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THE JOURNAL OF Organic Chemistry

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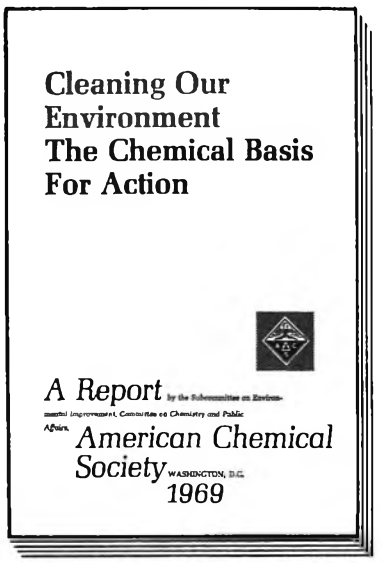
Cleaning Our Environment The Chemical Basis For Action



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Smiles Rearrangement on Borohydride Reduction of a Nitrophenoxy Ester[1]

MORTON HARFENIST* AND EDNA THOM

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Received September 18, 1970

An attempted preparation of the acetophenetidin metabolite 2-methyl-2-(4-acetamidophenoxy)propanol (**2**), which started with the reduction of the ester function of ethyl 2-methyl-2-(4-nitrophenoxy)propionate (**3a**) by $LiBH_4$ in diglyme, led to an isomer of **2**. Initial platinum/hydrogen reduction of the nitro function of **3a**, to give amino ester **4**, followed by $LiAlH_4$ reduction of the ester moiety, then acetylation, gave correct **2**. That a rearrangement had occurred at the borohydride reduction step was shown by reduction of the nitro acid **3b** by diborane to 2-methyl-2-(4-nitrophenoxy)propanol (**5**), different from the $LiBH_4$ product **8**, and rearranged to **8** by strong bases. Reduction of **3a**, labeled with ^{18}O at the aromatically bound O, and mass spectral analysis of the fragments showed that a Smiles rearrangement (intramolecular attack on a aromatic carbon) was the mechanism operating. Considerably less rearrangement during $LiBH_4$ reduction of the analogous monomethyl nitro ester, ethyl 2-(4-nitrophenoxy)propionate (**9a**), was shown by isolation of 2-(4-acetamidophenoxy)propanol starting with this step, as well as by using either diborane reduction of the corresponding acid **9b** to 2-(4-nitrophenoxy)propanol (**10**), or platinum and hydrogen reduction of ester **9a** as the initial step. The Smiles arrangement product, 1-(4-nitrophenoxy)-2-propanol (**11**), however, was present and could also be produced from **10** by strong bases. Under the reduction conditions used, the ratio of alcohols found after $LiBH_4$ reduction of **3a** or **9a** was identical with that produced by equilibration of either nitro alcohol with base.

The metabolic degradation of the commonly used mild analgesic *p*-acetophenetidin (Phenacetin) was shown some time ago[2] to occur largely by dealkylation to give *p*-acetamidophenol. Such dealkylations appear to be oxidative,[3] as if a hydrogen on the ethereal carbon of the aliphatic moiety is replaced by hydroxyl in the step leading to cleavage. Pursuing this, 4-acetamidophenyl *tert*-butyl ether (**1**), which has no such hydrogen, was made and found to be essentially unattacked by the drug-hydroxylating liver microsomal enzymes.[4] Preliminary testing in mice revealed that **1** appeared to have substantial analgesic activity, more prolonged in duration than that of phenacetin.[5] A metabolite was isolated as its glucuronide from the urine of dogs fed **1** and was postulated[6] to have the structure **2**. Since production of **2** would represent an unusual hydroxylation at an unactivated methyl group,[7] it seemed desirable to prove the structure of **2** by synthesis.

The route chosen involved preparation of ester **3a** (Scheme I) from the *p*-nitrophenol anion and ethyl 2-bromo-2-methylpropionate, to be followed by reduction of the ester function and of the nitro group. A single nitro ester was isolated. The alternatives to **3a**, either the product of ring alkylation rather than O-alkylation or the product of dehydrohalogenation of the bromo ester and subsequent Michael addition of *p*-nitrophenolate anion to the resulting ethyl 2-methylmethacrylate, could be ruled out by the hydrogen nmr (pmr)[8] of the nitro ester.

To avoid the necessity of doing a lithium aluminum hydride reduction of the amino ester **4**, with its two active hydrogens, use was made of the low activity toward the nitro group and the ability to reduce the ester function reported for complex borohydrides.[9] Although magnesium borohydride in hot diglyme showed no reaction, the more active lithium borohydride in hot diglyme reacted vigorously with **3a**. In addition to dark materials, presumably azo and/or azoxy compounds, which were not investigated further, a yield of about 70% of a seemingly pure (boiling point, tlc, and glpc) liquid was obtained which had the expected elemental analysis and pmr for the desired nitro alcohol **5**. This was then reduced with Adams' catalyst and hydrogen, and acetylated to an acetamino alcohol *isomeric*

(1) A portion of the material in this paper was presented in *Chem. Commun.*, 730 (1969).

(2) B. B. Brodie and J. Axelrod, *J. Pharmacol. Exp. Ther.*, **97**, 58 (1949).

(3) See R. T. Williams, "Detoxication Mechanisms," 2nd ed, Wiley, New York, N. Y., 1959, p 331.

(4) A. H. Conney, M. Sansur, and M. Harfenist, *Pharmacologist*, **7**, 160 (1965).

(5) A. H. Conney, M. Sansur, F. Soroko, R. Koster, and J. J. Burns, *J. Pharmacol. Exp. Ther.*, **151**, 133 (1966).

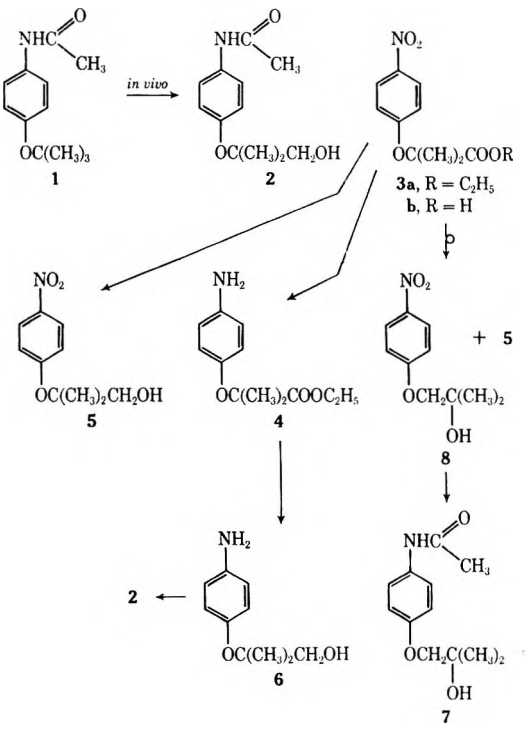
(6) A. Klutch and M. Bordun, *J. Pharm. Sci.*, **56**, 1654 (1967).

(7) Earlier reports of *in vivo* hydroxylations which occurred at nonethereal aliphatic carbons showed attack at *tertiary* carbons sufficiently activated that in some cases the same alcohols could be produced by chromic acid oxidations. *E.g.*, see E. W. Maynert, *J. Biol. Chem.*, **195**, 397 (1952). More recently attacks at *secondary* carbons not activated by α-ether bonding have been reported: R. W. Balsiger, Th. Leuenberger, W. Michaelis, and O. Schindler, *Helv. Chim. Acta*, **52**, 1323 (1969).

(8) Only the ethyl triplet and quadruplet, an isolated singlet for two CH_2 groups, and the A:B:B′:A′ quartet with meta splitting characteristic of a para-disubstituted benzene were found.

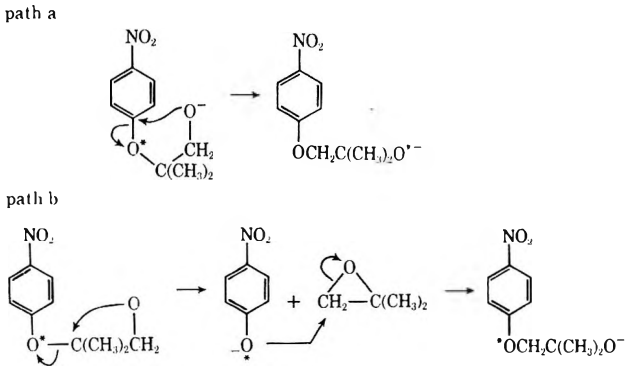
(9) R. F. Nystrom, S. W. Chaikin, and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 3245 (1949).

SCHEME I



with **2**, and with an almost identical pmr. This isomer of **2** gave *p*-acetamidophenol with acid, but only after more prolonged treatment than was required by the metabolite **2**. The structure best fitting these facts was **7**. (Evidence that the nitro alcohol antecedent to **7** was indeed **8** was obtained subsequently by mass spectral study of **8**, as described below.)

Two mechanistic routes could be postulated which would lead from **3a** eventually to **7**. The first of these, which we regarded as more likely, would involve the attack of a nucleophilic reduced species, here shown as the alkoxide of **5**, at the aromatic ethereal carbon para to the nitro group, to form a real or quasi five-membered ring in the transition state (path a). This would open



up preferentially to give predominantly the tertiary alcohol **8** convertible to **7**, because the rate of attack at the electrophilic aromatic carbon by the primary alkoxide of **5** would be more rapid than that of the tertiary alkoxide corresponding to **8**. The equilibrium constant would then represent the ratio of the two rate constants in the usual way, very much in favor of **8** upon equilibration.

The alternative route (path b) would involve attack of the same nucleophilic alkoxide oxygen or equivalent, but here at the *aliphatic* ethereal carbon to form the three-membered epoxide ring, with loss of *p*-nitrophenolate anion. Since base-catalyzed attack on such an epoxide would go at the least substituted carbon, isolation of **8** rather than **5** by this mechanism is explicable.

Either of these alternatives shows that such an arrangement would require an electron-withdrawing (here the para nitro) group, and would require a sufficiently strong base to form the alkoxide. The first of these requirements allowed a straightforward synthesis of the metabolite **2**, by the reduction of the nitro ester **3a** to the amino ester **4** with Adams' catalyst and hydrogen as the first step. Despite the active hydrogens, the reduction of **4** with lithium aluminum hydride in ether went in excellent yield to give **6**, unrearranged because the nitro group was not present during the hydride treatment. Compound **6** was acetylated with acetic anhydride in ethanol to give the desired metabolite **2**.

The second requirement for the rearrangement of nitro alcohol **5**, strong base, could be avoided completely by the use of a nonbasic reducing agent. Diborane, which has been reported[10] to reduce acids at a rapid rate but to be inert toward aromatic nitro groups, would be expected to be a Lewis acid rather than a base. Indeed, careful saponification of the nitro ester **3a** to give the nitro acid **3b**, followed by treatment of this acid with diborane in tetrahydrofuran, gave the unrearranged nitro alcohol **5**, different from that isolated from the borohydride reduction of the ester. Having samples of both nitro alcohols, it was now possible to show by column chromatography that the borohydride product, in accord with expectations, did contain a small proportion ($\lesssim 10\%$) of unrearranged **5**, while the borane product contained no detectible rearranged nitro alcohol **8**. This diborane reduction also made pure **5** available. Further, it was now possible to demonstrate the rearrangement of the nitro alcohol **5** in the presence of its alkoxide salt with any of several metals but without borohydride present. Rearrangement of **5** to the anticipated mixture, predominantly **8**, in hot diglyme was shown with **5** lithium alkoxide (from lithium butyl or from less than the theoretical amount of lithium borohydride) or **5** sodium alkoxide (from sodium hydride) or **5** potassium alkoxide (by addition of potassium *tert*-butoxide).[11]

Having pure **5** and **8** available also allowed us to find one absorption maximum each in the ir spectrum of **5** and **8** not present in the other, although the spectra were remarkably similar. These, as well as the slightly different positions of the pmr absorptions of the CH_2 hydrogens of **5** and of **8**, allowed crudely quantitative measurement of the proportion of **5** and **8** at base-catalyzed equilibrium approached from pure **5** and pure **8**. This was found to be essentially the same as that obtained from the borohydride reduction of nitro ester **3a**, almost wholly **8**.

It should be possible to distinguish a mechanism of rearrangement involving path a from the alternative path b by labeling one of the oxygens. For example, if the ether oxygen of the unrearranged nitro alcohol **5** were labeled, rearrangement by path a would lead to **8** with the terminal oxygen labeled. Conversely, the

(10) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962, p 29.

(11) Substantial amounts of *p*-nitrophenol (as anion) were also produced, as well as what appeared to be products of partial reduction of the nitro group.

epoxide of path b is produced without aryl-to-oxygen bond cleavage, and the attack on the epoxide by the aryloxy anion also proceeds with retention of the aryl-to-oxygen bond, so a labeled ether oxygen in **5** would remain as such in **8** produced by way of path b. An orienting experiment with unlabeled **8** showed that its mass spectrum[12] showed intense peaks attributable to $[O_2NC_6H_4OCH_3]^+$ and to $[(CH_3)_2COH]^+$, so that it would be possible to determine unequivocally the position of a labeled oxygen in **8**. Reduction with rearrangement of ether–oxygen labeled nitro ester **3a** seemed the approach most economical of synthetic effort.

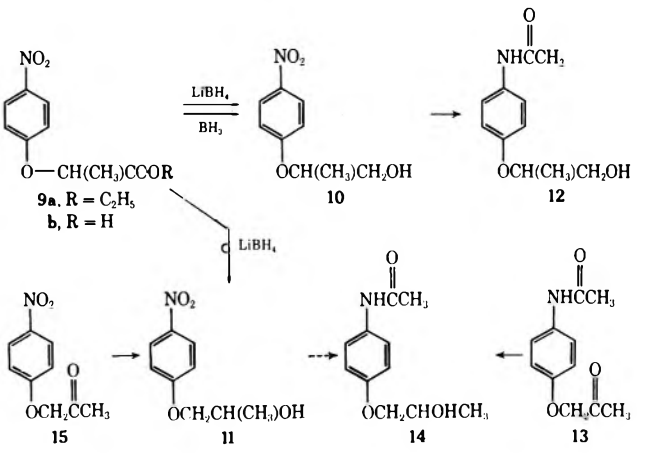
Labeled **3a** was made from *p*-fluoronitrobenzene; potassium hydroxide (40% ^{18}O) was made *in situ* from water (40% ^{18}O) and potassium *tert*-butoxide in *tert*-butyl alcohol.[13] The *p*-nitrophenol produced by reaction of this $K^{18}OH$ with *p*-fluoronitrobenzene in the same solvent was isolated. The ^{18}O-containing *p*-nitrophenol had mass spectral peaks at 139 and 141 mass units (parent) and at 93 and 95 mass units (parent less NO_2) in a ratio indicating approximately 38% ^{18}O at one of the three oxygens in the parent, and at the only oxygen in the fragments with *m/e* 93 and 95. This shows that exchange of oxygen had occurred neither with the alcoholic solvent nor between the $K^{18}OH$ and the nitro group.[14]

The product of the lithium borohydride reduction with rearrangement of the aryl ^{18}O-labeled **3a** made from this was found to show significant peaks: (a) at 211 and 213 (the product, *i.e.*, largely **8**) with the ratio showing 41% of ^{18}O at one oxygen; (b) at 153 and 155 (*i.e.*, $[O_2NC_6H_4OCH_3]^+$) showing not over 2% ^{18}O; (c) at 59 and 61 (*i.e.*, $[(CH_3)_2COH]^+$) showing 37% of ^{18}O.

The rearrangement, therefore, goes by path a and represents an example of the Smiles rearrangement.[15] This rearrangement can be described as an intramolecular attack at an aromatic carbon by a nucleophilic portion of the molecule, leading to displacement of a group previously attached at that carbon by the more nucleophilic portion. Although an example was found in the literature of attack by an alkoxide with displacement of a sulfurous acid amide,[16] and there are examples reported of internal displacement of alkoxide by an amino group leading to (*o*- and *p*-nitro-substituted) ω-hydroxypropylanilines[17] rather than the desired ω-aminopropyl aryl ethers, we do not know of any previously recognized examples of Smiles rearrangement by displacement of one alkoxide by another.

It was of interest to see whether this Smiles rearrangement would occur at a detectible rate with the *secondary* alkyl ether, 2-(4-nitrophenoxy)propanol (**10**). We therefore prepared ethyl 2-(4-nitrophenoxy)propionate (**9a**) and from it the corresponding nitro acid **9b**. Both lithium borohydride reduction in diglyme of the ester and reduction of the acid with diborane in THF gave what appeared to be the *same* nitro alcohol. Each of these nitro alcohol reduction products was reduced with hydrogen and Adams' catalyst to an amino alcohol, which was acetylated with acetic anhydride in ethanol to give, after purification (with substantial loss for the lithium borohydride product), the same acetanilide (shown by melting point and mixture melting point). This was assumed to be *unrearranged*, *i.e.*, **12**. Proof of this was obtained by an unequivocal synthesis of the isomeric *rearranged* acetamido alcohol **14** by the route shown in Scheme II, sodium borohydride reduction of **13**.[18]

SCHEME II



Isolation of **12**, suggesting that unrearranged nitro alcohol **10** was the major product of lithium borohydride reduction of ester **9a**, seemed in contradiction to the reasoning given as to the cause of preponderance of **8** over **5** in the corresponding reduction products of **3a** by borohydride. Rearrangement of **10** alkoxide should be comparable in speed to rearrangement of **5** alkoxide. This means that equilibrium would be reached here under our reaction conditions, as it was in the dimethyl case. Since the rate of attack of the primary alkoxide of **10** should be faster than the reverse attack of the secondary alkoxide of **11** (though the ratio should not be as overwhelming as in the **5** → **8** case), the equilibrium should favor **11**. We therefore made **11** from **15**, the chloroacetone plus *p*-nitrophenol product,[19] by reduction with sodium borohydride in aqueous ethanol. The product differed in pmr of the CH_2 and CH groups from that found for the diborane reduction product of **9b**, and neither **11** made from **15** nor the **10** made by BH_3 reduction had detectible quantities of the other, indicating the important point that rearrangement of **11** did not occur under conditions of the sodium borohydride reduction. The "pure" borohydride reduction product of ester **9a**, however, was found by pmr to be about 70%[20] rearranged, *i.e.*, **11**, and 30% **10**. Thus isolation of the unrearranged acetamido alcohol **12** was fortuitous and the rearrangement had occurred as predicted although not to the extent expected. It is of interest that neither of two tlc systems tried, nor two analytical glpc systems, could distinguish between **10** and **11**, nor could more than one substantial absorption

(12) Mass spectra were determined in most cases by the Morgan-Schaffer Co., Montreal, Canada. In the critical ^{18}O case (see below), they were independently corroborated through the courtesy of Dr. Keith Palmer of the Research Triangle Institute, Research Triangle Park, N. C.

(13) In one orienting run with unlabeled water, use of tetramethylene sulfone instead of the tertiary alcohol gave no detectible increase in yield.

(14) The lack of exchange in the nitro group was also indicated by a peak at *m/e* 46 with essentially nothing visible at *m/e* 48.

(15) A summary of the elegant work of S. Smiles, *et al.*, can be found in W. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1935), and also J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).

(16) K. G. Kleb, *Angew. Chem., Int. Ed. Engl.*, **7**, 291 (1968).

(17) W. T. Caldwell and G. C. Schweiker, *J. Amer. Chem. Soc.*, **74**, 5187 (1952).

(18) C. D. Hurd and P. Perletz, *ibid.*, **68**, 38 (1946).

(19) D. S. Tarbell, *J. Org. Chem.*, **7**, 251 (1942).

(20) An adequate separation required use of the Varian 220-MHz nmr instrument at Rockefeller University. We thank Dr. Earl Whipple for these data.

peak be found in which the ir curves of **10** and **11** differed in the 3–16-μ region.

Using the pmr, it was next shown that the same proportion of **11** and **10** was found starting with either pure isomer and heating with NaH in diglyme, a finding in keeping with the scheme presented.

Experimental Section[21]

Caution! Salts of *p*-nitrophenol can deflagrate if allowed to become dry, especially if heated.

Ethyl 2-Methyl-2-(4-nitrophenoxy)propionate (3a).—A solution of sodium ethoxide from 48.5 g of sodium (2.1 g-atoms) and 1800 ml of commercial absolute ethanol had 295 g (2.12 mol) of *p*-nitrophenol added with stirring and was stirred an additional 15 min. Much orange sodium salt precipitated. There was no obvious reaction when 476 g (2.45 mol) of ethyl 2-bromo-2-methylpropionate was added, so the reaction was stirred and heated on a steam bath under reflux (NaOH tube) for 48 hr. It was then concentrated on steam to approximately 1/4 of its volume (see Caution above) and partitioned between water and ether. The ethereal solutions were extracted with 0.5 *N* aqueous NaOH until acidification of an aliquot gave no oil (three portions, 1 l. each), washed with water, and dried ($MgSO_4$). The crude product was distilled at 132–166° (0.4 mm). This distillate was redistilled at a temperature varying markedly with the rate of distillation, nominally bp 125–138° (0.03 mm), yielding 297 g (56%) of a yellow liquid 97–100% pure by glpc.

Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.92. Found: C, 57.23; H, 6.20.

From the alkaline washes 84.5 g of *p*-nitrophenol was readily recovered.

2-Methyl-2-(4-nitrophenoxy)propionic Acid (3b).—Nitro ester **3a** (25.2 g, 0.1 mol) dissolved in 55 ml of 95% ethanol and 15 ml of water was treated with 12.4 g (0.11 mol) of potassium *tert*-butoxide. The reaction spontaneously heated to about 80°. It was stoppered and allowed to stand with occasional shaking for 3 hr and diluted with water to 500 ml. The clear solution was brought to pH 2 (test paper) cautiously, shaking to avoid local excess of strong acid, and extracted with ether, and the ether was washed with water and dried ($MgSO_4$). Removal of ether left 21 g of crude solid which sintered at 80° but with mp 124°. This, twice recrystallized from acetone–benzene–hexane, yielded 6.6 g of **3b** (mp 123.4–124.4°).

Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.65; H, 4.99; N, 6.06.

Ethyl 2-Methyl-2-(4-aminophenoxy)propionate (4).—Reduction of 50 g of nitro ester **3a** in 150 ml of 95% ethanol in a Parr hydrogenator at an initial H_2 pressure of 3 atm required 2 days and a change of the Adams' catalyst used to reach the calculated H_2 uptake. Filtration and solvent removal on steam at 15 mm pressure left 40.5 g of a liquid which darkened rapidly in air. Most was therefore immediately used to prepare **6**, and the by then dark remainder subsequently distilled, bp 100–103° (0.08 mm), and converted to the HCl salt. This was recrystallized from absolute ethanol–ether, mp 161–162°.

Anal. Calcd for $C_{12}H_{18}ClNO_3$: C, 55.49; H, 6.94; N, 5.39. Found: C, 55.30; H, 7.02; N, 4.99.

2-Methyl-2-(4-nitrophenoxy)propanol (5).—A solution of 155 ml of 1 *M* borane in tetrahydrofuran solution (Alfa Inorganics, Inc.) was added dropwise with stirring under nitrogen to a solution of 35 g (0.156 mol) of the acid **3a** in 70 ml of peroxide-free tetrahydrofuran. Gas was evolved. The solution was allowed to remain overnight, and water was added, slowly at first, to a total of 1200 ml. Extraction with three 300-ml portions of ether, drying ($MgSO_4$), and removal of the ether by distillation on steam left 33 g of yellow oil. Two distillations, each at 115–121° (0.01 mm), gave 24 g of product (73%): nmr ($CDCl_3$) δ 1.4 (s, 6, CH_3), 3.68 (s, 2, CH_2OH), 7.12 (d, 2, J = 9 Hz of d, J = 2 Hz, ArH ortho to OR), 8.20 (d, 2, J = 9 Hz of d, J = 2 Hz, ArH ortho to NO_2). A broad OH peak about δ 2.37 was observed when *p*-nitrophenol was absent.

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.80; H, 6.15; N, 6.63. Found: C, 56.33; H, 6.21; N, 6.57.

2-(4-Aminophenoxy)-2-methylpropanol (6). A. From Amino Ester 4.—A solution of 10.2 g (45.6 mmol) of crude **4** in 100 ml of anhydrous ether was added dropwise to 11 g (290 mmol) of $LiAlH_4$ in 350 ml of ether and then heated under reflux for 4 hr. Cautious addition of 22 ml of water, filtration, washing the solids with anhydrous ether, and removal of the ether on a water bath finally at reduced pressure left 7.2 g of a liquid **6** which was acetylated without further purification.

B. From Nitro Alcohol 5.—Use of Adams' catalyst, 95% ethanol as solvent, and 3 atm of initial hydrogen pressure in a Parr hydrogenator gave rapid uptake of the theoretical amount of hydrogen. The catalyst was removed by filtration, and the ethanolic solution of **6** was acetylated directly with 2 equiv of acetic anhydride.

2-(4-Acetamidophenoxy)-2-methylpropanol (2). A. From 6 Made from 4.—The 7.2 g of amino alcohol **6** from **4** was dissolved in 30 ml of ether, and 6 ml of acetic anhydride was added with swirling. After 5 min the resulting crystals were filtered off and washed with ether to remove the yellow color. Recrystallization from benzene–hexane gave 3.6 g, mp 119–119.5°. This was identical in ir (KBr pellet) and in tlc in the test system (silica gel, lower layer of the mixture of $CHCl_3$–H_2O–MeOH–HOAc = 1:1:0.5:0.025, all by volume) to the metabolite of **1** isolated from dog urine[6] and gave no mixture melting point depression with that metabolite. The R_f found for **2** was 0.185; that for the rearrangement product **7** was 0.235.

B. From 6 Made from 5.—The ethanolic solution was treated with a 200% excess of acetic anhydride, mixed, and heated on steam after 10 min, for 15 min. Crystallization followed addition of water. The product was **2**, identical in all tests with that isolated from natural sources or made from **4**.

1-(4-Acetamidophenoxy)-2-methyl-2-propanol (7).—The amino alcohol corresponding to **7** was made from rearranged nitro alcohol **8** (see below) by reduction in a Parr hydrogenator as in the conversion of **5** to **6**. It was not isolated but instead acetylated in ethanol following the same procedure used to make **2** from **6** and recrystallized to constant mp 142° from benzene, then from much water, final mp 144°.

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.47; H, 7.70; N, 6.27.

1-(4-Nitrophenoxy)-2-methyl-2-propanol (8). A. By $LiBH_4$ Reduction of 3a.—A mixture of 0.82 g (21.7 mmol) of $NaBH_4$ and 0.93 g (22 mmol) of oven-dried LiCl in 15 ml of dried (CaH_2) diglyme was heated (N_2) for 1 hr at 110° with stirring. A solution of 5.5 g (21.7 mmol) of nitro ester **3** in 10 ml of dried diglyme was added dropwise (15 min), and the reaction was stirred at 110° bath temperature for 2 hr more. The now dark orange solution was cooled under N_2 and 10 ml of H_2O added slowly. The reaction was then poured into 100 ml of water and extracted three time with Et_2O. The Et_2O layers were extracted in turn with 0.1 *N* HCl and 0.1 *N* NaOH (two 50-ml portions of each), dried ($MgSO_4$), concentrated, and distilled giving 3.3 g, bp 107–111° (0.007 mm).

The product was a yellow oil which appeared homogeneous when run on tlc[21] either in a mixture of hexane–ether–acetone–acetic acid, 30:4:2:0.75, or in benzene–ethanol, 22:3 (all solvents by volume), apart from a colored impurity which remained near the origin. This last was retained on an alumina column[21] developed with hexane containing increasing amounts of anhydrous ether. Combined column eluents were distilled to remove solvent and analyzed.

The pure product eventually crystallized and could be recrystallized from hexane: mp 60–61.5°; nmr ($CDCl_3$) δ 1.4 (s, 6, CH_3), 3.96 (s, $ArOCH_2$), 7.0 (d, 2, J = 9.5 Hz of d, J = *ca.* 1.5 Hz, ArH ortho to O), 8.22 (d, 2, J = 9.5 Hz of d, J = *ca.* 1.5 Hz, ArH ortho to NO_2). Unless *p*-nitrophenol was present, the OH absorption was at δ *ca.* 2.4.

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.15; N, 6.63; mol wt, 211.2. Found: C, 56.54; H, 6.14; N, 6.44; mol wt (mass spectrum), 211.

B. By Rearrangement of Nitro Alcohol 5.—A solution of 5 g (25 mmol) of **5** in 10 ml of dried (CaH_2) diglyme was heated at 115° for 1 hr after addition of 20 mmol each (separate experiments) of the bases, NaH (50% in mineral oil emulsion), and KH in mineral oil). In each case, after quenching in water, washing the ethereal solution with dilute HCl (amino compound was removed), dilute NaOH to remove *p*-nitrophenol, and water, the ethereal solution was dried ($MgSO_4$) and distilled All of the

(21) All melting points were taken on thermometers calibrated with standard compounds and are corrected. Nmr measurements were made using a Varian A-60 instrument by Mr. A. Ragouzeos. Column chromatography used Woelm neutral alumina, activity grade I. Tlc were run on Eastman K301R2 prepared silica gel.

fraction boiling within 10° of the boiling point was taken for pmr in $CDCl_3$.

Ethyl 2-(4-Nitrophenoxy)propionate (9a).—This was made from 155 g of *p*-nitrophenol similarly to **3** but using potassium *tert*-butoxide as base. Distillation was not required as the product solidified on removal of ether, mp 50–52° raised to 55–56° after two recrystallizations from hexane.

Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.44; N, 5.86. Found: C, 55.61; H, 5.54; N, 5.75.

Acidification of the basic aqueous extracts gave 34 g of *p*-nitrophenol.

2-(4-Nitrophenoxy)propionic Acid (9b).—A solution of 101 g (0.421 mol) of nitro ester **9a** in 800 ml of warm 95% ethanol was cooled to *ca.* 35° and treated, with stirring, with 50 ml of 50% w/v aqueous NaOH followed by 20 ml of water washes.

After 24 hr the mixture was concentrated *in vacuo* to a small volume, dissolved in *ca.* 200 ml of water, and filtered from a little water-insoluble material, and acidified with concentrated HCl. After overnight storage at 4°, the solid was filtered from the solution and recrystallized twice from benzene (*ca.* 2 l.), yielding 80 g of yellow crystals, mp 140–140.5°.

Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 50.94; H, 4.17; N, 6.37.

Reduction of Ester 9a by Lithium Borohydride.—The procedure used to reduce **3a** to **8** gave from 50 g of **9a**, 20.5 g of a liquid with bp 126–131° (0.03 mm).

2-(4-Nitrophenoxy)propanol (10). By Borane Reduction of the Acid 9b.—A solution of 60.2 g (0.283 mol) of acid **9b** in 250 ml of tetrahydrofuran (peroxide-free, dried over molecular sieves) was added dropwise to 250 ml of a molar solution of BH_3 in tetrahydrofuran, stirred under N_2. After remaining at 26° overnight, the reaction was treated with 1 l. of water added slowly with stirring, extracted with three 50-ml portions of 1 *M* $NaHCO_3$, dried ($MgSO_4$), and distilled, retaining fractions of bp 118–122° (0.06 mm): nmr ($CDCl_3$) δ 1.33 (d, 3, J = 6 Hz, CH_3), 2.37 (s, 1, OH), 3.80 (d, 2, J = 5 Hz, CH_2OH), 4.66 (q, 1, J = 7 Hz, CHOAr of d or m, J = *ca.* 1 Hz), 7.00 (d, 2, J = 9 Hz, *o*-ORArH, of d, J = *ca.* 2 Hz), 8.20 (d, J = 9 Hz, *o*-NO_2ArH, of d, J = *ca.* 2 Hz).

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.58; N, 7.11. Found: C, 55.11; H, 5.75; N, 7.16.

Ethyl 2-(4-Aminophenoxy)propionate.—A solution of 62 g (0.26 mol) of nitro ester **9a** in 250 ml of 95% ethanol had to be heated to 45° in a Parr hydrogenator to allow reduction with Adams' catalyst and hydrogen. The solvent was removed after filtration, using steam bath and water pump, to leave 56.3 g of residual oil. Most of this was used to make **10** but 6 g was converted to ethyl 2-(4-acetamidophenoxy)propionate by acetic anhydride in ethanol solution for analysis. Two recrystallizations from ethanol–water gave 3.2 g, mp 81–82°.

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.87; N, 5.65. Found: C, 61.84; H, 6.87; N, 5.65.

2-(4-Acetoamidophenoxy)propanol (12). A. By Reduction of Ethyl 2-(4-Aminophenoxy)propionate and Subsequent Acetylation.—A solution of 35.9 g (0.172 mol) of the named amino ester in 500 ml of commercial anhydrous ether was added to 25.8 g (0.68 mol) of $LiAlH_4$ in 1 l. of ether in the usual way and heated under reflux for 2 days. After cautious addition of 52 ml of H_2O and 0.5 hr of stirring, the solid was removed by filtration and washed with anhydrous ether, and then suspended in 100 ml of 95% ethanol and refiltered. The combined ether and ethanol solutions were treated with 50 ml of acetic anhydride with swirling over 10 min and then concentrated on steam at the water pump to a small volume. The residue was boiled with 1 l. of 95% ethanol for 1 hr and water was added at the boiling point to faint turbidity.

On cooling, 1.5 g of orange solid crystallized. This was recrystallized from benzene–hexane, mp 147–150°, and was shown to be 4,4'-bis(1-methyl-2-hydroxyethoxy)azobenzene (or an isomer) by elemental analysis, indicating that the starting amino ester had been contaminated with unreduced nitro ester.

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.40; H, 6.71; N, 8.48. Found: C, 65.22; H, 6.67; N, 8.45.

Concentration of the mother liquors and recrystallization of the residual 12.8 g of material from ethanol–water and from benzene–hexane gave 8 g of solid, mp 120–121°. An additional 10 g was obtained by further washings of the reduction "inorganic" solids with 95% ethanol, acetic anhydride treatment, and recrystallization.

B. By Adams' Catalyst and H_2 Reduction of 10 with Subsequent Acetic Anhydride Treatment.—Following the usual reduction procedure **10** yielded **12** of melting point undepressed on admixture with **12** prepared from the amino ester as outlined in A above, and with identical ir absorption in thin film. This was true for **12** made from **10** which had been prepared either by the $LiBH_4$ reduction of ester **9a** or BH_3 reduction of acid **9b**, but the $LiBH_4$ product initially was an oil requiring five recrystallizations to give an acceptable melting point, while that from **10** from the BH_3 reduction gave 93% of nearly pure material directly.

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 63.16; H, 7.18; N, 6.70. Found: C, 63.18; H, 7.43; N, 6.67.

1-(4-Acetamidophenoxy)-2-propanol (14).—A suspension of 10 g (50 mmol) of 1-(4-acetamidophenoxy)acetone[18] in 100 ml of 50% by volume of methanol–water was stirred, while 2.0 g of $NaBH_4$ dissolved in 20 ml of water was added dropwise, while cooling with flowing tap water. After addition was complete and an additional 45 min had elapsed, 2 ml of HOAc was added, and the solvents were removed on steam at water pump pressure. The resulting oil was extracted repeatedly with acetone, and the filtered acetone extracts were concentrated. The 5.8 g of oil crystallized after addition of water and was recrystallized from water, mp 122–123.5°. The ir absorption had lost the C=O peak present in the starting material and a peak attributed to OH was now present at 3300–3450 cm^{-1}. Elemental analysis showed that this product was isomeric with **12**, when taken with the mixture melting point depression found.

