 1,3-Diketones

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The reaction of β-keto esters with 5,5-dimethyl-1,3-cyclohexanedione and 1,3-indanedione in trifluoroacetic acid (TFA) shows an interesting contrast of the action

TABLE I

4-PYRONES FROM β-KETO ESTERS FROM 1,3-DIKETONES

No.	β-Keto ester used	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
	5,5 Dimethyl-1,3-cyclohexanedione(methone)									
1	Ethyl acetoacetate	207–208	84	$C_{12}H_{14}O_3$	69.88	6.84		69.69	7.06	
2	Ethyl *p*-nitrobenzoylacetate	203–204	96	$C_{17}H_{15}NO_5$	65.17	4.82	4.47	64.90	4.64	4.19
3	Ethyl benzoylacetate	123–125	52	$C_{17}H_{16}O_3$	76.10	6.01		75.94	6.08	
	1,3-Indanedione									
4	Ethyl acetoacetate	129	95	$C_{13}H_8O_3$	73.58	3.80		73.70	3.94	
5	Ethyl benzoylacetate	209–210	91	$C_{18}H_{10}O_3$	78.82	3.67		78.57	3.90	
6	Ethyl *p*-nitrobenzoylacetate	179–181	99	$C_{18}H_9NO_5$	67.71	2.84	4.38	67.43	2.59	4.17
7	Dimethyl acetone dicarboxylate	129–131	81	$C_{13}H_8O_3$	73.58	3.80		73.85	4.04	

1 = 7,8-Dihydro-2,7,7-trimethyl-4H-1-benzopyran-4,5(6H)-dione
2 = 7,8-Dihydro-7,7-dimethyl-2-(4-nitrophenyl)-4H-1-benzopyran-4,5(6H)-dione
3 = 7,8-Dihydro-7,7-dimethyl-2-phenyl-4H-1-benzopyran-4,5(6H)-dione
4 = 2-Methylindeno[1,2-*b*]pyran-4,5-dione
5 = 2-Phenylindeno[1,2-*b*]pyran-4,5-dione
6 = 2-(4-Nitrophenyl)indeno[1,2-*b*]pyran-4,5-dione
7 = 2-Methylindeno[1,2-*b*]pyran-4,5-dione

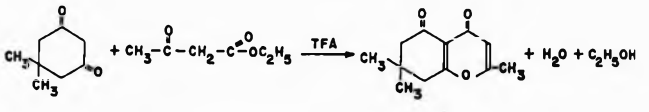
of the same reagents and catalyst with resorcinol and substituted resorcinols.

It has been shown that resorcinols, which under certain conditions have a 1,3-diketo structure, always react with β-keto esters *ortho* to one hydroxyl and *para* to the other, rather than at the position between the two hydroxyls, and that the product is always a coumarin.[1]

The two cyclic 1,3-diketones selected for this study react with β-diketones at the position between the two keto groups simply because it is either the only position having an active methylene group, as in 1,3-indanedione, or the only position having a single active methylene group available, as in 5,5-dimethyl-1,3-cyclohexanedione, because positions 4 and 6 are effectively covered and sterically hindered by the two methyl groups at position 5.

The chief product from 1,3-dimethyl-1,3-cyclohexanedione is a 4-pyrone, and the general course of the reaction may be considered to be the same as given in Scheme I for compound **1**. However, the difficulty in

SCHEME I

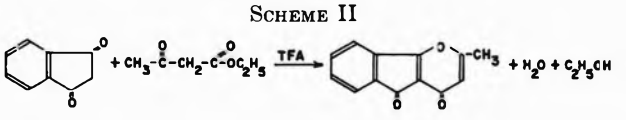


1

purification of compounds **1–3** appears to indicate that an appreciable amount of the product is 2-pyrone, which is removed along with occluded trifluoroacetic acid by the sodium bicarbonate treatment described in the Experimental Section.

No such difficulty, was encountered in the reaction of 1,3-indanedione with β-keto esters and Scheme II,

SCHEME II



4

giving the visualized reaction for compound **4**, may be considered to be a faithful representation of the general reaction for compounds **4–7**.

Hydrolysis and decarboxylation of compound **7** takes place during the course of the reaction and is the same as **4** by melting point, mixture melting point, and analysis.

A nuclear magnetic resonance study of compound **1** by the author and by an experienced spectroscopist[2] failed to show decisive results as to whether the compound was a 2-pyrone or a 4-pyrone. This indecision was resolved by preparing bis-2,4-dinitrophenylhydrazones from compounds **1** and **4** labeled as **1A** and **4A**, respectively. No structures other than those proposed in Schemes I and II would form such substances.

Table I records the essential data on the **1–7** series. Compounds **4–7** are powerful fluorescers.

Experimental Section[3]

Preparation of Members of 1–7 Series.—A mixture consisting of 0.1 mol of the 1,3-diketone, 0.1 mol of β-keto ester, and 40 ml of trifluoroacetic acid was refluxed for 24 hr in the case of the **1–3** compounds; however, in the case of the **4–7** compounds, the refluxing period was dropped to 2 hr because the product began to precipitate out of solution.

Upon the termination of the reflux period, each of the mixtures was poured into 400 ml of water. All of the compounds quickly crystallized except compounds **1** and **3**. In these two cases, the oils were separated from the water-diluted solutions and let into about 500 ml of a saturated solution of sodium bicarbonate in a 1000-ml beaker. Neutralization of the occluded acid in this manner permits the product to crystallize. All compounds were then filtered and the precipitates were dried in air.

Compounds **1–3** were purified three times by taking them up in boiling heptane followed by chilling. Compounds **4–7** were purified by extracting small powdered samples with boiling ethyl acetate and filtering. The precipitate was discarded and the compound was recovered by precipitating with heptane and chilling. The precipitate was again purified by repeating the process. Extreme care was taken on the second precipitation to use no more ethyl acetate than required to redissolve the compounds, and 10–20 times that volume of heptane was used.

(1) L. L. Woods and John Sapp, *J. Org. Chem.*, **27**, 3703 (1962).

(2) Sadtler Research Laboratories, Philadelphia, Pa. 19104.

(3) All analyses were performed by Dr. Carl Tiedcke, 705 George St., Teaneck, N. J. Melting points were taken on a Fisher–Johns melting point block.

An integrated nmr of compound I gave chemical shifts δ 1.10, 1.66, 2.20–2.80, 3.35, and 5.50, interpreted as 6, 2, 4, 0.4, and 0.6 protons, respectively.

2,4-Dinitrophenylhydrazones of Compounds 1 and 4.—Two grams each of compound 1 and 2,4-dinitrophenylhydrazine and 2 ml of concentrated hydrochloric acid were gently heated at 70–80° for 10 min in 70 ml of absolute ethanol. Compound 4 was treated in a similar manner. The cooled solutions were filtered and the filtrates were discarded. The air-dried precipitates were extracted with two successive 50-ml portions of boiling ethanol. The precipitates were again dried in air. The melting points of the hydrazones 1A and 4A were 205–207° and 248–249°, respectively.

Anal. Calcd for $C_{24}H_{22}N_8O_9$ (1A): N, 19.10. Found: N, 19.23. Calcd for $C_{25}H_{16}N_8O_9$ (4A): N, 16.66. Found: N, 16.49.

Registry No.—1, 20452-84-0; 1A, 20452-85-1; 2, 20452-86-2; 3, 20452-87-3; 4, 20452-88-4; 4A, 20452-89-5; 5, 20452-90-8; 6, 20452-91-9.

Acknowledgment.—The author acknowledges with thanks the financial support for this project by the Robert A. Welch Foundation and thanks Dr. Kurt Leoning of the Chemical Abstracts Service for his assistance in the naming of the compounds.

Bond Fission in the Hydrolysis of 2,4-Dinitrophenyl Phosphate[1]

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The hydrolyses of 2,4- and 2,6-dinitrophenyl phosphate differ from those of most simple monophosphates in that the dianion, rather than the monoanion, is the most reactive species.[2,3]

It is assumed that the dianion generates phenoxide and metaphosphate ions, and the inorganic phosphate

$$ArO\,PO_3^{2-} \xrightarrow{\text{slow}} ArO^- + PO_3^- \xrightarrow[\text{fast}]{H_2{}^{18}O} H_2P{}^{18}O_2^-$$

should therefore have 25% of the abundance of the water. Experiments in mixed aqueous organic solvents show that the phosphorus–oxygen bond is broken, as required by this mechanism. The aim of the present work was to confirm the phosphorus–oxygen bond fission for hydrolysis of the dianion in water, and in addition to determine the position of bond fission for hydrolysis at high pH, where part of the reaction involves attack of hydroxide ion upon the dianion.[3] (The over-all reaction rate is increased approximately sixfold by 1 *M* potassium hydroxide; however sodium and potassium chloride have marked salt effects on the spontaneous hydrolysis of the dianion, and, assuming that the potassium chloride and hydroxide exert similar salt effects, approximately half the reaction in 1 *M* hydroxide ion will involve attack of this reagent and the rest will be a salt-assisted spontaneous hydrolysis of the dianion.)

Inorganic phosphate was isolated after complete hydrolysis in ^{18}O-enriched water and its excess isotopic abundance, N, was determined. The results (Table I) show that hydrolysis of the dianion, at pH 6.0, introduces one oxygen of the water into inorganic phosphate, as expected.