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 63.16; H, 7.18; N, 6.70. Found: C, 62.69; H, 7.34; N, 6.73.

1-(4-Nitrophenoxy)-2-propanol (11).—Reduction of a solution of 10 g of *p*-nitrophenoxyacetone by $NaBH_4$ was carried out by the procedure used to prepare **14**, but work-up consisted of diluting the mixture after the addition of the acetic acid, extraction with ether, drying the ether over $MgSO_4$, and removal of solvent. The resulting orange oil crystallized and was recrystallized from ethanol–hexane and then from hexane: mp 90–92°; nmr ($CDCl_3$) δ 1.33 (d, 3, J = 6 Hz, CH_3), 2.56 (s, 1, OH), *ca.* 4.05 (m, 3, $ArOCH_2$ + CHOH), 7.00 (d, 2, J = 9 Hz, *o*-ORArH of d, J = *ca.* 2 Hz), 8.21 (d, 2, J = 9 Hz, *o*-NO_2ArH of d, J = *ca.* 2 Hz); ir showed no C=O absorption.

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.58; N, 7.11. Found: C, 54.92; H, 5.63; N, 7.09.

Preparation of ^{18}O-Enriched *p*-Nitrophenol.—Dry potassium *tert*-butoxide (21 g) (MSA Research Corp.) was added to 100 ml of *tert*-butyl alcohol which had been dried previously over calcium hydride. ^{18}O-Enriched water (3 ml, 3.061 g) [labeled 41.90% ^{18}O, containing 0.145% ^{17}O (Miles Laboratories)] was added, and the stoppered flask's contents were stirred for 1 hr. A 29.5-g portion of *p*-fluoronitrobenzene was then added, and the now red-brown solution was stirred for 22 hr at approximately 40°. It was then added to 500 ml of water and extracted with ether twice. The ethereal extracts were washed with 1 *N* aqueous sodium carbonate solution, and that combined with the initial aqueous solution brought to pH less than 2 (test paper) with concentrated HCl and extracted with ether (300 ml) and with benzene (100 ml). The combined organic layers were dried ($MgSO_4$) and solvent was removed on the steam bath at 15 mm pressure. The residue was 12.5 g, mp 112.6–113.5°.

Registry No.—**2**, 15971-28-5; **3a**, 23501-39-5; **3b**, 17431-97-9; **4**, 28048-87-5; **5**, 28048-88-6; **7**, 28048-89-7; **8**, 23501-60-2; **9a**, 28059-69-0; **9b**, 13794-10-0; **10**, 28059-71-4; **11**, 10572-15-3; **12**, 28059-73-6; **14**, 28059-74-7; ethyl 2-(4-aminophenoxy)propionate, 28059-75-8.

Reaction of Dialkyltin Dialkoxides with Carbon Disulfide at Higher Temperature. Preparation of Orthocarbonates[1]

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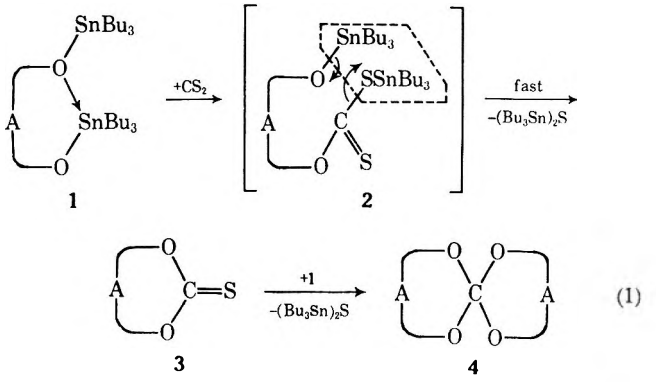
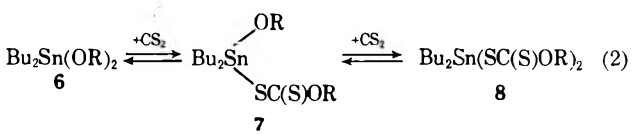
Five- and six-membered cyclic dibutyltin dialkoxides, except 4,4,5,5-tetramethyl-2-dibutylstanna-1,3-dioxolane, reacted with carbon disulfide at about 100–110° to give quantitatively five- and six-membered spiro orthocarbonates, respectively, along with dibutyltin sulfide. Seven-membered cyclic dibutyltin dialkoxide reacted with carbon disulfide at room temperature to form the inserted product of carbon disulfide to the tin–oxygen bond, which was converted at 50° to the corresponding spiro orthocarbonate and its decomposition products. Acyclic dibutyltin and dioctyltin dialkoxides derived from primary C_1–C_6 alcohols reacted with carbon disulfide giving good yields of tetraalkyl orthocarbonates, while the dialkoxides from secondary and tertiary alcohols gave dialkyl carbonates and olefin, respectively.

In our previous paper[2] a novel synthesis of spiro orthocarbonate and cyclic thioncarbonate from the reaction of bis(tributyltin) alkylene glycolate (**1**) with carbon disulfide at room temperature was reported (eq 1).



The formation of thioncarbonates and orthocarbonates from the reaction of carbon disulfide with the linear dialkoxides **1**, where the addition products **2** could not be detected even spectrometrically, exhibits a striking contrast to the reversible addition reaction of carbon disulfide with tributyltin monoalkoxide to give *O*-alkyl *S*-tributyltin dithiocarbonate.[3] This difference could be ascribed to the cyclization tendency assisted by coordination of a sulfur atom to a tributyltin group in the intermediate adduct **2**.

In 1967 Davies and Harrison found that the reaction of dibutyltin dimethoxide (**6**, R = Me) with carbon disulfide took place very fast at room temperature, affording *S*-dibutyl(methoxy)tin *O*-methyl dithiocarbonate (**7**, R = Me) and *S*-dibutyltin bis(*O*-methyl dithiocarbonate) (**8**, R = Me) (eq 2).[4]

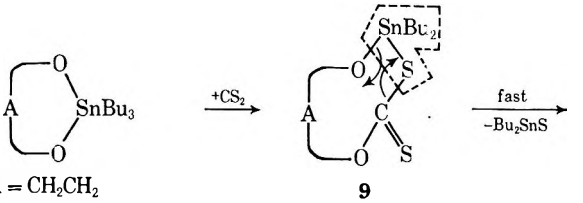


We confirmed their results in the reaction of carbon disulfide with dialkyltin dialkoxides at room temperature. However, when the reactions were carried out in a glass autoclave at higher reaction temperatures than the boiling point of carbon disulfide, orthocarbonates or their decomposition products were obtained in excellent yields.

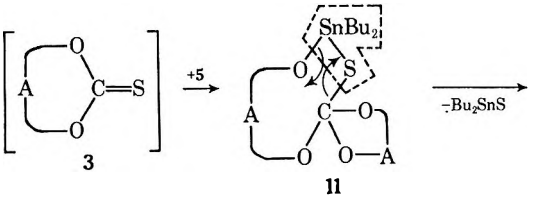
Hitherto, orthocarbonates have been prepared from sodium alkoxides and chloropicrin or thiocarbonylperchloride (Cl_3CSCl) through troublesome reaction steps.[5,6] In this publication the reactions of carbon disulfide with both cyclic and acyclic dialkoxides having an O–Sn–O bond were studied extensively for the purpose of establishing a novel preparative method for orthocarbonates from the dialkyltin dialkoxides which were easily obtained from dialkyltin dichloride or oxide.

Results and Discussion

Reaction of Cyclic Dibutyltin Dialkoxides.—Cyclic dibutyltin dialkoxide (**5**) and carbon disulfide reacted at 100–110° in ethylene dichloride in a glass autoclave to give spiro orthocarbonate and dibutyltin sulfide in good yields (eq 3). The reaction conditions and the yields of the products are summarized in Table I.



5a, A = CH_2CH_2
b, A = $CH(Me)CH_2$
c, A = $CH(Me)CH(Me)$
d, A = CMe_2CMe_2
e, A = $(CH_2)_3$



4a, A = CH_2CH_2
b, A = $CH(Me)CH_2$
c, A = $CH(Me)CH(Me)$ (3)
d, A = CMe_2CMe_2
e, A = $(CH_2)_3$

(1) Taken in part from our preliminary report in *Chem. Commun.*, 235 (1970).

(2) S. Sakai, Y. Kiyohara, K. Itoh, and Y. Ishii, *J. Org. Chem.*, **35**, 2347 (1970).

(3) A. J. Bloodworth, A. G. Davies, and S. C. Vasistha, *J. Chem. Soc. C*, 1309 (1967).

(4) A. G. Davies and P. G. Harrison, *ibid.*, 1313 (1967).

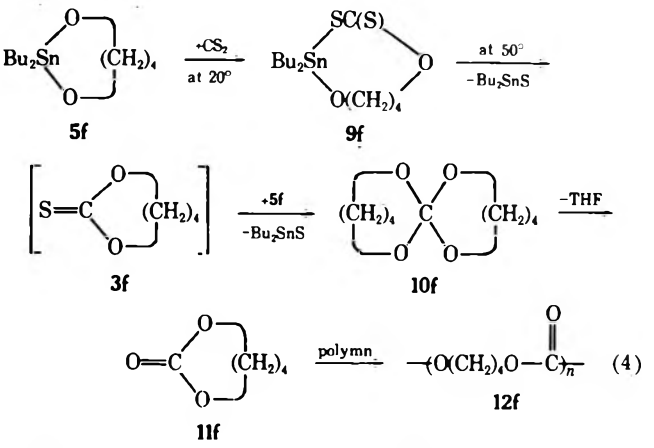
(5) J. D. Roberts and R. E. McMashon, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 457.

(6) H. Tieckelman and H. W. Post, *J. Org. Chem.*, **13**, 265 (1948).

Five- and six-membered[7] cyclic dialkoxides, **5a–e**, can be readily prepared by several methods[8–14] and are relatively stable against moisture in the air, so the reaction of **5a**, **5b**, **5c**, and **5e** with carbon disulfide at higher reaction temperature will be a convenient synthetic method for five- and six-membered spiro orthocarbonates. The spiro orthocarbonates **4a** and **4e** are stable and volatile solids, but **4b** and **4c** are relatively unstable liquids which were partially decomposed to the carbonates even when they were stored in sealed glass tubes at room temperature for 2 months. Cyclic dialkoxide **5d** reacted only slightly with carbon disulfide at 125° for 20 hr and was recovered from the reaction mixture in a 92% yield along with small amounts of a low boiling product which showed a strong $\nu_{C=O}$ band at 1790 cm^{-1} and the same retention time as that of the authentic sample of 2,3-dimethyl-2,3-butylene carbonate in the vapor phase chromatography. The carbonate would be presumably formed by the decomposition of the orthocarbonate **4d** as was reported in our previous papers.[1,15] Remarkable contrast between **5c** and **5d** in their reactivities could be attributed to a steric effect of methyl groups on the formation of spiro orthocarbonates, which was also observed in the case of the linear dialkoxide **1**.[1]

The reaction scheme (eq 3) would be a reasonable one, similar to eq 1 in the case of the linear dialkoxide, but in the reaction of the cyclic dialkoxide **5**, thioncarbonate **3** could not be detected even by ir and nmr spectroscopies, probably due to the higher reaction temperature employed which would accelerate further reaction of thioncarbonate with **5** to form spiro orthocarbonate. Moreover, in the case of **5a–e**, the inserted products **9** could not be detected in the reaction mixture at any temperature.

Contrary to the reaction of five- and six-membered cyclic dialkoxides, a seven-membered cyclic dialkoxide, 1,3-dioxa-2-dibutylstannacycloheptane (**5f**), reacted very rapidly at room temperature, and the reaction mixture showed the ir absorption bands at 1050 and 1175 cm^{-1} which would be assigned to dithiocarbonate structure in the inserted product **9f** in eq 4. Subsequent heating of **9f** at 50° for 2 hr gave a 37% yield of



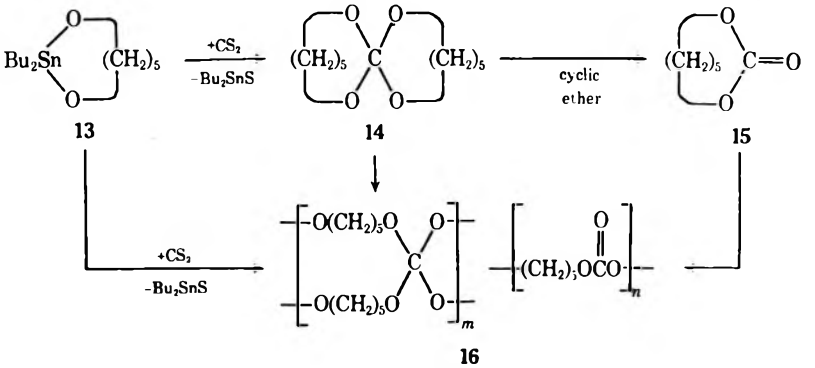
(4)

bis(1,4-butylene) orthocarbonate (**10f**), a 62% yield of poly(1,4-butylene carbonate), mp 141–153°, and trace amounts of tetrahydrofuran. The reaction course from the spiro compound **10f** to the polymer **12f** was confirmed by the redistillation of **10f** in the presence of dibutyltin sulfide to give **12f**.

The seven-membered spiro orthocarbonate **10f** is relatively unstable due to its ring strain in the two seven-membered rings and is decomposed to tetrahydrofuran and 1,4-butylene carbonate (**11f**), the latter polymerizing easily to give the polycarbonate **12f**.

As mentioned above, a remarkable contrast exists between the reactivity of the seven-membered cyclic dialkoxide **5f** and of the five- and six-membered cyclic dialkoxides **5a–e**. Pommier and Valade[7b] reported that the liquid seven-membered cyclic dialkoxide is monomeric, while the solid five- and six-membered cyclic dialkoxides are dimeric even in dilute solution. Therefore, the association degree of cyclic dialkoxides would be conceivable to be a dominating factor in their reactivities; monomeric dialkoxide can react more readily than dimeric one.

The attempt to prepare the eight-membered spiro orthocarbonate **14**, or the cyclic carbonate **15**, in eq 5



(5)

was unsuccessful. The reaction of the eight-membered cyclic dialkoxide **13** gave dibutyltin sulfide and an insoluble polymer of a net structure **16** having orthocarbonate and carbonate segments which would be formed

(7) (a) Five- and six-membered cyclic dialkoxides exist mainly as dimeric forms in solution, but, in this paper, they are conventionally depicted as monomeric forms. Dimer–monomer equilibrium was discussed by Pommier and Valade.[7b] (b) J. Pommier and J. Valade, *J. Organometal. Chem.*, **12**, 433 (1968).

(8) S. Sakai, Y. Fujimura, and Y. Ishii, *J. Org. Chem.*, **35**, 2344 (1970).

(9) H. E. Remsden and C. K. Banks, U. S. Patent 2,789,994 (1957); *Chem. Abstr.*, **51**, 14786 (1957).

(10) J. Bornstein, B. R. La Liberter, T. M. Andrews, and J. C. Montermoso, *J. Org. Chem.*, **24**, 886 (1959).

(11) W. J. Considine, *J. Organometal. Chem.*, **5**, 263 (1966).

(12) R. C. Mehrota and V. D. Gupta, *ibid.*, **4**, 145 (1965).

(13) R. K. Ingham and H. Gilman, *Chem. Rev.*, **60**, 459 (1960).

(14) Cyclic dialkoxide must be completely dried to avoid the hydrolysis of the orthocarbonate formed: *e.g.*, powdered dialkoxide was heated at 150° *in vacuo* (1 mm). Some spiro orthocarbonates are volatile solids or liquids at room temperature; so care should be taken, especially in the drying procedure.

(15) S. Sakai, Y. Asai, Y. Kiyohara, K. Itoh, and Y. Ishii, *Organometal. Chem. Syn.*, **1**, 45 (1970).

TABLE I
REACTION PRODUCTS FROM CYCLIC DIBUTYLTIN DIALKOXIDES AND CARBON DISULFIDE IN ETHYLENE DICHLORIDE

A in cyclic dialkoxide	Reaction condition Temp, °C	Time, hr	Yields of spiro orthocarbonate, %
CH_2CH_2 (5a)	105	10	82 (4a)
$CH_2CH(CH_3)$ (5b)	105	10	87 (4b)
$CH(CH_3)CH(CH_3)$ (5c)	110	10	90 (4c)
$C(CH_3)_2C(CH_3)_2$ (5d)	125	20	0[a]
$(CH_2)_3$ (5e)	105	10	92 (4e)
$(CH_2)_4$ (5f)	50	2[c]	37 (4f)[b]
$(CH_2)_5$ (13)	105	3	0[d]

[a] Trace amounts of 2,3-dimethyl-2,3-butylene carbonate were formed. [b] The polycarbonate 12f was formed in 62% yield. [c] Without solvent. [d] The polymer 16 was obtained.

TABLE II
REACTION PRODUCTS FROM $R'_2Sn(OR)_2$ AND CARBON DISULFIDE

Dialkoxide used R′	R	Reaction condition Temp, °C	Time, hr	Products and yields, %
Bu	CH_3 (6a)	100	10	$C(OCH_3)_4$ (18a), 95
Bu	C_2H_5 (6b)	96	5	$C(OC_2H_5)_4$ (18b), 80
Bu	n-C_3H_7 (6c)	120	20	$C(O$-n-$C_3H_7)_4$ (18c), 86
Bu	i-C_3H_7 (6d)	120	20	$O{=}C(O$-i-$C_3H_7)_2$ (19d), 90
Bu	$tert$-C_4H_7 (6e)	120	20	$CH_2{=}C(CH_3)_2$, *ca.* 80
Bu	n-C_4H_7 (6f)	120	20	$C(O$-n-$C_4H_9)_4$ (18f), 85
Bu	n-C_8H_{17} (6g)	120	20	$C(O$-n-$C_8H_{17})_4$ (18g), *a*
Oct	n-C_6H_{13} (6h)	120	20	$C(O$-n-$C_6H_{13})_4$ (18h), 49[b]
Oct	n-C_8H_{17} (6i)	120	20	$O{=}C(O$-n-$C_8H_{17})_2$ (19g), 80[a]

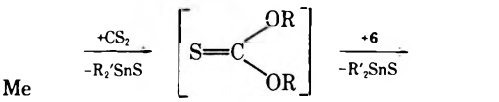
[a] The orthocarbonate, 18g, was formed but decomposed on the distillation to give the carbonate 19g. [b] The decomposition product from 18h, *i.e.*, 19h, was also obtained in 20% yield.

directly from 13 or indirectly *via* the intermediates 14 and 15.

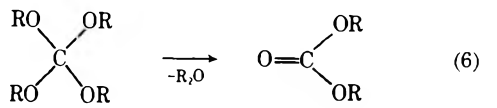
Reactions of Acyclic Dialkyltin Dialkoxides.—Dibutyltin diethoxide (6b) reacted with excess amounts of carbon disulfide at room temperature giving the insertion products 7 and 8 (R = Et in eq 2), as was reported by Davies and Harrison.[4] However, at higher reaction temperature we obtained tetraethyl orthocarbonate and dibutyltin sulfide in quantitative yields. Tetraalkyl orthocarbonates, 18a, 18b, 18c, 18f, and 18g, were formed in good yields in the reaction of carbon disulfide with dibutyltin di(primary)alkoxides, 6a, 6b, 6c, 6f, and 6g, respectively, at 110–120° for 5–20 hr. These results are tabulated in Table II.

In the reaction of dibutyltin dialkoxide from *n*-hexyl or *n*-octyl alcohol with carbon disulfide at 120°, the formation of the orthocarbonate was confirmed by a strong ν_{CO} band at 1120 cm^{-1} and a nmr peak at about τ 6.4 of methylene oxy group in the spectra of the reaction mixture. However, on distillation the mixture of dibutyltin sulfide and the orthocarbonate or its decomposition products was obtained. Column chromatographic separation was unsuccessful because the orthocarbonate was hydrolyzed in the column to afford the carbonate.

Dioctyltin dihexoxide (6h) reacted also with carbon disulfide at 120° for 20 hr to form tetrahexyl orthocarbonate from which the orthocarbonate 18h (49% yield) and its decomposition product, dihexyl carbonate 19h (20% yield), were obtained on the distillation. Dioctyltin dioctoxide (6i) was allowed to react with carbon disulfide under the same reaction condition and tetraoctyl orthocarbonate (18g) was formed, but dioctyl carbonate 19g was only obtained as a decomposed product in 80% yield by distillation (eq 6).



6a, R′ = Bu; R = Me
b, R′ = Bu; R = Et
c, R′ = Bu; R = *n*-Pr
d, R′ = Bu; R = *i*-Pr
f, R′ = Bu; R = *n*-Bu
g, R′ = Bu; R = *n*-Oct
h, R′ = Oct; R = *n*-Hex

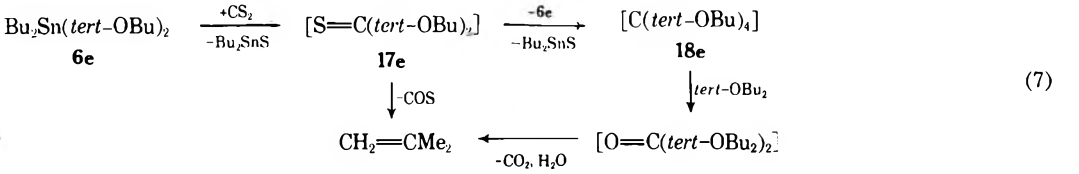


18a, R = Me
b, R = Et
c, R = *n*-Pr
f, R = *n*-Bu
g, R = *n*-Oct
h, R = *n*-Hex

19d, R = *i*-Pr
g, R = *n*-Oct
h, R = *n*-Hex

(6)

In contrast to the reaction of a dibutyltin primary dialkoxide, such as di-*n*-propoxide 6c, the reaction of dibutyltin diisopropoxide with carbon disulfide under the same reaction condition (at 120° for 20 hr) afforded diisopropyl carbonate in a 90% yield (based on eq 6), probably because the secondary orthocarbonate is so thermally unstable that it is decomposed. Dibutyltin di-*tert*-butoxide did not react completely at 100° for 20 hr, and a mixture of the starting dialkoxide and isobutene was obtained. In the reaction with carbon disulfide at 120° for 20 hr, tetra-*n*-butyl orthocarbonate (18f) was formed from dibutyltin di-*n*-butoxide (6f), while isobutene was obtained in about 80% yield from dibutyltin di-*tert*-butoxide (6e) (eq 7).



(7)

The evolution of a gas containing isobutene and carbonyl sulfide was observed, and isobutene was formed from the decomposition of the thioncarbonate 17e. However, small amounts of carbon dioxide were found in the reaction mixture; so the formation of isobutene *via* the orthocarbonate 18e was undeniable.

Experimental Section

General.—Melting and boiling points were uncorrected. Microanalyses were performed by the Analysis Centre of Kyoto University. Ir and nmr (TMS as an internal standard) were recorded on a JASCO Model IR-S spectrometer and on a Japan Electron Optics Laboratory Co., Model JMN-MH60 spectro-

meter, respectively. Vapor phase chromatography was carried out on a Yanagimoto Manufacturing Co., Ltd., Type GCG-5DH chromatograph using an Apiezon column.

Materials.—All alcohols, glycols, and toluene were dried with sodium metal or calcium hydride and distilled before use. Carbon disulfide and 1,2-dichloroethane were dried over phosphorus pentoxide and distilled. Dibutyltin and dioctyltin chloride were purified, but dibutyltin oxide of industrial grade was used without any purification.

Cyclic dialkoxides were prepared from the glycols and dialkyltin dichloride,[9] dimethoxide,[11,12] or oxide,[10] and were strictly dried.[14] Their melting points were as follows: **5a**, 224–226°; **5b**, 183–185°; **5c**, 119–121°; and **5e** 86–88°. Boiling points of **5d**, **5f**, and **13** were 188–189° (0.1 mm), 177–178° (0.6 mm), and 165–175° (0.5 mm), respectively. Dibutyltin dimethoxide, diethoxide, di-*n*- or -isopropoxide, and di-*n*- or -*tert*-butoxide were prepared from dibutyltin dichloride and sodium alkoxides in excess amounts of the corresponding alcohols by the common method.[13] Their boiling points were as follows: **6a**, 131–132° (0.3 mm); **6b**, 115–120° (0.2 mm); **6c**, 119–121° (0.25 mm); **6d**, 81–85° (0.15 mm); **6e**, 152–154° (27 mm); **6f**, 125–127° (0.1 mm); and **6g**, 173–175° (0.4 mm), respectively. Dioctyltin dihexoxide (**6h**) and octaoxide (**6i**) were prepared by a transalcoholysis reaction of dioctyltin dimethoxide with equimolar amounts of the corresponding alcohol by heating to 150° *in vacuo* and were used as starting materials in the reactions with carbon disulfide without further purification, because these dialkoxides were decomposed on the distillations.[16]

Reaction of the Cyclic Dialkoxide 5a with CS_2.—Powder of **5a** (8.7 g, 30 mmol), ethylene dichloride (40 ml), and excess amounts of CS_2 (5 ml) were introduced into a glass autoclave equipped with a mechanical stirrer and gauge, and the mixture was heated for 10 hr in a oil bath kept at 100–110°. The reaction was heterogeneous in the initial stage but became a clear solution after several hours. Nitrogen atmosphere was not applied in the autoclave, because dimeric dialkoxide is relatively stable against moisture. The reaction pressure was about 1.5–3.0 kg/cm². After evaporation of excess amounts of CS_2 and the solvent, a large quantity of *n*-hexane was added to the reaction mixture to precipitate bis(ethylene) orthocarbonate (**4a**): yield 82%; mp (toluene) 143–144° (lit.[2] 143.0–143.5°); the ir and nmr spectra coincided well with those of an authentic sample prepared in a previous paper.[2] Dibutyltin sulfide was obtained in a 94% yield by the distillation of the filtrate.

Reaction of the Cyclic Dialkoxide 5b with CS_2.—The cyclic dialkoxide **5b** was allowed to react with CS_2 at 105° for 10 hr analogously, and the distillation gave an 87% yield of bis(1,2-propylene) orthocarbonate (**4b**): bp 71–73° (2 mm) [lit.[2] 73° (2 mm)]; the ir and nmr spectra were the same as those reported in the previous paper.[2] The orthocarbonate **4b** was stored in a sealed glass tube, but it showed a strong carbonyl band which was assigned to the carbonyl group of 1,2-propylene carbonate by comparison of the retention time and the ir and nmr spectra of the decomposed product with those of an authentic sample.

Reaction of the Cyclic Dialkoxide 5c with CS_2.—The cyclic dialkoxide **5c** was allowed to react with CS_2 at 110° for 10 hr as was mentioned above, and distillation of the reaction mixture gave the spiro orthocarbonate **4c** in a 90% yield. The ir and nmr spectra of the product were the same as those reported in our previous paper.[2]

Reaction of the Cyclic Dialkoxide 5d with CS_2.—The cyclic dialkoxide **5d** (20 mmol) and CS_2 (5 ml) were allowed to react at 110° for 10 hr in ethylene dichloride (40 ml) in an autoclave, but no reaction occurred. Further heating of the mixture at 125° for 20 hr and vacuum distillation gave small amounts of low boiling product in a cold trap which showed a strong $\nu_{C=O}$ band at 1790 cm^{-1} and the same retention time as that of the authentic 2,3-dimethyl-2,3-butylene carbonate. The unreacted dialkoxide **5d** was recovered in a 92% yield on distillation of the residue.

Reaction of the Cyclic Dialkoxide 5e with CS_2.—The cyclic dialkoxide **5e** was allowed to react with CS_2 at 105° for 10 hr in ethylene dichloride, and the reaction mixture was refrigerated and filtrated to give a 92% yield of crude bis(1,3-propylene) orthocarbonate (**4e**) which was sublimated and recrystallized, mp (CCl_4–*n*-hexane) 132–133° (lit.[2] 132–133°). The distillation of the filtrate gave a 95% yield of dibutyltin sulfide.

Reaction of the Cyclic Dialkoxide 5f with CS_2.—The cyclic dialkoxide **5f** (20 mmol) was added to 5 ml of CS_2 under nitrogen at room temperature. The reaction mixture showed strong ir bands at 1175 and 1050 cm^{-1}, suggesting the formation of the inserted product **9f**. Subsequent heating of the mixture at 50° for 2 hr and distillation gave a 37% yield of bis(1,4-butylene) orthocarbonate (**10f**): bp (with sublimination) 80° (0.1 mm); mp (toluene) 109–110° (lit.[2] 109–110°); ir and nmr spectra coincided well with those of the authentic sample.[2] The tetrahydrofuran formed was detected by ir spectroscopic and gas chromatographic measurements of the condensed product in a cold trap of the distillation.

Large amounts of *n*-hexane were added to the distillation residue to precipitate the polymer formed, **12f**, mp about 141–153°, which showed a strong carbonyl band at 1750 cm^{-1} in the ir spectrum ($CHCl_3$) and two broad resonance peaks at τ 5.83 (OCH_2CH_2) and 8.24 (OCH_2CH_2) in the nmr spectrum ($CHCl_3$), and gave 1,4-butylene glycol by basic hydrolysis suggesting the polycarbonate structure **12f**. The redistillation of the orthocarbonate **10f** in the presence of dibutyltin sulfide afforded the polycarbonate **12f**.

Reaction of the Cyclic Dialkoxide 13 with CS_2.—The mixture of cyclic dialkoxide **13** (20 mmol), CS_2 (5 ml), and ethylene dichloride (40 ml) was heated at 105° for 3 hr in a glass autoclave, giving a solid polymer (80% yield) and dibutyltin sulfide which was isolated by distillation after the separation of the polymer by filtration. The polymer was insoluble in dimethylformamide, phenol, or formic acid, showed a very strong ν_{C-O} band at 1120 cm^{-1} and a weak $\nu_{C=O}$ band at 1745 cm^{-1} in the ir spectrum, and gave carbon dioxide and pentamethylene glycol on the acid hydrolysis in 20% sulfuric acid at 100°.

Reaction of Dibutyltin Dimethoxide (6a) with CS_2.—The methoxide **6a** (20 mmol, 5.9 g) and CS_2 (1.2 ml) were mixed at room temperature and gave a solid inserted product as reported by Davies and Harrison,[4] which was heated at 100° for 5–10 hr in a sealed glass tube. The liquid reaction mixture was distilled giving a 95% yield of tetramethyl orthocarbonate (**18a**): bp 62–63°; ir ($CHCl_3$) 1125 cm^{-1} (strong ν_{C-O}); nmr (CCl_4) τ 6.78 (s, 12, CH_3O).

Anal. Calcd for $C_5H_{12}O_4$: C, 44.11; H, 8.88. Found: C, 43.95; H, 8.68.

Further distillation of the residue gave dibutyltin sulfide (97%).

Reaction of Dibutyltin Diethoxide (6b) with CS_2.—The diethoxide **6b** (6.44 g, 20 mmol) and CS_2 (1.2 ml, 20 mmol) were allowed to react at 96° for 5 hr in a glass tube giving tetraethyl orthocarbonate (**18b**) in 80% yield on distillation: bp 47–52° (24 mm) (lit.[5] 158–161°); ir ($CHCl_3$) 1195, 1120 (strong ν_{C-O}), and 1035 cm^{-1}; nmr ($CHCl_3$) τ 6.39 (q, 8, J = 6.9 Hz, OCH_2) and 8.77 (t, 12, J = 6.9 Hz, CH_2CH_3).

Reaction of Dibutyltin Di-*n*-propoxide (6c) with CS_2.—The dialkoxide **6c** (20 mmol) and CS_2 were allowed to react at 120° for 20 hr as in the case of **6b**, and the reaction mixture was distilled giving an 86% yield of tetra-*n*-propyl orthocarbonate (**18c**): bp 56.5–57.5° (0.5 mm); ir ($CHCl_3$) 1119 (ν_{C-O}); nmr ($CHCl_3$) τ 6.45 (t, 8, J = 7.1 Hz, OCH_2), 8.35 (sextet, 8, J = 7, 1 Hz, CCH_2), and 9.07 (t, 12, J = 7.1 Hz, CCH_3).

Anal. Calcd for $C_{13}H_{28}O_4$: C, 62.87; H, 11.36. Found: C, 63.03; H, 11.22.

Reaction of Dibutyltin Diisopropoxide (6d) with CS_2.—The dialkoxide **6d** (20 mmol) and equimolar amounts of CS_2 were allowed to react at 120° for 20 hr as in the case of **6c**, and the reaction mixture was distilled giving diisopropyl carbonate (**19d**) in a 90% yield (calculated assuming the reaction occurred as in eq 6): bp 67–69° (0.5 mm); ir ($CHCl_3$) 1735 ($\nu_{C=O}$), 1268, and 1098 cm^{-1}; nmr (CCl_4) τ 8.75 (d, 12, J = 6.2 Hz, CH_3C) and 5.27 (seven, 2, J = 6.2 Hz, OCH).

Reaction of Dibutyltin Di-*tert*-butoxide (6e) with CS_2.—The dialkoxide **6e** (20 mmol) and equimolar amounts of CS_2 were sealed in a glass tube and heated at 120° for 20 hr giving an ~80% yield of isobutene (based on **6e** used) which was identified by comparison of the nmr spectrum and the retention time in the gas chromatogram with those of a commercially available sample. The mixture condensed in a cold trap on distillation showed a strong ir band at 2050 cm^{-1} (COS) and a weak band at 2450 cm^{-1} (CO_2) in its ir spectrum.

On the other hand, the reaction at 110° for 20 hr gave an ~40% yield of isobutene and an ~45% yield of the unreacted dialkoxide **6e** which was isolated by distillation.

Reaction of Dibutyltin Di-*n*-butoxide (6f) with CS_2.—The dialkoxide **6f** (20 mmol) and equimolar amounts of CS_2 were allowed to react, as in the case of **6c**, giving an 85% yield of

(16) The dialkoxides of dioctyltin were decomposed at about 160° on distillations.

tetra-*n*-butyl orthocarbonate (**18f**): bp 85–89° (0.4 mm); ir ($CHCl_3$) 1175, 1120 (ν_{C-O}), 1050, and 970 cm^{-1}; nmr ($CHCl_3$) τ 6.44 (t, 8, J = 6.2 Hz, OCH_2), 8.1–8.8 (m, 16, CCH_2CH_2C), and 9.07 (t, 12, J = 6.1 Hz, CCH_3).

Reaction of Dibutyltin Di-*n*-octoxide (6g) with CS_2.—The dialkoxide **6g** (20 mmol) and equimolar amounts of CS_2 were heated at 120° for 20 hr, and the reaction mixture showed a strong ν_{C-O} band at 1115 cm^{-1} and a very weak $\nu_{C=O}$ band at 1750 cm^{-1} in the ir spectrum, suggesting the formation of tetra-*n*-octyl orthocarbonate. However, the pure orthocarbonate could not be obtained on distillation or column chromatography of the mixture, because it was decomposed to dioctyl carbonate in these procedures.

Reaction of Dioctyltin Di-*n*-hexoxide (6h) with CS_2.—Crude dialkoxide **6h** (10 mmol),[16] prepared *in situ* from dioctyltin dimethoxide and dried 1-hexanol by heating the mixture in a distillation flask to 120° *in vacuo* (20 mm), was allowed to react with CS_2 (0.6 ml) at 120° for 20 hr under argon to give a 49% yield of tetra-*n*-hexyl orthocarbonate (**18h**) and a 20% yield of di-*n*-hexyl carbonate (**19h**) (yields based on the crude **6h** used).

18h: bp 119–121° (0.04 mm); ir ($CHCl_3$) 1118 cm^{-1} (ν_{C-O}); nmr ($CHCl_3$) τ 6.51 (t, 8, J = 6.0 Hz, OCH_2), 8.3–8.9 (m, 32, $C(CH_2)_4C$), and 9.13 (t, 12, J = 5.8 Hz, CCH_3).

Anal. Calcd for $C_{25}H_{52}O_4$: C, 72.06; H, 12.58. Found: C, 72.25; H, 12.74.

(16) The dialkoxides of dioctyltin were decomposed at ~160° on distillation.

19h: bp 61–63° (0.03 mm); ir ($CHCl_3$) 1742 (ν_{C-O}) and 1260 cm^{-1}; nmr (CCl_4) τ 5.87 (t, 4, J = 6.0 Hz, OCH_2), 8.1–8.9 (m, 16, $C(CH_2)_4C$), and 9.11 (t, 6, J = 5.7 Hz CCH_3).

Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.80; H, 11.19.

Reaction of Dioctyltin Di-*n*-octoxide (6i) with CS_2.—Crude dialkoxide **6i** (10 mmol),[16] prepared from dioctyltin dimethoxide and dried 1-octanol as was discussed above, reacted with CS_2 (0.6 ml) at 120° for 20 hr. The reaction mixture showed a strong ether band of tetraalkyl orthocarbonate at 1115 cm^{-1}, but, on distillation (the oil bath temperature used was increased to 220°), di-*n*-octyl carbonate (**19i**) was obtained in a 80% yield suggesting the decomposition of **18g** to **19g**: bp 120° (0.04 mm); ir ($CHCl_3$) 1740 (ν_{C-O}) and 1265 cm^{-1}; nmr ($CHCl_3$) τ 5.85 (t, 4, J = 6.2 Hz, OCH_2), and 8.1–9.3 (m, 30, CC_7H_{15}).

Anal. Calcd for $C_{17}H_{35}O_4$: C, 71.28; H, 11.96. Found: C, 71.46; H, 11.89.

Registry No.—**5a**, 3590-59-8; **5b**, 3590-60-1; **5c**, 3590-63-4; **5d**, 3590-67-8; **5e**, 3744-99-8; **5f**, 3590-62-3; **6a**, 1067-55-6; **6b**, 1067-41-0; **6c**, 3349-35-7; **6d**, 14538-83-1; **6e**, 3349-40-4; **6f**, 3349-36-8; **6g**, 3349-38-0; **13**, 3590-65-6; **18a**, 1850-14-2; **18b**, 78-09-1; **18c**, 597-72-8; **18f**, 25335-30-2; **18h**, 28131-23-9; **19d**, 6482-34-4; **19h**, 7523-15-1; **19i**, 1680-31-5; carbon disulfide, 75-15-0.

The Reactions of Amines, Alcohols, and Pivalic Acid with Di-*tert*-butyl Dithiol Tricarbonate and Di-*tert*-butyl Tricarbonate[1,2]

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Nucleophilic attack by amines on di-*tert*-butyl dithiol tricarbonate and di-*tert*-butyl tricarbonate is shown to take place at the central carbonyl group. Primary aromatic amines give rise to symmetrical ureas, secondary amines produce the corresponding carbonic carbamic anhydrides, and tertiary amines catalyze the decomposition of the tricarbonates to their corresponding dicarbonates. Ethyl and isopropyl alcohols react to produce the corresponding mixed dicarbonates. Pivalic acid reacts to produce RSCOOCOOCOR (R = *tert*-Bu), almost certainly by attack at the central carbonyl group of the tricarbonate.

The present paper describes the action of primary and secondary amines, of alcohols, and of pivalic acid on the tricarbonates whose preparation and properties were reported previously. The present work will be described most clearly by reference to some of our earlier observations.

The thermal decomposition of di-*tert*-butyl dithiol tricarbonate (**1**) has been shown to give di-*tert*-butyl dithiol dicarbonate (**2**), which may be further decomposed to the corresponding monocarbonate **3**[3-5] (eq 1).

$$\underset{\mathbf{1}}{RSCOCOCSR} \xrightarrow{75^\circ} \underset{\mathbf{2}}{RSCOCSR} \xrightarrow{170^\circ} \underset{\mathbf{3}}{RSCSR} \qquad (1)$$

R = *tert*-Bu

In contrast to this behavior, di-*tert*-butyl tricarbonate (**4**), when thermally decomposed, fragments into three molecules of carbon dioxide, one molecule of *tert*-butyl alcohol, and one molecule of isobutene[4,5] (eq 2). By refluxing in carbon tetrachloride with a trace of triethylamine, the decomposition is arrested at the di-*tert*-butyl dicarbonate[6,7] **5** stage. Under all of the conditions tried, **5** could not be converted into the known monocar-

$$\underset{\mathbf{4}}{ROCOCOCOR} \xrightarrow{65^\circ} 3CO_2 + ROH + \text{alkene}$$

$$\downarrow Et_3N\text{-}CCl_4 \qquad (2)$$

$$\underset{\mathbf{5}}{ROCOCOR} \xrightarrow{\Delta} 2CO_2 + ROH + \text{alkene}$$

(1) Aided by Grant GP-7874 from the National Science Foundation.

(2) The nomenclature of the di- and tricarbonates described in this and the preceding papers of this series is a vexing problem. The dicarbonates, ROCOOCOR, have been known for some time (ref 6 and 7 below) and are usually called "pyrocarbonates;" they have received considerable attention as mild acylating agents for compounds of biochemical importance [*e.g.*, N. J. Leonard, J. J. McDonald, and M. E. Reichmann, *Proc. Nat. Acad. Sci. U. S.*, **67**, 93 (1970), and references therein]. R. Sayre [*J. Amer. Chem. Soc.*, **74**, 3647 (1952)] has named EtOCOSCSOEt "diethyl thionothiodiformate" and gives other less descriptive names. In our work, we have preferred the "dicarbonate" and "tricarbonate" scheme to emphasize the similarities between the two types, derived formally from HOCOOCOOH and HOCOOCOOCOOH, as well as from the corresponding sulfur carbonic acids, HSCOOCOSH and HSCOOCOOCOSH. The di- and triphosphates, as in adenosine triphosphate and adenosine diphosphate, are reasonable analogs to our usage.

(3) A. W. Friederang and D. S. Tarbell, *Tetrahedron Lett.*, **55**, 5535 (1968).

(4) C. S. Dean and D. S. Tarbell, *Chem. Commun.*, 728 (1969).

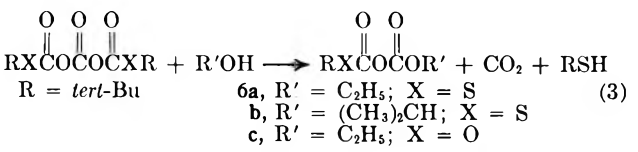
(5) C. S. Dean, D. S. Tarbell, and A. W. Friederang, *J. Org. Chem.*, **35**, 3395 (1970).

(6) J. W. Howe and L. R. Morris, *ibid.*, **27**, 1901 (1962).

(7) W. Thoma and H. Rinke, *Justus Liebigs Ann. Chem.*, **624**, 31 (1959); T. Boehm and D. Mehta, *Ber.*, **71**, 1797 (1938).

bonate,[8] the products being two molecules of carbon dioxide, one molecule of isobutene, and one molecule of *tert*-butyl alcohol (eq 2). The contrast in the decompositions between the oxygen compounds and the sulfur compounds is readily understandable on the basis of the ready ability of *tert*-butyl oxygen compounds to form *tert*-butyl carbonium ions and the well-known failure of *tert*-butyl thiol compounds to reciprocate this behavior.[9] However, the ability of a catalytic quantity of triethylamine to arrest the decomposition of the oxygen tricarbonate at the dicarbonate stage is striking. The action of tertiary amines on the di- and tricarbonates is being investigated further.

The reaction of tricarbonates with alcohols appears to be general. Di-*tert*-butyl dithiol tricarbonate reacts with ethanol in chloroform or carbon tetrachloride solution to give *tert*-butyl thiol ethyl dicarbonate (**6a**) (eq 3). The formation of carbon dioxide in this and the



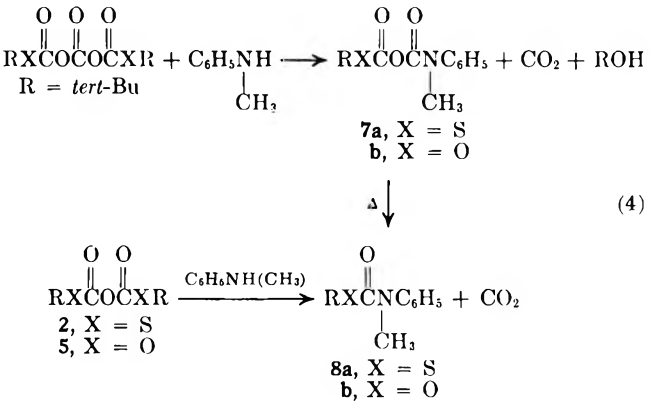
(3)

other reactions of nucleophiles with the tricarbonates was shown by a strong band in the ir at 2370 cm^{-1} which disappeared when reaction was complete. Similarly, di-*tert*-butyl tricarbonate reacts with ethanol to produce the corresponding mixed oxygen dicarbonate, *tert*-butyl ethyl dicarbonate (**6c**). A further example is furnished by the reaction of isopropyl alcohol with di-*tert*-butyl dithiol tricarbonate to form *tert*-butyl thiol isopropyl dicarbonate (**6b**).

Compounds **6a**, **6b**, and **6c** were obtained pure by distillation, and the structures were assigned on the basis of ir and nmr spectra, and the elemental analysis; mass spectroscopy is not useful in the polycarbonate series, because even the monocarbonates fragment extensively, without giving a molecular ion.[10]

All attempts to produce *tert*-butyl thiol *tert*-butyl dicarbonate from di-*tert*-butyl dithiol tricarbonate were unsuccessful. The methods tried included refluxing the tricarbonate in carbon tetrachloride in the presence of *tert*-butyl alcohol, allowing the tricarbonate to stand at room temperature in carbon tetrachloride containing *tert*-butyl alcohol and a catalytic quantity of triethylamine or potassium *tert*-butoxide, and using equimolar quantities of the tricarbonate and potassium *tert*-butoxide at room temperature in tetrahydrofuran solution. In all cases, the decomposition of the tricarbonate, to di-*tert*-butyl dithiol dicarbonate, takes precedence over the formation of the mixed dicarbonate. A similar effect is seen in the reaction of di-*tert*-butyl dithiol tricarbonate with mercaptans. The decomposition of the tricarbonate to di-*tert*-butyl dithiol dicarbonate competes with the formation of the mixed dithiol dicarbonate. Both isopropyl mercaptan and benzyl mercaptan were used and the corresponding mixed dicarbonates, *tert*-butyl thiol isopropyl thiol dicarbonate and *tert*-butyl thiol benzyl thiol dicarbonate were formed in 10–15% yield (nmr).

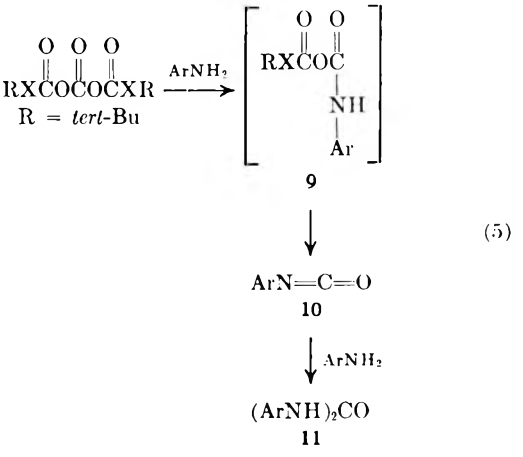
N-Methylaniline reacts similarly to alcohols, producing carbonic carbamic anhydrides; with di-*tert*-butyl dithiol tricarbonate (**1**) at room temperature, the product formed is *tert*-butyl thiol *N*-methylphenylcarbamic anhydride (**7a**) (eq 4). Similarly, di-*tert*-butyl



(4)

tricarbonate with *N*-methylaniline produces *tert*-butyl *N*-methylphenylcarbamic anhydride (**7b**). Both of these anhydrides are thermally unstable and may be decomposed with the loss of one molecule of carbon dioxide, the thiol compound giving the known *tert*-butyl thiol *N*-methylphenylcarbamate (**8a**) and the oxygen compound giving *tert*-butyl *N*-methylphenylcarbamate (**8b**). Both of these carbamates can be obtained from di-*tert*-butyl dithiol dicarbonate (**2**) and di-*tert*-butyl dicarbonate (**5**), respectively, by refluxing the dicarbonate with *N*-methylaniline in carbon tetrachloride.

With primary aromatic amines, both tricarbonates give the isocyanate, which then reacts with a second molecule of amine to give the urea. On the basis of the reactions with alcohols and secondary amines, the reaction presumably proceeds through an intermediate of the type **9** (eq 5) which immediately then forms the isocyanate **10** and finally the symmetrical urea **11**. The primary amines used were aniline, 2,4-dimethylaniline, and 2,6-dimethylaniline. The isocyanates were not isolated, but their presence was shown by the characteristic absorption[11] in the ir at 2270 cm^{-1}, which appeared



(5)

(8) A. R. Choppin and J. W. Rogers, *J. Amer. Chem. Soc.*, **70**, 2967 (1948).

(9) (a) D. S. Tarbell and L. Wei, *J. Org. Chem.*, **33**, 1884 (1968); (b) C. J. Michejda and D. S. Tarbell, *ibid.*, **29**, 1168 (1964); (c) T. Parasaran and D. S. Tarbell, *ibid.*, **29**, 2471 (1964); (d) R. Altschul, *J. Amer. Chem. Soc.*, **68**, 2605 (1946).

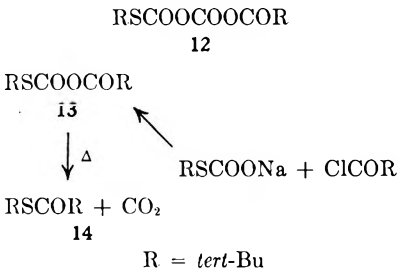
(10) P. Brown and C. Djerassi, *ibid.*, **88**, 2469 (1966); H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 484 ff.

(11) W. H. T. Davison, *J. Chem. Soc.*, 3712 (1953); H. Hoyer, *Chem. Ber.*, **89**, 2677 (1956).

during the reaction and then disappeared, because of the reaction with amine to form the urea. The rate of formation of the ureas decreased sharply in going from aniline to 2,6-dimethylaniline, ascribable to the steric effect of the methyl groups.

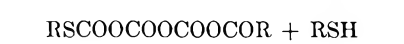
The reaction of *N*-methylaniline with di-*tert*-butyl and di-*tert*-butyl dithiol dicarbonate can be logically linked to the well-documented reactions with nucleophiles of the *tert*-butyl carbonic carboxylic,[9b] *tert*-butyl thiol carbonic carboxylic,[9c] and *tert*-butyl carbonic phosphoric anhydrides.[12]

Pivalic acid reacted with the sulfur tricarbonate **1** to yield a mixture of the compounds **12** and **13** (nmr and ir), which gave on distillation at bath temperature of 75° the pure mixed anhydride **13**. This was obtained crystalline and was identical with the product prepared by the usual procedure. Compound **13** readily yielded



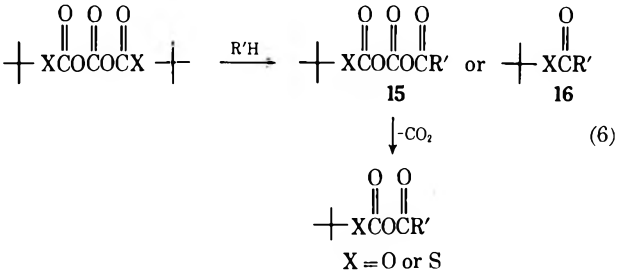
the simple ester, *tert*-butyl thiol pivalate (**14**). Other acids (benzoic, *p*-nitrobenzoic, and acetic) did not give satisfactory results, partly because the products could not be purified and also because they appeared to disproportionate (especially the acetic acid product). The highly substituted pivalic derivatives did not show this behavior.

Pivalic acid is believed to attack **1** at the central carbonyl group; however, it cannot be stated definitely on the basis of present evidence that the primary product from **1** and pivalic acid is not **15**, formed by attack at the terminal carbonyl. If **15** is formed, however, there is



no evidence for it in the ir, which would be very distinctive.

The tricarbonates, however, are a new class of compounds to which there are no close analogies.[13] Even so, all of their above reactions with nucleophilic reagents can be readily rationalized on the basis of nucleophilic attack at the central carbonyl group. Alcohols and mercaptans produce the corresponding mixed dicarbonates **6**, primary amines give the isocyanates *via* the carbonic carbamic anhydride intermediate **9**, and secondary amines give the carbamic anhydrides **7**. (Pivalic acid is discussed above.) Little support can be found for any alternative mechanism whereby one of the other two equivalent carbonyl centers is attacked, as depicted in eq 6.



R' = RNH, R_2N, RO, $OCOC(CH_3)_3$

One would expect to see at least some, if not exclusive, formation of a monocarbonyl compound of the type **16**, or an indication of the presence of an intermediate of the type **15**, which in itself should be susceptible to further nucleophilic attack as well as decomposition. Such was not the case. Hence the ability of a catalytic quantity of triethylamine to arrest the decomposition of di-*tert*-butyl tricarbonate at the dicarbonate stage, along with its ability to speed up the decomposition of di-*tert*-butyl dithiol tricarbonate to its corresponding dicarbonate, can readily be linked with the above nucleophilic reactions, in that an association of the tertiary amine with the central carbonyl group must be involved. Therefore the evidence would strongly suggest that the thermal decomposition of both tricarbonates involves the loss of the central carbonyl group. Kinetic studies[5] have shown that these decompositions are first order and that the rates are essentially the same for both tricarbonates in chlorobenzene and the same in decalin. Further the rate of reaction decreases sharply in going from the polar solvent chlorobenzene to the nonpolar solvent decalin, which supports an ionic mechanism for the decomposition process.

Experimental Section[14]

Reactions of Alcohols with Tricarbonates. ***tert*-Butyl Thiol Ethyl Dicarbonate** (**6a**).—A solution of 294 mg (0.001 mol) of di-*tert*-butyl dithiol tricarbonate[3,5] in 10 ml of chloroform containing 75 mg (0.00166 mol) of ethyl alcohol was heated on a steam bath for 10 min. Removal of the solvent followed by distillation gave 150 mg (73%) of colorless mobile *tert*-butyl thiol ethyl dicarbonate (**6a**) (0.01 mm, bath temperature 80°). The ir spectrum showed carbonyl absorptions at 1800 and 1735 cm^{-1}. The nmr spectrum showed a triplet at 1.37 (J = 7 cps, 3 H), a singlet at 1.33 (9 H), and a quartet at 4.3 (J = 7 cps, 2 H).

Anal. Calcd for $C_8H_{14}O_4S$: C, 46.58; H, 6.68. Found: C, 46.57; H, 6.82.

***tert*-Butyl Ethyl Dicarbonate** (**6c**).—A similar procedure using ethanol and di-*tert*-butyl tricarbonate[4,5] gave the dicarbonate **6c** in 52% yield, distilled at a bath temperature of 55° (0.025 mm). The ir spectrum showed carbonyl absorptions at 1815 and 1775 cm^{-1}. The nmr spectrum showed a triplet at 1.37 (J = 7 cps, 3 H), a singlet at 1.53 (9 H), and a quartet at 4.25 (J = 7 cps, 2 H).

Anal. Calcd for $C_8H_{14}O_5$: C, 50.53; H, 7.41. Found: C, 50.53; H, 7.38.

***tert*-Butyl thiol isopropyl dicarbonate** (**6b**) was prepared similarly from the sulfur tricarbonate **1** and isopropyl alcohol in 68% yield as a colorless mobile liquid, distilled at a bath temperature of 80° (0.025 mm). The ir spectrum showed carbonyl

(12) (a) D. S. Tarbell and M. A. Insalaco, *Proc. Nat. Acad. Sci. U. S.*, **57**, 233 (1967); (b) A. W. Friederang, D. S. Tarbell, and S. Ebine, *J. Org. Chem.*, **34**, 3825 (1969). *Cf.* also K. H. Slotta and H. Dressler *Ber.*, **63**, 888 (1930); R. Sayre, N. J. Leonard, *et al.*, in ref 2 above; J. E. Hodkins, W. P. Reeves, and Y. Liu, *J. Amer. Chem. Soc.*, **83**, 2532 (1961).

(13) M. Zbirovsky and V. Ettel, *Chem. Listy*, **50**, 670 (1956), report compounds obtained from thiophosgene and xanthates of type ROCSSCSSCSOR, which appear to dimerize readily.

(14) Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. All melting points and boiling points are uncorrected unless otherwise specified. Infrared spectra were recorded on a Beckman IR-10 spectrometer and nmr spectra were recorded on a Varian A-60 spectrometer, using TMS as internal standard; nmr spectra are given in parts per million.

peaks at 1800 and 1730 cm^{-1}. The nmr spectrum showed a doublet at 1.34 (J = 6.5 cps, 6 H), a singlet at 1.52 (9 H), and a septet at 4.93 (J = 6.5 cps, 1 H).

Anal. Calcd for $C_9H_{16}O_4S$: C, 49.07; H, 7.32; S, 14.55. Found: C, 49.22; H, 7.33; S, 14.54.

Reactions of Primary Amines with Tricarbonates. Aniline and Di-*tert*-butyl Dithiol Tricarbonate (1).—A solution of 150 mg (0.0016 mol) of freshly distilled aniline in 3 ml of carbon tetrachloride was added to a solution of 150 mg (0.00051 mol) of di-*tert*-butyl dithiol tricarbonate (1) in 3 ml of carbon tetrachloride at 0°. The reactants were allowed to warm to room temperature and stand for 1 hr. A white precipitate formed shortly after the addition was complete. Filtration gave 100 mg (theoretical yield, 92 mg) of product, mp 241–242°, whose ir spectrum was identical with that of diphenylurea. Recrystallization from ethanol–water gave white needles, mp 241–242°. Nothing was isolated from the filtrate.

Aniline and di-*tert*-butyl tricarbonate[4,5] (4) reacted similarly to give 82% of diphenylurea.

2,4-Dimethylaniline and Di-*tert*-butyl Dithiol Tricarbonate (1).—2,4-Dimethylaniline (redistilled, 83 mg) was allowed to react with 100 mg of the sulfur tricarbonate 1 in 5 ml of CCl_4 at room temperature; CO_2 was evolved and a white solid began to precipitate after 3 min. The ir spectrum of the reaction mixture showed a strong isocyanate band at 2270 cm^{-1}. The mixture was heated on the steam bath for 15 min, and 75 mg (62%) of bis-2,4-dimethylphenylurea was obtained which melted, from ethanol, at 268–270° (sealed tube) (reported[15] 263–265°).

2,4-Dimethylaniline and di-*tert*-butyl tricarbonate (4) gave 89% of the same urea.

2,6-Dimethylaniline (purified by distillation) with the sulfur tricarbonate 1, and with the oxygen tricarbonate 4, gave similarly a strong absorption for the isocyanate during the reaction, and the corresponding bis(2,6-dimethylphenyl)urea was formed in 50–60% yield, mp 331–332° (sealed tube).[16]

Reactions of Tertiary Amines with Tricarbonates. Triethylamine and *N*-Methylpiperidine.—The decomposition of di-*tert* butyl tricarbonate (4) is arrested at the dicarbonate[4,5] 5, and the decomposition of di-*tert*-butyl dithiol tricarbonate (1) to the dithiol dicarbonate 2 is catalyzed.

Reactions of *N*-Methylaniline with Tricarbonates. A. Di-*tert*-butyl Dithiol Tricarbonate (1).—A solution of 364 mg (0.000356 mol) of *N*-methylaniline (purified by distillation) in 3 ml of CCl_4 was added to a solution of 100 mg (0.00034 mol) of the dithiol tricarbonate 1 at room temperature. The solution became warm and the ir spectrum indicated that reaction was complete after 30 min. Removal of the solvent gave 32 mg (91%) of *tert*-butyl thiol carbonic *N*-methylphenylcarbamic anhydride (**7a**) as a pale yellow oil. The material could not be purified on account of its instability. The ir spectrum showed absorptions at 1775, 1725, and 1020 cm^{-1}, and the nmr spectrum showed singlets at 1.43 (9 H), 3.33 (3 H), and a broad singlet at 7.27 (5 H).

B. Di-*tert*-butyl Dithiol Dicarbonate (2).—A solution of 107 mg (0.001 mol) of *N*-methylaniline in 4 ml of CCl_4 was added to a solution of 240 mg (0.001 mol) of the dicarbonate 2. The reactants were heated on a steam bath for 1 hr after which time carbamate formation was complete. Removal of the solvent gave 180 mg (81%) of crystalline *tert*-butyl thiol *N*-methylphenylcarbamate (**8a**). Recrystallization from ethanol–water gave white needles of **8a**, mp 54–55.5°.

The same compound was obtained in 45% yield (of recrystallized material) by refluxing *N*-methylaniline with the thiol carbonic carbamic anhydride 7a in CCl_4 for 4 hr. None of the symmetrical bis-*N*-methylphenylurea was found.

C. Di-*tert*-butyl Tricarbonate (4). Formation of *tert*-Butyl Carbonic *N*-Methylphenylcarbamic Anhydride (7b).—A solution of 60 mg (0.00056 mol) of *N*-methylaniline in 3 ml of CCl_4 was added to a solution of 150 mg (0.00057 mol) of the tricarbonate 4 in 3 ml of CCl_4 at room temperature. The solution became warm and carbon dioxide was evolved. The ir spectrum of the reactants showed that the tricarbonate bands had disappeared after 30 min. Removal of the solvent gave 130 mg (92%) of colorless mobile *tert*-butyl carbonic *N*-methylphenylcarbamic anhydride (**7b**) which was not purified further on account of its instability. The ir spectrum showed absorptions at 1795 and 1745 cm^{-1}. The nmr spectrum showed singlets at 1.43 (9 H), 3.31 (3 H), and 7.28 (5 H).

Thermal Decomposition of *tert*-Butyl Thiol Carbonic *N*-Methylphenylcarbamic Anhydride (7a).—In an apparatus[5] for the estimation of carbon dioxide, 171 mg of the carbonic anhydride **7a** was heated at 170–180° in the presence of a trace of *N*-methylpiperidine as catalyst. The decomposition was complete after about 30 min; 26 mg of carbon dioxide (92% of 1 mol) was evolved. The yield of residue was 114 mg (80%). Recrystallization from ethanol–water gave white needles, mp 54–55°, identical with an authentic sample of *tert*-butyl thiol *N*-methylphenylcarbamate (**8a**).

Thermal Decomposition of *tert*-Butyl Carbonic *N*-Methylphenylcarbamic Anhydride (7b).—The anhydride, 184.5 mg (0.000735 mol), was decomposed at 170–180° exactly as described for the corresponding thiol compound **7a**. The yield of carbon dioxide was 37 mg (103% of 1 mol). Distillation of the residue gave 116 mg (76%) of colorless mobile *tert*-butyl *N*-methylphenylcarbamate (**8b**), bp *ca.* 70° (1 mm). The ir spectrum showed a carbonyl absorption at 1700 cm^{-1}, and the nmr spectrum showed singlets at 1.42 (9 H), 3.21 (3 H), and a broad singlet at 7.18 (5 H).

Anal. Calcd for $C_{12}H_{17}NO$: C, 69.52; H, 8.27; N, 6.76. Found: C, 70.13; H, 8.40; N, 6.85.

The same compound was obtained in 89% yield by the action of *N*-methylaniline on di-*tert*-butyl dicarbonate 5 in refluxing CCl_4.

Reaction of Di-*tert*-butyl Dithiol Tricarbonate (1) with Pivalic Acid.—Pivalic acid (90 mg, 0.01 mol) and di-*tert*-butyl dithiol tricarbonate (294 mg, 0.01 mol) dissolved in 10 ml of CCl_4 were heated on a steam bath for 2 hr, after which time reaction was complete. Removal of the solvent gave 200 mg of crude product which consisted of a mixture of the tri- and dicarbonyl compounds **12** and **13**. Distillation caused the tricarbonyl compound to decompose to the dicarbonyl compound, *tert*-butyl thiol carbonic pivalic anhydride (**13**), which occurred as a white wax, boiling at a bath temperature of about 75°, mp 40–49°. A second distillation gave 100 mg (46%) of a waxy solid, mp 56–59°; the ir spectrum showed absorptions at 1790 and 1725 cm^{-1}. The nmr spectrum showed a singlet at 1.52 (3 H) and at 1.24 (3 H).

Anal. Calcd for $C_{10}H_{18}O_3S$: C, 55.03; H, 8.31; S, 14.69. Found: C, 54.81; H, 8.29; S, 14.44.

***tert*-Butyl Thiol Carbonic Pivalic Anhydride (13).**—Sodium *tert*-butyl thiol carbonate was prepared from 4.5 g (0.05 mol) of *tert*-butyl mercaptan as previously described. A solution of 6.03 g (0.05 mol) of pivaloyl chloride in 30 ml of THF was added dropwise to the stirred carbonate at −60°. The reactants were stirred at this temperature for 2 hr and then for a further 2 hr at 0°. Ice-cold pentane (500 ml) was added, the precipitated NaCl was filtered off, and the solvent was removed at 0°. Distillation gave 4.5 g (41.3%) of the pure anhydride, bp 73° (0.025 mm), mp 57–59°, which was identical with **13** obtained above.

Thermal Decomposition of *tert*-Butyl Thiol Carbonic Pivalic Anhdride (13).—The mixed anhydride (330 mg) was decomposed at 120–140° in the presence of a trace of triethylamine. The yield of residue was 230 mg, which was distilled at a bath temperature of 100° and water pump pressure, to yield 165 mg (75%) of colorless *tert*-butyl thiol pivalate. The ir spectrum showed an absorption at 1675 cm^{-1}, and the nmr showed a singlet at 1.43 (3 H) and at 1.28 (3 H).

Reaction of Di-*tert*-butyl Tricarbonate with Pivalic Acid.—The tricarbonate, 262 mg (0.001 mol), and pivalic acid, 90 mg (0.001 mol), in 10 ml of CCl_4 were heated on a steam bath for 20 min. The ir spectrum indicated that reaction was complete. The nmr spectrum showed the material to consist probably of the symmetrical dicarbonate 5 and the mixed anhydride 13 (O instead of S).

Registry No.—**1**, 22085-39-8; **4**, 24424-95-1; **6a**, 28058-92-6; **6b**, 28058-93-7; **6c**, 19935-69-4; **8b**, 28131-24-0; **13**, 28058-95-9; **14**, 28058-96-0; pivalic acid, 75-98-9.

(15) J. K. Thomson and F. J. Wilson, *J. Chem. Soc.*, 1262 (1933).

(16) R. A. Franz, *et al.*, *J. Org. Chem.*, **26**, 3309 (1961), report that this urea melts above 300°.

Small-Ring Epoxides. III. Further Studies on 2,2,5,5-Tetramethyl-4-isopropylidene-1-oxaspiro[2.2]pentane[1a]

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Solvolysis of 2,2,5,5-tetramethyl-4-isopropylidene-1-oxaspiro[2.2]pentane (1) in acetic acid–methanol leads initially to 2,5-dimethyl-3-(1-methyl-1-methoxyethyl)hexa-3,4-dien-2-ol (3). Further reaction gives 2,5-dimethyl-3,5-dimethoxy-4-isopropylidenehex-2-ene (5) and 2,5-dimethyl-4-(1-methyl-1-methoxyethyl)-5-methoxyhexa-2,3-diene (4) and subsequently 2,5-dimethyl-3-isopropenyl-2-methoxyhexa-3,4-diene (6), 2,5-dimethyl-4-isopropenyl-3-methoxyhexa-2,4-diene (7), and 2,5-dimethyl-4-isopropylidenehex-5-en-3-one (8). Treatment of 1 with sodium methoxide produces 2,5-dimethyl-4-isopropylhex-1,4-dien-3-one (16), 2,5-dimethyl-2-methoxy-4-isopropylhex-4-en-3-one (17), and 2-isopropylidene-3,3,4,4-tetramethylcyclobutanone (2). The use of either potassium *tert*-butoxide or lithium diethylamide transforms 1 into a mixture of 1-isopropenyl-2-(1-methyl-1-hydroxyethyl)-3,3-dimethylcyclopropene (19) and 8. Reaction of 19 with sulfuric acid in acetic acid also leads to 8. The mechanistic details of these transformations are discussed.

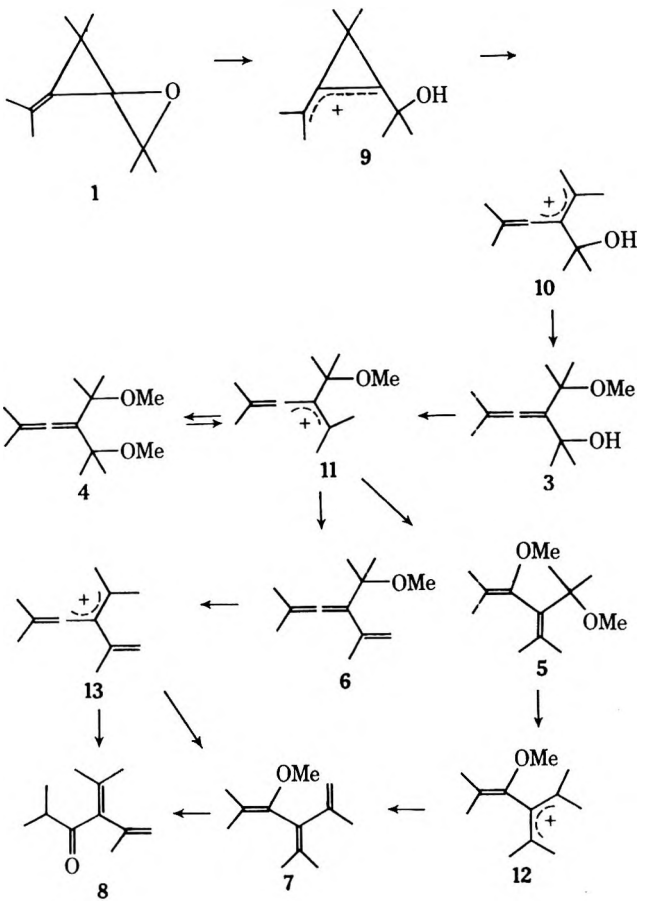
In connection with our interests in highly strained epoxides[2] and in the reactions of epoxides with strong bases,[3] we have further examined the chemistry of oxaspiropentane 1.[4] Experimental complications associated with facile solvolysis reactions of 1 in methanol prompted an examination of these processes prior to study of base-promoted reactions.

Solvolysis of carefully purified 1 in freshly distilled methanol proceeded smoothly to yield two products in a 77:19 ratio which were identified as cyclobutanone 2[4] and allene alcohol 3. Structure 3 follows from its ir (weak 5.1 μ allene absorption) and nmr spectra (three six-proton methyl singlets, a methoxy signal, and a hydroxyl proton at appropriate chemical shifts).