TABLE I

BOND FISSION IN THE HYDROLYSIS OF 2,4-DINITROPHENYL PHOSPHATE[a]

Reagent	N_{H_2O}[b]	N_P[b]	% N_P/N_{H_2O}
pH 6.0[c]	0.80	0.21	26
pH 6.0[c]	0.78	0.18	23
1 *M* KOH	1.37	0.31	23
1 *M* KOH	1.37	0.33	24
1 *M* KOH	0.73	0.19	26

[a] At 25.0° unless specified. [b] Atom per cent excess above normal. [c] At 45.0° with acetate buffer; the pH was readjusted during the reaction.

The dianion with alkoxide ion in methanol or ethanol gives both phenol and phenolic ether, showing that phosphorus– and aryl–oxy fission are occurring.[3] In water we find predominantly phosphorus–oxygen fission (Table I). The spontaneous hydrolysis of the dianion makes some contribution to the over-all reaction, even with 1 *M* hydroxide ion, but not enough to account for all the phosphorus–oxygen fission, and therefore the hydroxide ion is attacking the phosphorus atom, although attack upon the aryl group is important with alkoxide ion in alcohol.[3] For nucleophilic attack upon 2,4-dinitrophenyl tosylate it was found that the more polarizable reagents tended to attack the aryl group preferentially,[4] but amines have been shown to attack the phosphorus atom of 2,4-dinitrophenyl phosphate.[5] These changes in the site of attack with changes in reagent accord with Pearson's classification of "hard" and "soft" reagents.[6]

However there was some nucleophilic attack upon the aryl group in the reaction between the bis-2,4-dinitrophenyl phosphate monoanion and hydroxide ion.[7] In this system two aryl groups are available for attack, and the spontaneous hydrolysis makes little contribution to the over-all reaction in alkali. These results provide other examples of phosphorylation by anions of phosphate esters.[3,5,7] Phosphorylations of one anion by another have been considered as models for degradations of several biologically important phosphates.[8]

Experimental Section

Materials.—2,4-Dinitrophenyl phosphate was prepared and isolated as its cyclohexylamine salt, mp 145° (lit.[3] mp 147°). The water was distilled from $KMnO_4$ (twice) and its isotopic abundance was determined by equilibration with CO_2 which was analyzed mass spectrometrically.

Reaction Conditions.—The following conditions are typical. The aryl phosphate (1 g), as its cyclohexylamine salt, was dis-

(1) (a) Abstracted from the thesis of J. M. Hellyer, submitted in partial fulfillment of the requirements of the Doctor of Philosophy degree of the University of California at Santa Barbara. (b) Support of this work by the National Institute of Arthritis and Metabolic Diseases of the U. S. Public Health Service is gratefully acknowledged.

(2) A. J. Kirby and A. G. Varvoglis, *J. Amer. Chem. Soc.*, **89**, 415 (1967).

(3) C. A. Bunton, E. J. Fendler, and J. H. Fendler, *ibid.*, **89**, 1221 (1967).

(4) J. F. Bunnett and J. Y. Bassett, *ibid.*, **81**, 2014 (1959).

(5) A. J. Kirby and A. G. Varvoglis, *J. Chem. Soc., Phys. Org.*, 135 (1968).

(6) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963).

(7) C. A. Bunton and S. J. Farber, *J. Org. Chem.*, **34**, 767 (1969).

(8) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 343 (1964); J. R. Cox and J. P. Cleveland, in the Symposium on Naturally Occurring Phosphate Esters, Newcastle, The Chemical Society, London, 1967; D. G. Oakenfull, D. I. Richardson, and D. A. Usher, *J. Amer. Chem. Soc.*, **89**, 5491 (1967).

solved in $H_2{}^{18}O$ (150 ml) and the solution was made alkaline and extracted with pentane to remove the cyclohexylamine. The pH of the solution was then adjusted and the hydrolysis was carried to completion. For reactions at pH 6 the dinitrophenol was extracted with chloroform; this step was omitted for reaction in alkali. Barium phosphate was then precipitated, redissolved in acid and reprecipitated, following procedures already described, and then converted into potassium dihydrogen phosphate using Dowex 50W-X8 resin in its acid form followed by neutralization with KOH. Potassium dihydrogen phosphate was then isolated following procedures already described,[9] and its ^{18}O abundance was determined by heating it *in vacuo* with phenylenediamine hydrochloride and guanidine hydrochloride and analyzing the evolved CO_2 mass spectrometrically.[10]

Registry No.—2,4-Dinitrophenyl phosphate, 2566-26-9.

(9) C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3574 (1958).
(10) C. A. Bunton and B. N. Hendy, *ibid.*, 627 (1963).

Base-Catalyzed Formation and Reactions of o-Nitrophenylacetamides[1a,b]

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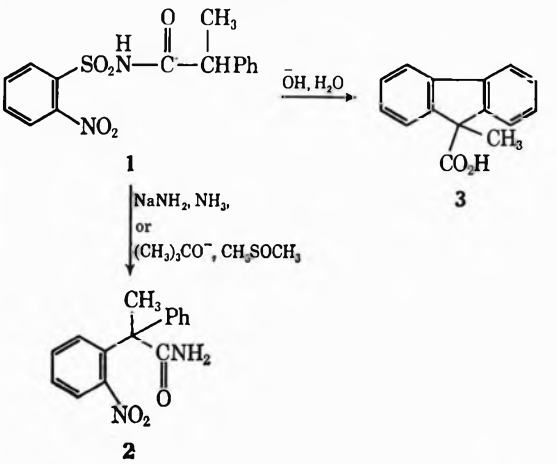
Naito and coworkers[2] have shown that Smiles rearrangement of N-(nitrophenylsulfonyl)acetamides can be a useful synthetic route to nitrophenylacetamides. We subjected N-(*o*-nitrophenylsulfonyl)-2-phenylpropionamide (**1**) to prolonged heating (26 hr) with 10% aqueous sodium hydroxide in an attempt to synthesize 2-(*o*-nitrophenyl)-2-phenylpropionamide (**2**) (Scheme I). The principal product of the reaction was found to

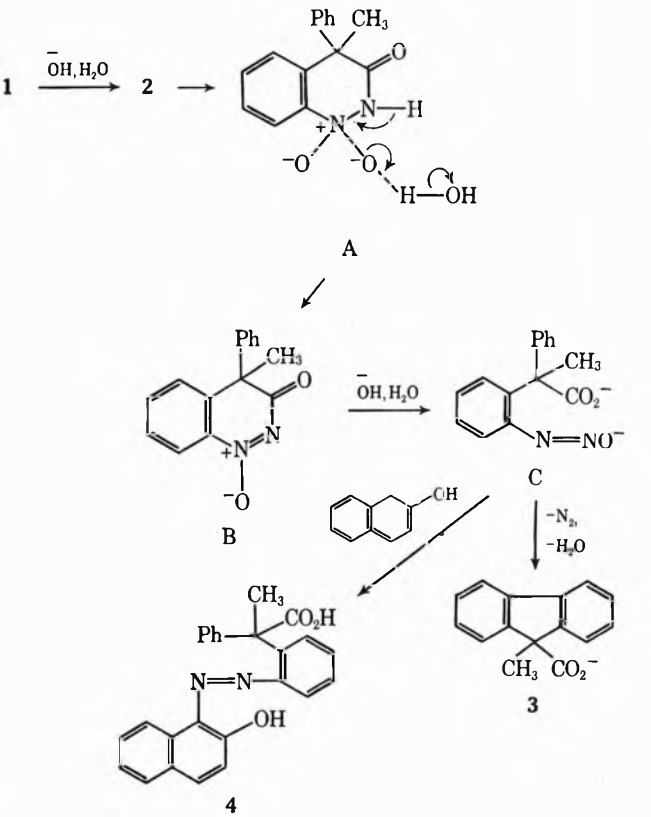
SCHEME I



be a nitrogen-free acid (30% yield). Spectral evidence and comparison with an authentic sample showed the acid to be 9-methylfluorene-9-carboxylic acid (**3**). It proved to be possible to synthesize **2** from **1** by using alternative basic catalysts. Sodium amide in liquid ammonia effects the transformation in 43% yield, whereas use of potassium *t*-butoxide in dimethyl sulfoxide gave **2** in 67% yield.

We propose that the formation of **3** results from base-catalyzed intramolecular condensation of the amide and nitro groups in **2** and that the reaction follows the course outlined in Scheme II.

SCHEME II

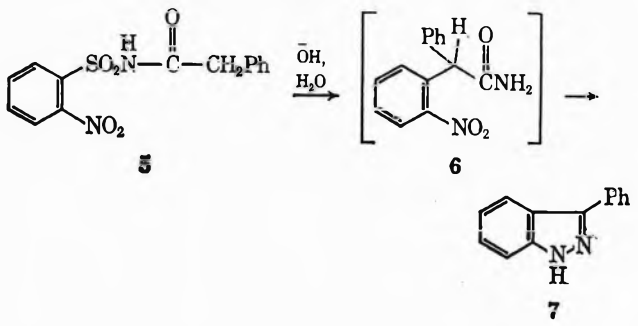


The following observations can be cited in support of this proposal. When **2** is subjected to reaction with aqueous base, **3** is formed in 59% yield after 4.5 hr. Reaction of **1** with aqueous sodium hydroxide in the presence of β-naphthol leads to an azo compound believed to be **4** on the basis of analytical and spectral data. The formation of **4** suggests the intermediacy of a diazonium hydroxide (C) in the reaction. If C is formed by intramolecular condensation from **2**, the final step in the formation of 9-methylfluorene-9-carboxylic acid can readily be explained as a Pschorr cyclization.[3]

The intramolecular condensation between an amide group and nitro group which is proposed to account for the formation of intermediate B is an example of a relatively rare class of reactions, although condensations with many other types of carbon and nitrogen nucleophiles and nitro groups are quite common.[4] The formation of 3-phenylindazole when N-(*o*-nitrophenylsulfonyl)-2-phenylacetamide (**5**) is heated with aqueous base is believed to involve a similar condensation[2,4] proceeding *via* the Smiles rearrangement product **6** (Scheme III). An attempt was made to trap a di-

(1) (a) Supported in part by NIH Grant GM-14344. (b) Abstracted from the Ph.D. Thesis of D. E. Blackburn, University of Virginia, 1969. (c) NASA Trainee, 1964–1967.
(2) T. Naito, R. Dohmori, and O. Nagase, *J. Pharm. Soc. Japan*, **74**, 593 (1954); T. Naito, R. Dohmori, and M. Sano, *ibid.*, **74**, 596 (1954); T. Naito, R. Dohmori, and M. Shimoda, *Pharm. Bull.* (Tokyo), **3**, 34 (1955).
(3) D. F. DeTar, *Org. Reactions*, **9**, 409 (1957).
(4) J. D. Loudon and G. Tennant, *Quart. Rev.* (London), **18**, 389 (1964).

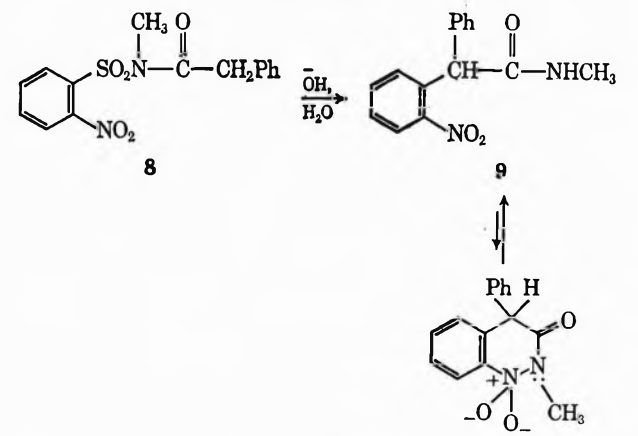
SCHEME III



azonium intermediate by treating **5** with aqueous base in the presence of β-naphthol. No azo compound was formed and the formation of 3-phenylindazole was not inhibited. The diazonium intermediate from **6** may cyclize to **7** faster than it can be trapped by β-naphthol. It is interesting to note that, in contrast to **2** and **6**, the parent compound *o*-nitrophenylacetamide undergoes hydrolysis in preference to intramolecular condensation.[5] The presence of the substituents α to the carbonyl group in **2** and **6** may be important in retarding the rate of hydrolysis sufficiently to permit intramolecular condensation to compete successfully.

Further evidence that condensation reactions involving the amido and nitro functions of **2** lead to the formation of **3** can be inferred from the results obtained with N-methyl-N-(*o*-nitrophenylsulfonyl)-2-phenylacetamide (**8**). Unlike **5**, the N-methyl homolog **8** gives the normal Smiles rearrangement product **9** on reaction with aqueous base (Scheme IV). The N-

SCHEME IV



methyl group can interfere with the intramolecular condensation by preventing loss of water and the formation of a nitrogen–nitrogen double bond.

A convenient synthesis of 2-phenylpropionic acid (hydratropic acid) based on alkylation of the disodio salt[6] of phenylacetic acid was developed during the course of this work and is described in the Experimental Section.

Experimental Section

2-Phenylpropionic Acid.—A solution of sodium amide was prepared by addition of small pieces of sodium (10.4 g, 0.45 g-atom) to liquid ammonia (750 ml) containing a small amount of ferric nitrate. Phenylacetic acid (28.2 g, 0.208 mol) was added and the mixture was stirred for 0.5 hr. Methyl iodide (29.6 g, 0.208 mol) in ether (40 ml) was added. After the reaction mixture had been stirred for 1.5 hr, the ammonia was allowed to evaporate. Ether (250 ml) was added to the residue and the mixture was evaporated to dryness on the steam bath. This procedure was repeated and the residue was then dissolved in water (600 ml) and washed with ether. The aqueous solution was filtered and acidified with hydrochloric acid. The organic layer was separated and distilled to yield pure 2-phenylpropionic acid (24.4 g, 0.162 mol, 78%), bp 92–97° (0.3 mm).

N-(*o*-Nitrophenylsulfonyl)-2-phenylpropionamide (1).—2-Phenylpropionyl chloride was prepared from the acid by reaction with thionyl chloride and then distilled. The acid chloride (33.7 g, 0.200 mol) and *o*-nitrobenzenesulfonamide (40.4 g, 0.200 mol) were mixed and heated in an oil bath at 170–180° for 1.5 hr. Crushed ice was added with stirring until the viscous reaction mixture solidified. The water was decanted and the residue was crystallized from ethanol–water giving 74.3 g of crude product, mp 144–155°. Treatment with charcoal and several recrystallizations gave pure **1** (34.3 g, 0.103 mol, 51%): mp 152.5–155°; ν_{NH} 3210, ν_{CO} 1720, ν_{NO_2} 1525, 1350 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.88; H, 4.22; N, 8.38. Found: C, 54.10; H, 4.45; N, 8.67.

Reaction of 1 with Aqueous Sodium Hydroxide.—A solution of **1** (1.7 g, 0.0050 mol) and 10% sodium hydroxide (20 ml, ~0.05 mol OH) was heated on a steam bath for 26 hr. The reaction mixture was acidified causing the separation of an oil which solidified on standing. The mixture was extracted with chloroform and, after concentration, the product was chromatographed on silicic acid. Chloroform eluted 9-methylfluorene-9-carboxylic acid (**3**) which was recrystallized from ethanol–water giving pure **3** (0.33 g, 0.0015 mol, 29%): mp 172–173° (lit.[7] mp 170–171°); λ_{max} (in absolute methanol) 256 mμ s (log ε 4.24), 265 (4.30), 277 s (4.08), 288 (3.75), and 299 (3.73); nmr peaks in $CDCl_3$ at δ 1.75 (3 H, s), 7.2–7.8 (8 H, m) and 10.5 (1 H, s).

The sample was identical (mixture melting point and superimposable infrared spectra) with an authentic sample of **3** prepared by the method of Anet and Bavin.[7]

2-(*o*-Nitrophenyl)-2-phenylpropionamide (2).—A solution of **1** (3.34 g, 0.0100 mol) in dimethyl sulfoxide (10 ml) was added to a solution of potassium *t*-butoxide (3.36 g, 0.0300 mol) in dimethyl sulfoxide (50 ml). The solution was heated at 80–85° for 24 hr. The reaction mixture was diluted with saturated aqueous sodium chloride (500 ml) and extracted thoroughly with ether. The ether solution was washed with water and dried over magnesium sulfate. The solution was filtered and evaporated. Crystallization of the residue from benzene–petroleum ether gave **2** (1.10 g, 0.0041 mol, 67% based on unrecovered **1**): mp 129–131°; ν_{NH_2} 3470 and 3360, ν_{CO} 1670, ν_{NO_2} 1535 and 1365 cm^{-1}; nmr peaks in $CDCl_3$ at δ 2.15 (3 H, s), 5.87 (2 H, broad singlet), and 6.9–7.9 (8 H, m).

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.64; H, 5.40; N, 10.35.

Unreacted **1** (1.30 g, 0.0039 mol, 39%) was recovered by acidification of the alkaline aqueous layer remaining from the extraction of **2**.

Reaction of **1** with sodamide (2 mol) in liquid ammonia for 2.5 hr led to formation of a 43% yield of **2** (based on unrecovered **1**) and recovery of 65% of the starting material.

Reaction of 2 with Aqueous Sodium Hydroxide.—2-(*o*-Nitrophenyl)-2-phenylpropionamide (0.63 g, 0.0023 mol) was heated with 10% aqueous sodium hydroxide (7.5 ml, ~0.018 mol OH^-) for 4.5 hr on a steam bath. The reaction mixture was cooled, acidified, and extracted with ether. The ether extract was washed with water, dried, and concentrated using a rotary evaporator. The residue was chromatographed on silicic acid. Chloroform eluted 9-methylfluorene-9-carboxylic acid (0.30 g, 0.0013 mol, 59%), mp 170–172° after recrystallization from ethanol–water.

Reaction of 1 with Aqueous Sodium Hydroxide in the Presence of β-Naphthol.—A mixture of **1** (1.67 g, 0.0050 mol) and β-naphthol (0.72 g, 0.0050 mol) in 10% aqueous sodium hydroxide (30 ml) was heated on a steam bath for 26 hr. The reaction mixture was acidified giving a partially crystalline precipitate. Recrystallization from ethanol–water gave pure 2-phenyl-2-[2-(2-hydroxy-1-naphthylazo)phenyl]propionic acid (**4**, 0.8 g, 0.002 mol, 40%): mp 214–216° dec; ν_{OH} 3450 and 2200–3200,

(5) C. W. Muth, N. Abraham, M. L. Linfield, R. B. Wotring, and E. A. Pacofsky, *J. Org. Chem.*, **25**, 736 (1960).