In the presence of added acetic acid up to five additional products could be isolated depending on the exact reaction conditions. These reactions were faster than those performed in the absence of acid and furthermore did not yield cyclobutanone 2. A reaction utilizing 12% acetic acid in methanol could be followed conveniently by glpc analysis. Starting epoxide was transformed extremely rapidly to alcohol 3 which was itself depleted by further reaction. Dimethoxyallene 4 accumulated and then decreased in quantity, whereas the isomeric dimethoxydiene 5 was formed more slowly but continued to increase in amount. Finally, trienes 6 and 7 appeared and increased in quantity as long as the reaction was monitored. Prolonged reaction eventually led to ketone 8 in accord with the earlier work[4] on the isomerization of 1 in acetic acid containing small amounts of sulfuric acid. Alcohol 3 was also converted to 8 by these latter conditions. Reaction of diene 5 with methanol–acetic acid slowly produced triene 7.

The mecahnistic details of these solvolyses are complex in that a variety of processes are occurring concurrently, but a reasonable outline can be constructed as illustrated in Scheme I. Competitive isomerizations of 1 to cyclobutanone 2 and materials with the allene skeleton were observed in our earlier work.[4] At that time acid-catalyzed pathways were suggested for both types of reactions. The predominance of 2 under neutral conditions and its absence in the faster reactions catalyzed by acetic acid suggest that an acid-catalyzed

SCHEME I



mechanism is probably not operative (*vide infra*). However, the acid-catalyzed route to allene alcohol 3 *via* cations 9 and 10 remains attractive, as well as fully consistent with the data. (Direct rearrangement of 1 to 10 is an equally viable alternative.) The isomeric dimethoxy compounds 4 and 5 result from solvolysis of 3 *via* cation 11. The kinetically controlled product is the allene 4, but this material is gradually converted to its isomer 5 and monomethoxyallene 6, presumably through reversible formation of 11. The remaining monomethoxytriene 7 arises from 5 *via* cation 12 and possibly from 6 *via* cation 13. Ketone 8 arises from attack of water on 13 or by multistep hydrolysis of 7. Other possible interconversions can be visualized, but

(1) (a) Supported by a research grant from the National Science Foundation; (b) Alfred P. Sloan Fellow, 1968–1970; (c) NIH Predoctoral Fellow, 1966–1968.

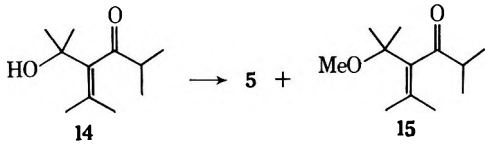
(2) J. K. Crandall and D. R. Paulson, *J. Org. Chem.*, **33**, 3291 (1968).

(3) J. K. Crandall and L. H. C. Lin, *ibid.*, **33**, 2375 (1968).

(4) J. K. Crandall and D. R. Paulson, *ibid.*, **33**, 991 (1968).

these do not change the essential features of the reaction course.

The characteristic spectral properties of the compounds discussed above define the assigned structures and are detailed in the Experimental Section. Noteworthy, however, is the nmr spectrum of **5** which displays eight distinct methyl resonances. This observation demands that the two CCH_3 groups of the $-C(CH_3)_2OMe$ moiety be magnetically nonequivalent. Hindered rotation of this group[5] or about the single bond of the conjugated diene function[6] can account for this result. The large steric perturbation of **5** is also indicated by its rather low wavelength ultraviolet maximum (212 nm).[7] Nonetheless, an alternate preparation of **5** was considered desirable to confirm the assigned structure. This was smoothly accomplished by reacting keto alcohol **14**[2] with triethyl orthoformate in methanol containing a trace of strong acid. A minor product of this reaction was methoxy ketone **15**.



14 15

The reaction of epoxide **1** with sodium methoxide in refluxing methanol led gradually to cyclobutanone **2**, acyclic ketone **16**, and methoxy ketone **17** in a 48:36:8 ratio. The spectroscopic data for **16** define the structural units clearly, hydrogenation leads to the known compound **18**, and alternate structure **8** has already been given to a nonidentical ketone. These data secure the above assignment. Likewise, the spectral data for **17** and its nonidentity with isomer **15** ensure the structure portrayed. Methoxy ketone **17** was found to be stable to the reaction conditions, thereby ruling out its intermediacy in the formation of **16**.

Use of the stronger, more sterically hindered base, potassium *tert*-butoxide, in refluxing benzene resulted in the production of cyclopropenylcarbinol **19** and minor amounts of the ubiquitous ketone **8**. When the basic medium was lithium diethylamide in ether, the same two products were found; however, despite some variance from experiment to experiment, the predominant component was always **8**.

The structural assignment for **19** is derived from its nmr spectrum (two identical pairs of saturated methyl groups, an isopropenyl moiety, and a hydroxyl proton), a cyclopropene band[8] at 5.47 μ in the ir, and a conjugated diene chromophore in the uv. Treatment of **19** with sulfuric acid in acetic acid resulted in facile isomerization to ketone **8**, presumably *via* an initial cyclopropenylcarbinyl–allenylcarbinyl cationic rearrangement.[4,9] One possible pathway is **19** → **9** → **10** → **8**. (An alternate but essentially equivalent series of steps can be envisaged following ionization of the hydroxyl group.) Analogy for this type of rearrangement can be found in the work of Closs and Böll.[9] Of course, the reactions of **1** are proposed to generate the same allylic cation from an alternate source.[4] In the minimum, these results are fully consistent with the intervention of cation **9** in both processes.

It is possible to rationalize the transformations of **1** effected by methoxide in terms of simple nucleophilic displacement to yield cyclopropanol anion **20** and β elimination[10] to related intermediate **21**. Further isomerization of these species to **17** and **16**, respectively, is anticipated from the available information on the chemistry of cyclopropanols.[11] In this light, it is a little puzzling that *tert*-butoxide promotes elimination in an entirely different manner to yield **19**. Reservations may also be expressed with regard to the likelihood of nucleophilic displacement resulting from attack of methoxide at the tertiary epoxide center. Therefore, the consideration of more obscure pathways to these materials may not be altogether without justification. The absence of allene alcohol **3** in basic media supports the proposed scheme for the formation of this material under neutral and acidic conditions.

The isomerization of **1** to cyclobutanone **2** occurs with roughly equal facility in both neutral and strongly basic methanol, but other processes are more effective under acidic conditions. This seems to implicate some type of purely thermal isomerization for the **1** → **2** transformation. In fact, this same conversion has been shown to result from the gas-phase pyrolysis of **1**.[4] However, it must be noted that relatively high temperatures were utilized to effect this thermal reaction, which was considered to take place by a biradical mechanism. It is possible that in solution an alternate process obtains, for example, reaction *via* zwitterion **22**. This species should be generated more readily in polar solvents and, in addition to being a logical precursor of **2**, reaction of **22** with methoxide provides rational alternate pathways to ketones **16** and **17**. On the other hand, it is not easy to see why epoxide **1** would prefer to open in one fashion when protonated (to **9**) but in a rather different way (to **22**) when unassisted by acid. The peculiar response of the transformations of **1** to the reaction medium thus remains incompletely understood. See Scheme II.

The formation of cyclopropene alcohol **19** was unexpected owing to the highly strained nature of this compound, but a 1,4-elimination mechanism is apparent *a posteriori*. The absence of ketone **16** among the products of the reaction of **1** with *tert*-butoxide or diethylamide is conspicuous, particularly since this compound is an important product with methoxide. This ketone was expressly shown to be absent from the product mixture of the lithium diethylamide reaction and, furthermore, it was demonstrated to be stable to these conditions.

The source of ketone **8**, the second product in the strong base isomerizations of **1**, is not certain, but the most likely explanation for this material is that it results from a secondary transformation of **19**, probably in an acid-catalyzed process during work-up. Such a transformation under more acidic conditions is described

(5) J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, Oxford, 1965, pp 559–573; M. L. Martin and G. J. Martin, *Bull. Soc. Chim. Fr.*, 2117 (1966); B. Halpern, J. W. Westley, and B. Weinstein, *Chem. Commun.*, 160 (1967); M. Kajtar and L. Radics, *ibid.*, 784 (1967); P. D. Bartlett and T. T. Tidwell, *J. Amer. Chem. Soc.*, **90**, 4421 (1968).

(6) F. P. Boer, G. A. Doorakian, H. H. Freedman, and S. V. McKinley, *ibid.*, **92**, 1225 (1970).

(7) W. F. Forbes, R. Shilton, and A. Balasubramanian, *J. Org. Chem.*, **29**, 3527 (1964); R. Criegee, U. Zirngibl, H. Furrer, D. Seebach, and G. Freund, *Chem. Ber.*, **97**, 2942 (1964).

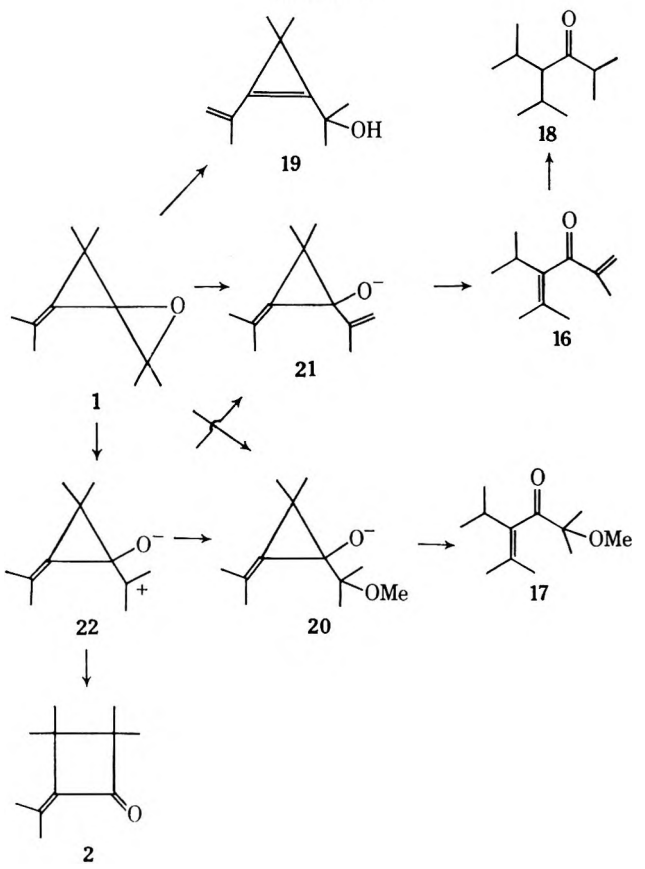
(8) G. L. Closs, L. E. Closs, and W. A. Böll, *J. Amer. Chem. Soc.*, **85**, 3796 (1963).

(9) Unpublished results cited in G. L. Closs, *Advan. Acyclic Chem.*, **1**, 98 (1966).

(10) B. Rickborn and R. P. Thummel, *J. Org. Chem.*, **34**, 3583 (1969).

(11) C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

SCHEME II



above, and support for this contention is found in the variability of the ratio of **19** to **8** in different experiments with lithium diethylamide. It was specifically shown that cyclobutanone **2** was recovered from the reaction conditions without transformation to **8**, thereby ruling out **2** as an intermediate in the formation of **8**. Consequently, the formation of cyclobutanone is not favored by strong, nonnucleophilic bases in aprotic solvents, in accordance with the ideas expressed above concerning the mode of conversion of **1** to **2**.

Experimental Section

General.—Infrared spectra (ir) were obtained with Perkin-Elmer Model 137 and 137G Infracord spectrophotometers. Unless otherwise specified, these were taken in carbon tetrachloride solution. Nuclear magnetic resonance (nmr) spectra were obtained with Varian Associates A-60 and HR-100 spectrometers in carbon tetrachloride solution. Ultraviolet spectra (uv) were recorded on a Cary 14 spectrophotometer. Raman spectra were taken on a Cary 81 spectrophotometer. Mass spectra were obtained with an AEI MS-9 mass spectrometer at 70 eV. Gas chromatography (glpc) was performed on Aerograph Model 600, Model 1200 (analytical, hydrogen flame detector) chromatographs. The analytical column was 10 ft × $^1/_8$ in. of 15% Carbowax 20M on 60–80 Chromosorb W; preparative columns were 10 ft × $^3/_8$ in. of either 30% FFAP or 15% Carbowax 20M on 60–80 Chromosorb W. Percentage composition data were estimated by peak areas (uncorrected). Anhydrous magnesium sulfate was used for all drying operations. Microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind.

Solvolysis of 1 in Methanol.—A solution of 0.22 g of **1** in 50 ml of methanol was refluxed for 18 hr, diluted with 50 ml of water, and extracted with four 25-ml portions of pentane. The combined pentane extracts were washed with 25 ml of saturated sodium chloride solution and dried. Removal of the solvent by flash evaporation gave 0.20 g of crude product. Glpc analysis showed two major products as 19 and 77% of the volatile reaction products. The products were purified by glpc collection.

The minor product was identified as 2,5-dimethyl-3-(1-methyl-1-methoxyethyl)hexa-3,4-dien-2-ol (**3**): ir 2.9, 5.1 (weak), 9.4, and 10.4 μ; nmr τ 8.73 (s, 6), 8.63 (s, 6), 8.30 (s, 6), 6.77 (s, 3, OCH_3), and 5.9 (s, 1, OH).

Anal. Calcd for $C_{12}H_{22}O$: C, 72.68; H, 11.18. Found: C, 72.56; H, 11.08.

The major product was identified as ketone **2** by comparison with an authentic sample.[4]

Solvolysis of 1 in 12% Acetic Acid–Methanol.—To a solution of 7 ml of glacial acetic acid in 60 ml of methanol was added 0.79 g of **1**, and the resulting mixture was refluxed for 56 hr, poured into 100 ml of saturated sodium bicarbonate solution, and extracted with four 50-ml portions of pentane. The pentane extracts were combined and dried. Removal of the pentane by flash evaporation gave 0.83 g of a crude oil. Four compounds were isolated by preparative glpc as 58, 20, 16, and 6% of the volatile reaction mixture.

The major material was identified as 4-isopropylidene-3,5-dimethoxy-2,5-dimethylhex-2-ene (**5**): ir 5.95 (weak), 6.10, 8.35, 8.55, 8.92, 9.28, and 9.72 μ; nmr τ 8.82 (s, 3), 8.75 (s, 3), 8.52 (s, 3), 8.39 (s, 3), 8.35 (s, 3), 8.02 (s, 3), 6.95 (s, 3, OCH_3), and 6.75 (s, 3, OCH_3); uv max (hexane) 212 nm (ϵ 12,700); Raman (CCl_4) 1380, 1445 (very strong), 1635, and 1678 cm^{-1} (strong). The mass spectrum shows a weak molecular ion at m/e 2.12.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.68; H, 11.41.

The second product was ketone **8** as established by glpc isolation and comparison with an authentic sample.

The third product is assigned as 4-isopropenyl-3-methoxy-2,5-dimethylhex-2,4-diene (**7**): ir 3.24, 6.0, 6.14, 8.35, 8.88, and 11.21 μ; nmr τ 8.53 (s, 3), 8.33 (s, broad, 9), 8.18 (m, 3, CH_2=CCH_3), 6.72 (s, 3, OCH_3), 5.31 (m, 1, C=CH_2), and 5.02 (m, 1, C=CH_2). The mass spectrum shows a molecular ion at m/e 180.1518 (calcd for $C_{12}H_{20}$, 180.1514).

The fourth product is assigned as 3-isopropenyl-2,5-dimethyl-2-methoxyhexa-3,4-diene (**6**): ir 5.10 (weak), 6.19, 8.56, 11.1, and 12.6 μ; nmr τ 8.72 (s, 6, $C(CH_3)_2OCH_3$), 8.26 (s, C=C=C-$(CH_3)_2$), 8.25 (m, 3, H_2C=CCH_3), 6.96 (s, 3, OCH_3), 5.10 (m, 1, C=CH_2), and 4.58 (m, 1, C=CH_2). The mass spectrum shows a molecular ion at m/e 180.1513 (calcd for $C_{12}H_{20}O$, 180.1514).

Solvolysis of 1 in 2% Acetic Acid–Methanol.—To a solution of 0.5 ml of glacial acetic acid in 25 ml of methanol was added 50 mg of **1**. The resulting solution was refluxed for 36 hr, poured into 100 ml of saturated sodium bicarbonate solution, and extracted with two 50-ml portions of pentane. The combined pentane extracts were dried. Glpc analysis showed formation of 70% **5** and 30% of a new compound identified as 2,5-dimethyl-4-(1-methyl-1-methoxyethyl)-5-methoxyhexa-2,3-diene (**4**): ir 5.1 (weak, allene), 8.2, 8.6, 8.9, and 9.4 μ (strong); nmr τ 8.74 (s, 12), 8.29 (s, 6, C=C=$C(CH_3)_2$), and 7.0 (s, 6, $(OCH_3)_2$).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.41. Found: C, 73.74; H, 11.28.

Solvolysis of 5 in Acetic Acid–Methanol.—To a 5-ml solution of 12% acetic acid–methanol was added 10 mg of **5**. After 24 hr of reflux, the reaction mixture was poured into 25 ml of water and extracted with four 25-ml portions of pentane. The combined pentane extracts were washed with 25 ml of saturated sodium bicarbonate solution and dried. Glpc analysis of the crude product showed 15% **8**, 18% **7**, and 67% unreacted **5**.

Acid-Catalyzed Rearrangment of 3.—A 15-mg sample of **3** was dissolved in 3 ml of methanol containing 5 mg of *p*-toluenesulfonic acid. The resulting solution was refluxed for 3 hr, cooled to room temperature, neutralized with solid potassium hydroxide, poured into 25 ml of water, and extracted with three 25-ml portions of pentane. The combined pentane extracts were dried and the pentane was removed by flash evaporation to give 12 mg of crude product. Glpc and spectral analysis showed this material to be essentially pure ketone **8**.

2,5-Dimethyl-3,5-dimethoxy-4-isopropylidenehex-2-ene (5).—A solution of 5 ml of methanol, 0.20 g of 14, 0.10 g of trimethyl orthoformate, and 2 mg of *p*-toluenesulfonic acid was stirred at room temperature for 12 hr, poured into 50 ml of water, and extracted with four 50-ml portions of pentane. The combined pentane extracts were dried and the pentane was removed by flash evaporation to give 0.21 g of crude oil. Glpc analysis showed four components as 38, 50, 8, and 4% of the volatile reaction products. The two major components were purified by glpc collection. The major product was shown to be **5**, identical in every respect with that obtained from the acetic acid catalyzed

solvolysis of 1. The minor product is assigned as 2,5-dimethyl-5-methoxy-4-isopropylidenehexan-3-one (15): ir 5.91, 6.10, 7.95, 8.55, 9.35 (strong), and 10.5 μ; nmr τ 8.93 (d, 6, J = 7 Hz), 8.71 (s, 6), 8.42 (s, 3), 8.12 (s, 3), 7.38 (septet, 1, J = 7 Hz), and 6.94 (s, 3).

Rearrangement of 1 with Sodium Methoxide.—To a solution of 1.9 g of metallic sodium in 50 ml of anhydrous methanol was added dropwise a solution of 0.50 g of 1 in 5 ml of methanol. After heating to reflux for 18 hr, the mixture was poured into 100 ml of water and extracted with four 25-ml portions of pentane. The combined pentane extracts were washed with saturated sodium chloride solution and dried. Removal of the solvent by flash evaporation gave 0.38 g of crude oil. Glpc analysis showed three major products as 36, 48, and 8% of the volatile reaction product. No other product amounted to more than 1%. The products were purified by glpc.

The first component (36%) was identified as 2,5-dimethyl-4-isopropyl-1,4-hexadien-3-one (16): ir (neat) 6.02, 6.14, and 10.69 μ; nmr τ 9.03 (d, 6, J = Hz, $CH(CH_3)_2$, 8.51 (s, 3), 8.26 (s, 3), 8.15 (m, 3, $H_2C{=}CCH_3$), 7.92 (septet, 1, $CH(CH_3)_2$), and 4.2 (m, 2, $C{=}CH_2$); uv max (hexane) 215 nm (ε 2050) and 255 (190). The mass spectrum of 16 shows a molecular ion at *m/e* 166.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.43; H, 10.76.

The second product was identified as 2-isopropylidene-3,3,4,4-tetramethylcyclobutanone (2) by comparison with an authentic sample.[4]

The third product was identified as 2,5-dimethyl-4-isopropyl-2-methoxyhex-4-en-3-one (17): ir 5.94, 6.09, 8.35, 8.65, and 9.35 μ; nmr τ 8.71 (s, 6, $C(CH_2)_2$), 8.48 (s, 3), 8.29 (s, 3), 7.35 (septet, 1, J = 7.0 Hz, $CH(CH_3)_2$), 9.05 (d, 6, J = 7.0 Hz, $CH(CH_3)_2$), and 6.78 (s, 3, OCH_3). The mass spectrum of 17 shows a molecular ion at *m/e* 198.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.72; H, 11.07.

Rearrangement of 1 with *tert*-Butoxide in Benzene.—To a mixture of 1.2 g of potassium *tert*-butoxide and 70 ml of benzene was added a solution of 0.58 g of 1 in 10 ml of benzene. After heating to reflux for 6 hr, the mixture was shaken with 100 ml of water, the layers were separated, and the aqueous layer was extracted with 50 ml of benzene. The benzene layers were combined and dried. Removal of the solvent by flash evaporation gave 0.53 g of crude product. Glpc collection gave three compounds as 7, 10, and 83% of the volatile reaction product.

The first compounds was identified as starting material 1; the second compound was shown to be ketone 8. The major product was a new compound assigned as 1-isopropenyl-2-(1-methyl-1-hydroxyethyl)-3,3-dimethylcyclopropene (19): ir 2.71, 2.82, 3.20, 5.47, 6.20, and 11.20 μ; nmr τ 8.78 (s, 6, $C(CH_3)_2$), 8.60 (s, 6, $C(CH_3)_2OH$), 8.06 (m, 3, $H_2C{=}CCH_3$), 7.06 (s, 1, OH), 4.91 (m, 2, $C{=}CH_2$); uv max (hexane) 242 nm (ε 4475). The mass spectrum of 19 shows a molecular ion at 166.1358 (calcd for $C_{11}H_{18}O$, 166.1358). Similar results were obtained when *tert*-butyl alcohol was used as solvent in place of benzene.

Rearrangement of 1 with Lithium Diethylamide.—To a predried flask were added 50 ml of anhydrous ether, 0.16 g of anhydrous diethylamine, and 1.5 ml of 1.6 *N* *n*-butyllithium solution in hexane. The resulting solution was stirred for 30 min under a nitrogen atmosphere, 0.25 g of 1 in 5 ml of ether was added dropwise, and the resulting solution was refluxed for 18 hr. The reaction mixture was poured into 100 ml of water, the layers were separated, and the aqueous layer was washed with 25 ml of ether. The combined ethereal solutions were dried and the ether was removed by flash evaporation to give 0.22 g of crude product. Glpc analysis showed three major components as 11, 57, and 28% of the reaction product. Glpc collection and comparison with known samples showed these to be unreacted epoxide 1, ketone 8, and cyclopropenol 19, respectively. This reaction was repeated under identical conditions on several occasions with varying percentages of 8 (57–90%) and 19 (39–10%) observed.

A second reaction was followed closely by removing aliquots and analyzing by glpc. All of the 1 was gone after 2 hr when the ratio of 8:19 was 59:41. Subsequent work-up gave a 75:25 ratio of these same two materials in good yield.

Acid-Catalyzed Rearrangement of 19.—To an 87-mg sample of 19, in 75 ml of glacial acetic acid, was added 9 drops of concentrated sulfuric acid, and the resulting mixture was stirred for 4 hr, poured into 200 ml of water, and extracted with five 25-ml portions of pentane. The pentane extracts were washed with two 25-ml portions of saturated sodium bicarbonate solution and dried. The solvent was removed by flash evaporation to give 82 mg of crude product. Two products were isolated by preparative glpc as 66 and 34% of the volatile reaction product. The major material was shown to be ketone 18, and the minor product was the enol acetate of ketone 8 as established by glpc isolation and comparison with authentic materials.[4]

Hydrogenation of 16.—A solution of 50 mg of 16 in 24 ml of methanol was hydrogenated at atmospheric pressure using 30% palladium on charcoal as catalyst. After the uptake of 2 mol of hydrogen, the resulting mixture was filtered to remove the catalyst and the filtrate was poured into 100 ml of water and extracted several times with 25-ml portions of pentane. The pentane extracts were combined and dried. After removal of the solvent, a single product was isolated in almost quantitative yield. Ketone 18 was shown to be 2,5-dimethyl-4-isopropylhex-3-one by comparison with an authentic sample.[4]

Registry No.—**1**, 15448-69-8; **3**, 28054-75-3; **4**, 28054-76-4; **5**, 28054-77-5; **6**, 28054-78-6; **7**, 28054-79-7; **15**, 28054-80-0; **16**, 28054-81-1; **17**, 28054-82-2; **19**, 28054-83-3.

Reductive Elimination of Epoxides to Olefins with Zinc–Copper Couple

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A new direct and single-step reductive elimination of epoxides to olefins by treatment with zinc–copper couple in ethanol is described. The scope and stereochemistry of the reaction have been studied with epoxides of sesquiterpenes, steroids, styrene, stilbenes, and octenes. The reaction has been compared with reductive elimination of epoxides with the Cr^{II}–ethylenediamine complex.

In the course of structural studies of sesquiterpene lactones from *Eupatorium rotundifolium*,[1] an attempt was made to dehydrochlorinate eupachloroxin (1) to eupatundin (2) with zinc–copper couple in boiling ethanol.[2] The desired product was not obtained, but treatment for 3 days resulted primarily in reductive elimination of the 3,4 epoxide to yield eupachlorin (3) as the principal isolable product. Treatment for 4 days resulted in reductive elimination of the epoxide *and* dehydrochlorination to give deoxyeuparotin (4) in 31% yield.

(1) S. M. Kupchan, J. E. Kelsey, M. Maruyama, and J. M. Cassady, *Tetrahedron Lett.*, 3517 (1968); S. M. Kupchan, J. E. Kelsey, M. Maruyama, J. M. Cassady, J. C. Hemingway, and J. R. Knox, *J. Org. Chem.*, **34**, 3876 (1969).

(2) J. Elks, G. H. Phillipps, T. Walker, and L. J. Wyman, *J. Chem. Soc.*, 3440 (1956).

TABLE I

REDUCTIVE ELIMINATION OF SESQUITERPENE, STEROID, STYRENE, AND STILBENE OXIDES

Starting material	Reaction time	Product isolated (% yield)
Eupachloroxin (1)	3 days	Eupachlorin (3, 28)
1	4 days	Deoxyeuparotin (4, 31)
Euparotin (5)	3 days	4 (75)
Euparotin acetate (6)	3 days	Deoxyeuparotin acetate (7, 20) + 4 (25)
Eupatundin (2)	5 days	4 (9) + 2 (recovery, 8)
Eupatoroxin (8)	5 days	4 (15) + 2 (27)
10-*epi*-Eupatoroxin (9)	5 days	4 (10) + 2 (10)
Elephantopin (10)	3 days	Deoxydihydroelephantopin (11, 63)
2β,3β-Oxido-22a-5α-spirostan-12-one (12)	10 hr	22a-5α-Spirost-2-en-12-one (13, 88)
16α,17α-Oxido-3α-acetoxy-16β-methyl-5β-pregnane-11,12-dione (14)	2 days	3α-Acetoxy-16-methyl-5β-pregn-16-ene-11,12-dione (15, 75)
Cholesterol α-oxide (16)	3 days	Cholesterol (17, 68)
3α-Acetoxy-11β,12β-oxido-5β-pregnan-20-one (18)	8 days	3α-Acetoxy-11β,12β-oxido-5β-pregnan-20-ol (19, 58) + starting material (18, 9)
Styrene oxide	4 hr	Styrene (90) + ethylbenzene (≤)
Styrene oxide	6 hr	Styrene (47) + ethylbenzene (≤7)
cis-Stilbene oxide	6 hr	*cis*-Stilbene (13) + *trans*-stilbene (80)
trans-Stilbene oxide	6 hr	*trans*-Stilbene (95)

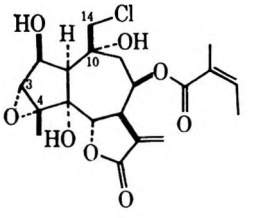
Zinc–copper couple is widely used as a reagent for abstraction of halogen atoms,[3] but our results appear to be the first reported one-step reductive eliminations with zinc–copper couple of an epoxide and a chlorohydrin to yield the corresponding olefins.

To explore the scope of the reductive elimination of epoxides, several other sesquiterpene lactone epoxides[1,4] and steroid epoxides[5] were treated in the same manner. In general, a mixture of the epoxide, zinc–copper couple, and ethanol was heated under reflux for several days. The results are summarized in Table I.

Reductive elimination of the C-3,4 epoxide in eupachloroxin (1) proceeded more rapidly than the dehydrochlorination at C-10,14. However, diepoxides 8 and 9 yielded deoxyeuparotin (4) and eupatundin (2), in which the epoxide at C-3,4 remained intact. The less sterically hindered epoxide at C-10,14 of the sesquiterpenes thus appears to be more reactive than the epoxide at C-3,4. In the case of the steroid derivatives, the epoxide at C-2,3 was most reactive and that at C-11,12, which is sterically hindered, was not reduced. Apparently, styrene oxide was first reduced to styrene and saturation of the terminal double bond followed to give ethylbenzene as a final product. Saturation of the terminal double bond was also observed in the case of elephantopin.

Cis–trans isomerization was not observed when *cis*- or *trans*-stilbene was treated with zinc–copper couple under the same reaction conditions. To explore further the stereochemistry of the reaction, several octene oxides[6] were reduced (Table II). In a typical experiment, a mixture of 2-*cis*-octene oxide, zinc–copper couple, and ethanol was heated in a sealed tube at 140° for 2 days.

The product from 1-octene oxide was *n*-octane, presumably formed *via* epoxide elimination and saturation of the terminal double bond, as observed earlier. Accordingly, zinc–copper treatment of 1-octene yielded *n*-octane in 12% yield. In contrast to the stilbene oxides, reductive elimination of octene epoxides gave mixtures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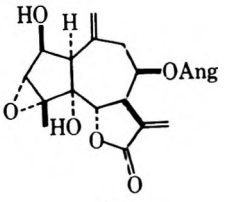
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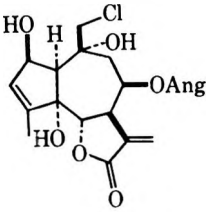
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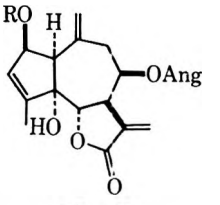
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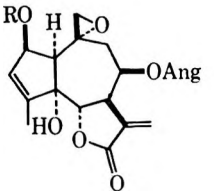
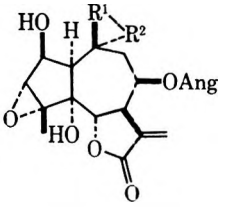
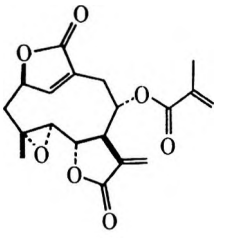
7, R = Ac


5, R = H
6, R = Ac


8, $R^1 = CH_2$; $R^2 = O$
9, $R^1 = O$; $R^2 = CH_2$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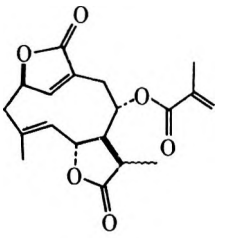
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(3) C. R. Noller, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 184; T. F. Corbin, R. C. Halm, and H. Shechter, *Org. Syn.*, **44**, 30 (1964).

(4) S. M. Kupchan, J. C. Hemingway, J. M. Cassady, J. R. Knox, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **89**, 467 (1967); S. M. Kupchan, Y. Aynehchi, J. M. Cassady, A. T. McPhail, G. A. Sim, H. K. Schnoes, and A. L. Burlingame, *ibid.*, **88**, 3674 (1966).

(5) The authors acknowledge with thanks the generosity of Dr. D. Taub, Merck & Co. Inc., in supplying samples of steroid oxides.

(6) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).

TABLE II
REDUCTIVE ELIMINATION OF OCTENE OXIDES

Starting material	Total yield, %	Product (ratio)
1-Octene oxide	25	*n*-Octane
2-*cis*-Octene oxide	8	4-*cis*-Octene (67) + 2-*trans*-octene (33)
2-*trans*-Octene oxide	13	2-*cis*-Octene (39) + 2-*trans*-octene (61)
3-*cis*-Octene oxide	8	3-*cis*-Octene (54) + 3-*trans*-octene (46)
3-*trans*-Octene oxide	33	3-*cis*-Octene (18) + 3-*trans*-octene (82)
4-*cis*-Octene oxide	16	4-*cis*-Octene (55) + 4-*trans*-oetene (45)
4-*trans*-Octene oxide	82	4-*cis*-Octene (11) + 4-*trans*-octene (89)

stilbene oxides proceeded rapidly at room temperature, reduction of the epoxides of the octenes and of cholesterol proceeded very slowly under the conditions described earlier.[7] The latter compounds were reduced most effectively at 90° in 4.5–5 hr.

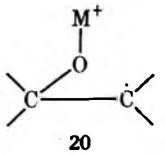
No cis–trans isomerization or saturation of double bonds in olefins with Cr^{II}(en) complex was observed. Both *cis*- and *trans*-stilbene oxides gave mixtures of *cis*- and *trans*-stilbenes in which the trans isomer predominated. The products from *cis*- and *trans*-octene oxides were mixtures of *cis*- and *trans*-octenes, and there appeared to be no stereoselectivity in this reaction. In contrast, limited stereoselectivity *was* observed in the zinc–copper couple reductive eliminations of *cis*- and *trans*-octene oxides.[8]

TABLE III
RESULTS OF Cr^{II}(en) REDUCTION

Starting material	Conditions	Product	Yield, %	Isomer ratio Cis	Isomer ratio Trans
cis-Stilbene oxide	Room temp, 20 hr	*cis*- and *trans*-stilbenes	80	10	90
trans-Stilbene oxide	Room temp, 20 hr	*cis*- and *trans*-stilbenes	96	7	93
1-Octene oxide	90°, 4.5 hr	1-Octene	49		
2-*cis*-Octene oxide	90°, 4.5 hr	2-*cis*- and -*trans*-octenes	46	62	38
2-*trans*-Octene oxide	90°, 4.5 hr	2-*cis*- and -*trans*-octenes	56	57	43
3-*cis*-Octene oxide	90°, 4.5 hr	3-*cis*- and -*trans*-octenes	43	55	45
3-*trans*-Octene oxide	90°, 4.5 hr	3-*cis*- and -*trans*-octenes	54	52	48
4-*cis*-Octene oxide	90°, 4.5 hr	4-*cis*- and -*trans*-octenes	42	53	47
4-*trans*-Octene oxide	90°, 4.5 hr	4-*cis*- and -*trans*-octenes	52	53	47
Cholesterol α-oxide	90°, 5 hr	Cholesterol	39		

of *cis*- and *trans*-octenes. *cis*-Octenes predominated among the products from *cis*-epoxides and *trans*-octenes predominated from *trans*-epoxides. When *cis*-2-octene was treated under the same conditions, the product, in quantitative yield, was a mixture of 7% of *n*-octane, 80% of 2-*cis*-octene, and 13% of 2-*trans*-octene. 2-*trans*-Octene gave a mixture of 3% of *n*-octane, 7% of 2-*cis*-octene, and 90% of 2-*trans*-octene, in quantitative yield. Some cis–trans isomerization of olefins appears to occur under the reaction conditions.