(6) C. R. Hauser and W. R. Dunnavent, *Org. Syn.*, **40**, 38 (1960).

(7) F. A. L. Anet and P. M. G. Bavin, *Can. J. Chem.*, **34**, 991 (1956).

ν_{CO} 1730 cm^{-1}; λ_{max} (in 95% ethanol) 228 mμ (log ϵ 4.59), 315 (3.98), 485 (4.08); nmr peaks in DMSO-d_6 at δ 2.0 (3 H, s), 7.2 (15 H, m), and 13.8 (1 H, s).

Anal. Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.09; N, 7.07. Found: C, 75.78; H, 5.00; N, 6.83.

Reaction of 5 with Aqueous Sodium Hydroxide in the Presence of β-Naphthol.—N-(*o*-Nitrophenylsulfonyl)-2-phenylacetamide (1.6 g, 0.005 mol) and β-naphthol (0.72 g, 0.005 mol) were mixed with 10% aqueous sodium hydroxide (30 ml) and heated on a steam bath for 14 hr. A gummy precipitate was present. After crystallization from ethanol and elution through a short column of alumina, 3-phenylindazole (0.66 g, 0.0034 mol, 68%), mp 116–118°, was obtained.

Acidification of the aqueous reaction solution precipitated β-naphthol (0.70 g, 0.0049 mol, 97%), mp 121–122° after purification by chromatography.

Reaction of *o*-Nitrophenylacetamide with Aqueous Sodium Hydroxide.—A mixture of *o*-nitrophenylacetamide (1.8 g, 0.010 mol) and 10% aqueous sodium hydroxide was heated on a steam bath for 7 hr. Acidification of the reaction mixture followed by recrystallization of the precipitate from ethanol–water gave *o*-nitrophenylacetic acid (1.0 g, 0.05 mol, 55%), mp 138–141°.

N-Methyl-N-(*o*-nitrophenylsulfonyl)-2-phenylacetamide (8).—N-Methyl-*o*-nitrobenzenesulfonamide (10.8 g, 0.050 mol) and phenylacetyl chloride (12.4 g, 0.080 mol) were heated together at 150–160° in an oil bath for 2 hr. Crushed ice was added to the reaction mixture with stirring and the precipitate was collected by filtration. Several recrystallizations from ethanol gave pure **8** (12.1 g, 0.036 mol, 72%): mp 126.5–128°; ν_{CO} 1700, ν_{NO_2} 1540 and 1355, ν_{SO_2} 1175 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.88; H, 4.22, N, 8.38. Found: C, 53.80; H, 4.17; N, 8.21.

Reaction of 8 with Aqueous Sodium Hydroxide.—A solution of **8** (1.67 g, 0.050 mol) in 10% aqueous sodium hydroxide (12.5 ml) was heated on a steam bath for 4.5 hr. The reaction mixture contained an oil which was dissolved in ether. The aqueous solution was extracted with ether. The combined ether solutions were washed with water, dried, and evaporated. The residue was chromatographed on silicic acid. N-Methyl-(*o*-nitrophenyl)phenylacetamide (**9**) was eluted with chloroform and recrystallized from ethanol (0.37 g, 1.4 mol, 88% based on unrecovered **8**): mp 142–144°; ν_{NH} 3250, ν_{CO} 1645, ν_{NO_2} 1525 and 1345 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.43, H, 5.39; N, 10.32.

Acidification of the aqueous reaction mixture gave unreacted **8** (1.15 g, 0.034 mol, 68% recovery).

Registry No.—**1**, 20512-89-4; **2**, 20512-90-7; **4**, 20512-91-8; **8**, 20512-92-9; **9**, 20512-93-0.

The Synthesis of (+)-, (−)-, and (±)-Dimethyl 3-Methyl-1-cyclopentene-1,2-dicarboxylates and the Corresponding Acids

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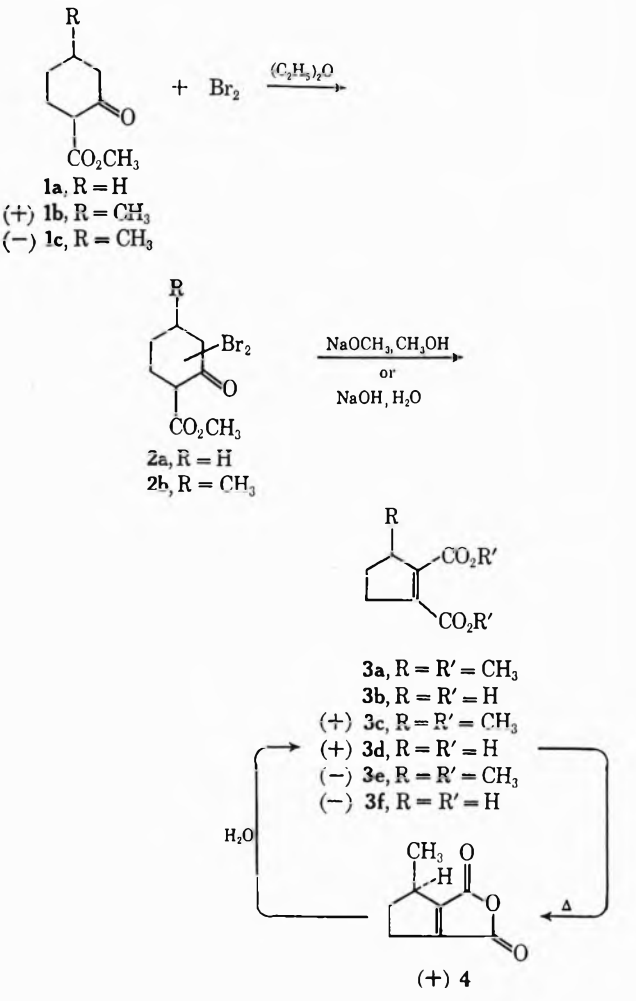
The synthesis of 1-cyclopentene-1,2-dicarboxylic acid and its dimethyl ester has been reported.[3] However, the reported synthesis of comparable esters with alkyl substitution at positions C-3 and C-4 are time consuming and multistep, and the over-all yields are low.[3c] We describe a convenient two-step general synthesis for esters or acids of these types. This reaction sequence, a Favorskii-type rearrangement of dibromo derivatives of β-keto esters, was first applied to 4,4-dibromo-2-methylacetoacetic acid.[4]

As shown in Scheme I, methyl 2-oxocyclohexanecarboxylate (**1a**), (+)-methyl 4-methyl-2-oxocyclohexanecarboxylate (**1b**), and (−)-methyl 4-methyl-2-oxocyclohexanecarboxylate (**1c**) on treatment with 2.2 molar equiv of bromine afforded the dibromides **2a** and **2b**.[5] These crude unidentified dibromides were then separately treated with a methanolic solution of sodium methoxide. Subsequent work-up provided the new esters (+)-dimethyl (3*R*)-methyl-1-cyclopentene-1,2-dicarboxylate (**3c**) and (−)-dimethyl (3*S*)-methyl-1-cyclopentene-1,2-dicarboxylate (**3e**). Hydrolysis of **2b**[5] yielded the new acids (+)-(3*R*)-methyl-1-cyclopentene-1,2-dicarboxylic acid (**3d**) and (−)-(3*S*)-methyl-1-cyclopentene-1,2-dicarboxylic acid (**3f**).

Dimethyl 1-cyclopentene-1,2-dicarboxylate (**3a**) and the acid **3b** were prepared and identified as described in the Experimental Section. The racemic forms of **3c**

SCHEME I



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(3) (a) E. Haworth and W. H. Perkin, *J. Chem. Soc.*, **65**, 978 (1894); (b) L. L. McCoy, *J. Amer. Chem. Soc.*, **89**, 1673 (1967); (c) R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, *ibid.*, **80**, 3413 (1958).

(4) (a) M. Demarcay, *Ann. Chim. Phys.*, **20**, 433 (1880); (b) P. Walden, *Ber.*, **24**, 2025 (1891).

(5) Structure **2b** is used to represent the dibromide from both (+) **1b** and (−) **1c**.

and **3d** are also known.[3c] The absolute configuration assignments of (+) **3c**, (+) **3d**, and (+) **4** as *R*[6] as well as (−) **3e** and (−) **3f** as *S*[6] are based on the use of (+)-(3*R*)-methylcyclohexanone[7a,b] and (−)-(3*S*)-methylcyclohexanone[7c] in the synthesis of (+) **1b** and (−) **1c**.

We found it convenient to use sodium methoxide in methanol to cause the Favorskii-type rearrangement since the product was thus directly available for distillation. However, aqueous sodium hydroxide may be used to cause the direct formation of the sodium salts of the dibasic acids **3b**, (+) **3d**, and (−) **3f**.

The nmr spectra of **3c** and/or **3e** show δ 1.15 (d, 3, J = 7 Hz), which is in agreement with a methyl-group split by a proton allylic to a double bond; 3.72 (s, 3) and 3.73 (s, 3) assigned to the two carboxymethyl groups; and a series of highly coupled resonances between 1.30 and 3.30 (m, 5) attributed to the protons of the cyclopentene ring. Their ir absorption (ester C=O) at 1720 cm^{-1} is comparable with that of maleic acid and not with the 1680-cm^{-1} value obtained for fumaric acid. Their ultraviolet spectra are in agreement with the reported value for the (±) form.[3c] The molecular ion peak at *m/e* 198 from their mass spectra lends additional support to the assigned structures.

The nmr spectrum of the acid **3d** in NaOD showed peaks compatible with the assigned structure. However, as expected, downfield shifts of about 29 Hz were observed and the methyl-group split appeared at δ 1.58 (d, 3, J = 7 Hz).

Experimental Section[8]

Dibromo Keto Ester 2a.—To a well-stirred solution of 25 g (0.16 mol) of methyl 2-oxocyclohexanecarboxylate (**1a**) and 200 ml of anhydrous ether at 0° was added dropwise 56 g (0.35 mol) of bromine. After the addition was complete, the solution was stirred for an additional hour at 0° and then added to 100 g of crushed ice and 100 ml of a saturated solution of sodium bicarbonate. The ether layer was separated and the aqueous layer was extracted with three additional 100-ml portions of ether. The ether layers were combined, dried ($MgSO_4$), and concentrated to 40 g (78%) of crude **2a**: nmr (neat) δ 3.80 (s, 3), 2.90 (m, 2), 2.40 (m, 2), and 1.80 (m, 2); ir (liquid film) 2950, 1730, 1650, 1620, 1440, 1360, 1340, 1240, 790, and 730 cm^{-1}. This crude material was used directly in the next step.

Dimethyl 1-Cyclopentene-1,2-dicarboxylate (3a).—To a well-stirred solution of sodium methoxide (12 g, 0.52 g-atom of sodium) in 200 ml of methanol was added dropwise at room temperature 40 g (0.127 mol) of **2a**. After the addition was complete, the solution was allowed to stir for 1 hr, poured into 200 ml of 5% hydrochloric acid solution, and extracted with five 100-ml portions of ether. The ether extracts were combined and washed with distilled water until neutral to pH paper, dried ($MgSO_4$), concentrated, and distilled, giving 19 g (81%) of dimethyl 1-cyclopentene-1,2-dicarboxylate (**3a**): bp 63° (0.4 mm); ir (liquid film) 2950, 1730, 1640, 1440, 1330, 1275, and 1200 cm^{-1}; nmr (CCl) δ 3.65 (s, 3), 3.64 (s, 3), 2.60 (t, 4, J = 6 Hz), 2.00 (q, 2, J = 7 Hz); mass spectrum (70 eV) molecular ion peak at *m/e* 184.[9] Hydrolysis of 450 mg of **3a** in 1 ml of 10% NaOH at room temperature yielded 210 mg (55%) of brown leaflets of 1-cyclopentene-1,2-dicarboxylic acid (**3b**), mp 150–160° and 176–177° after recrystallization from ethyl acetate (lit.[7a] mp 178–179°).

Dibromo Keto Ester 2b.—The procedure described for the preparation of **2a** was applied to 29 g (0.17 mol) of **1b**, which was dibrominated to yield 41.3 g (75%) of crude **2b**: ir (liquid film) 2950, 1730, 1660, 1620, 1440, 1360, 1260, 1250, 1220, 1160, 1100, 960, 810, 780, and 740 cm^{-1}.

(+)-Dimethyl (3*R*)-Methyl-1-cyclopentene-1,2-dicarboxylate (3c).—The procedure described for the preparation of **3a** was used to convert 41.3 g (0.126 mol) of **2b** into 22 g (88%) of **3c**: bp 45° (0.2 mm); $[\alpha]^{23}D$ +29.6° (c 1.2, CH_3OH); nmr (CCl_4) δ 3.73 (s, 3), 3.72 (s, 3), and 1.15 (d, 3, J = Hz); the remaining five protons were observed as complex resonances between 1.7 and 3.5; ir (liquid film) 2950, 1725, 1640, 1430, and 1260 cm^{-1}; uv max (CH_3OH) 223 mμ (log ϵ 4.33); mass spectrum 70 eV molecular ion *m/e* 198.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.39; H, 7.11.

(+)-(3*R*)-Methyl-1-cyclopentene-1,2-dicarboxylic Acid (3d).—To a well-stirred solution of 20 g (0.5 mol) of sodium hydroxide in 200 ml of distilled water at room temperature was added 41.3 g (0.126 mol) of **2b** prepared from (+) **1b**. After the addition was complete, the solution was allowed to stir for an additional hour and it was then added to 200 ml of a 5% solution of hydrochloric acid and extracted with five 100-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and concentrated to 20 g (80%) of brown crystals, mp 105–125°. Recrystallization from petroleum ether (bp 60–68°) gave 14 g of colorless crystals of **3d**: mp 135–136°; nmr ($CDCl_3$) δ 8.75 (s, 2), 4.25 (m, 1), 3.60 (m, 2), and 1.30 (d, 3, J = 7 Hz); ir ($CHCl_3$) 3000, 1720, 1625, 1420, 1250, 1040, and 930 cm^{-1}; uv max (C_2H_5OH) 236 mμ (log ϵ 4.05); $[\alpha]^{24}D$ +12.1° (c 0.5, CH_3OH).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.38; H, 5.97.

(−)-Dimethyl (3*S*)-Methyl-1-cyclopentene-1,2-dicarboxylate (3e) and (−)-(3*S*)-Methyl-1-cyclopentene-1,2-dicarboxylic Acid (3f).—A 1.7-g sample of (−) 1c[7a,c] was converted into 1.06 g (53%) of (−) **3e**: bp 88–90° (0.1 mm); $[\alpha]D$ −28.7° (c 6.6, CH_3OH); molecular ion peak *m/e* 198. The mass, nmr, and ir spectra of (+) **3c** and (−) **3e** were essentially identical.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.40; H, 7.22.

An 0.2-g sample of (−) **3e** was treated with aqueous alkali as described for **3c** to give 0.11 g (64%) of (−) **3f**. Recrystallization of (−) **3f** from pentane afforded colorless crystals: mp 132–133°; $[\alpha]D$ −12.6° (c 1.0, CH_3OH). The nmr, ir, and uv spectra of (−) **3f** were essentially identical with those of (+) **3d**.

Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.51; H, 5.96.

(+)-(3*R*)-Methyl-1-cyclopentene-1,2-dicarboxylic Acid Anhydride (4).—A 0.28-g sample of crude **3d** was distilled at 180° (1 mm) to give 0.21 g (83%) of **4**: $[\alpha]^{23}D$ +17.4° (c 2.1 $CHCl_3$); ir (liquid film) 2945, 1840, 1770, 1650, 1450, 1325, 1265, 1105, 1075, 1030, 866, 729, and 718 cm^{-1}; nmr (CCl_4) δ 2.70 (m, 3), 2.20 (m, 2), and 1.25 (d, 3, J = 7 Hz). A sweep past δ 8.75 showed absence of absorption due to carboxyl proton.

Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.45; H, 5.01.

Hydrolysis of **4** with warm water and recrystallization of the product from ethyl acetate gave **3d**, mp 135–136°.

Registry No.—**3a**, 13368-79-1; **3c**, 20512-95-2; **3d**, 20512-96-3; **3e**, 20512-97-4; **3f**, 20512-98-5; **4**, 20512-99-6.

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(6) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Intern. Ed. Engl.*, **5**, 385 (1966).

(7) (a) E. J. Eisenbraun, P. G. Hanel, K. S. Schorno, S. St. Francis Dilgen, and Jeanne Osiecki, *J. Org. Chem.*, **32**, 3010 (1967). (b) E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.*, **77**, 3383 (1955). (c) The (−)-(3*S*)-methylcyclohexanone was obtained by resolution of racemic ketone through use of the amine bisulfite technique: R. Adams and J. D. Garber, *ibid.*, **71**, 522 (1949).

(8) Spectral data were obtained from Varian A-60, Beckman IR-5a, and Beckman DK-1 spectrometers. The nmr measurements are in δ 0 ppm from tetramethylsilane standard: m, multiplet; q, quartet; t, triplet; d, doublet; and s, singlet.

(9) This mass spectrum and others were obtained from a Consolidated Electrodynamics Corp. Model 21-103C spectrometer.

Studies on the Constituents of *Corydalis* sp. VI.[1] Alkaloids from Chinese Corydalis and the Identity of *d*-Corydalmine with *d*-Corybulbine

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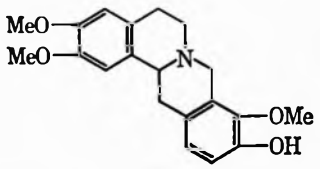
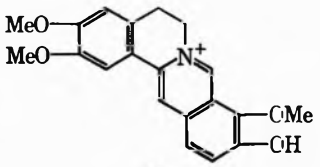
Several years ago, the first isolation of two new protoberberine bases named corydalmine (I), $C_{20}H_{23}O_4N$ (mp 238–239°, $[\alpha]D$ 337.4°), and dehydrocorydalmine (II), $C_{20}H_{20}O_4N^+$ (iodide, $C_{20}H_{20}O_4NI \cdot 2H_2O$, mp 238–



I

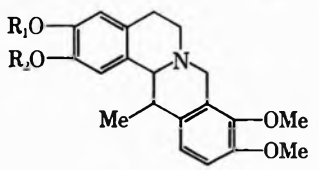


II

240° dec), from the commercially available *Corydalis* species[2] cultivated for use in Chinese medicine, and their structural assignments were reported by Imaseki and Taguchi.[3]

Recently, Telang and Bradsher[4] synthesized *dl*-10-hydroxy-2,3,9-trimethoxydibenzo[*a*,*g*]quinolizidine corresponding to the structure of I, and more recently Doskotch, *et al.*,[5] isolated dehydrocorydalmine iodide from *Stephania glabra*. It was noted by the above authors[4,5] and by Jeffs[6] that there were large differences in melting points between the synthetic product of *dl*-corydalmine,[4] mp 187.5–188.5°, and the natural *dl*-corydalmine,[3] mp 213–215°, and also between dehydrocorydalmine iodide from *Corydalis* species,[3] mp 238–240° dec, and that from *Stephania glabra*,[5] mp 195°. Up to now, those discrepancies in the melting points have remained unresolved because of the absence of a sample for direct comparison, and there is still some uncertainty which cannot be resolved satisfactorily by the accepted formulas I and II for these alkaloids.