The zinc–copper couple reductive elimination reaction is presumed to proceed *via* C–O bond cleavage to a radical like **20**. The observed limited stereoselectivity



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in the reduction of octene oxides suggests that the rate of C–C bond rotation in the intermediate may be comparable to the rate of formation of the olefin.

While this work was in progress, the reductive elimination of three epoxides to olefins with Cr^{II}–ethylenediamine complex [Cr^{II}(en)] was reported.[7] To compare this reaction with zinc–copper couple reductive elimination, the reduction of epoxides of stilbenes, octenes, and cholesterol with Cr^{II}(en) complex was carried out (Table III). Whereas reduction of the

(7) J. K. Kochi, D. M. Singleton, and L. J. Andrews, *Tetrahedron*, **24**, 3503 (1968).

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Values of $[\alpha]_D$ were determined on a Zeiss-Winkel polarimeter and have been approximated to the nearest degree. Ultraviolet absorption spectra were determined on a Coleman Hitachi EPS-3T recording spectrophotometer. Infrared absorption spectra were determined on a Beckman Model 9 recording spectrophotometer. Nmr spectra were determined on Varian A-60 spectrometer. Vapor phase chromatography was carried out on F & M Model 770, 700, and Varian Aerograph Model 1860-1 gas chromatographs. Thin layer chromatography (tlc) was carried out on precoated silica gel and precoated alumina (Brinkmann) plates. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Petroleum ether refers to the fraction of bp 35–40°. Silica gel refers to silica gel, Merck, 0.05–0.2 mm for column chromatography. Previously known products showed melting points within 2° of the reported values and were identified by mixture melting point, mixture tlc, and ir and nmr spectral comparison with authentic material.

Zinc–Copper Couple Reduction of Eupachloroxin (1). A.—A mixture of eupachloroxin (1, 20 mg), zinc–copper couple prepared from zinc dust (800 mg), and ethanol (8 ml) was heated under reflux for 3 days. The precipitate was filtered off and the solution was evaporated *in vacuo* to give an oil, which was chromatographed on a silica gel (20 g) column. Elution with chloroform, acetone, and ethanol (85:15:1 vol) gave a crystalline fraction (11 mg). Rechromatography on silica gel (15 g) gave crystals (6 mg), which were recrystallized from methanol to give pure eupachlorin (**3**, 4 mg, 28%).

B.—Eupachloroxin (1, 80 mg) was reduced in the same way for 4 days. The product was separated by tlc on silica gel ($CHCl_3$–EtOH 19:1) to give crystals[9] (21 mg, 31%) which were re-

(8) After completion of this work, reductive elimination of epoxides to olefins with magnesium bromide and magnesium amalgam was reported: F. Bertini, P. Grasselli, G. Zubiani, and G. Cainelli, *Chem. Commun.*, 144 (1970).

(9) The homogeneity of crystalline products for which yields are cited was shown to be higher than 90% by nmr spectroscopy.

crystallized from acetone to yield deoxyeuparotin (4), identical with the product from euparotin (5).

Zinc–Copper Couple Reduction of Euparotin (5).—Euparotin (5, 44 mg) was reduced in the same way for 3 days. The product was chromatographed on silica gel (30 g) and elution with chloroform, acetone, and ethanol (85:15:1 vol) gave crystals (32 mg, 75%). Recrystallization from acetone gave deoxyeuparotin (4): mp 200–204°; $[\alpha]^{26}D$ −138.8° (*c* 0.36, MeOH); uv end (MeOH) 210 mμ (ε 18,600); ir (KBr) 5.88 and 5.66 μ.

Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.77; H, 6.92.

Zinc–Copper Couple Reduction of Euparotin Acetate (6).—Euparotin acetate (6, 100 mg) was reduced in the same way for 3 days. The product was separated by tlc on silica gel to give high R_f noncrystalline material (25 mg, 25%) and low R_f crystals (18 mg, 20%). The high R_f amorphous material was a homogeneous solid (tlc) and the ir spectrum was identical with that of deoxyeuparotin acetate [Calcd for $C_{22}H_{26}O_7$: mol wt, 446. Found: mol wt (mass spectrum), 446] prepared by acetylation of deoxyeuparotin (4) with acetic anhydride in pyridine. The low R_f crystals were recrystallized from aqueous acetone to give deoxyeuparotin (4, 8 mg).

Zinc–Copper Couple Reduction of Eupatundin (2).—Eupatundin (2, 100 mg) was reduced in the same way for 5 days. The product was separated by tlc on alumina to give high R_f crystals (9 mg, 9%) and low R_f crystals (8 mg, 8%). Recrystallization of the high R_f material from aqueous acetone gave deoxyeuparotin (4, 2 mg). Recrystallization of the low R_f product from a mixture of chloroform, benzene, and petroleum ether gave eupatundin (2, 2 mg).

Zinc–Copper Couple Reduction of Eupatoroxin (8).—Eupatoroxin (8, 100 mg) was reduced in the same way for 5 days. The product was separated by tlc on alumina to give high R_f crystals (14 mg, 15%) and low R_f crystals (26 mg, 27%). Recrystallization of the high R_f product from acetone gave deoxyeuparotin (4, 4 mg). Recrystallization of the low R_f product from a mixture of chloroform, benzene, and petroleum ether gave eupatundin (2, 13 mg).

Zinc–Copper Couple Reduction of 10-Epi-eupatoroxin (9).—10-Epi-eupatoroxin (9, 100 mg) was reduced in the same way for 5 days. The product was separated by tlc on alumina to give high R_f crystals (10 mg, 10%) and low R_f crystals (10 mg, 10%). Recrystallization of the high R_f product from aqueous acetone gave deoxyeuparotin (4, 2 mg). Recrystallization of the low R_f product from a mixture of chloroform, benzene, and petroleum ether gave eupatundin (2, 2 mg).

Zinc–Copper Couple Reduction of Elephantopin (10).—A mixture of elephantopin (10, 300 mg), zinc–copper couple prepared from zinc dust (12 g), and ethanol (150 ml) was heated under reflux for 3 days. The product (280 mg) was chromatographed on acid-washed alumina (100 g, Merck) with alcohol-free chloroform to give homogeneous (tlc, 220 mg) material. Recrystallization from ethanol gave colorless needles of deoxydihydroelephantopin (11, 180 mg, 63%): mp 212–216° dec; $[\alpha]^{22}D$ +13.8° (*c* 1.2, acetone); uv end (MeOH) 210 mμ (ε 17,600); ir (KBr) 5.57, 5.73, 5.82, and 5.84 μ.

Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.43; mol wt, 346. Found: C, 65.89; H, 5.88; mol wt (mass spectrum), 346.

Zinc–Copper Couple Reduction of 2β,3β-Oxido-22a-5α-spirostan-12-one[10] (12).—2β,3β-Oxido-22a-5α-spirostan-12-one (12, 95 mg) was reduced in the same way for 10 hr. The product (90 mg) was chromatographed on silica gel (30 g) with chloroform containing 1% acetone to give crystals (88 mg, 88%). Recrystallization from ethanol gave 22a-5α-spirost-2-en-12-one[10] (13).

Zinc–Copper Couple Reduction of 16α,17α-Oxido-3α-acetoxy-16β-methyl-5β-pregnane-11,12-dione[11] (14).—16α,17α-Oxido-3α-acetoxy-16β-methyl-5β-pregnane-11,12-dione (14, 100 mg) was reduced in the same way for 2 days. The product was chromatographed on silica gel (50 g) with chloroform, acetone, and ethanol (98:2:0.5 vol) to give crystals (72 mg, 75%). Recrystallization from ethanol gave 3α-acetoxy-16-methyl-5β-pregn-16-ene-11,12-dione (15, 33 mg): mp 167–168.5°; $[\alpha]^{26}D$ +69.5° (*c* 1.90, $CHCl_3$); ir (KBr) 5.75, 5.88, 6.06 μ.

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87; mol wt, 386. Found: C, 74.53; H, 8.96; mol wt (mass spectrum), 386.

Zinc–Copper Couple Reduction of Cholesterol α-Oxide (16).—Cholesterol α-oxide (16, 200 mg) was reduced in the same way for 3 days. The product was purified by tlc on silica gel to give crystals (125 mg, 68%). Recrystallization from ethanol gave cholesterol (17, 100 mg).

Zinc–Copper Couple Reduction of 3α-Acetoxy-11β,12β-oxido-5β-pregnan-20-one[12] (18).—3α-Acetoxy-11β,12β-oxido-5β-pregnan-20-one (18, 100 mg) was reduced in the same way for 8 days. The product was chromatographed on silica gel to give starting material (9 mg, 9%) and product (60 mg, 58%), which was recrystallized from petroleum ether to give 3α-acetoxy-11β,12β-oxido-5β-pregnan-20-ol (19, 18 mg): mp 149–151°; $[\alpha]^{26}D$ +14.5° (*c* 1.35, $CHCl_3$); ir (KBr) 2.86, 5.84 μ.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; mol wt, 376. Found: C, 73.79; H, 9.53; mol wt (mass spectrum), 376.

Zinc–Copper Couple Reduction of Styrene Oxide. A.—A mixture of styrene oxide (500 mg), zinc–copper couple prepared from zinc dust (8 g), and ethanol (50 ml) was heated under reflux for 4 hr. The precipitate was filtered off, water (20 ml) was added, and the solution was extracted with petroleum ether (15 ml, three times). The combined petroleum ether extract was washed with $CaCl_2$ solution and NaCl solution, and dried (Na_2SO_4). The solution was distilled through a Vigreux column to yield a mixture of styrene (388 mg, 90%) and ethylbenzene (17 mg, 4%). The products were analyzed by vpc with an SE-30 column at 64°.

B.—The reaction was carried out for 6 hr in the same way to give a mixture of styrene (203 mg, 47%) and ethylbenzene (212 mg, 47%).

Zinc–Copper Couple Reduction of Octene Oxides or Octene.—A mixture of octene oxide (1 g, or octene, 1 g), zinc–copper couple prepared from zinc dust (6 g), and ethanol (20 ml) was heated in a sealed tube at 140° for 2 days. After the precipitate was filtered off, the solution was diluted with water (20 ml) and extracted with petroleum ether (15 ml, three times). The combined petroleum ether extract was washed with $CaCl_2$ solution and NaCl solution, dried (Na_2SO_4), and distilled through a Vigreux column. No octene was detected in the distillate. The residue was analyzed by vpc by comparison with standard mixtures of the products with an SE-30 column to determine yield and a β,β-oxydipropionitrile column to determine the ratio of cis and trans isomers.

Zinc–Copper Couple Reduction of Stilbene Oxides.—A mixture of stilbene oxide (196 mg), zinc–copper couple prepared from zinc dust (4 g), and ethanol (50 ml) was heated under reflux for 6 hr. After the precipitate was filtered off, the solution was evaporated to dryness *in vacuo*. The ratio of *cis*- and *trans*-stilbenes in the product was determined by nmr spectroscopy.

Preparation of Cr^{II} Solution.—Chromium pellets (8 g) were treated with concentrated HCl (10 ml) until the reaction began. The pellets were washed well with water and added to water (60 ml) covered with purified nitrogen. Perchloric acid (60%, 30 ml) was added and the mixture was allowed to stand at room temperature under an atmosphere of purified nitrogen. The reagent was ready for use after 2 days.

Cr^{II}(en) Reduction of Stilbene Oxides.—To a mixture of stilbene oxide (100 mg) and dimethylformamide (30 ml) under purified nitrogen, Cr^{II} solution (3 ml) and ethylenediamine (0.1 ml) were added, and the solution was allowed to stand for 20 hr at room temperature. The solution was poured into 2 *N* HCl (20 ml) and the solution was extracted with petroleum ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a mixture of stilbenes. The ratio of cis and trans isomers in the product was determined by nmr spectroscopy.

Cr^{II}(en) Reduction of Octene Oxide.—To a mixture of dimethylformamide (30 ml) and octene oxide (100 mg) under purified nitrogen, Cr^{II} solution (3 ml) and ethylenediamine (0.15 ml) were added and the solution was heated at 90° for 4.5 hr. The solution was poured into 2 *N* HCl (20 ml) and separated into two equal portions. One was extracted with petroleum ether (2 ml) after addition of *n*-nonane (50 mg) as a standard, and the petroleum ether extract was analyzed by vpc with an SE-30 column to determine the yield of octenes. The other portion of the aqueous solution was extracted with petroleum ether (2 ml) and analyzed by vpc with a β,β-oxydipropionitrile column to determine the ratio of cis and trans isomers.

(10) H. L. Slates and N. L. Wendler, *J. Amer. Chem. Soc.*, **78**, 3749 (1956).

(11) D. Taub, N. L. Wendler, and R. D. Hoffsommer, Jr., U. S. Patent 3,309,272 (1967); *Chem. Abstr.*, **67**, 3196n (1967).

(12) P. L. Julian, and A. Magnani, U. S. Patent 2,944,052 (1960); *Chem. Abstr.*, **55**, 1710e (1961).

Cr^{II}(en) Reduction of Cholesterol α-Oxide.—To a solution of cholesterol α-oxide (100 mg) in dimethylformamide (30 ml) under purified nitrogen, Cr^{II} solution (3 ml) and ethylenediamine (0.15 ml) were added. The solution was kept at 90° for 5 hr and then poured into 2 *N* HCl (20 ml). The aqueous solution was extracted with ether (20 ml, three times) and the combined ether extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to dryness. The crystalline residue was chromatographed on silica gel with a mixture of chloroform, acetone, and ethanol (96:4:1, vol) to give 37 mg (39%) of crystals. Recrystallization of the product from ethanol gave cholesterol (23 mg).

Registry No.—**1**, 20071-52-7; **2**, 20071-53-8; **4**, 28180-56-5; **5**, 10191-01-2; **6**, 10215-89-1; **8**, 20071-51-6; **9**, 20071-54-9; **10**, 13017-11-3; **11**, 28180-62-3; **12**, 28180-63-4; **14**, 28291-99-8; **15**, 28180-64-5; **16**, 20230-31-3; **18**, 28312-59-6; **19**, 28180-66-7; styrene oxide, 96-09-3; *cis*-stilbene oxide, 1689-71-0; *trans*-stilbene oxide, 1439-07-2; 1-octene oxide, 2984-50-1; 2-*cis*-octene oxide, 23024-54-6; 2-*trans*-octene oxide, 28180-70-3; 3-*cis*-octene oxide, 28180-71-4; 3-*trans*-octene oxide, 28180-72-5; 4-*cis*-octene oxide, 1439-06-1; 4-*trans*-octene oxide, 1689-70-9.

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The Acetylation of Cyclononene

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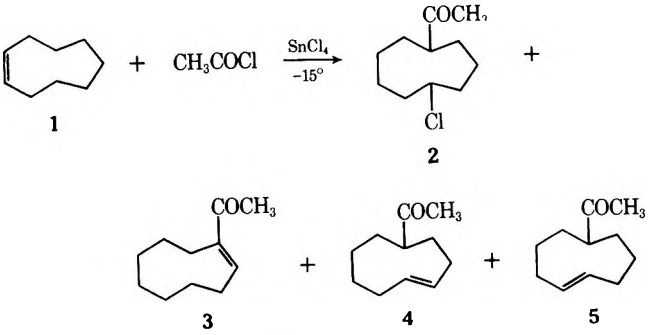
The acetylation of *cis*-cyclononene with acetyl chloride in the presence of stannic chloride yields 50–60% of 1-acetyl-5-chlorocyclononane and ~20% of 4- and 5-acetylcyclononenes, the products of 1,5-transannular hydride transfer. Use of acetic anhydride-trifluoroacetic acid gave similar results. Acetylation in the presence of active aluminum chloride led to ring contraction, with six- and seven-membered ring compounds being formed. The major (35%) product was shown to be a chloro derivative of 1-acetyl-4-isopropylcyclohexane. The other products are chlorine-bearing derivatives of 4-ethyl-1-acetylcycloheptane and, possibly, 4- or 5-methyl-1-acetylcyclooctane.

The Lewis acid catalyzed acylation of cyclic olefins and polyolefins containing seven- and eight-membered rings, including cycloheptene,[2] cycloheptatriene,[3] cyclooctene,[4,5] and 1,3- and 1,5-cyclooctadiene,[6] has been the subject of considerable recent investigation. Transannular hydride transfers were frequently observed as well as ring contraction and ring-bridging reactions. Thus, acetylation of cyclooctene in the presence of stannic chloride or added deactivated aluminum chloride gave predominantly 1-acetyl-4-chlorocyclooctane, the product of a sequence of steps which includes a 1,5-transannular hydride transfer.[5,6] When fresh, active aluminum chloride was employed, the acetylation gave a mixture of 1-acetyl-4-chloro-4-ethylcyclohexane and 1-acetyl-4-methylcycloheptane, products of ring-contraction reactions. Since of the medium rings, the nine-membered ring appears to possess the most severe transannular interactions,[7] it was considered worthwhile to extend our previous investigations to nine-membered ring olefins. We present herewith the results of our studies on the acetylation of *cis*-cyclononene.

Results

Our initial experiments were of acetylations employing acetyl chloride in the presence of stannic chloride, performed in methylene chloride as solvent. This system might, by analogy with cyclooctene, favor the formation of products resulting from transannular hydride transfer, with ring-contraction and bridging reactions being avoided. In fact, acetylation of *cis*-cyclononene (**1**) in the presence of stannic chloride in methylene chloride at −15° gave as the major product 1-acetyl-5-chlorocyclononane (**2**, 42–55%) and a mixture of 1-, 4-, and 5-acetylcyclononene (**3**, **4**, and **5**, 20–25%). The yields were erratic and depend particularly on the purity of the catalyst. Larger amounts of the unsaturated ketones **3** and **4** were obtained when stannic chloride from a freshly opened bottle was used. The structures of **2**, **3**, **4**, and **5** were assigned initially on the bases of analytical and spectral data. The mass spectrum of chloro ketone **2** showed molecular ion peaks at *m/e* 202 and 204; its infrared spectrum displayed bands for a

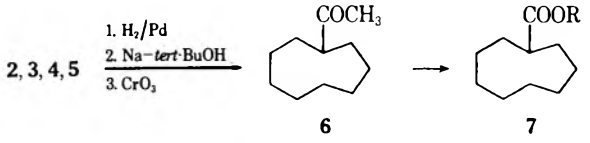


saturated ketone function at 1709 cm^{-1}. The nmr spectrum of **2** exhibited, *inter alia*, a one-hydrogen multiplet at τ 5.83 attributable to the hydrogen on the chlorine-bearing carbon (C-5) and an acetyl methyl singlet at τ 7.85; no signals in the τ 8.6–9.2 region which might be attributable to *C*-methyl groups were present. The lower boiling fraction from the acetylation of **1** showed two partially resolved peaks on several gas chromatography columns. The infrared spectrum

(1) NDEA Fellow, 1965–1968.
(2) (a) N. Jones, H. T. Taylor, and E. Rudd, *J. Chem. Soc.*, 1342 (1961); (b) L. Rand and R. J. Dolinski, *J. Org. Chem.*, **31**, 3063 (1966).
(3) J. A. Blair and C. J. Tate, *Chem. Commun.*, 1506 (1969).
(4) T. S. Cantrell, *J. Org. Chem.*, **32**, 1669 (1967).
(5) J. K. Groves and N. Jones, *J. Chem. Soc. C*, 1718 (1969).
(6) T. S. Cantrell and B. L. Strasser, *J. Org. Chem.*, **36**, 670 (1971).
(7) V. Prelog, "Perspectives in Organic Chemistry," A. R. Todd, Ed., Wiley–Interscience, New York, N. Y., 1956.

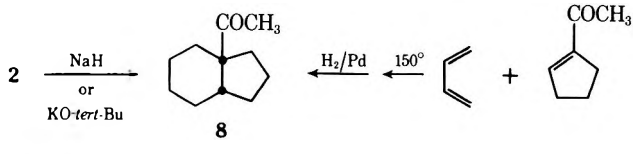
of the mixture displayed carbonyl stretching bands at 1662 and 1708 cm^{-1}; the nmr spectrum of the mixture showed vinyl hydrogen signals at τ 3.11 (hydrogen β to carbonyl) and 4.3 (unconjugated vinyl) and singlets indicative of conjugated and nonconjugated acetyl groups at τ 7.71 and 7.90. The intensities of the infrared bands suggest a **3**:**4** + **5** ratio of 55:45. The products exhibiting the 1708-cm^{-1} band are assigned structures **4** and **5** by analogy, since they are the result of pathways involving a 1,5 hydride transfer, shown to be important in acylations of cyclooctene.[5,6] In studies on cyclooctene, no 3-acetylcyclooctene was found.

That all of these compounds did possess an intact nine-membered ring was confirmed by conversion of the total reaction mixture to methyl cyclononanecarboxylate. The mixture of **2**, **3**, **4**, and **5** obtained by rapid distillation (without fractionation) of the acetylation reaction mixture was subjected to catalytic hydrogenation and was then reduced with sodium borohydride. Dechlorination of the material thus obtained, using sodium–*tert*-butyl alcohol–tetrahydrofuran, gave crude methyl cyclononylcarbinol. Oxidation with Jones reagent gave acetylcyclononane (**6**) in 41% overall yield. For positive identification the acetylcyclononane was



subsequently oxidized under haloform conditions and the crude product esterified directly with diazomethane. The methyl cyclononanecarboxylate (**7**) thus obtained was identical (ir, gc, nmr) with an authentic sample prepared from cyclodecanone according to Schenker and Prelog.[8]

The relative positions of the acetyl group and chlorine atom of **2** were established by base-effected ring closure to 1-acetylbicyclo[4.3.0]nonane (**8**), *via* intramolecular alkylation. Distillation of **2** from 1,5-diazabicyclo[5.4.0]undecene gave mainly unchanged starting material. However, treatment of **2** with sodium hydride in dimethoxyethane afforded a chlorine-free product (**8**) which showed no olefinic absorption in its infrared or nmr spectrum. The absence of signals due to cyclopropyl hydrogens in its nmr spectrum eliminated the possibility of a bicyclo[6.1.0]nonane skeleton having been formed. Compound **8** was conclusively identified as 1-acetyl-



cis-bicyclo[4.3.0]nonane by comparison with a sample prepared by an unambiguous synthesis.[9] Thus, Diels–Alder addition of butadiene to 1-acetylcyclopentene, followed by subsequent hydrogenation, gave a saturated ketone identical with the product of intramolecular alkylation of **2**. Use of potassium *tert*-butoxide as the base in the intramolecular alkylation of **2** gave a 70:30 mixture of two products, **8** and **9**. The minor component was identified as hydrindan **8** by direct comparison. The major component exhibits an infrared spectrum very similar to, but not identical with, that of **8**. The nmr spectrum of **9** shows no signals attributable to vinyl hydrogens, and the mass spectra of **8** and **9** show parent and major fragment ions of the same mass. It seems most likely that **9** is the trans-fused isomer of **8**, rather than 1-acetylbicyclo[5.2.0]nonane. One explanation for the behavior of **2** on treatment with the different bases begins with the observation that **2** appears to be a single isomer; many other processes involving transannular hydride transfer have been found to be stereospecific.[10] On treatment of **2** with sodium hydride a concerted transannular elimination is effected, producing the *cis*-hydrindan **8**. The weaker base, *tert*-butoxide, on the other hand, effects prior epimerization of **2** to a mixture of cis and trans isomers *via* a reversibly formed enolate; the cis and trans isomers of **2** undergo 1,5 elimination to give both acetylbicyclo[4.3.0]nonanes. Very recently Jones and Groves have employed potassium *tert*-butoxide to effect a similar conversion of 1-acetyl-4-chlorocyclooctane to 1-acetylbicyclo[4.2.0]octane.[11] Only the cis product was obtained; however, the trans-fused bicyclo[4.2.0]octanes are appreciably less stable than the cis isomers, whereas in the bicyclo[4.3.0]nonane series, the trans isomer is actually slightly more stable (~1 kcal).[12]

Acetylation of cyclononene with acetic acid–trifluoroacetic anhydride without additional solvent gave a mixture of acetylcyclononenes, **3**, **4**, and **5**, and an acetyltrifluoroacetoxycyclononane, presumably the 1,5 isomer. Attempted hydrolysis of the trifluoroacetoxy group afforded only the elimination product, **4**, or 5-acetylcyclononene, identical with the material obtained in the stannic chloride catalyzed acetylation of cyclononene.

Attention was then turned to acylations employing the more active catalyst, aluminum chloride, with the expectation of observing deep-seated changes in the nine-membered ring. In fact, acetylation of *cis*-cyclononene in the presence of aluminum chloride in methylene chloride at −20° gave a mixture of five products which appeared to contain (as shown by nmr) *C*-methyl groups, indicative of rings smaller than nine-membered. This mixture was not resolvable on any of wide variety of gas chromatography columns, with exception of the peak of shortest retention time, which amounted to 2% of the mixture. For determination of the carbon skeleton, a mixture of the four chlorine-containing products was subjected to a chemical degradative sequence in order to remove the chlorine atoms and convert the acetyl groups to ring ketone functions. Thus, Baeyer–Villiger oxidation followed by lithium aluminum hydride reduction gave a mixture of alcohols which was dechlorinated with sodium–*tert*-butyl alcohol. Oxidation with Jones reagent gave a mixture of cyclanones which could be separated and was found to consist of

(8) K. Schenker and V. Prelog, *Helv. Chim. Acta*, **36**, 896 (1953).

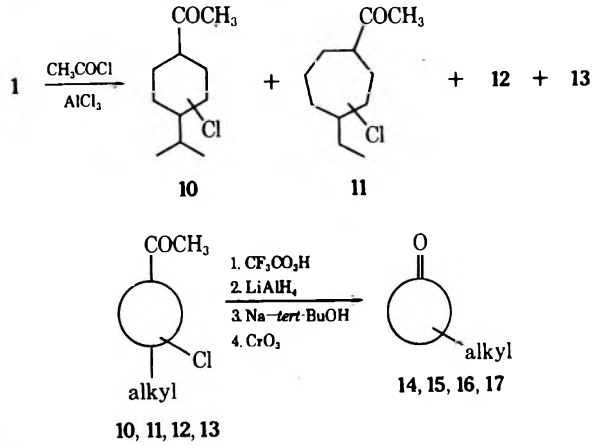
(9) R. L. Kronenthal and E. I. Becker, *J. Amer. Chem. Soc.*, **79**, 1095 (1957).

(10) See, for example, A. C. Cope, S. W. Fenton, and C. F. Spencer, *ibid.*, **74**, 5884 (1952); for further references, see J. G. Traynham and V. Prelog in "Molecular Rearrangements," Vol. I, Wiley, New York, N. Y., 1963, Chapter VIII.

(11) J. K. Groves and N. Jones, *J. Chem. Soc. C*, 2350 (1969).

(12) (a) E. L. Eliel, N. L. Allinger, H. Angyal, and H. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, pp 225–226; (b) E. L. Eliel, "The Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 274–275.

4-isopropylcyclohexanone (**14**, 63%), 4-ethylcycloheptanone (**15**, 12%), and two components of unknown



structure, which may be 4- or 5-methylcyclooctanone (**16** or **17**). The first two compounds were positively identified (ir, gc, nmr) by comparison with samples prepared by unambiguous routes.[13] That neither the third nor the fourth components are cyclononanone was established by comparison with an authentic sample of that compound. The two unidentified products seem unlikely to be hydrindanones, since *C*-methyl absorption is present.

The acylation of cyclononene follows a course similar to that of cyclooctene, in that the milder catalyst systems such as stannic chloride lead to products resulting from 1,5-hydride transfers, albeit containing intact nine-membered rings. The stronger Lewis acid aluminum chloride induced ring contraction, with a cyclohexane derivative predominating among the products.

Experimental Section

General.—The aluminum chloride used was from a freshly opened bottle of Baker and Adamson sublimed reagent grade material, unless stated otherwise. Stannic chloride was Baker and Adamson Reagent Grade. The methylene chloride and carbon disulfide were reagent grade materials, used without further purification. Magnesium sulfate was used for all drying operations. The infrared spectra were obtained on a Beckman IR-8 instrument and the nmr spectra on a Varian A-56/60-A instrument operating at 46°. Gas chromatographic work was performed on a Varian Aerograph Model 202-1 instrument (thermal conductivity detector) utilizing the following columns: column A, 5 ft × 0.25 in. 20% SE-30 on Chromosorb P; column B, 6 ft × 0.25 in., 10% QF-1 fluorosilicone on Chromosorb W; column C, 5 ft × 0.25 in. 15% Carbowax 20M on Chromosorb P; column D, 5 ft × 0.25 in., 20% diethylene glycol succinate on Chromosorb W; column E, 10 ft × 1/8 in. Carbowax 20M on Chromosorb P; and column F, 20 ft × 1/8 in. SE-30 on Chromosorb W. Elemental analyses were performed by Elek Laboratories, Torrance, Calif.

Acetylation of *cis*-Cyclononene with Acetyl Chloride in the Presence of Stannic Chloride.—To a solution of stannic chloride (12.5 g, 0.05 mol) in methylene chloride (50 ml) was added dropwise a solution of cyclononene (6.1 g, 0.05 mol) and acetyl chloride (3.9 g, 0.05 mol) in 20 ml of methylene chloride at −25° over 0.5 hr. The reaction mixture was stirred at −15° for an additional 1 hr, allowed to warm to 0°, and then poured onto crushed ice. The organic layer was combined with an ethereal extract (40 ml) of the water layer and the combined organic phases were washed with water (three 50-ml portions), dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow oil (7.9 g). Analysis of this material on column A at 175° indicated the presence of seven components. Distillation of the yellow oil gave three fractions.

Fraction A, bp 25–60° (0.3 mm) (1.8 g), appeared to be a mixture of unchanged cyclononene and chlorocyclononanes; the infrared spectrum showed bands indicative only of C–H and C–Cl bonds at 2940 and ~700 cm^{-1}.

Fraction B, bp 75–95° (0.3 mm) (2.1 g), appeared to be a mixture of **3**, **4**, and **5**, the acetylcyclononene isomers: ir (film) max 1710, 1662, and 1620 cm^{-1}; nmr (*inter alia*) (CCl_4) τ 3.10 (t, 1 H, H-2 of 3), 3.9 (2 H, m, vinyl hydrogens of **4** and **5**), 7.72 and 7.90 (3 H each, s, $COCH_3$). Analysis on column E showed the presence of three components in the ratio 55:25:20. From the nmr and infrared spectra of the mixture, the conjugated ketone was the major isomer. The mixture was not sufficiently well resolved on other gc columns to allow collection of pure samples.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.52; H, 10.92. Found: C, 79.36; H, 10.63.

Fraction C, bp 96–101° (0.2 mm), was ~92% 1-acetyl-5-chlorocyclononane (**2**). A sample collected from column B exhibited ir (film) 1711 (C=O) and 665 cm^{-1} (CCl); nmr (CCl_4) τ 5.8 (1 H, pentet, J ~ 5 Hz, CHCl), 7.6 (1 H, broad, CHCO), 7.85 (3 H, s, $COCH_3$), and 8.3–8.7 (14 H, multiplet). Ketone **2** darkened on storage, even at 0°, and an accurate analysis could not be obtained. The compound was characterized as the semicarbazone. This derivative, obtained in the usual fashion, was recrystallized twice from ethanol to give shiny white leaflets, mp 159–160°.

Anal. Calcd for $C_{12}H_{22}ON_3Cl$: C, 55.49; H, 8.54. Found: C, 56.05; H, 8.69.

Degradation of the Cyclononene Acylation Mixture.—A reaction mixture obtained as described above, distilled once without fractionation, was employed here. The ketone mixture (5.0 g, 75% of **2** present by gc) in 75 ml of methanol was shaken with 100 mg of 10% palladium on charcoal under 15 psig of hydrogen for 3 hr; 96% of 1 molar equiv was absorbed. The catalyst was removed by filtration and washed with methanol, and the filtrates were concentrated to *ca.* 25 ml. To this solution, cooled to 10–15°, was added, with stirring, a solution of sodium borohydride (0.8 g) in methanol (30 ml) over 0.5 hr. The solution was stirred at ambient temperature for 1 hr and poured into excess ice and water, and the whole solution extracted with three 50-ml portions of ether. The ethereal extracts were combined, washed twice with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated under reduced pressure to give the carbinol mixture as a faintly yellow oil (4.2 g): ir (film) 3360 (br) cm^{-1}; no carbonyl absorption was present.

The alcohol mixture thus obtained was dechlorinated by the addition of sodium (10 g, 0.43 g-atom) in small pieces to a stirred refluxing solution of the crude alcohol mixture as obtained above (6.5 g, 0.034 mol) and *tert*-butyl alcohol (100 ml) in tetrahydrofuran (400 ml). The reaction mixture was stirred and refluxed an additional 15 hr. The bulk of the solvents was removed by evaporation under reduced pressure leaving a yellow slurry which was poured into ice water. The resulting mixture was extracted with ether; the combined extracts were washed with 5% hydrochloric acid and twice with water, dried, and concentrated under reduced pressure. Distillation of the residue gave 1-cyclononylethanol (3.5 g, 58%) as a colorless oil: bp 93–95° (0.3 mm); ir (film) 3360 and 1152 cm^{-1}; analysis on column C indicated the alcohol sample to be about 91% pure.

The entire sample of 1-cyclononylethanol obtained above (3.5 g) was oxidized with Jones reagent (2.8 ml, 8 *N* in oxygen) in dry acetone at 20–30° and worked up by the usual procedure involving evaporation of solvent, treatment with water, and repeated extraction with ether. Distillation gave 3.0 g (85%) of acetylcyclononane: bp 82–85° (0.2 mm); ir (film) 1705 cm^{-1}. Analysis on column C indicated the material to be *ca.* 90% pure. A semicarbazone was prepared and recrystallized twice from ethanol to give white leaflets, mp 172°.

Anal. Calcd for $C_{12}H_{23}N_3O$: C, 63.96; H, 10.29. Found: C, 63.77; H, 10.40.

For positive identification, the ketone was oxidized to cyclononanecarboxylic acid as described below.

Haloform Oxidation of Acetylcyclononane.—To a solution of acetylcyclononane (1.6 g, 90% pure, 0.008 mol) and 20 ml of 10% sodium hydroxide in 60% aqueous dioxane (100 ml) was added dropwise 10% aqueous iodine–potassium iodide until an excess was indicated (50 ml). The reaction mixture was stirred overnight at room temperature, filtered to remove iodoform, acidfied,

(13) (a) R. L. Frank, R. E. Berry, and O. L. Shotwell, *J. Amer. Chem. Soc.*, **71**, 3889 (1949); (b) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 181 (1939).

and extracted with three 40-ml portions of ether. The combined ether extracts were washed with 20% sodium thiosulfate solution and with water, dried, and concentrated to give 0.94 g of crude cyclononanecarboxylic acid; ir (film) 3400–2900 (broad) and 1702 cm^{-1}. Analysis on columns A and B showed only one peak. This material was esterified directly by treatment at 0° with ethereal diazomethane prepared from *N*-nitrosomethylurea (10 g). After the solution had been stirred overnight at room temperature, the ether was evaporated and the residue distilled to give methyl cyclononanecarboxylate: bp 90° (0.3 mm); ir (film) 1736, 1250 cm^{-1}. The infrared and nmr spectra, as well as gc retention times on columns A and B, were identical with those of an authentic sample prepared from cyclodecanone (bromination followed by Favorskii rearrangement) as previously described.[8]

Intramolecular Alkylation of 1-Acetyl-5-chlorocyclononane (2) with Sodium Hydride. Preparation of *cis*-1-Acetylbicyclo[4.3.0]nonane.—To a cold (0°) suspension of sodium hydride (0.8 g of a 52% dispersion in mineral oil) in dry dimethoxyethane (100 ml) under nitrogen was added a solution of chloro ketone 2 (2.0 g, 0.01 mol) in dry dimethoxyethane (40 ml). The solution was stirred for 1.5 hr while warming to room temperature and was then poured into water. The resulting mixture was extracted with ether (three 30-ml portions); the ether extracts were washed with saturated sodium chloride solution, dried, and concentrated to give an orange oil (1.1 g) which showed on column D at 148° three small peaks of short retention time which appeared to possess the same retention times as the impurities in the sample of 2 used. The major peak (retention time 4.2 min, 75% of total area) was collected and identified as 1-acetylbicyclo[4.3.0]nonane: ir (film) 1705 cm^{-1}; nmr (CCl_4) τ 7.91 (3 H, s, CH_3CO) and 8.2–8.8 (15 H, multiplets); mass spectrum: *m/e* (parent) 166. The infrared and nmr spectra were identical with those of an authentic sample (*vide infra*).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 16.92. Found: C, 79.19; H, 10.93.