In this paper, we wish to reveal that the alkaloid having mp 238–239°, and named *d*-corydalmine by Imaseki and Taguchi,[3] is identical with *d*-corybulbine[7]



III, $R_1 = H$; $R_2 = Me$
IV, $R_1 = Me$; $R_2 = H$

having the structure of III, and also to report further investigations on the tertiary alkaloids from the same plant.[2]

Reexamination of the tertiary alkaloid fraction from the plant resulted in the isolation of eleven crystalline alkaloids (Table I). From the tertiary nonphenolic alkaloid fraction, *d*-corydaline, *dl*-tetrahydropalmatine, *l*-tetrahydrocoptisine, and protopine were isolated by means of alumina column chromatography in the manner described by Imaseki and Taguchi.[3] Further elution with methanol from the alumina column gave a large amount of a crystalline aporphine-type alkaloid which was identified as *d*-glaucine[8,9] by direct comparison. On the other hand, the tertiary phenolic base fraction showed more than ten spots on the thin layer chromatogram, and eight alkaloids were isolated by means of silica gel column chromatography. Five of them were identified as *l*-tetrahydrocolumbamine,[3] *d*-corydaline, *l*-scoulerine,[10] noroxyhydrastinine,[11] and *α*-allocryptopine,[1c] respectively, by direct comparison, *i.e.*, thin layer chromatography, infrared and nmr spectra, and mixture melting point determinations. One new base, mp 248–250°, having a characteristic infrared absorption at 1715 cm^{-1}, was isolated in so small an amount that it could not be further investigated. The other two tertiary phenolic bases were tentatively designated as base A and B.

TABLE I

ALKALOIDS ISOLATED FROM COMMERCIALLY AVAILABLE CHINESE CORYDALIS[a]

Name	Yield,[b] %
Tertiary Phenolic Alkaloids	
l-Tetrahydrocolumbamine	0.0474
d-Corybulbine	0.0054
l-Scoulerine	0.0021
d-Tetrahydrojatrorrhizine	0.0015
Tertiary Nonphenolic Alkaloids	
d-Corydaline	0.1161
d-Glaucine	0.0822
dl-Tetrahydropalmatine	0.0530
Protopine	0.0282
l-Tetrahydrocoptisine	0.0182
α-Allocryptopine	0.0003
Noroxyhydrastinine	0.0001

[a] Reference 2. [b] Per cent yields calculated from the dried material.

Base A was obtained not only by the method previously reported for the isolation of *d*-corydalmine[3] but also by means of column chromatography described in the Experimantal Section. Base A, mp 220–222° dec, $[\alpha]D$ 307°, analyzed for $C_{21}H_{25}O_4N$. Its infrared spectrum taken in a Nujol mull was superimposable on the reported spectrum of the "*d*-corydalmine" of Imaseki and Taguchi,[3] although we were unable to obtain an authentic sample for a direct comparison. The nmr spectrum of base A taken in DMSO-d_6 solution was

(1) For part V, see S. Naruto, S. Arakawa, and H. Kaneko, *Tetrahedron Lett.*, 1705 (1968).

(2) The original plant of Chinese corydalis is described as *Corydalis bulbosa* D. C. in the official Chinese pharmacognostical book "Chung Yao Chih," Vol. 1, Peking, 1959, p 263, but is quite different from *C. bulbosa* D. C. occuring in Europe. It rather seems to be morphologically a variety of *C. ambigua* Cham. et Schlecht. The pharmacognostical data of this plant will be reported elsewhere by our coworkers, Dr. S. Takahashi and Mr. K. Namba.

(3) I. Imaseki and H. Taguchi, *Yakugaku Zasshi*, **82**, 1214 (1962).

(4) S. A. Telang and C. K. Bradsher, *J. Org. Chem.*, **30**, 752 (1965).

(5) R. W. Doskotch, M. Y. Malik, and J. L. Beal, *ibid.*, **32**, 3253 (1967).

(6) P. W. Jeffs, "The Alkaloids, Chemistry and Physiology," Vol. 9, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1967, pp 71–72.

(7) R. H. F. Manske, *Can. J. Res.*, **21B**, 13 (1943).

(8) J. Gadamer, *Arch. Pharm.*, **249**, 224 (1911).

(9) The isolation of *d*-glaucine served to identify one of the main spots which had not been identified hitherto on the two-dimensional thin layer chromatogram of the total alkaloid fraction of this plant. On the other hand, it was found that the peak of *d*-corydaline contained that of *d*-glaucine on the gas chromatogram of the total alkaloid, since the retention times of both alkaloids were almost equal on 2% QF-1 column: J. Iwasa, S. Naruto, and Y. Utsui, *Yakugaku Zasshi*, **86**, 396 (1966).

(10) R. H. F. Manske, *Can. J. Res.*, **14B**, 347 (1936).

(11) W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **97**, 305 (1910).

most informative, showing four aromatic protons at δ 6.85 (2 H), 6.72 (1 H), and 6.47 (1 H), three methoxyl groups at δ 3.85 (3 H) and 3.81 (6 H), one phenolic hydroxyl proton at δ 8.70, and a secondary methyl group at δ 0.83 (3 H) as a doublet (J = 6.8 cps). This secondary methyl signal could not be explained by the structure of I proposed for *d*-corydalmine.[3] Its methylation with diazomethane to *d*-corydaline served to characterize it as a 13-methylated protoberberine base having a 2,3,9,10-oxygenation pattern. The position of the phenolic hydroxyl group remained to be settled. Among the four possible isomers, two bases, *d*-corybulbine (III) and *d*-isocorybulbine (IV), were already known, the former of which was similar to base A in respect to physical constants. As a result, it was found that base A was identical with *d*-corybulbine by comparison of nmr and infrared spectra, thin layer chromatographic behavior, and mixture melting point. Accordingly, the name of *d*-corydalmine and its proposed structure I, first reported by Imaseki and Taguchi,[3] should be revised to those of *d*-corybulbine (III). Furthermore, it is suggested that the accompanying quaternary base, "dehydrocorydalmine," which on reduction afforded an optically inactive *dl*-corydalmine,[3] was identical with dehydrocorybulbine. Therefore the genuine "dehydrocorydalmine," represented by structure II, is considered to be that from *Stephania glabra*.[5] Recent investigation on the constituents of *S. glabra* has confirmed the presence of (−)-10-hydroxy-2,3,9-trimethoxydibenzo[*a*,*g*]quinolizidine (so-called *l*-corydalmine) as a natural product.[12]

Base B, mp 214–215°, $[\alpha]_D$ 302°, $C_{20}H_{23}O_4N$, gave *d*-tetrahydropalmatine by methylation with diazomethane. The infrared spectrum taken in the chloroform solution was superimposable on the infrared spectrum of *dl*-tetrahydrojatrorrhizine synthesized from berberine according to the method of Späth and Quietensky.[13] These results, in conjunction with the nmr spectrum of base B, indicated that it was *d*-tetrahydrojatrorrhizine.

In conclusion, *d*-glaucine, *l*-scoulerine, *d*-tetrahydrojatrorrhizine, noroxyhydrastinine, and α-allocryptopine were isolated for the first time from Chinese corydalis[2] cultivated in China. It is interesting to note from the chemotaxonomical viewpoint that three main alkaloids, *d*-corydaline, *d*-corybulbine, and dehydrocorydaline,[14] in this plant are identical with the major alkaloids of *Corydalis ambigua* Cham. *et* Schlecht. *var. amurensis* Maxim.[15,16] This fact suggests that the original plant of Chinese corydalis[2] is closely related to *C. ambigua* Cham. *et* Schlecht.

Experimental Section

Melting points are uncorrected. Ultraviolet spectra were measured in ethanol on a Hitachi Model EPS-2U recording spectrophotometer, and infrared spectra were taken in KBr disks unless otherwise specified, with a Hitachi Model EPI-S2 infrared spectrophotometer. Nmr spectra were determined in deuteriochloroform or DMSO-d_6 solution, with tetramethylsilane as an internal standard, with a Varian A-60 spectrometer. The optical rotations were determined with a Rex Model NEP-2 photoelectric polarimeter. Thin layer chromatography (tlc) was carried out with the use of silica gel G (Merck) and the solvent system used in tlc is abbreviated as follows: chloroform–methanol, 25:1 (solvent a). Alkaloid spots or bands were detected by spraying with Dragendorff's reagent. Microanalyses were performed by Mr. Y. Utsui and his associates.