Intramolecular Alkylation of 1-Acetyl-5-chlorocyclononane (2) with Potassium *tert*-Butoxide. Preparation of 8 and 9.—To a solution of potassium (0.40 g) in dry *tert*-butyl alcohol (50 ml) was added a solution of 2 (0.62 g, 90% pure) in *tert*-butyl alcohol. The reaction mixture was stirred and refluxed for 1 hr under nitrogen and was then concentrated under reduced pressure; water was added to the residue and the resulting suspension was extracted with ether (three 30-ml portions). The ether extracts were washed three times with water, dried, and concentrated to give an orange oil which was distilled to give 0.29 g of colorless oil: bp 55–65° (bath) (0.2 mm); ir (film) 1704 cm^{-1}. Analysis on column C at 145° indicated the material to be a 70:30 mixture of two components: the major component, of shorter retention time, was collected from this column and exhibited the following spectral parameters: ir (film) 1704 cm^{-1}; nmr (CCl_4) τ 8.02 (3 H, s, CH_3CO) and 8.2–8.8 (15 H, m); no signals at 2–6; mass spectral parent peak at 166.

The minor peak was collected and found to be identical with the ketone 8 obtained using sodium hydride as base.

The infrared spectrum of ketone 9 was very similar to that of 8 but exhibited definite differences. It seems likely that 9 is the trans-fused 1-acetylbicyclo[4.3.0]nonane.

Preparation of Authentic 8.—The cis-fused ketone 8 was prepared according to a modified procedure of Kronenthal and Becker. A mixture of butadiene (24 g, 0.44 mol) and 1-acetylcyclopentene[14] (11 g, 0.10 mol) and hydroquinone (0.5 g) was placed in a steel tube and heated to 170–180° for 12 hr. Rapid distillation of the black residue gave 6.8 g, bp 55–60° (0.5 mm), of crude product, in addition to a large amount of black tar. Fractionation of the crude product through a helice-packed column gave 1-acetyl-*cis*-bicyclo[4.3.0]non-3-ene: bp 52–54° (0.5 mm); ir (film) 1705 cm^{-1}. The 2,4-dinitrophenylhydrazone crystallized from ethanol as orange flakes, mp 131–132° (lit.[8] mp 130–131°).

A solution of the above ketone (1.8 g) in 95% ethanol (100 ml) was shaken with 10% palladium on charcoal under 2 atm of hydrogen pressure until uptake had ceased (15 min). Filtration of the catalyst, evaporation of the solvent, and distillation of the residue gave authentic 1-acetyl-*cis*-bicyclo[4.3.0]nonane (8), bp 52–55° (0.5 mm). This sample showed ir and nmr spectra identical with those of the sample obtained by intramolecular alkylation of 2 (*vide supra*).

Acylation of *cis*-Cyclononene with Trifluoroacetic Anhydride–Acetic Acid.—To a mixture of trifluoroacetic anhydride (3.5 g) and acetic acid (1.0 g) was added dropwise cyclononene (2.0 g) over 15 min at 25–28°, according to the procedure of Henne and Tedder.[15] The dark brown solution was stirred at this temperature for an additional 1.5 hr, poured into ice water, and worked up in the manner described for previous acylations to give 3.7 g of a yellow oil. Analysis on column A indicated this material to be composed of two major components and three minor ones, the latter comprising *ca.* 12% of the total area. Fractional distillation of the oil through a Vigreux column gave first 89% pure 5- (or 6-) acetylcyclononene (4 or 5) as a colorless liquid, bp 68–74° (0.6 mm); the infrared spectrum of this material was essentially identical with that of the sample obtained in the acetylation of 1 using stannic chloride. A second fractionation, bp 100–130° (0.5 mm), appeared to be, on the basis of gc analysis on column A, a 1:4 mixture of 4 or 5 and an isomer of acetyltrifluoroacetoxycyclononane, probably the 1,5 isomer. The infrared spectrum of the mixture showed bands at 1760, 1708, and 1245 cm^{-1}; the nmr spectrum exhibited signals at τ 5.8 (1 H, m, $-CHOOCCF_3$), 7.3 (1 H, m CHCOR), and 7.6–8.9 (16 H, m).

Acetylation of Cyclononene Using Aluminum Chloride.—Aluminum chloride (from a freshly opened bottle of sublimed reagent grade material, 13.5 g, 0.1 mol) was added to methylene chloride and acetyl chloride (7.8 g, 0.1 mol) and swirled at 0°. The solution was decanted from the insoluble solid and cooled to −15 to −20°. To the stirred solution at this temperature was added dropwise a solution of cyclononene (11.2 g, 0.10 mol) in methylene chloride (100 ml) over 20 min. The solution was allowed to warm to 0° and was then poured onto crushed ice. The organic layer was separated and the aqueous layer extracted once with methylene chloride (50 ml). The combined organic layers were washed with water (three 50-ml portions), dried ($MgSO_4$), and concentrated. The residual liquid was distilled to give the product mixture as an almost colorless liquid, bp 85–100 (0.5 mm) (9.7 g, 56%). Attempts at analysis by gc were inconclusive due to decomposition of the chloro compounds at the temperatures required. Analysis on column A showed the presence of five poorly resolved components. The reaction was repeated, using aluminum chloride from a bottle which had been opened and exposed to the air several weeks previously. The composition of the reaction mixture was very similar, with the exception that the smallest peak (*ca.* 3% of total area) was absent.

Degradation of the Aluminum Chloride Produced Acetylation Mixture.—Sodium (10 g, 0.43 g-atom) was added in small pieces to a stirred, refluxing mixture of the aluminum chloride produced acetylation mixture, obtained as described above (8.7 g, 0.042 mol), *tert*-butyl alcohol (90 ml), and tetrahydrofuran (200 ml). The reaction mixture was stirred and refluxed for 24 hr and the bulk of the solvent was evaporated. The residue was poured into an ice–water slurry and the resulting suspension extracted with ether (four 50-ml portions). The combined extracts were washed with 2% hydrochloric acid and with water, dried, and concentrated. Distillation of the residue gave 4.7 g (64%) of a chlorine-free (negative Beilstein test) oil, bp 86–98° (1.0 mm), whose infrared spectrum indicated it to be composed of alcohols (relative intensities of bands at *ca.* 1710 and 3500 cm^{-1}). This mixture, dissolved in reagent grade acetone (30 ml), was treated with Jones reagent (8 *N* in oxygen, 3 ml) at room temperature over 40 min. After being stirred at room temperature for an additional 2 hr, the solvent was evaporated under reduced pressure and the residue treated with water. Repeated ether extraction of the resulting mixture, followed by washing of the extracts with 5% sodium bicarbonate and with water, drying, and concentration, gave a ketone mixture which was used directly in the Baeyer–Villiger reaction. A solution of the ketone mixture obtained above (4.3 g), disodium phosphate (25 g), and methylene chloride (100 ml) was treated dropwise with trifluoroperacetic acid (from 1 g of 90% hydrogen peroxide and 7 g of trifluoroacetic anhydride in cold methylene chloride) and then stirred and refluxed for an additional 1 hr. The salts were filtered and washed twice with methylene chloride; the combined filtrates were dried and evaporated. The residue was distilled to give the acetate mixture as a faintly yellow oil: bp 78–95° (1.0 mm); infrared absorption at 1708 and 1730 cm^{-1} indicated the acetate mixture contained *ca.* 10% unchanged ketone. The product was treated with Girard's reagent T (0.8 g) by the standard procedure. The acetate mixture recovered from this treatment was ketone

(14) N. Jones and H. T. Taylor, *J. Chem. Soc.*, 4017 (1959).

(15) A. L. Henne and J. M. Tedder, *ibid.*, 3628 (1953).

free as shown by the absence of infrared absorption maxima or shoulders at 1700–1720 cm^{-1}.

A solution of the acetate mixture obtained above (4.0 g) in ether (40 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.8 g) in ether (50 ml); after completion of the addition, the reaction mixture was refluxed 2 hr more. The reaction mixture was cooled and treated slowly with water (0.7 ml), 15% sodium hydroxide (1.0 ml), and water (3 ml), and stirred for 1 hr. The white salts were filtered and washed well with ether; the combined filtrates were dried and concentrated to give the mixture of ring alcohols and as a colorless, slightly cloudy oil (1.2 g); ir (film) 3450–3500 cm^{-1}.

The mixture of ring alcohols (1.2 g) in reagent grade acetone (30 ml) was treated with Jones reagent (1.3 ml, 8 *N* in oxygen at 25–30° and stirred at ambient temperature for 5 hr. Evaporation of the solvent, treatment with water, and extraction as usual gave, after evaporation of the solvent and distillation, 0.82 g (16% overall) of colorless liquid, ir (film) 1712 cm^{-1}. This mixture of ring ketones showed four peaks on column E at 170°. The retention times of these and the per cent of total peak area represented by each are (a) 5.5 (63%); (b) 6.5 (12%); (c) 7.4 (16%); and (d) 8.3 min (9%). Peaks a and b were collected from column C, on which they were partially resolved. Rechromatography on column A afforded first 4-isopropylcyclohexanone, identical (ir, gc on two columns, mixture melting point of 2,4-DNP) with material prepared from authentic 4-isopropylphenol by a hydrogenation–oxidation sequence. Peak b was identical with a sample of 4-ethylcycloheptanone prepared by ring expansion with diazomethane of authentic 4-ethylcyclohexanone. Peaks c and d both exhibited gc retention times which were significantly different from that of authentic cyclononanone and of 4-*n*-propylcyclohexanone. It seems most likely that at least one of these compounds is 4- or 5-methylcyclooctanone; however, samples of these isomers were not available for comparison.

Registry No.—**2**, 27921-40-0; 2 semicarbazone, 27921-41-1; **3**, 27921-42-2; **4**, 27921-43-3; **5**, 27921-44-4; *cis*-cyclononene, 933-21-1; acetylcyclononane, 19207-40-0; acetylcyclononane semicarbazone, 27921-46-6.

Acid-Catalyzed Cyclization of 4-(2,6,6-Trimethylcyclohexenyl)-2-methylbutanal. X-Ray Structure Analysis of the Major Product

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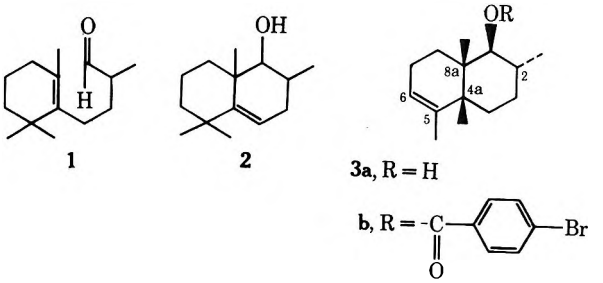
The cyclization of 4-(2,6,6-trimethylcyclohexenyl)-2-methylbutanal (luciferin aldehyde) with phosphoric acid has been found to give (±)-1,2,3,4,4a,7,8,8a-octahydro-2α,4aβ,5,8aβ-tetramethylnaphthalen-1β-ol as the major product. The structure and stereochemistry of this bicyclic alcohol, the formation of which involves an interesting Wagner–Meerwein rearrangement, was established by X-ray analysis of the 4-bromobenzoate derivative. The alcohol is probably identical with a product obtained (cyclization and degradation) from β-monocyclofarnesic acid by Kitahara, *et al.*

Some time ago, we became interested in the cyclization of the aldehyde **1** which is readily available from the "β-C_{14}-aldehyde"[2] by partial hydrogenation with palladium on charcoal in acetone solution. The same aldehyde (**1**, "luciferin aldehyde") has recently been obtained[3] upon hydrolysis of luciferin, which is the enol formate derived from **1**, and by subsequent synthesis[4,5] from dihydro-β-ionone. It was hoped that the aldehyde **1** might cyclize to give the bicyclic alcohol **2**, thus offering a new approach to the preparation of certain sesqui- and higher terpenoids. A precedent for this type of reaction is the well-known cyclization of citronellal, which affords isopulegol.[6]

Results

Upon mixing the aldehyde **1** with 85% phosphoric acid, a solid mass was produced in an exothermic reaction. After alkaline work-up and crystallization, the bicyclic alcohol **3a** was obtained as the major product in 35–45% yield. The structure **3a**, rather than **2**, followed from the nmr spectrum (100 mc, $CDCl_3$) δ 0.86, 0.93 (s, 2 × 3, 4a- and 8a-CH_3), 0.94 (d, 3, J = 6 Hz, 2-CH_3), 1.60 (t, J = 1 Hz, 5-CH_3), 3.28 (d, 1, J = 10 Hz, H_1), and 5.38 (m, 1, H_6).



1 **2** **3a**, R = H

b, R = -C(=O)-C$_6$H$_4$-Br

In order to assign the stereochemistry unambiguously, the alcohol **3a** was converted into its 4-bromobenzoate **3b** and the latter subjected to single crystal X-ray structure analysis. As a result, proof for the relative stereochemistry shown in formula **3a** was obtained. A product with the same structure and "tentative" relative stereochemistry was recently described by Kitahara, Kato, and Kanno.[7] These authors obtained **3a** *via* its acetate by lead tetraacetate oxidation of the bicyclic acid **6**. The latter was formed as a

(1) The portion of this work carried out at the California Institute of Technology was made possible by a grant from the Hoffmann-La Roche Foundation, and this support is gratefully acknowledged.

(2) Intermediate of the technical synthesis of vitamin A; *cf.* O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947).

(3) O. Shimomura and F. H. Johnson, *Biochemistry*, **7**, 1734 (1968).

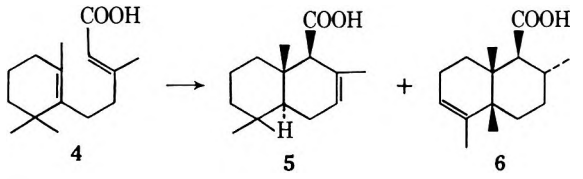
(4) M. G. Fracheboud, O. Shimomura, R. K. Hill, and F. H. Johnson, *Tetrahedron Lett.*, 3951 (1969).

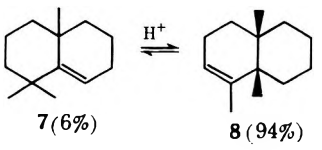
(5) F. Nakatsubo, Y. Kishi, and T. Goto, *ibid.*, 381 (1970).

(6) A. R. Pinder, "The Chemistry of the Terpenes," Wiley, New York, N. Y., 1960, p 38.

(7) Y. Kitahara, T. Kato, and S. Kanno, *J. Chem. Soc. C*, 2397 (1968).

minor product together with the unrearranged acid **5** upon cyclization of β-monocyclofarnesic acid **4** with boron trifluoride in benzene. On the basis of the published[7] nmr data, the two products (**3a**) seem to be identical, although we found a somewhat higher melting point (79–80° *vs.* 71–73°) for our sample. From a study of models, it would appear that the stereochemical result of the cyclization **1** → **3a** is consistent with a concerted mechanism. However, Marshall and Hochstettler[8] have very recently shown that the analogous octalins **7** and **8** are interconvertible *via* acid-catalyzed equilibration, **8** being the predominant isomer. Therefore, the hydroxy octalin **3a** may arise from its isomer **2**, which could be the primary cyclization product. Treatment of the hydroxy octalin **3a** and its acetate with sulfuric acid in acetic acid[8] has so far failed to produce the isomeric octalin **2**, other products forming instead.





Experimental Section[9]

(±)-4-(2,6,6-Trimethylcyclohexenyl)-2-methylbutanal (1, Luciferin Aldehyde).—The C_{14} β aldehyde[2] (200 g) was dissolved in acetone (400 ml) and hydrogenated under normal conditions using 5% palladinum/carbon catalyst (30 g). After takeup of 1 mol of hydrogen, the hydrogenation was stopped and the catalyst was removed by filtration. The crude aldehyde **1** (200.5 g) obtained upon evaporation of the filtrate was found to be sufficiently pure (95% or better by gc) for the cyclization step. A pure sample of **1** was obtained by fractional distillation on a spinning-band column, bp 93.5° (1.6 mm), $n^{21}D$ 1.4821. The ir, nmr, and mass spectra of **1** were identical with those reported[3-5] for luciferin aldehyde.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.59; H, 11.31.

(±)-1,2,3,4,4a,7,8,8a-Octahydro-2α,4aβ,5,8aβ-tetramethylnaphthalen-1β-ol (3a) from 1.—The aldehyde **1** (100 g, crude hydrogenation product) was mixed, with stirring, with 85% phosphoric acid (100 ml). A red emulsion was obtained and the temperature rose to about 50° within 15 min. After standing at room temperature for 24 hr, the reaction mixture had solidified. Water (200 ml) was added and the solid residue was broken up with a spatula. The solid material (probably a phosphoric ester) was filtered and washed with three 100-ml portions of hot water. The solid residue was placed in a flask with ice (200 g), ether (500 ml), and concentrated sodium hydroxide solution (100 ml) and stirred until all solids had dissolved. The ether phase was washed with 3 *N* sodium hydroxide (200 ml) and three 100-ml portions of water. All of the aqueous washings were back extracted in two separatory funnels with more ether (500 ml each). The combined, neutral ether extracts were dried over sodium sulfate and evaporated *in vacuo* at 60° to give 95–98 g of a yellow oil. This was crystallized from petroleum ether (200 ml, boiling range of 40–60°) at Dry Ice temperature. After filtration, washing with cold (−50°) petroleum ether (50 ml), and drying *in vacuo* at room temperature, the alcohol **3a** was obtained as a crystalline, colorless solid (35–54 g), mp 77–80°. An analytically pure sample, mp 79–81°, was made by repeated crystallization from the same solvent.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.64; H, 11.92.

(±)-1,2,3,4,4a,7,8,8a-Octahydro-2α,4aβ,5,8aβ-tetramethylnaphthalen-1β-ol 4-Bromobenzoate (3b).—To a solution of 600 mg (2.88 mmol) of the alcohol **3a** in 60 ml of dry pyridine was added 1.188 g (5.40 mmol) of 4-bromobenzoyl chloride and, after brief agitation, the homogeneous mixture was allowed to stand at 23° for 36 hr under a nitrogen atmosphere. After the mixture was treated with ice and 3 *N* hydrochloric acid, the precipitated ester was isolated by ether extraction. The ethereal extract was washed successively with water, three 100-ml portions of 2% aqueous sulfuric acid, water, and saturated salt solution and then dried (Na_2SO_4). The residue (1.185 g), obtained after evaporation of the ether, was chromatographed on 50 g of silica gel and 825 mg (76%) of the ester **3b**, mp 79–81°, was eluted with 500 ml of 1:1 ether–petroleum ether (bp 30–60°). Analytically pure material suitable for single crystal X-ray analysis was obtained after two crystallizations from hexane and melted at 80.0–81.5°: ir ($CHCl_3$) 1710 (ester C=O) and 1590 cm^{-1} (aromatic absorption); nmr ($CDCl_3$) δ 0.83 (d, 3, J = 5 Hz, C_2 CH_3), 0.99 (s, 3, C_{8a} CH_3), 1.09 (s, 3, C_{4a} CH_3), 1.13 (m, 3, C_5 CH_3), 5.15 (d, 1, J = 10 Hz, C_1 H), 5.50 (m, 1, C_6 H), and 7.50, 7.64, 7.85, 8.00 (A_2B_2q, 4, para-substituted ArH).

Anal. Calcd for $C_{21}H_{27}BrO_2$: C, 64.45; H, 6.96; Br, 20.42. Found: C, 64.51; H, 6.84; Br, 20.35.

X-Ray Analysis of 3b.—Suitable crystals of the 4-bromobenzoate derivative **3b** were grown from a mixture of methanol–ether by slow evaporation. The resulting plate-like crystals were cut to a size of 0.05 × 0.15 × 0.20 mm and surveyed on a precession camera. Both the survey and data collection were performed at ambient room temperature. The survey is summarized in Table I.

TABLE I
DETAILS OF CRYSTAL SURVEYS

Solvent system	Methanol–ether
a(Å) =	6.67 ± 0.01
b(Å) =	13.60 ± 0.01
c(Å) =	21.05 ± 0.01
β (degrees) =	95.84 ± 0.08
Systematic extinctions	$h0l$, l odd $0k0$, k odd
Space group	$P2_1/c$
Molecules/unit cell	4
Density calculation	1.368 g/cm³
Density observed	1.38 g/cm³
Number of reflections	1986
Nonzero reflections	1837

One-angstrom intensity data were collected on a General Electric Datex diffractometer using nickel-filtered copper radiation and a scintillation counter. A θ–2θ scan technique was employed, the background was counted for 30 sec at each end of the scan, and the scan rate was 2° per minute in 2θ. A single check reflection (023) was monitored every 30 reflections; this reflection indicated no crystal damage and was reproducible well within counting statistics.

The diffractometer output was processed using subprograms of the CRYRM crystallographic computer system.[10] The processing included corrections for background and for Lorentz and polarization effects. Absorption effects on the relative intensities would be less than 2% and, therefore, no corrections for this effect were made. The data processing also included calculation of the F^2 value and its standard deviation for each of the 1986 reflections (149 reflections having observed intensities less than or equal to zero were assigned a value of zero intensity). The standard deviations were assigned on the basis of the following equation

$$\sigma^2(I) = S + (B_1 - B_2)\alpha^2 + (dS)^2$$

(8) J. A. Marshall and A. R. Hochstettler, *J. Amer. Chem. Soc.*, **91**, 648 (1969).

(9) Boiling and melting points are uncorrected. Nmr spectra were determined with Varian Model A-60 and HA-100A spectrometers at 60 MHz and 100 MHz, respectively. The mass spectra were determined on a Consolidated Electrodynamics Corp. mass spectrometer, Model 21-110.

(10) D. J. Duchamp, Annual Meeting of the American Association of Crystallographers, Abstracts, Paper B-14, Bozeman, Mont., 1964, p 29.

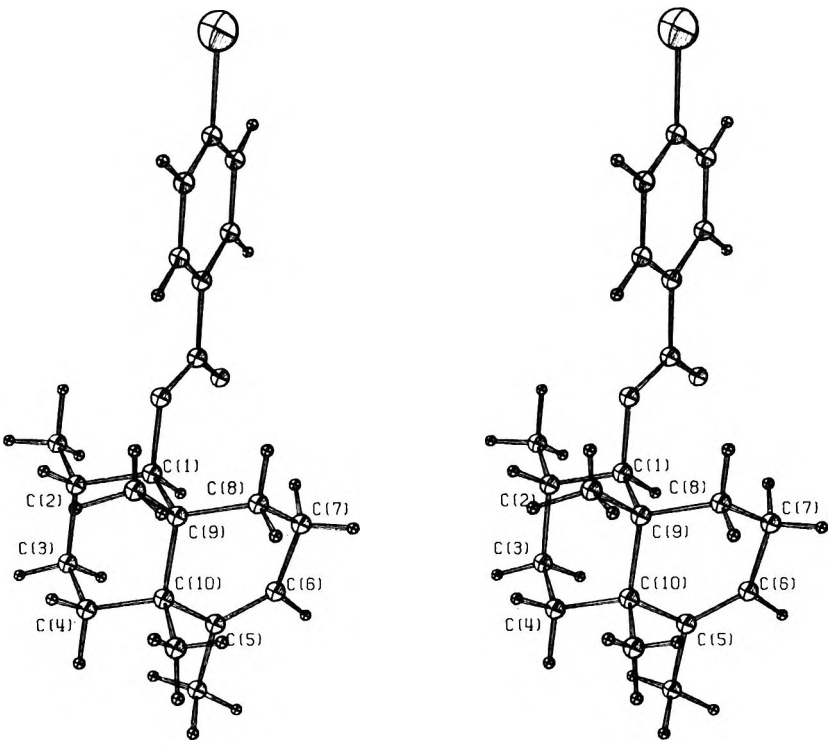


Figure 1.—Stereoplot of the *p*-bromobenzoate **3b**.

where S is the scan count, B_1 and B_2 are the background counts, d is an empirical constant equal to 0.02, and $\alpha = n/2mt$ where n = scan range, m = scanning speed, and t = time for background count in seconds. Finally, the data were placed on an absolute scale by means of Wilson statistics.[11] The atomic scattering factor for bromine includes the real part of the anomalous dispersion correction.

Determination and Refinement of Structure.—The trial structure was derived by the usual Patterson and Fourier techniques in three dimensions. Full-matrix least-squares refinement of coordinates, isotropic temperature factors (bromine anisotropic), and scale factor reduced the R index to 14.4%. The quantity minimized by the least-squares procedure is $\Sigma w(F_o^2 - F_c^2)^2$, where $w = \sigma^2(F_o^2)$. The difference Fourier indicated no misplaced or missing Br, C, or O atoms. The difference Fourier was also utilized to locate the hydrogen atoms. The addition of the hydrogen atoms, without refinement, to the structure factor calculation and the application of anisotropic temperature factors and secondary extinction factor[12] to the refinement reduced the R index to its final value of 8.7%.

Results of X-Ray Analysis.—The structure obtained in the analysis was stereographically plotted (Figure 1) using the ORTEP computer program of C. K. Johnson.[13] An estimate of errors in positional parameters, bond lengths, and bond angles is summarized in Table II. Bond distances and bond angles found together with the crystallographic numbering are given in Figure 2. Other pertinent crystallographic data and parameters may be found in the microfilm addition.[14]

TABLE II
DATA FIT AND DEVIATIONS

Final R index ($\Sigma(\|\|F_o - F_c\|\|)/\Sigma\|F_o\|$)	0.087
Standard deviations[a] of coordinates	
Br	0.001 Å
C, O	0.008 Å
Uncertainties in C, O, Br bond lengths	0.01 Å
Uncertainties in C, O, Br bond angles	0.5°

[a] Standard deviations in the coordinates were derived from the residuals and the diagonal elements of the inverse matrix of the final least-squares cycle.

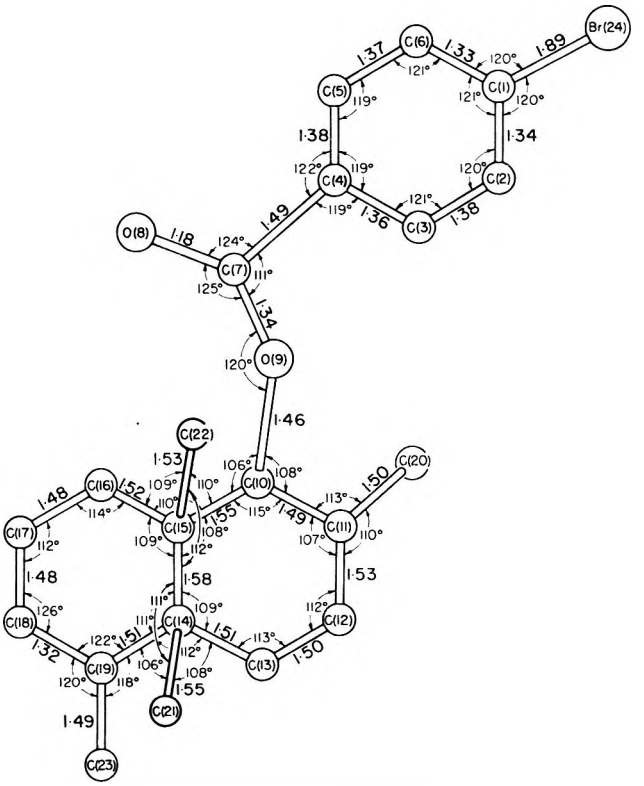


Figure 2.—Plot of bond distances and angles for the *p*-bromobenzoate **3b**.

Registry No.—**1**, 28058-97-1; **3a**, 28058-98-2; **3b**, 28058-99-3.

(11) A. J. C. Wilson, *Nature*, **150**, 152 (1942).
(12) A. C. Larson, *Acta Crystallogr.*, **23**, 664 (1967).
(13) C. K. Johnson, ORTEP, ORNL-3794, Oak Ridge National Laboratories, Oak Ridge, Tenn.
(14) *F* tables, atomic coordinates, anisotropic temperature factors, bond angles, and distances appear immediately following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

Synthesis of Bridgehead Derivatives by Chromic Acid Oxidation

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The chromic acid oxidation of hydrocarbons is a rather selective process strongly influenced by strain factors. In competition with attack at the methylene groups, no significant oxidation occurs at the bridgehead positions of the smaller bicycloheptane and bicyclooctane bridged systems. With adamantane, bicyclo[3.3.1]nonane (I, X = H), bicyclo[3.2.2]nonane (II, X = H), and bicyclo[3.3.2]decane (III, X = H), attack at the bridgehead positions predominates, and chromic acid oxidation becomes a synthetically useful reaction for the preparation of the corresponding bridgehead alcohols. From these alcohols, other bridgehead derivatives can be prepared. As a substitution method for the larger bridged hydrocarbons, chromic acid oxidation has definite advantages as a general method. Free-radical chlorination is less selective, and ionic substitution processes may give rise to rearranged products.

Since it is often easy to prepare polycyclic hydrocarbons by rearrangement or by other means, substitution methods are needed to synthesize functional derivatives.[2] High selectivity is a desirable characteristic of such reactions.

The chromic acid oxidation of hydrocarbons has synthetic utility in special cases.[3-5] In ordinary structures, oxidation of tertiary C–H bonds predominates over CH_2 attack; methyl groups are essentially unaffected (the relative rates of oxidation of typical primary, secondary, and tertiary hydrogens are 1:110:7000).[3] One problem is that the oxidized products tend not to be stable to the reaction conditions; tertiary alcohols may be dehydrated to olefins which are further attacked, and ketones also are oxidizable. Bridgehead alcohols should be stable, since dehydration (to give bridgehead olefins) occurs poorly, if at all.[2] Such bridgehead alcohols were the objective of the present work.

Table I summarizes the results of an earlier investigation in this laboratory.[4a] With adamantane, reaction with CrO_3 in acetic acid–acetic anhydride solvent gave mainly 1-adamantanol, but some adamantanone also formed. More recent studies have confirmed this result.[4b,d] In addition, if excess oxidant is employed, good yields of 1,3-diols can be obtained in the adamantane series.[4d] However, norbornane, bicyclo[2.2.2]octane, and bicyclo[3.2.1]octane give no bridgehead products; only ketones (and some secondary acetates) result (Table I).[4a]

This inhibition of bridgehead oxidation of small bicyclic systems is consonant with the accepted mechanism of chromic acid–hydrocarbon oxidation.[3,6] The initial step is believed to be hydrogen atom abstraction to give a caged radical pair, collapse of which can occur to give retention of configuration[6] (in addition to literature cases,[3] see the results with *cis*- and *trans*-decalin in Table I). Electron transfer in the radical pair can also occur to give carbonium ions, from which certain products, *e.g.*, those involving skeletal rearrangement, occasionally result. This mechanism is preferred over a direct insertion process, which would also give retention of configuration. It is known that carbonium ion, free-radical, and insertion reactions are all inhibited to a decreasing degree at the bridgehead positions of the smaller bicyclanes (Table II).[7]

TABLE I[a]

CHROMIC ACID OXIDATION OF POLYCYCLIC HYDROCARBONS

Triphenylmethane	98% triphenylcarbinol
Adamantane	71% 1-adamantanol, 9% 2-adamantanone
Norbornane	23% 2-norbornanone, 6% 2-*exo*-norbornyl acetate
Bicyclo[2.2.2]-octane	40% 2-bicyclo[2.2.2]octanone, 4% 2-bicyclo[2.2.2]octyl acetate
Bicyclo[3.2.1]-octane	15% 6-bicyclo[3.2.1]octanone, 7% 3-bicyclo[3.2.1]octanone, 8% 2-bicyclo[3.2.1]octanone, 10% 2-bicyclo[2.2.2]-octanone, 4% acetate ester, mostly 2-bicyclo[2.2.2]octyl acetate
cis-Decalin	32% *cis* 9-decalol, 5% 9,10-*cis*-dihydroxydecalin, 4% decalones
trans-Decalin	7% *trans*-9-decalol, 3% 9,10-*trans*-dihydroxydecalin, 8% decalones

[a] Reproduced from ref 4a. Oxidations were carried out in AcOH–Ac_2O. The products were analyzed by a combination of column and gas chromatography, in most cases by comparison with authentic materials. 1-Bicyclo[2.2.1]heptanol, 7-bicyclo[2.2.1]heptanol, 1-bicyclo[2.2.2]octanol, and 1-bicyclo[3.2.1]-octanol were specifically sought among the products but were not detected. For details see R. D. Nicholas, Ph.D. Thesis, Princeton University, 1960; R. E. Lehr, A.B. Thesis, Princeton University, 1964.

TABLE II

COMPARISON OF BRIDGEHEAD RELATIVE REACTIVITIES[a]

			
Nitrene insertion	1	0.3	0.07
Free radical (*tert*-butyl perester decomposition)[b]	1	0.07	0.001
Carbonium ion (bromide solvolyses)[c]	1	10^{-3}	10^{-10}

[a] Reference 7. [b] Reference 10. [c] Reference 2.

(1) National Institutes of Health Predoctoral Fellow, 1968–1970; Ph.D. Thesis, Princeton University, 1970.

(2) A good example is afforded by adamantane. Reviews: R. C. Fort, Jr., and P. v. R. Schleyer, *Chem. Rev.*, **64**, 277 (1964); *Advan. Alicyclic Chem.*, **1**, 283 (1966); R. C. Bingham and P. v. R. Schleyer, *Fortschr. Chem. Forsch.*, in press.

(3) Review: K. B. Wiberg in "Oxidation in Organic Chemistry," K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, pp 109–124.

(4) (a) P. v. R. Schleyer and R. D. Nicholas, Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961, p 75Q; (b) S. Landa, J. Vais, and J. Burkhard, *Z. Chem.*, **7**, 233 (1967); (c) P. v. R. Schleyer and V. Buss, *J. Amer. Chem. Soc.*, **91**, 5880 (1969); (d) R. E. Moore, private communication; *cf.* Sun Oil Co., Neth. Patent Appl., 6,516,807 [*Chem. Abstr.*, **65**, 15249e (1966)].

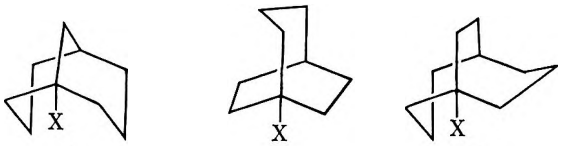
(5) L. A. Paquette, G. V. Meehan, and S. J. Marshall, *J. Amer. Chem. Soc.*, **91**, 6779 (1969).

(6) J. Roček, *Tetrahedron Lett.*, 135 (1962).

(7) D. S. Breslow, E. I. Edwards, R. Leone, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **90**, 7097 (1968).