Separation of the Crude Alkaloid.—The ether extract of the total tertiary alkaloids was obtained from the tubers of Chinese corydalis imported from China (5.0 kg) according to the procedure described previously.[14] This ether extract was concentrated to 0.05 volume and allowed to stand for 1 week. The crude crystals of *l*-tetrahydrocolumbamine were deposited. The etherial mother liquor was extracted with 5% aqueous sodium hydroxide solution. The ether layer was dried over anhydrous potassium carbonate and evaporated to dryness to give the nonphenolic alkaloid fraction (22 g). The 5% aqueous sodium hydroxide layer was saturated with ammonium chloride and extracted with ether. The ether layer was dried over anhydrous potassium carbonate and the solvent was removed to give the crude phenolic alkaloid fraction (4.5 g).

Isolation of the Alkaloids. A. Nonphenolic Alkaloids.—The crude alkaloid fraction (22 g) was placed on a column of basic alumina (350 g, activity I, Merck). *d*-Corydaline, mp 132–134° (3.87 g), *dl*-tetrahydropalmatine, mp 143–145° (0.37 g), *l*-tetrahydrocoptisine, mp 197–200° (0.35 g), and protopine, mp 205–207° (1.05 g), were isolated in the manner described by Imaseki and Taguchi[3] and were each identified with authentic samples. The mother liquors of *l*-tetrahydrocoptisine, *dl*-tetrahydropalmatine, and *d*-corydaline were combined and concentrated. The residue (9.56 g) was rechromatographed on silica gel column (100 g, silica gel, Merck). From benzene (6 l.) and benzene–ether (1:1) (1 l.) elutes, *d*-corydaline (0.97 g), *l*-tetrahydrocoptisine (0.57 g), and *dl*-tetrahydropalmatine (1.3 g) were isolated in a manner similar to the above procedure.[3] Ether (3 l.) and methanol (0.8 l.) elutes were combined and concentrated to give the residue (5.3 g), which was treated with a small amount of ether. The ether-soluble fraction was concentrated and crystallized from ether–petroleum ether to yield crystals of *d*-glaucine: mp 120–121.5° (2.958 g); $[\alpha]_D$ 125° (*c* 1.0, methanol); λ_{max}^{EtOH} 219 mμ (log ε 4.58), 282 (4.18), 302 (4.17).

Anal. Calcd for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.89; H, 6.92; N, 4.24.

The hydrobromide melted at 234–236° (from ethanol).

Anal. Calcd for $C_{21}H_{25}O_4N \cdot HBr$: C, 57.80; H, 6.01; N, 3.21; Br, 18.32. Found: C, 57.71; H, 6.08; N, 3.05; Br, 18.12. Identity was established by comparisons of the infrared spectrum of this hydrobromide with that of an authentic sample, and by mixture melting point determination.

The methanol elute from the first alumina column chromatography and the mother liquor of protopine were combined and concentrated. The residue (6.242 g) was applied to the top of the silica gel column (30 g). The chromatography was developed with chloroform to obtain further amounts of *d*-glaucin (1.150 g) and protopine (0.363 g).

B. Phenolic Alkaloids.—The crude phenolic alkaloid fraction (4.1 g) was combined with the similar material from another extraction (total, 19.6 g), and treated with chloroform (200 ml). The chloroform-insoluble fraction was recrystallized from chloroform–methanol to give *l*-tetrahydrocolumbamine, mp 222–224°, (4.3 g), which was identical with an authentic sample of *l*-tetrahydrocolumbamine. The mother liquor was combined with the chloroform-soluble fraction and concentrated. The brown residue (15.3 g) was dissolved in 4% methanol–chloroform applied to the top of a silica gel column (200 g, 4.8 × 23.4 cm, silica gel, Merck) and eluted in six fractions as shown in Table II.

TABLE II
COLUMN CHROMATOGRAPHY OF PHENOLIC ALKALOID (1)

Fraction	Eluent	Volume, ml	Yield, mg	R_f values on tlc, solvent a
1-1	4% MeOH–$CHCl_3$	100	911	0.93, 0.83
1-2	4% MeOH–$CHCl_3$	360	8890	0.66, 0.55, 0.43
1-3	4% MeOH–$CHCl_3$	360	1750	0.55, 0.43, 0.33 0.24
1-4	4% MeOH–$CHCl_3$	180	680	0.15, 0.11, 0.05
1-5	4% MeOH–$CHCl_3$	800	807	0.11, 0.05
1-6	6% MeOH–$CHCl_3$	800	310	0.02

Fraction 1-1 showed two spots (R_f 0.93 and 0.83) on tlc. These two components were separated by rechromatography on silica

(12) M. P. Cava, K. Nomura, S. K. Talapatra, M. J. Mitchell, R. H. Schlessinger, K. T. Buck, J. L. Beal, B. Douglas, R. F. Raffauf, and J. A. Weisbach, *J. Org. Chem.*, **33**, 2785 (1968).
(13) E. Späth and H. Quietensky, *Ber.*, **58**, 2267 (1925).
(14) J. Iwasa, S. Naruto, and N. Ikeda, *Yakugaku Zasshi*, **86**, 437 (1966).
(15) H. Taguchi and I. Imaseki, *ibid.*, **83**, 578 (1963).
(16) H. Taguchi and I. Imaseki, *ibid.*, **84**, 773 (1964).

gel column (20 g, 2.3 × 13 cm) with methanol–chloroform (1:100) as a developing solvent. The component of R_f 0.93 was obtained as colorless needles, mp 248–250°, after recrystallization from methanol. This material, showing an infrared absorption at 1715 cm^{-1}, was obtained in such a small amount (3 mg) that it could not be further investigated. The other component (R_f 0.83) was *d*-corydaline, mp 132–134°, identical (tlc behavior, infrared spectrum, and mixture melting point determination) with an authentic sample. Fraction 1–2 showed three spots (R_f 0.66, 0.55, and 0.43) on tlc. Repeated crystallization of this fraction from chloroform–methanol yielded a material showing R_f 0.55, which proved to be identical with *l*-tetrahydrocolumbamine by direct comparison. The mixture consisted of *l*-tetrahydrocolumbamine, and a material showing R_f 0.66 was deposited from the mother liquor. These two components were separated by means of silica gel column chromatography with methanol–chloroform (3:100) as a developing solvent. The component (R_f 0.66) was obtained from the first elute in pure form, which was designated as base A described below. The last elute gave *l*-tetrahydrocolumbamine. The mother liquors of these two bases were combined and concentrated to yield the residue (2.0 g) which was rechromatographed on silica gel column (60 g, 2.8 × 20 cm) and eluted in four fractions as shown in Table III.

TABLE III

COLUMN CHROMATOGRAPHY OF PHENOLIC ALKALOID (2)

Fraction	Eluent	Volume, ml	Yield, mg	R_f values on tlc, solvent a
2-1	4% MeOH–$CHCl_3$	50	150	0.83, 0.66
2-2	4% MeOH–$CHCl_3$	100	804	0.66, 0.55, 0.43
2-3	4% MeOH–$CHCl_3$	40	494	0.43, 0.33
2-4	4% MeOH–$CHCl_3$	40	285	0.33, 0.24

Additional amounts of *l*-tetrahydrocolumbamine (200 mg) and base A (500 mg) were obtained by recrystallization of fraction 2-2 from chloroform–methanol. The mother liquors were combined with the fraction 2-3 and recrystallized from the same solvent to give base B (R_f 0.43) (341 mg). Fraction 2-4 was converted to the hydrochloride and crystallized from ethanol–ether to yield pale yellow crystals of *l*-scoulerine hydrochloride (74 mg). Identity was established by comparison of the infrared spectrum of its base (mp 194–196°, R_f 0.24) with that of an authentic sample, and by mixture melting point determination.

Fraction 1-3 was recrystallized from chloroform–methanol to give *l*-tetrahydrocolumbamine (351 mg). This mother liquor was concentrated to give the residue (1.4 g), which was rechromatographed on silica gel column (70 g, 3.2 × 20 cm) and eluted in three fractions as shown in Table IV.

TABLE IV

COLUMN CHROMATOGRAPHY OF PHENOLIC ALKALOID (3)

Fraction	Eluent	Volume, ml	Yield, mg	R_f values on tlc, solvent a
3-1	4% MeOH–$CHCl_3$	20	198	0.55, 0.43
3-2	4% MeOH–$CHCl_3$	60	1250	0.33, 0.24
3-3	4% MeOH–$CHCl_3$	60	68	0.33, 0.24

Fraction 3-1 was treated as in the case of fraction 2-2 to give *l*-tetrahydrocolumbamine (51 mg) and base B (108 mg). Fraction 3-2 was converted to the hydrochloride and treated as in the case of fraction 2-4 to give *l*-scoulerine hydrochloride (451 mg). The mother liquor of the hydrochloride was reconverted to the base. This basic fraction (714 mg) showed the presence of a component of R_f 0.33 which was isolated by means of silica gel column chromatography (24 g, 2.1 × 16.5 cm) using chloroform–methanol (25:1) as a developing solvent. The compound, isolated as pale yellow needles (R_f 0.33), mp 189–190°, was identical with an authentic sample of noroxyhydrastinine.