However, the degree of bridgehead inhibition observed with norbornane and the bicyclooctanes would appear to be of a magnitude larger than would be expected of typical insertion processes.[7]

The solvolytic reactivity of 1-bicyclo[3.3.1]nonyl derivatives are known to be greater than adamantane compounds.[8,9] Since bridgehead radical reactivities seem to parallel carbonium ion reactivities,[7,10] it is reasonable to expect that chromic acid oxidation of bicyclo[3.3.1]nonane (I, X = H) would proceed well at the 1 position. This, in fact, is the case. In addition, bicyclo[3.2.2]nonane (II, X = H) and bicyclo[3.3.2]decane (III, X = H) give moderately good

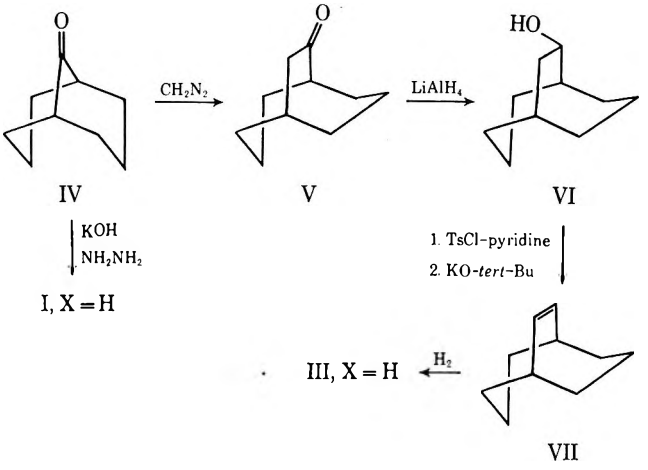


I II III

yields (40–50%) of the corresponding bridgehead alcohols. Side reactions interfere only with bicyclo[3.3.2]decane (III, X = H), where small amounts of 1,5-bicyclo[3.3.2]decanediol and unidentified ketones were found.

1-Bicyclo[3.3.1]nonanol (I, X = OH)[8,9] and 1-bicyclo[3.2.2]nonanol (II, X = OH)[11] have been obtained previously, generally *via* multistep reaction sequences. The physical properties observed, *e.g.*, mp 180–182° for I (X = OH) and 195–197° for II (X = OH), agree well with literature data.[8,9,11] However, a discrepancy exists for 1-bicyclo[3.3.2]decanol (III, X = OH). The literature reports mp 64–65°,[12] which seems much too low for such a bridgehead alcohol. Our value, mp 191–194°, and other evidence[13] support our structural assignment.

The starting hydrocarbons, I,[9] II,[14] and III (all X = H), are all readily available compounds. A new synthesis of III (X = H) was developed. 9-Bicyclo[3.3.1]nonanone (IV) may be prepared in one step by treatment of 1,5-cyclooctadiene with nickel carbonyl.[15] Wolff–Kishner reduction[16] gives I (X = H) in reasonable yield.[9] Homologation of IV with diazomethane[17] gives 9-bicyclo[3.3.2]decanone (V) which may be converted to III (X = H) as shown below.



Comparison with Other Substitution Methods.—Chromic acid oxidation may well be one of the best *general* substitution methods to gain access to various bridgehead derivatives of structures I–III. The alcohols, I (X = OH), II (X = OH), and III (X = OH), can readily be converted to other functional groups. On the other hand, ionic substitution reactions on the parent hydrocarbons, although working well with adamantane,[2] have drawbacks or give undesired products.

Although good yields of 1-bromobicyclo[3.3.1]nonane (I, X = Br) may be obtained by treatment of the hydrocarbon (I, X = H) with molecular bromine,[9] only rearrangement products (possibly 1-bicyclo[3.2.1]-octyl carbinyl bromide and 1-bicyclo[2.2.2]octyl carbinyl bromide)[18] are obtained from II (X = H) under similar conditions. Such rearrangements have also been observed for the bromination of homoadamantane, which gives 1-adamantylcarbinyl bromide.[19] Apparently, the bromination reaction (conducted in liquid bromine, a Lewis acid) is a thermodynamically controlled process. Because of ring strain, the primary rearrangement products are more stable than the tertiary bromides obtained by direct substitution. For this reason, similar rearrangements are likely for III (X = H) and the bromination of this hydrocarbon was not attempted.

In contrast, the alcohols I (X = OH), II (X = OH), and III (X = OH) can readily be converted without rearrangement to the corresponding bridgehead halides under milder conditions. Thus, I (X = Cl),[8] II (X = Cl),[11a] and III (X = Cl) are obtained from the treatment of the alcohols with thionyl chloride. II (X = Br) can be prepared using thionyl bromide.

Similarly, the Koch–Haaf reaction[20] works well with I (X = OH) to give a 75% yield of 1-bicyclo[3.3.1]-

(8) W. G. Dauben and C. D. Poulter, *J. Org. Chem.*, **33**, 1237 (1968).

(9) P. v. R. Schleyer, P. R. Isele, and R. C. Bingham, *ibid.*, **33**, 1239 (1968).

(10) (a) J. P. Lorand, S. D. Chodroff, and R. W. Wallace, *J. Amer. Chem. Soc.*, **90**, 5266 (1968); (b) R. C. Fort, Jr., and R. E. Franklin, *ibid.*, **90**, 5267 (1968); (c) L. B. Humphrey, B. Hodgson, and R. E. Pincock, *Can. J. Chem.*, **46**, 3099 (1968); (d) C. Rüchardt, K. Herwig, and S. Eichler, *Tetrahedron Lett.*, 421 (1969); (e) A. Oberlinner and C. Rüchardt, *ibid.*, 4685 (1969); (f) R. C. Bingham and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, in press; (g) C. Rüchardt, *Angew. Chem.*, **82**, 845 (1977); *Angew. Chem., Int. Ed. Engl.*, **9**, 830 (1970).

(11) (a) C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958); (b) J. R. Wiseman and J. A. Chong, *J. Amer. Chem. Soc.*, **91**, 7775 (1969).

(12) K. H. Baggerley, W. H. Evans, S. H. Graham, D. A. Jonas, and D. H. Jones, *Tetrahedron*, **24**, 3445 (1968). Dr. Graham (private communication) now concurs that the alcohol, mp 64–65°, is not III (X = H).

(13) Conversion of the alcohol to the corresponding chloride (III, X = Cl) followed by reduction of the chloride with triphenyltin hydride regenerates the original bicyclo[3.3.2]decane starting material. This, coupled with the absence of a carbinyl (CHOH) resonance in the nmr spectra, requires the assigned structure III (X = OH).

(14) M. Hartman, *Z. Chem.*, **7**, 101 (1967).

(15) B. Fell, W. Seide, and F. Asinger, *Tetrahedron Lett.*, 1003 (1968).

(16) A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *J. Amer. Chem. Soc.*, **87**, 3130 (1965), and references cited therein.

(17) *Cf.* T. J. deBoer and H. J. Backer, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 225.

(18) The treatment of 1-acetoxybicyclo[3.2.2]nonane with toluenesulfonic acid in acetic acid gives a mixture of 1-bicyclo[3.2.1]octyl- and 1-bicyclo[2.2.2]octylcarbinyl acetates. See J. A. Chong and J. R. Wiseman, Abstracts, 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, No. ORGN 114.

(19) S. H. Liggero, unpublished observations; *cf.* J. E. Norlander, S. P. Jindal, P. v. R. Schleyer, R. C. Fort, Jr., J. J. Harper, and R. D. Nicholas, *J. Amer. Chem. Soc.*, **88**, 4475 (1966).

(20) H. Koch and W. Haaf, *Angew. Chem.*, **72**, 628 (1960), and references cited therein.

nonylcarboxylic acid (I, X = COOH).[21] While the same acid can be prepared directly from I (X = H) by use of *tert*-butyl alcohol–formic acid–sulfuric acid,[22] the yield is poorer (45%) and the separation of the pivalic acid by-product is difficult. The literature records the preparation of II (X = NHCHO)[11b] by the Ritter reaction[23] on II (X = OH) and the Koch–Haaf synthesis of III (X = COOH) starting with I (X = CH_2OH).[21b] Both Ritter and Koch–Haaf reactions are governed by kinetic attack on the most stable (tertiary) carbonium ions; monosubstituted acetic acid derivatives [*e.g.*, I (X = CH_2COOH)] are not formed.[23]

Free-radical chlorination is normally a rather unselective process (primary, secondary, and tertiary C–H substitution relative rates are 1:4:2:6.0),[24] and the bridged ring systems which have been studied give mixtures of products.[2,4c,25] Free-radical bromination is much more like chromic acid in selectivity[3] (primary, secondary, tertiary relative rates are given as 1:100:3000[3] or 1:220:19,400[24]), but the behavior of bridged ring systems (other than adamantane[25]) does not appear to have been studied. Such a selective free-radical substitution method might be a good choice as an alternative to chromic acid oxidation for the preparation of bridgehead derivatives I, II, and III.

Experimental Section

Bicyclo[3.3.1]nonane (I, X = H)[9] and **bicyclo[3.2.2]nonane** (II, X = H)[14] were prepared following literature procedures.

9-Bicyclo[3.3.2]decanone (V).—To a solution of 9-bicyclo[3.3.1]nonanone (IV)[16] (20 g, 0.145 mol), potassium hydroxide (9 g), and water (30 ml) in 200 ml of methanol cooled in an ice bath was added *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, "Diazald" (60 g, 0.28 *M*), in 400 ml of methanol over a period of 1 hr.[17] After being stirred overnight the reaction mixture was diluted with 1500 ml of water and extracted with ether (three times). The ether was then removed *in vacuo* to give a viscous oil which was a mixture of 9-bicyclo[3.3.2]decanone (V) and methyl tosylate. This mixture was dissolved in 200 ml of 50% aqueous ethanol and refluxed for 15 hr. The reaction mixture was then diluted with water and extracted with pentane (three times). The pentane extracts were washed once with water and dried ($MgSO_4$). The pentane was removed by distillation and the product sublimed to give 15 g (68%) of V: mp 182–184°; nmr (CCl_4) δ 1.70 (13 H, b s), 2.35 (2 H, m), and 2.78 (1 H, m); ir (CCl_4) 1689.5 cm^{-1} (C=O). The corresponding tosylhydrazone had mp 184–187°.

Anal. Calcd for $C_{17}H_{24}N_2SO_2$: C, 63.75; H, 7.50; N, 8.75. Found: C, 63.46; H, 7.45; N, 8.87.

9-Bicyclo[3.3.2]decanol (VI).—To a suspension of lithium aluminum hydride (1.5 g, 0.04 mol) in anhydrous ether (50 ml) was added 9-bicyclo[3.3.2]decanone (18 g, 0.12 mol) dissolved in 100 ml of anhydrous ether. After addition was complete (1.5 hr) the reaction mixture was refluxed for 3 hr. The excess lithium aluminum hydride was then decomposed by the cautious addition of 10% Na_2CO_3 and water and dried (Na_2SO_4–$MgSO_4$). The product obtained after removal of solvent was recrystallized from hexane to give 14.5 g (78%) of VI: mp 213–215° (sealed tube); nmr ($CDCl_3$) δ 1.62 (14 H, b s), 2.00 (1 H, s, OH), 2.20 (2 H, m), and 4.10 (1 H, m); ir (CCl_4) 3600, 3300 cm^{-1} (OH).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.92; H, 11.69. Found: C, 77.76; H, 11.78.

9-Bicyclo[3.3.2]decyl Tosylate (VI OTs).—The tosylate was prepared by the method described in Fieser and Fieser[26] in 60% yield: mp 66–68°; nmr (CCl_4) δ 1.55 (16 H, b m), 2.38 (3 H, s), 4.62 (1 H, b m), and 7.35 (4 H, q).

Anal. Calcd for $C_{17}H_{24}SO_3$: C, 66.23; H, 7.79. Found: C, 66.36; H, 8.00.

9-Bicyclo[3.3.2]dec-9-ene (VII).—To a solution of potassium *tert*-butoxide (12 g) in dimethyl sulfoxide (100 ml) was added a solution of 9-bicyclo[3.3.2]decyl tosylate (11 g, 0.036 mol) in dimethyl sulfoxide (100 ml). After addition was complete (1.5 hr), the reaction mixture was heated at 60° for 30 min. Water (500 ml) was then added and the product was extracted with pentane (two times). The extracts were dried ($MgSO_4$), the solvent was removed by distillation, and the product was sublimed and recrystallized from methanol to give 4 g of VII (83%): mp 128.4–130°; nmr (CCl_4) δ 1.53 (12 H, m) 2.43 (2 H, b s), and 5.77 (2 H, m).

Bicyclo[3.3.2]decane (III, X = H).—A solution of 9-bicyclo[3.3.2]decene (4.6 g, 0.034 mol) and a catalytic amount of platinum oxide in ether was placed in a Parr apparatus under 50 psi of hydrogen. After 4 hr when the theoretical amount of hydrogen had been absorbed, the reaction mixture was filtered and the solvent removed by distillation. Sublimation of the product gave 5 g (86% yield) of III (X = H): mp 177–178° (lit. mp 162°[27] and 179–181°[28]); nmr (CCl_4) δ 1.52 (16 H, m) and 2.20 (2 H, m).

General Procedure for Chromic Acid Oxidations.—To a solution of the hydrocarbon (1 g, approximately 8 mmol), acetic acid (15 ml), and acetic anhydride (15 ml) was added chromium trioxide (1.6 g, 16 mmol) in small portions over a period of 1 hr. During addition the reaction mixture was kept below 35° by external cooling. After addition was complete the reaction was stirred at room temperature for 6 hr. (Reaction times on the order of 1 hr were required for the preparation of 1-bicyclo[3.3.2]decanol; see below.) Dilution with ice water (50 ml) was followed by extraction with ether (five times). The ether extracts were then washed with 10% Na_2CO_3 (to remove all acetic acid) and with water. After drying ($MgSO_4$) solvent was removed *in vacuo* to give a product which was a mixture of the desired alcohol and the corresponding acetate. This mixture was added to a solution of lithium aluminum hydride in ether and stirred for 1 hr. The excess hydride was then destroyed by the addition of 10% H_2SO_4, the Li salts were separated by filtration, and the ether solution was dried ($MgSO_4$). After removal of the ether the desired alcohol was obtained in yields of 40–50%.

The alcohols prepared in this manner had the following physical properties. 1-Bicyclo[3.3.1]nonanol (I, X = OH): mp 180–182° (lit.[8] mp 182.5–184°); nmr (CCl_4) δ 1.63 (14 H, m), 2.17 (2 H, m), 2.27 (1 H, s, OH); ir (CCl_4) 3600, 3350 cm^{-1} (OH). 1-Bicyclo[3.2.2]nonanol (II, X = OH): mp 195–197° (lit.[11a] mp 199–201°); nmr (CCl_4) δ 1.65 with a shoulder at δ 1.85; ir (CCl_4) 3600, 3350 cm^{-1} (OH). 1-Bicyclo[3.3.2]decanol (III, X = OH): mp 191–194° (lit.[12,29] mp 64–65°); nmr (CCl_4) δ 1.55 (1 H, sh, OH), 1.75 (16 H, m), and 2.22 (1 H, m); ir (CCl_4) 3600, 3420 cm^{-1} (OH).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.92; H, 11.69. Found: C, 77.58; H, 11.61.

If the oxidation of bicyclo[3.3.2]decane (III, X = H) was allowed to continue longer than 1 hr, significant amounts of 1,5-bicyclo[3.3.2]decanediol were formed in addition to the monoalcohol. These compounds may be readily separated by differential crystallization or column chromatography. The diol is only slightly soluble in ether and nearly insoluble in hexane. Recrystallization of the diol from ether gave mp 214–217°: nmr ($CDCl_3$) δ 1.42 (2 H, s, OH) and 1.80 (16 H, d); ir ($CDCl_3$) 3580, 3400 cm^{-1} (OH).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70.24; H, 10.71.

(21) For direct syntheses of this acid *via* ring closure reactions, see (a) J. R. Wiseman, *J. Amer. Chem. Soc.*, **89**, 5966 (1967); (b) Smith Kline and French Laboratories, British Patent 1,104,058 [*Chem. Abstr.*, **69**, 51739e (1968)]; (c) S. H. Graham and D. A. Jonas, *J. Chem. Soc. C*, 188 (1969); (d) J. R. Wiseman and W. A. Pletcher, *J. Amer. Chem. Soc.*, **92**, 956 (1970); *J. Org. Chem.*, **35**, 3164 (1970).

(22) *Cf.* H. Koch and W. Haaf, *Org. Syn.*, **44**, 1 (1964).

(23) L. I. Krimen and D. J. Cota, *Org. React.*, **17**, 213 (1969).

(24) G. A. Russell and C. DeBoer, *J. Amer. Chem. Soc.*, **85**, 3138 (1963).

(25) I. Tabushi, J. Hamuro, and R. Oda, *ibid.*, **89**, 7127 (1967); *J. Org. Chem.*, **33**, 2108 (1968); I. Tabushi, T. Okada, Y. Aoyama, and R. Oda, *Tetrahedron Lett.*, 4069 (1969); P. H. Owens, G. J. Gleicher, and L. M. Smith, Jr., *J. Amer. Chem. Soc.*, **90**, 4122 (1968); G. J. Gleicher, J. L. Jackson, P. H. Owens, and J. D. Unruh, *Tetrahedron Lett.*, 833 (1969). However, *cf.* V. A. Nekrasova and N. I. Shiukin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 714 (1969).

(26) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1968, p 1180.

(27) K. Alder, S. Harting, and G. Hausmann, *Ber.*, **89**, 1972 (1956).

(28) G. Schröder, *ibid.*, **97**, 3140 (1964).

(29) See text and ref 13.

1-Chlorobicyclo[3.2.2]decane (III, X = Cl).—A procedure similar to that reported[11a] for the preparation of 1-chlorobicyclo-[3.2.2]nonane was employed. Thus, 1-bicyclo[3.3.2]decanol (187 mg, 1.2 mmol) was added to freshly purified thionyl chloride[30] (2 ml) and stirred for 12 hr. Chips of ice were then added to the reaction mixture until all excess thionyl chloride had decomposed. The product was extracted with ether and the ether extracts were washed with 10% Na_2CO_3, water, and brine and dried ($MgSO_4$). Removal of solvent by distillation and sublimation of the residue gave a white waxy solid (140 mg, 67%): mp 85–87°; nmr (CCl_4) δ 1.67 (11 H, m) and 2.28 (6 H, m); ir (CCl_4) 2900, 1450 cm^{-1}.

Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.56; H, 9.86; Cl, 20.58. Found: C, 69.54; H, 9.71; Cl, 20.25.

Reduction of 1-Chlorobicyclo[3.3.2]decane (III, X = Cl).—To a solution of 1-chlorobicyclo[3.3.2]decane (75 mg, 0.44 mmol), lithium aluminum hydride (5 mg, 0.13 mmol), and 2,2-azobisisobutyronitrile (catalytic amount) in 5 ml of anhydrous ether was added triphenyltin chloride (193 mg, 0.5 mmol) in ether (15 ml) at room temperature.[31] Care was taken to exclude moisture. A fine, light-colored precipitate developed during the course of the addition (30 min). The reaction mixture was then refluxed for 3 hr, filtered, washed with water (two times) and brine, and dried ($MgSO_4$). Removal of solvent and sublimation of the residue gave a product (67%) whose physical (mp 177–178°) and spectroscopic properties were identical in every respect with those of bicyclo[3.3.2]decane (III, X = H).

Bromination of Bicyclo[3.2.2]nonane (II, X = H).—To bromine (5 ml) cooled in an ice bath was added bicyclo[3.2.2]-nonane[14] (1 g). The reaction mixture was then gradually raised to room temperature and stirred for 20 hr. After addition of CCl_4 (35 ml), the excess bromine was destroyed with an aqueous solution of $NaHSO_3$. The organic layer was then separated, washed twice with water, and dried ($CaCl_2$). The solvent was removed *in vacuo* and the product distilled (1 g, 61%), bp 53–54° (0.3 mm). A sharp singlet attributable to $-CH_2Br$ appears at δ 3.33 in the nmr spectra indicating that rearrangement had occurred. The integration of this signal indicated that rearrangement was complete within experimental error. No conditions could be found for the separation of the two most likely products,[18] 1-bicyclo[3.2.1]octylcarbinyl bromide and 1-bicyclo-[2.2.2]octyl carbinyl bromide.

1-Bromobicyclo[3.2.2]nonane (II, X = Br).—To freshly distilled thionyl bromide (0.56 ml, 7 mmol) was added 1-bicyclo-[3.2.2]nonanol (0.5 g, 3.5 mmol) at room temperature. The reaction mixture was stirred at that temperature for 12 hr and heated at 85° for an additional 4 hr. Chips of ice were then added to decompose the excess thionyl bromide. The product was extracted with ether (two times) and the combined extracts were washed with 10% Na_2CO_3, water, and brine. After drying ($MgSO_4$) the solvent was removed *in vacuo* and the oily product was distilled (0.4 g, 55%): bp 123–125° (20 mm); nmr (CCl_4) δ 1.70 (9 H, m) and 2.40 (6 H, m); ir (CCl_4) 2925, 2860, 1460, 640 cm^{-1}.

Anal. Calcd for $C_9H_{15}Br$: C, 53.20; H, 7.39; Br, 39.41. Found: C, 53.27; H, 7.29; Br, 39.24.

1-Bicyclo[3.3.1]nonylcarboxylic Acid (I, X = COOH). A.—To a solution of 96% H_2SO_4 (125 ml), CCl_4 (50 ml), and 1-bicyclo-[3.3.1]nonanol (6.5 g, 0.046 mol) cooled in an ice–salt bath was added 28 g of HCOOH with vigorous stirring over a period of 1.5 hr. The reaction temperature was not allowed to rise above 15°. After stirring for an additional hour, the reaction mixture was poured over ice (350 g). The organic layer was separated and the acid layer was extracted with CCl_4 (three times). The combined CCl_4 extracts were washed with two 50-ml portions of 15 *N* NH_4OH. The alkaline washes were then acidified with 12 *N* HCl. The precipitated product was extracted with chloroform, the chloroform extracts were dried (Na_2SO_4), and the solvent was removed to give 5.8 g (75%) of crude product. Recrystallization from methanol–water (7:1) gave I (X = COOH): mp 96–97.5° (lit. mp 98–99°,[21a] 95.5–97°,[21b] 82–84°[21c]); nmr (CCl_4) δ 1.70 (15 H, m) and 11.95 (1 H, s); ir (CCl_4) 3100, 2925, 1695 cm^{-1}.

B.—Similar results in somewhat decreased yield were obtained when bicyclo[3.3.1]nonane was used instead of the 1-alcohol and *tert*-butyl alcohol (15 g) was added with the formic acid.[22] Separation of the 1-bicyclo[3.3.1]nonylcarboxylic and pivalic acids obtained in this manner was accomplished by distillation. A fraction boiling at 113–118° (0.1 mm) gave a 47% yield of 1-bicyclo[3.3.1]nonylcarboxylic acid (I, X = COOH).

Registry No.—I (X = OH), 15158-56-2; I (X = CO_2H), 17530-63-1; II (X = OH), 28054-86-6; II (X = Br), 28054-87-7; III (X = OH), 18216-08-5; III (X = Cl), 28054-89-9; III 1,5-diol, 28054-90-2; V, 28054-91-3; V tosylhydrazone, 28054-94-6; VI, 19388-80-8; VI OTs, 28054-92-4; VII, 6571-74-0; chromic acid, 7738-94-5.

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(30) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 345.

(31) For leading references concerning tin hydride reductions, see H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968).

Correlation Constants in the Chemistry of Organophosphorus Compounds

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Two correlation methods of ionization constants of the organophosphorus acids are discussed. The first involves application of σ^{Φ} constants characteristic of the substituents bonded to phosphorus. In the second approach the σ_I and σ_R constants found for the substituents bonded to carbon are used. The best correlations are obtained for σ^{Φ} constants. Correlation of σ^{Φ} constants with σ_I and σ_R values employing the Taft equation gives only a fairly good correlation coefficients. Electronic effects of the substituents at phosphorus are of the same nature as those at carbon atom, but some specific difference in the resonance effects is observed probably owing to the difference between p–π or π–π and p–d or π–d overlaps. Thus the use of σ^{Φ} constants for correlation of the organophosphorus reactions is preferable.

Jaffé, Freedman, and Doak were the first to employ the Hammett equation in the chemistry of organophosphorus compounds in 1953.[1] They found that the ionization constants of aromatic phosphonic acids show linear correlation with σ_m and σ_p values reported by Jaffé.[2] In 1956 one of us found[3,4] that, besides for aromatic acids, the Hammett equation

$$pK = pK^0 - \rho\Sigma\sigma^{\Phi} \quad (1)$$

(1) H. H. Jaffé, L. D. Freedman, and G. O. Doak, *J. Amer. Chem. Soc.*, **75**, 2209 (1953).

(2) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(3) M. I. Kabachnik, *Dokl. Akad. Nauk SSSR*, **110**, 393 (1956).

(4) M. I. Kabachnik, *Z. Chem.*, **1**, 2893 (1961).

can be applied to a variety of phosphorus acids when σ^{ϕ} constants specific for the substituents directly bonded to phosphorus atom are used. Work was done on approximately 150 ionization constants of phosphorus acids in water and 50% aqueous alcohol in order to determine σ^{ϕ} constants. Excellent correlations were obtained in the majority of cases. In a later study the σ^{ϕ} constants were used many times to correlate the ionization constants of the organophosphorus acids and bases and rate constants of some reactions in various media.[5-10]

Recently[11] we discussed in detail the application of the correlational analysis in the chemistry of organophosphorus compounds. In all we treated 124 reaction sets involving nearly 1300 rate and equilibrium constants. It was found that in the case of ionization of organophosphorus acids and bases the use of σ^{ϕ} constants gives the best results and provides a universal correlation system. Thus for 27 reaction sets in correlations of pK_a values of different phosphorus acids with σ^{ϕ} values 77.6% were excellent or good (r varied from 0.970 to 1.000), 18.5% were rather satisfactory (r varied from 0.950 to 0.969), and 3.7% had correlation coefficients below 0.950. Analysis of the nucleophilic substitution reactions at a phosphorus atom and some other reactions showed that good correlations are obtained by using eq 2, where σ_I^{ϕ} and σ_R^{ϕ} are, re-

$$\log k = \log k^0 + \rho\Sigma(\sigma_I^{\phi} + \alpha\sigma_R^{\phi}) \quad (2)$$

spectively, the inductive and resonance components of σ^{ϕ}. A method was advanced for the estimation of these constants from the experimental data, and a unified system of correlations of the rate and equilibrium constants was developed for a variety of organophosphorus reactions. The correlations were good or excellent in 62% of the 124 reaction sets, 20% were rather satisfactory, and 18% had a correlation coefficient below 0.950.

It should be pointed out that a comparison of the σ^{ϕ} and σ constants derived from reactions of the pure carbon compounds revealed that in general these two sets of constants are not in any simple correlation. The linear dependences of σ^{ϕ} and σ were only found for certain types of substituents. Thus Palm[12] was the first to find the linear correlation between the σ^{ϕ} constants of the unsubstituted alkyl groups and the σ^* Taft constants (eq 3). (The parameters of this equa-

$$\sigma^{\phi} = -0.960 + 1.99\sigma^* \quad (3)$$

tion were corrected in our work.[11]) The σ^{ϕ} constants of the substituted aromatic groups at phosphorus were shown to be linearly dependent on the σ_p and σ_m (or σ^0) values of the aromatic ring substituents (eq 4).[13] Thus the σ^{ϕ} constants of the alkyl and cyclo-

$$\sigma_{XC_6H_4}^{\phi} = -0.415 + 0.634\sigma_X \quad (4)$$

alkyl groups at phosphorous are purely inductive whereas those of the substituted aromatic groups contain the inductive and resonance components in the same ratio as σ_p and σ_m. For other groups (RO, RS, or R_2N, etc.) a dependence between the σ^{ϕ} and σ constants of the substituents at carbon was not established. Thus the contribution of the inductive and resonance components to σ^{ϕ} varies depending on the nature of the group bonded to phosphorus. It was due to these reasons that the derivation of the specific σ^{ϕ} constants became necessary.

Recently Charton has published a paper in which he deals with this problem.[14] He examines the possible application of the σ_I and σ_R constants, obtained for the substituents at carbon, to the correlation of the ionization constants of organophosphorus acids and bases. Charton used the Taft equation[15]

$$Q_X = \alpha\sigma_I + \beta\sigma_R + h \quad (5)$$

σ_I values were those obtained earlier by Charton,[16] and the σ_R constants were obtained from the equation

$$\sigma_R = \sigma_p - \sigma_I \quad (6)$$

using σ_p values of McDaniel and Brown.[17]

In the correlation of σ^{ϕ} values[18] with σ_I and σ_R the following values were obtained (eq 5): $\alpha = 4.01 \pm 0.34$, $\beta = 0.760 \pm 0.243$, $h = -0.915 \pm 0.067$, the multiple correlation coefficient $R = 0.946$. In the correlation of ionization constants with the σ_I and σ_R constants, Charton obtained correlations of which 57.9% were good or very good, 10.5% were satisfactory, and 31.6% had correlation coefficients below 0.950. It should be noted that good correlations can be obtained from the data of various authors only for certain combinations of their reaction sets or by division of the data of one work into several reaction sets and by omitting some substances that fall out of the linear correlation from the pK_a sets. It should also be mentioned that Charton's α and β differ significantly for acids of the same type measured under very similar conditions.

For example, for pK_1 in water for set 2 the α and β values -3.62 and -0.797 were obtained (β/α, 0.22), and for set 4 the α and β values were -3.52 and -1.74 (β/α, 0.49). Thus, in this case, the resonance contribution to the total substituents electronic effect difference is more than double. It is impossible to ascribe this difference to the temperature change from 20 to 25°.

Thus Charton came to the conclusion that the effect of the substituents bonded to pentavalent phosphorus

(5) T. A. Mastryukova, T. A. Melentyeva, A. E. Shipov, and M. I. Kabachnik, *Zh. Obshch. Khim.*, **29**, 2178 (1959).
(6) M. I. Kabachnik, T. A. Mastryukova, A. E. Shipov, and T. A. Melentyeva, *Dokl. Akad. Nauk SSSR*, **124**, 1061 (1959).
(7) M. I. Kabachnik, T. A. Mastryukova, T. A. Melentyeva, and A. E. Shipov, *Tetrahedron*, **9**, 10 (1960).
(8) M. I. Kabachnik and G. A. Balueva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 536 (1962).
(9) T. Ya. Medved, B. A. Korolev, K. S. Yudina, B. I. Stepanov, and M. I. Kabachnik, *Teor. Eksp. Khim.*, **6**, 116 (1968).
(10) G. K. Genkina, B. A. Korolev, V. A. Gilyarov, B. I. Stepanov, and M. I. Kabachnik, *Zh. Obshch. Khim.*, **39**, 326 (1969).
(11) T. A. Mastryukova and M. I. Kabachnik, *Usp. Khim.*, **38**, 1751 (1969).
(12) V. A. Palm, *ibid.*, **30**, 1069 (1961).
(13) T. A. Mastryukova and M. I. Kabachnik, *Zh. Obshch. Khim.*, **38**, 677 (1968).
(14) M. Charton, *J. Org. Chem.*, **34**, 1877 (1969).
(15) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **80**, 2436 (1958).
(16) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
(17) D. H. McDaniel and H. C. Brown, *ibid.*, **23**, 420 (1958).
(18) The Charton list of σ^{ϕ} values had some errors:[14] for the OH group the -0.393 value should be used instead of -0.343; for the C_2H_5O group -0.214 should be used instead of -0.314; for the $ClCH_2$ group -0.051[19] should be used instead of -0.034. Besides, recently we have corrected the σ^{ϕ} value for CF_3 group: 0.7 should be used instead of 0.50.[11]
(19) M. I. Kabachnik, T. A. Mastryukova, and S. T. Ioffe, *Zh. Obshch. Khim.*, **30**, 2763 (1960).

TABLE I

σ_X^{ϕ} CONSTANTS OF X SUBSTITUENTS[a]

No.	X	σ_X^{ϕ}	No.	X	σ_X^{ϕ}	No.	X	σ_X
1	H	0.00	15	$(C_6H_5)_2CH$	−0.73	29	C_4H_9O	−0.41
2	CH_3	−0.96	16	$HOCH_2$	−0.55	30	$C_5H_{11}O$	−0.39
3	C_2H_5	−1.10	17	$ClCH_2$	−0.05	31	i-$C_5H_{11}O$	−0.38
4	C_3H_7	−1.18	18	$BrCH_2$	0.0	32	c-$C_5H_{11}O$	−0.35
5	i-C_3H_7	−1.30	19	ICH_2	−0.1	33	C_6H_5O	−0.06
6	C_4H_9	−1.22	20	$(CH_3)_3SiCH_2$	−1.6	34	CH_3S	+0.15
7	i-C_4H_9	−1.30	21	$CHCl_2$	+0.27	35	C_2H_5S	+0.09
8	sec-C_4H_9	−1.36	22	CCl_3	+0.3	36	C_3H_7S	−0.06
9	$tert$-C_4H_9	−1.55	23	CF_3	+0.7	37	i-C_4H_7S	−0.06
10	i-C_5H_{11}	−1.27	24	OH	−0.39	38	$(CH_3)_2N$	−1.22
11	Neo-C_5H_{11}	−1.44	25	CH_3O	−0.12	39	F	+0.56
12	c-C_6H_{11}	−1.19	26	C_2H_5O	−0.21	40	Cl	+0.93
13	$C_6H_5CH_2$	−0.69	27	C_3H_7O	−0.32	41	C_6H_5	−0.48
14	CH_2=CH	−0.68	28	i-C_3H_7O	−0.29			

[a] Reference 11.

may be described as a function of the σ_I and σ_R constants obtained for the substituents bonded to carbon and that it is unnecessary to define the new substituent constants, *i.e.*, σ^{ϕ}.

It is evident from the above that one can outline two approaches in the correlation of the rate and equilibrium constants of the organophosphorous reactions. The first is associated with the use of the σ^{ϕ} constants specific to the substituents bonded to phosphorus. The second approach is based on application of the σ_I and σ_R constants obtained for the substituents bonded to carbon. In this regard we have carried out a comparative study of both these correlation methods.

Results

For the comparative correlations one can use only the data for the substituents with the three known constants σ^{ϕ}, σ_I, and σ_R. Table I shows the σ^{ϕ} constants of such substituents.[11] The σ_I values were taken according to Charton.[16] The σ_R constants were estimated from eq 6 using the σ_p constants of McDaniel and Brown.[17] In some cases they were taken from Jaffé's review.[2] We also used σ_I constants for the RO and RS groups calculated from the σ^* constants of these groups[11] from the relation $\sigma_I = \sigma^*/6.23$. Other constants employed are listed in Table II.

TABLE II

SUBSTITUENT CONSTANTS OF SOME X GROUPS

X	σ_I	σ_p	Ref	X	σ_I	σ_p	Ref
OH	0.29		*a*	$CHCl_2$		0.185	*b*
CH_2=CH		0.14	*c*	CCl_3		0.407	*b*
$C_6H_5CH_2$		−0.109	*d*	F	0.52		*a*
$(C_6H_5)_2CH$		−0.038	*d*	Cl	0.47		*e*

[a] V. A. Palm, "Osnovy kolichestvennoy teorii organicheskikh reaktsii," Khimiya, Leningrad, 1967, p 164. [b] J. Hine and W. C. Bailey, *J. Amer. Chem. Soc.*, 81, 2075 (1959). [c] B. A. Zaitsev, *Reakts. Sposobnost Org. Soedin.*, 4, No. 4 (14), 726 (1967). [d] W. F. Little, C. N. Reilley, J. D. Johnson, and A. P. Sanders, *J. Amer. Chem. Soc.*, 86, 1381 (1964). [e] O. Eksner, *Proc. Conf. Use Correlational Equations Org. Chem., Tartu*, 1, 67 (1962).