Fraction 1-4 was converted to the hydrochloride and allowed to stand for 4 days. Pale yellow crystals of protopine hydrochloride separated, which, after recrystallization from ethanol, were converted to the base. This base was identified with an authentic sample of protopine by comparison of the infrared spectrum and by mixture melting point determination. The mother liquor of fraction 1-4 and fraction 1-5 contained more than two components (R_f 0.15 and 0.11), none of which could be isolated in pure form.

Crystallization of fraction 1-6 from ethanol yielded a small amount (120 mg) of the material showing R_f 0.02, mp 163–164°, which proved to be identical with α-allocryptopine. Identity was established by comparison of the infrared spectrum with that of an authentic sample, by tlc behavior, and by mixture melting point determination. The remainder of the fraction could not be separated into pure components.

Base A (*d*-**Corybulbine** = *d*-**Corydalmine**) (III).—Base A, mp 220–222° dec, $[\alpha]_D$ 307° (*c* 0.38, chloroform), was identical with *d*-corybulbine [nmr (described in the text) and infrared spectra, tlc behavior, and mixture melting point determination].

Anal. Calcd for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.30; H, 6.96; N, 3.84.

A solution of 5 mg of base A in 10 ml of methanol was added to a solution of an excess of diazomethane in ether, and the mixture was allowed to stand for 3 hr. The solution was concentrated under reduced pressure and the residue was recrystallized from ethanol to give pale yellow prisms of mp 134–136°. This compound was identified with *d*-corydaline by comparison of its infrared spectrum and by mixture melting point determination.

Base B (*d*-**Tetrahydrojatrorrhizine**).—Base B had mp 214–215°, $[\alpha]_D$ 302.2° (*c* 0.65, chloroform).

Anal. Calcd for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.57; H, 7.09; N, 4.04. Infrared (in chloroform solution) and nmr spectra and tlc behavior of this compound were identical with those of synthetic *dl*-tetrahydrojatrorrhizine.[13] Base B was methylated as in the case of base A by diazomethane to give pale yellow prisms, mp 143–145°. Tlc behavior and infrared spectrum of this methylated compound were identical with those of *dl*-tetrahydropalmatine.

Registry No.—*l*-Tetrahydrocolumbamine, 20504-94-3; *d*-corybulbine, 518774; *l*-scoulerine, 6451-73-6; *d*-tetrahydrojatrorrhizine, 6018-39-9; *d*-corydaline, 3907-48-0; *d*-glaucine, 475-81-0; *dl*-tetrahydropalmatine, 2934-97-6; protopine, 130-86-9; *l*-tetrahydrocoptisine, 20504-98-7; α-allocryptopine, 485-91-6.

Acknowledgment.—The authors are very grateful to Dr. S. Ose, Director of this laboratory, for his encouragement and also to Professor Sheng-Teh Lu, Kaohsiung Medical College, for the kind supply of the authentic sample of *d*-glaucine hydrobromide. Thanks are also due to the members of Analytical Center of this laboratory for microanalyses and nmr measurements.

A Novel Method of Converting Aldehydes into Nitriles under Mild Conditions. The Reaction of Dialkyl Hydrogen Phosphonates with Oximes

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Present methods of converting aldehydes into nitriles generally require rather vigorous conditions.[2] We wish to report a very mild method of effecting this conversion in two simple steps.

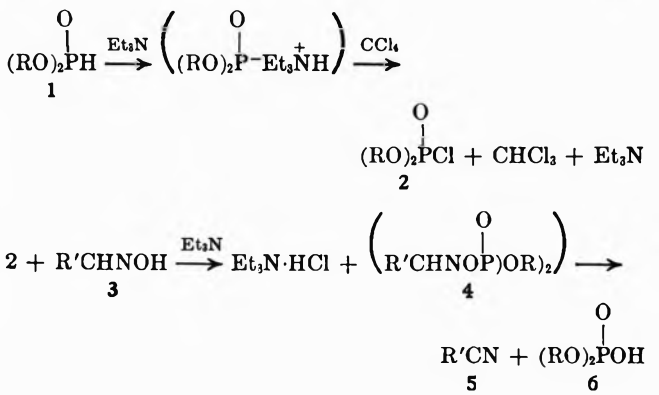
(1) Plastics Department, E. I. du Pont de Nemours and Co., Experimental Station Laboratory, Wilmington, Del. 19898.

(2) See, for example, W. Theilheimer ["Synthetic Methods of Organic Chemistry," Vol. 1–22, S. Karger, A G., Basel, Switzerland, 1946–1968] for representative techniques. For a mild method, see J. H. Pomeroy and C. A. Craig, *J. Amer. Chem. Soc.*, **81**, 6340 (1959).

Treatment of various aldoximes (**3**), readily available from the aldehydes, with dialkyl hydrogen phosphonates (**1**, R = phenyl, methyl, *n*-butyl) at room temperature in the presence of carbon tetrachloride and a tertiary amine (triethylamine) produced a high yield of the corresponding nitrile. Aliphatic, aromatic, and olefinic oximes all reacted cleanly to give good yields of the nitriles, but it was found that diphenyl hydrogen phosphonate gave higher yields than either the dimethyl or di-*n*-butyl compounds. The stereochemistry of the aldoxime (*syn* or *anti*) had little effect on the reaction, although it is possible that the oximes are isomerized under the reaction conditions.[3]

The oximes used and the yields of the purified nitriles produced in the reactions with diphenyl hydrogen phosphonate are *syn*-benzaldoxime, 88%; *syn*-anisaldoxime, 85%; *syn*-*p*-nitrobenzaldoxime, 85%; *syn*-cinnamaldoxime, 95%; butyraldoxime (stereochemistry unknown), 40%; and *anti*-furaldoxime, 60%.

The mechanism of this reaction is undoubtedly reaction of the phosphonate (**1**) with carbon tetrachloride and triethylamine to produce the dialkyl phosphorochloridate (**2**) and chloroform,[4] followed by esterification of the aldoxime (**3**) and Beckmann fragmentation[5] of this ester (**4**) to the nitrile (**5**) and the dialkylphosphoric acid (**6**).



Although the intermediate ester (**4**) could not be isolated, the likelihood of the correctness of this mechanism was shown by treating *syn*-benzaldoxime with diphenylphosphorochloridate (**2**, R = Ph) under the same conditions used in the phosphonate reactions. An 85% yield of benzonitrile was obtained directly, in support of the intermediacy of the dialkyl phosphorochloridate (**2**) in the dialkyl hydrogen phosphonate reactions.

Experimental Section

The oximes were either purchased or prepared by standard routes. The nitriles were identified by comparison of their ir spectra and gc retention times with those of authentic material, and by their melting points, in the case of solids.

A solution of 0.1 mol of the oxime and 0.1 mol of triethylamine in 250 ml of carbon tetrachloride was treated over 30 min with 0.1 mol of diphenyl hydrogen phosphonate and the solution was stirred for 4 hr at ambient temperature. The triethylamine hydrochloride was removed by filtration and the filtrate was poured into water. The organic layer was separated, washed twice with dilute aqueous sodium hydroxide, and dried (Na_2SO_4), and the solvent was removed at reduced pressure. The resulting nitrile was purified by distillation or recrystallization.

Registry No.—**1** (R = Ph), 4712-55-4; **1** (R = Me), 868-85-9; **1** (R = Bu), 1809-19-4; *syn*-benzaldoxime, 13830-84-7; *syn*-anisaldoxime, 20707-68-0; *syn*-*p*-nitrobenzaldoxime, 20707-69-1; *syn*-cinnamaldoxime, 20707-70-4; butyraldoxime, 110-69-0; *anti*-furaldoxime, 20728-36-3.

(3) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, p 34.

(4) G. M. Steinberg, *J. Org. Chem.*, **15**, 637 (1950); G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).

(5) P. A. S. Smith, in "Molecular Rearrangements," Vol. 1, P. de Mayo Ed., Interscience Publishers, New York, N. Y., 1963, p 504.

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1. L.F. Fieser and M. Fieser. Reagents for Organic Synthesis, Wiley, 1967, p. 940.
2. G.M. Goldberg and J.E. Lavalle. U.S. 2,938,793.

3a. H. Gehlen and G. Dase. *Z. anorg. allgem. Chem. 275 327 (1954).*
3b. H. Gehlen. *Ber. 70B* 1980 (1937).

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REFERENCES

(1) A. McKillop et al, Tetrahedron Letters, *29*, 2423 (1969)
(2) A. McKillop et al, *ibid.*, *29*, 2427 (1969)
(3) A. McKillop, D. Bromley and E. C. Taylor, *ibid*, *21*, 1623 (1969)
(4) A. South Jr. and R. J. Ouellette, J. Am. Chem. Soc. *90*, 7064 (1968)
(5) M. E. Kuehne and T. J. Giacubbe, J. Org. Chem. *33*, 3359 (1968)
(6) W. Kitching, Organometal. Chem. Rev. *3*, 35 (1968)
(7) A. McKillop, D. Bromley and E. C. Taylor, J. Org. Chem. *34*, 1172 (1969)
(8) E. C. Taylor, Y. Maki and A. McKillop, *ibid*, *34*, 1170 (1969)
(9) A. McKillop, M. J. Zelesko and E. C. Taylor, Tetrahedron Letters, *48*, 4945 (1968)

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