First of all we correlated σ^{ϕ} with the σ_I and σ_R constants. Table III (set 1) shows the results of this correlation.[20] It can be seen that our α and β values of

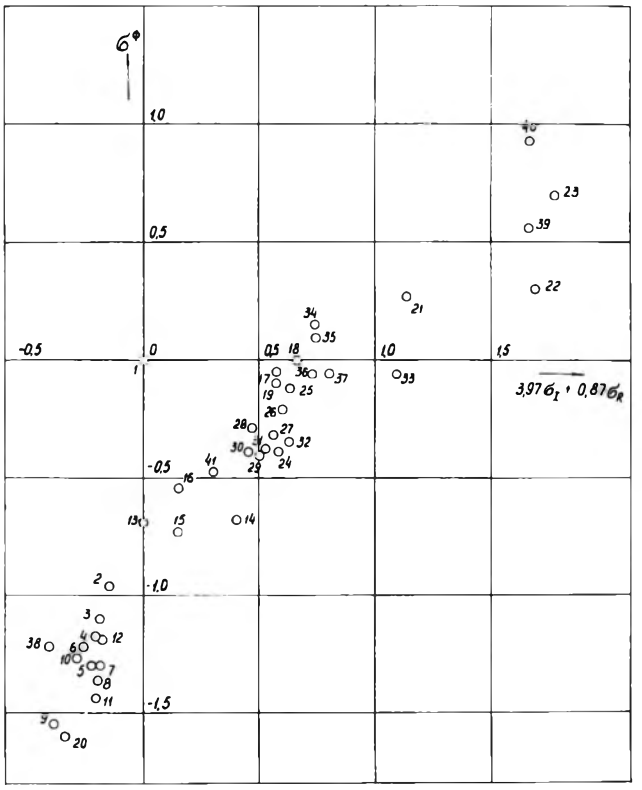

Figure 1.—σ^{ϕ} constants *vs.* σ_I and σ_R constants.

eq 5 differ only slightly from Charton's data (α = 3.97 and 4.01, and β = 0.87 and 0.760). Values of h are also close (−0.89 compared with Charton's value, −0.915), but the multiple correlation coefficient was less good (0.931 compared with Charton's 0.946).[22] Probably such disagreements are a result of some inaccuracy in the σ^{ϕ} constants of Charton (see footnote 18.). Moreover Charton correlated only a part of the known σ^{ϕ} constants (20), whereas the present paper employs a larger number (41) of constants. Figure 1 shows a dependence of the σ^{ϕ} constants on $\sigma_{eff} = 3.97\sigma_I + 0.87\sigma_R$).[23] Because of the low correlation coefficient, the points corresponding to the particular substituents lie in a wide band. Several separate linear dependences can be differentiated within this band.

(20) Statistical analysis was performed as described in ref 21.

(21) L. M. Batuner and M. E. Pozin, "Matematicheskie metody v khimicheskoi tekhnike," Khimiya, Leningrad, 1968, p 689.

(22) The correlation coefficient becomes a little higher (0.957 compared with 0.931) by the exclusion of the value for h but it is still lower than that required for a good correlation.

(23) $\sigma_0^{\phi} = -0.89$, $\rho = 1.000$, $r = 0.931$, $s = 0.24$, $s_\rho = 0.06$.

TABLE III
RESULTS OF CORRELATION WITH EQ 7

Set no.	$-\alpha$	$-\beta$	h	R	r_s	s_α	s_β	s_h	n
1	−3.97	−0.87	−0.89	0.931	0.372	0.25	0.06	0.24	41
2	6.83	3.02	2.31	0.919	0.983	0.81	0.35	0.15	15
3	13.30	−0.44	7.99	0.749	0.352	4.44	0.15	0.24	9
4	4.78	4.05	0.23	0.874	0.715	1.01	0.86	0.20	9
5	12.18	4.80	7.26	0.851	0.717	4.24	1.70	0.15	5
6	3.78	0.62	3.02	0.913	0.841	0.48	0.08	0.33	14
7	3.98	1.14	4.24	0.954	0.918	0.20	0.14	0.20	9
8	4.13	0.70	4.98	0.939	0.852	0.40	0.07	0.32	16
9	7.56	3.91	3.80	0.780	0.918	1.47	3.91	0.63	19
10	8.93	4.67	4.32	0.744	0.929	2.14	1.12	0.73	16
11	0.65	−0.08	−3.34	0.981	0.960	0.04	0.01	0.05	10

Thus alkyl substituents and hydrogen are likely to form a sharply inclined secondary band (no. 1–12). Partial linear correlation can be observed for the alkoxy- and alkylthio groups with normal chains (points 24–27, 29, 30, and 34–36). There are separate points corresponding to the strong electronegative substituents (CCl_3, CF_3, F, and Cl, no. 22, 23, 39, and 40). With an almost constant σ_{eff}, the value of σ^ϕ varies within 0.30–0.93.

In order to estimate both these correlation methods we have carried out a comparative correlation of the ionization constants (pK_a) of phosphorus acids using both methods. Table IV shows the reaction sets em-

TABLE IV
THE REACTION SETS USED FOR CORRELATION

Set no.	Reaction set	pK	Conditions: Medium	°C	Ref
1	Constants σ^ϕ		...	...	...
	Ionization Constants of XYPOOH				
2	Set of Crafts and Kosolapoff[a]	pK_1	H_2O	25	*b*
3	Set of Crafts and Kosolapoff[a]	pK_2	H_2O	25	*b*
4	Set of Kumler and Eiler	pK_1	H_2O	25	*c*
5	Set of Kumler and Eiler	pK_2	H_2O	25	*c*
6	Set of Mastryukova, *et al.*	pK_1	7% EtOH	20	*d*
7	Set of Mastryukova, *et al.*	pK_1	50% EtOH	20	*d*
8	Set of Mastryukova, *et al.*	pK_1	80% EtOH	20	*d*
9	Set of Peppard, *et al.*	pK_1	75% EtOH	22.5	*e*
10	Set of Peppard, *et al.*[f]	pK_1	95% EtOH	22.5	*e*
11	XYPSSNa + $C_6H_5CH_2Cl$		95.5% EtOH	25	*g*

[a] Data for *tert*-$C_5H_{11}P(O)(OH)_2$ are excluded since the authors assume that their acid obtained is not sufficiently pure. [b] P. C. Crofts and G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 3379 (1953). [c] W. D. Kumler and J. J. Eiler, *ibid.*, **65**, 2355 (1943). [d] T. A. Mastryukova, Doctoral Thesis, INEOS, Moscow, 1967 (autoreferate, 26). [e] D. F. Peppard, G. W. Mason, and C. M. Andreyasich, *J. Inorg. Nucl. Chem.*, **27**, 697 (1965). [f] Data for $(C_6H_5O)_2POOH$ are excluded since the pK_a value (1.91) is below that found in 75% alcohol (2.28); all other acids show the reverse relations. [g] M. I. Kabachnik, T. A. Mastryukova, G. A. Balueva, E. E. Kugucheva, A. E. Shipov, and T. A. Melentyeva, *Zh. Obshch. Khim.*, **31**, 140 (1961).

ployed. Each of the sets relates to the data from a single paper, obtained by the same procedure and under analogous conditions. Use was made of all the constants published by the authors except in a very few cases when there were no literature data on the σ_I and σ_R[24] constants. The additivity principle was used in the correlation which was found to be very reasonable in the correlation analysis of organophosphorus reactions. Thus for acids of the type XYPOOH we used eq 7 for the correlations in accordance with

$$Q_X = \alpha\Sigma\sigma_I + \beta\Sigma\sigma_R + h \quad (7)$$

Charton's method and eq 1 for the correlation with the σ^ϕ constants. In the calculations of correlation parameters from eq 7, when di- and tribasic acids were taken in the same set with monobasic ones, statistical factors of 0.30 and 0.48 pK_a unit have been used. No statistical factor was used in eq 1 since this has already been included in σ^ϕ of the hydroxy group. Table III (sets 2–10) shows the data of the correlations of ionization constants for organophosphorus acids with the σ_I and σ_R constants in accordance with the Charton procedure. Table V lists the results of the correla-

TABLE V
RESULTS OF CORRELATIONS WITH EQ 1

Set no.	ρ	pK^0	r	s_ρ	s	n
2	1.07	0.87	0.989	0.04	0.08	15
3	1.90	5.93	0.995	0.07	0.04	9
4	1.09	0.98	0.910	0.19	0.10	9
5	1.66	6.17	0.958	0.29	0.07	5
6	1.05	1.00	0.995	0.03	0.08	14
7	1.20	2.10	0.998	0.05	0.08	9
8	1.20	2.71	0.992	0.04	0.12	16
9	1.47	2.44	0.946	0.12	0.32	19
10	1.56	2.93	0.949	0.14	0.34	16
11[a]	−0.25	Log k^0				
		−3.91	0.990	0.01	0.04	10

[a] Calculated from the equation $\log k = \log k^0 + \rho\Sigma\sigma^\phi$.

tions of the same reaction sets with the σ^ϕ constants.

Discussion

A comparison of Tables III and V shows that the use of the σ^ϕ constants for correlation of the ionization and rate constants of organophosphorus reactions is much more preferable than the use of σ_I and σ_R. The mean correlation coefficient in the first case was 0.972,[25]

(24) The nine reaction sets presented in Table IV practically correspond to 19 reaction sets of Charton[14] and differ only in their compilation. Since Charton has separated the data of one set into several reaction sets, it is natural that he had a larger number of reaction sets than those in Table IV. For example, set 9 corresponds to the six sets of Charton (no. 5, 11, 13, 15, 17, and 19[14]) and set 10 to the five reaction sets (no. 12, 14, 16, 18, and 20[14]). The total number of the constants employed is approximately the same (122).

(25) It should be emphasized that the use of σ^ϕ provides high correlation coefficients not only for correlations with the ionization constants of XYPOOH acids but for many other reaction sets. Thus in our paper in *Uspekhi Khimii* we refer to 59 different reaction sets with an average correlation coefficient of 0.970.[11]

in the second 0.870. In accordance with Student's criterion a probability of the coincidence of these mean values is below 0.01. Moreover in the correlations employing σ^ϕ, the reaction sets of different authors under equivalent or very like conditions lead to the same correlation parameters. For example, sets 2, 4, and 6, respectively, yield ρ 1.07, 1.09, and 1.05 and pK^0 = 0.87, 0.98, and 1.00. Sets 3 and 5 give ρ 1.90 and 1.66, and pK^0 = 5.93 and 6.17. Differences in these values do not exceed the mean deviations. The correlation with Charton's method gives substantially different parameters. The sets 2, 4, and 6 give h = 2.31, 0.23, and 3.02, α = −6.83, −4.78, and −3.78, β = −3.02, −4.05, and −0.62, respectively. The sets 3 and 5 give h = 7.99 and 7.26, α = −13.30 and −12.18, β = 0.44 and −4.80. There is obviously no physical sense in these differences. Thus the Charton correlations, although giving satisfactory results, may lead to serious errors when analyzing the substituent effects on the properties of organophosphorus compounds. This danger may be avoided by using the σ^ϕ constants.

The correlation of σ^ϕ with σ_I and σ_R using eq 7 gives approximately linear dependence with the deviations mentioned above. Such a dependence shows that for organophosphorus compounds the substituent electronic effects are transmitted to the reaction center through inductive and mesomeric mechanisms. It may be assumed that the inductive mechanisms at phosphorus and carbon are in principle the same. This is confirmed by a good linear correlation between σ^ϕ values of alkyl groups and the σ^* Taft constants. As for the resonance effects, there is only a rough similarity between them for purely carbon and phosphorus compounds. For the aryl group bonded to phosphorus a contribution of the resonance component in σ^ϕ coincides with that of the aryl groups at carbon. For the RO, RS, and R_2N groups these contributions are different. For example, for the R_nX groups where X is an atom of the second row (N, O, or F; n varies, respectively, from 2 to 0), the two-parameter correlation of the σ^ϕ constants with σ_I and σ_R leads to the following results: h = −0.46 ± 0.08, α = 2.69 ± 0.16, β = 1.23 ± 0.08, r_3 = 0.648,[26] R = 0.983. However, one should not pay too much attention to this good correlation, but it does indicate that a contribution of the resonance component in the effective constant σ_{eff} is equal to 0.48.

Thus, the contribution of the resonance component to the σ^ϕ constants is determined essentially by the nature of the group attached. The overlap of p and π orbitals of a bonded group with the phosphorus d orbitals obviously differs from that with the π orbitals of benzene ring or some other purely carbon π system. Its dependence on the distances and angles is other than that for the p–p or p–π overlap, and this explains the different contribution of the resonance components to the substituent constants. Thus Charton's dependence of σ^ϕ on σ_I and σ_R is confirmed. In spite of the low correlation coefficient this dependence indicates a common similarity of the substituent effects at phosphorus and carbon. Certainly it would be tempting to employ the σ_I and σ_R constants in the correlation analysis of the organophosphorus reactions, but a more detailed discussion reveals specific differences in the resonance effects of groups at phosphorus and carbon. Certainly one cannot take into account such differences in the correlation with σ_I and σ_R, but this can be done by using the σ^ϕ constants. Therefore in correlation of the reaction rate and equilibrium constants of the organophosphorus compounds the results are better with the σ^ϕ constants. Thus it is the σ^ϕ constants that one should use in solving the correlation problems in the organophosphorus chemistry.

(26) Pair correlation coefficient for σ_R and σ_I.

Calculation of the pK_a Values of Alcohols from σ^* Constants and from the Carbonyl Frequencies of Their Esters

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As an alternative to direct measurement, the pK_a values of primary alcohols (RCH_2OH) may be calculated from σ^* constants by use of the equation pK_a (RCH_2OH) = $-1.316\sigma^*(R) + 15.74$ for alcohols in which C-2 is sp^3 or sp hybridized. For those alcohols in which C-2 is sp^2 hybridized, pK_a (RCH_2OH) = $-1.316\sigma^*(R) + 16.23$. Values of σ^* are based on pK_a data for the corresponding carboxylic acids (RCOOH) or on the carbonyl stretching frequencies of esters of RCH_2OH. Frequencies can be related to σ^* by bonding type: for C-2 (sp^3 or sp^2), $\sigma^*(R) = 0.08996\nu - 156.000$; for C-2 (sp), $\sigma^*(R) = 0.11757\nu - 203.991$; for C-2 ($sp^3$) but R = H or alkyl, $\sigma^*(R) = 0.10828\nu - 188.316$. For secondary alcohols, pK_a values can be calculated from $\Sigma\sigma^*$, the latter values being obtained by use of the additivity principle or from carbonyl frequencies of esters. Measurement of carbonyl frequency offers a novel and facile method for determination of σ^* values.

Aliphatic substituent constants (σ^* or σ_I) provide a measure of the relative effect of chain substituents on the electron density at a reactive atom or functional group. Originally, these constants were derived by Taft from ratios of the rates of acid and alkaline hydrolysis of esters and were shown, subsequently, to be applicable to a wide variety of reaction series, including the dissociation of carboxylic acids and alcohols.[2]

In connection with studies on alcohols as nucleophiles, reliable pK_a values were needed. The available

(1) Associate in the Visting Program, National Institutes of Health, 1967–1970.

(2) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

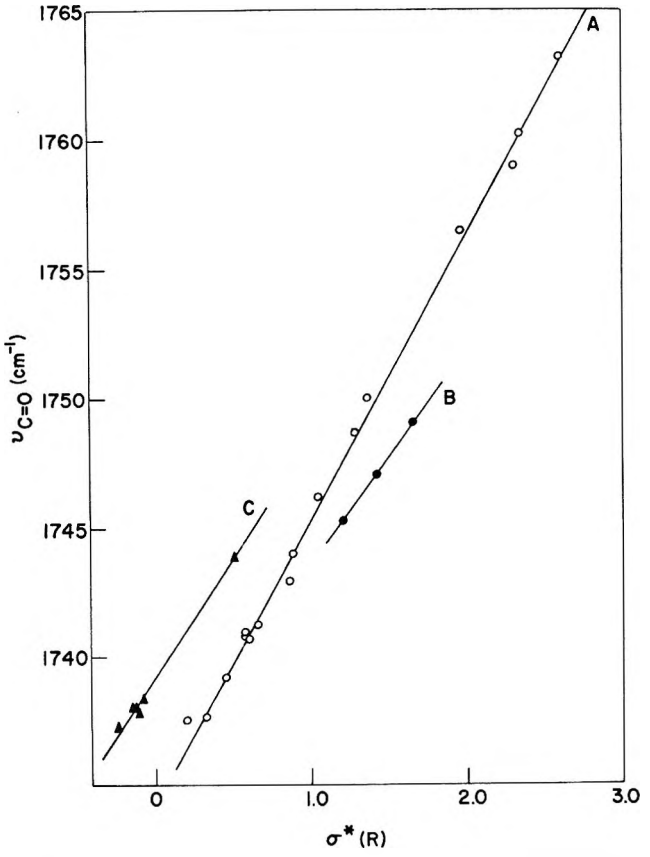

Figure 1.—Plots of σ^*(R) *vs.* $\nu_{C=O}$ ($RCH_2OCOCH_2CH_2Ph$). Line A includes esters of alcohols in which C-2 = sp^3 and carries an electronegative substituent, or C-2 = sp^2; line B for C-2 = sp; line C for C-2 = sp^3 and R = H or alkyl.

literature data[3-6] are scanty and sometimes inconsistent. In addition to the inaccuracies inherent in pH measurement in strongly alkaline media, the instabilities of some β-halogen-substituted alcohols in such media present special problems.[5] We, therefore, chose to calculate new pK_a values from substituent constants and an appropriate linear free energy relationship.[7] Correlations of σ^* with the pK_a values of some alcohols in water[5,6] and in isopropyl alcohol[2] have been demonstrated. We wished to enlarge the scope of the correlation with respect to the pK_a range as well as to secondary and tertiary alcohols. The validity of the calculated pK_a values might be examined by direct determination of pK_a or by correlation with rates of reaction.[8] An independent and particularly facile test was found, however, in our observation that the carbonyl stretching frequencies of esters can be correlated with the σ^* values of substituents in the alcohol moiety.

Results

In his derivation of σ^* values, Taft depended primarily on rate data for acid and alkaline hydrolysis of esters, assuming that steric effects are equivalent in the transition states for the two reactions. The substantial, though not universal, validity of this assumption is borne out in the excellent correlations of σ^* with various other physical and chemical parameters. Charton[9a] has presented arguments, however, in favor of deriving new substituent constants (σ_I) from pK_a values of carboxylic acids, as Hammett had done originally for the aromatic series. The substituent constants used in this study are also based on pK_a values of carboxylic acids, the substituent being defined as R in RCOOH.[3,9b] Regression analysis of pK_a *vs.* σ^* for 40 aliphatic acids provided the line of eq 1 (n =

$$pK_a\,(RCOOH) = -1.700\sigma^*(R) + 4.644 \qquad (1)$$

40, r = 0.9986, s = 0.0142).[10] Our result differs slightly from that obtained by Taft[2] (based on 16 acids) and by Barlin and Perrin.[7] The pK_a and σ^* values of some of the acids used to establish eq 1 are given in Table I, columns 2 and 3. Values of σ^* (calcd) were then obtained from eq 1 (Table I, column 4). Taft has noted the failure of eq 1 for α,β-unsaturated acids.[11] Analysis of pK_a/σ^* data for acids containing an sp^2 carbon at C-2 provides a regression line (eq 2; n = 5,

$$pK_a\,(RCOOH\text{-}sp^2) = -1.795\sigma^*(R) + 5.275 \qquad (2)$$

r = 0.9999, s = 0.0106) of slope similar to that of eq 1. It is noteworthy that α,β-acetylenic acids follow eq 1 rather than eq 2.

Six primary alcohols, whose measured pK_a values were deemed reliable, were used to establish eq 3 (n =

$$pK_a\,(RCH_2OH) = -1.316\sigma^*(R) + 15.74 \qquad (3)$$

6, r = 0.999, s = 0.0273) relating pK_a (RCH_2OH) with σ^* (calcd). This regression line differs slightly from that obtained by Ballinger and Long.[5] For alcohols in which C-2 is sp^2 hybridized, eq 4 is applicable.

$$pK_a\,(RCH_2OH\text{-}sp^2) = -1.316\sigma^*(R) + 16.23 \qquad (4)$$

By use of these equations and σ^* (calcd), pK_a values for a large number of primary alcohols were calculated (Table I, column 6). For comparison, available literature values are given in Table I, column 8.

In connection with another investigation,[8c] 3-phenylpropionate esters of several moderately acidic alcohols had been prepared. It was noted that the carbonyl stretching frequencies of these esters showed a trend consistent with the acidities of the respective alcohol components. Careful measurement of the carbonyl frequencies, at high resolution and under standardized conditions (in CCl_4), of these and numerous other esters of the same acid, provided the values given in Table I, column 5. From a plot of the carbonyl frequency of $PhCH_2CH_2COOCH_2R$ *vs.* σ^*(R) (Figure 1), it became evident that the esters fell into three distinct groups, dependent on the nature of the bond between C-1 and C-2

(3) W. P. Jencks and J. Regenstein in "Handbook of Biochemistry," H. A. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, p J-159.

(4) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 353 (1963).

(5) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **81**, 1050 (1959); **82**, 795 (1960).

(6) J. Murto, *Acta Chem. Scand.*, **18**, 1043 (1964).

(7) See also G. B. Barlin and D. D. Perrin, *Quart. Rev. (London)*, **20**, 75 (1966).

(8) (a) T. C. Bruice, T. H. Fife, J. T. Bruno, and N. E. Brandon, *Biochemistry*, **1**, 7 (1962); (b) J. R. Robinson and L. E. Matheson, *J. Org. Chem.*, **34**, 3630 (1969); (c) S. Takahashi and L. A. Cohen, *ibid.*, **35**, 1505 (1970).

(9) (a) M. Charton, *ibid.*, **29**, 1222 (1964); (b) K. Bowden, M. Hardy, and D. C. Perry, *Can. J. Chem.*, **46**, 2929 (1968).

(10) Regression lines were obtained by use of a General Electric 265 computer: n = number of compounds, r = correlation coefficient, and s = standard deviation of the slope.

(11) Reference 2, p 640.

TABLE I

ACIDITIES OF PRIMARY ALCOHOLS (RCH_2OH) AND CARBONYL FREQUENCIES OF THEIR ESTERS[a]

R	pK_a, RCOOH[b]	σ^* Lit.[c]	σ^* Calcd[d]	$\nu_{C=O}$, cm^{-1}	pK_a (RCH_2OH) Calcd[e]	pK_a (RCH_2OH) Lit.
F_3C	0.23	2.61[f]	2.60	1763.2	12.32	12.37[g,h]
F_2CH	1.24	2.05	2.00		13.11	~ 13.3[h]
FCH_2	2.66	1.10	1.17		14.20	
Cl_3C	0.65	2.65	2.35	1760.2	12.65	12.24[h]
Cl_2CH	1.30	1.94	1.97	1756.5	13.15	12.89[h]
$ClCH_2$	2.86	1.05	1.05	1746.2	14.36	14.31[g,h]
Br_3C	0.72	2.3[i]	2.31	1759.0	12.70	
Br_2CH	1.48	1.6[i]	1.86		13.29	
$BrCH_2$	2.90	1.02[j]	1.03		14.38	
ICH_2	3.12	0.88[j]	0.90	1744.0	14.56	
$NCCH_2$	2.43	1.30	1.30	1748.7	14.03	
CH_3OCH_2	3.53	0.66[j]	0.66	1741.3	14.87	14.82[g,h]
$C_2H_5OCH_2$	3.65		0.58	1741.0	14.98	15.12[k]
$PhOCH_2$	3.17	0.85	0.87	1743.0	14.60	15.1[l]
$PhCH_2$	4.31	0.22	0.20	1737.5	15.48	
$HOCH_2$	3.83	0.56	0.48		15.11	15.07[h]
H	3.77	0.49	0.51	1743.9	15.07	15.09,[g,m] 15.49[h]
CH_3	4.76	0	−0.068	1738.2	15.83	15.90,[g,h] 15.93[m]
C_2H_5	4.88	−0.10	−0.14	1738.0	15.92	16.10[l]
C_3H_7	4.82	−0.12	−0.10	1737.8	15.87	16.10[l]
i-C_3H_7	4.86	−0.19	−0.13	1738.0	15.91	16.10[l]
$(CH_3)_3C$	5.04	−0.30	−0.23	1737.3	16.04	
$HC\equiv C$	1.84[n]	1.7[o]	1.65	1749.1	13.57	13.55[g,h]
$CH_3C\equiv C$	2.60[n]		1.20	1745.3	14.16	
$PhC\equiv C$	2.23[n]	1.35	1.42	1747.1	13.87	
$CH_2=CH$	4.25	0.56[f]	0.57	1740.8	15.48	15.52[h]
$CH_3CH=CH$	4.69	0.36	0.33	1737.6	15.80	
$PhCH=CH$	4.44	0.41	0.46	1739.2	15.62	
Ph	4.20	0.60	0.60	1740.7	15.44	15.4[l]
3,5-Di-NO_2Ph	2.82[p]		1.37	1750.0	14.43	
OHC	3.32	1.1[i]	1.09		14.80	
CH_3CO	2.50	1.65	1.55		14.19	
PhCO	1.32[q]	2.2[f]	2.20		13.33	

[a] With 3-phenylpropionic acid. [b] Taken from ref 3 and 9b except as noted. [c] Taken from ref 2 except as noted. [d] Calculated by use of eq 1 and 2. [e] Calculated by use of eq 3 and 4. [f] Reference 7. [g] Value used to establish eq 3. [h] Reference 5. [i] I. P. Biryukov and M. G. Voronkov, *Latv. PSR Zinat. Akad. Vestis*, 39 (1966); *Chem. Abstr.*, **68**, 44645 (1968). [j] P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968, p 38. [k] Estimated from Figure 1 of ref 6. [l] Reference 6. [m] Derived from kinetic data, ref 6. [n] G. H. Mansfield and M. C. Whiting, *J. Chem. Soc.*, 4761 (1956). [o] J. Hine and W. C. Bailey, Jr., *J. Amer. Chem. Soc.*, **81**, 2075 (1959). [p] J. F. J. Dippy, B. D. Hawkins, and B. V. Smith, *J. Chem. Soc.*, 154 (1964). [q] J. Böeseken, *Recl. Trav. Chim. Pays-Bas*, **40**, 568 (1921).

in the alcohol. The correlations are expressed by eq 5, for esters in which C-2 of the alcohol is sp^3 and carries an electronegative substituent, as well as for esters in which C-2 is sp^2 hybridized; eq 6 for esters in which C-2 is sp hybridized; and eq 7 for esters in which C-2

$$\sigma^*(R) = 0.08996\nu - 156.000 \quad (5)$$

$$\sigma^*(R) = 0.11757\nu - 203.991 \quad (6)$$

$$\sigma^*(R) = 0.10828\nu - 188.316 \quad (7)$$

is sp^3 but R = H or alkyl. The excellent correlations observed[12] demonstrate that the electronic influence of R in RCOOH is linearly related to its influence on the oxygen atom in RCH_2OH and on the carbonyl frequency in RCH_2OCOR'. Thus, new values of σ^*, or reevaluation of older values, may be obtained either from pK_a data on carboxylic acids or from carbonyl frequencies of esters of the corresponding primary alcohols. In turn, pK_a values of the alcohols may be calculated from such σ^*constants. For 22 primary alcohols, pK_a values calculated from σ^*(RCOOH ionization) and from σ^*(ester carbonyl frequency) agreed to within ±0.05 pK unit; three others (R = $PhCH_2$, $PhOCH_2$, and Br_3C) differed by 0.1 pK unit.

The validity of eq 3 and 4 for secondary and tertiary alcohols was also examined. Values of $\Sigma\sigma^*$ (Table II, column 5) were obtained by addition of the appropriate σ^* values (Table I, column 4), followed by subtraction of σ^*(H) for each hydrogen atom replaced in RCH_2OH. Values of $\Sigma\sigma^*$, calculated from carbonyl frequencies, are given in Table II, column 6. Although a critical test is limited by the scarcity of experimental pK_a values (Table II, column 8), the calculated pK_a values (Table II, column 7) are reasonably satisfactory, at least for secondary alcohols. The values of $\Sigma\sigma^*$ obtained for the two tertiary alcohols by the alternate methods differ significantly, those based on spectral data being considered the more reliable.

Discussion

The acidities of alcohols may be determined by direct measurement of ionic equilibria or, indirectly, from kinetic or spectral data. The difficulties inherent in

(12) Statistical data: (for eq 5) $n = 14$, $r = 0.999$, $s = 0.002$; (for eq 6) $n = 3$, $r = 0.9999$, $s = 0.002$; (for eq 7) $n = 6$, $r = 0.994$, $s = 0.005$.

TABLE II

ACIDITIES OF SECONDARY AND TERTIARY ALCOHOLS AND CARBONYL FREQUENCIES OF THEIR ESTERS

R	R′	R″	$\nu_{C=O}$, cm^{-1}	$\Sigma\sigma^{*a}$	$\Sigma\sigma^{*b}$	pK_a —(RR′R″COH)— Calcd[c]	Lit.
F_3C	F_3C	H	1785.8	4.69	4.65	9.62	9.3[d]
Cl_3C	Cl_3C	H	1780.0	4.19	4.13	10.30	
F_3C	CH_3	H	1765.5	2.02	2.02	13.08	11.8[e]
Ph	Ph	H	1741.7	0.69	0.68	15.34	15.63[f]
CH_3	CH_3	H	1733.3	−0.65	−0.63	16.57	17.1[g]
CH_3	CH_3	CH_3	1731.4	−1.23	−0.84	16.84	15.8,[h] 19.2[g]
F_3C	F_3C	F_3C	1820[i]	6.78	7.73	5.57	5.4[d]

[a] Calculated from the values in Table I, column 4. [b] Calculated by use of eq 5–7. [c] Calculated by use of eq 3 and 4, and the values of $\Sigma\sigma^*$ in column 6. [d] B. L. Dyatkin, E. P. Mochalina, and I. L. Knunyants, *Tetrahedron*, 21, 2991 (1965). [e] A. L. Henne and R. L. Pelley, *J. Amer. Chem. Soc.*, 74, 1426 (1952); the validtiy of this value is doubtful (see ref 5). [f] Estimated from Figure 1 of ref 6. [g] Derived from kinetic data, ref 6. [h] M. Martin, *J. Chim. Phys.*, 59, 736 (1962). [i] Reference 16, as the acetate ester.

Although carbonyl frequencies have been measured for a large number of esters, variation in the nature of the alcohol component has been limited, largely, to the simplest alkyl cases. It is, therefore, not surprising that little range in carbonyl frequency has been observed for esters of a single acid. Infrared data for the acetates of a number of polyfluoro alcohols have been reported, together with qualitative evidence for a dependence of the band position on the pK_a of the alcohol involved.[16] By measuring the carbonyl frequencies of a large number of esters whose alcohol components cover a range of 8 pK units in their acidities, we have been able to demonstrate the existence of linear correlations between frequency and σ^*, and, indirectly, with alcohol pK_a. Accurate measurement of the carbonyl frequencies of esters of other alcohols should permit the calculation and prediction of their acidities, as well. A few random measurements indicated that the carboxylic acid component of the ester should not vary in order to obtain linear correlations.

TABLE III

ESTERS OF 3-PHENYLPROPIONIC ACID[a]

Ester	Registry no.	Mp or bp (mm), °C	Ester	Registry no.	Mp or bp (mm), °C
Ethyl	2021-28-5	83–84 (1)	Benzhydryl (A)[b]	28049-02-7	53–54
Propyl	13326-06-2	75 (0.3)	Chloroethyl	28049-03-8	118–119 (0.8)
Isopropyl	22767-95-9	89 (0.9)	Dichloroethyl	28049-04-9	134 (1.5)
Butyl	20627-49-0	91 (0.3)	Tribromoethyl	28049-05-0	159 (0.4)
Isobutyl	28048-94-4	99 (0.6)	Hexachloroisopropyl (B)	28049-06-1	36–37
tert-Butyl[c]	16537-10-3	84–85 (0.5)	1,1,1-Trifluoro-2-propyl	28049-07-2	84 (1.4)
Neopentyl	28048-96-6	82 (0.3)	Methoxyethyl	28049-08-3	113–115 (0.6)
Allyl	15814-45-6	97–98 (0.8)	Ethoxyethyl	22524-30-7	116 (0.4)
Cinnamyl	28048-98-8	162–163 (0.3)	Phenoxyethyl	28049-09-4	143 (0.1)
2-Butynyl	28048-99-9	108 (0.3)	Phenethyl	28049-10-7	142 (0.2)
Phenylpropargyl	28049-00-5	163 (0.3)	Iodoethyl	28049-11-8	115 (0.1)
Benzyl	22767-96-0	165 (2)	Cyanoethyl	28049-12-9	121 (0.2)

[a] All compounds provided acceptable elemental analyses. The methyl, propargyl, trichloroethyl, trifluoroethyl, hexafluoroisopropyl, and 3,5-dinitrobenzyl esters have been reported previously (ref 8c). [b] Solvents for recrystallization: A, cyclohexane; B, petroleum ether. [c] Prepared by an alternative method, bp 86–88° (1.5 mm): W. v. E. Doering and R. M. Haines, *J. Amer. Chem. Soc.*, 76, 482 (1954).

direct measurement have already been noted.[5] Kinetic methods may involve the use of alcohols or their anions as nucleophiles[6] or may be based on the relative reactivities of their esters toward various nucleophilic species.[8] Although several impressive correlations of alcohol acidity with rate data have been obtained, the complications which may result from variable steric interactions[13] and solvation requirements cannot be ignored. We were, therefore, led to consider the advantages of acquiring such data by use of spectral characteristics of esters, for which concentration, solvent, and steric effects should be minimal.

Efforts to correlate the stretching frequencies of alcohols with the electronic nature of substituents have been unsuccessful, due to complications such as association, internal hydrogen bonding, conformational effects, and a low sensitivity of the frequency to acidity changes.[14] On the other hand, the intensities of the same absorption bands have been related to σ^* for a moderate number of compounds.[15]

As may be seen from Figure 1, separate plots are required to correlate alcohols containing electron-withdrawing and electron-releasing substituents, as well as those with α,β-acetylenic linkages. Since the physical basis of any correlation of infrared frequency with electronic effects is poorly understood, the existence of these separate categories is, for the present, best left in the realm of empirical observation.

The results also indicate that the transmission coefficient, for induction through a lone pair atom, need not vary with the electronegativity of the substituent. Although the constancy of such a coefficient is often taken for granted, few studies have been available which permit a clarification of the question.

Experimental Section[17]

Alcohols.—The alcohols employed were of the highest purity commercial materials available. Hexachloro-2-propanol, mp 86–87°, was prepared by reduction of hexachloroacetone with sodium borohydride in tetrahydrofuran.[18] Similarly, phenyl-

(13) R. W. A. Jones and J. D. R. Thomas, *J. Chem. Soc. B*, 661 (1966).
(14) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen & Co., London, England, 1968, Chapter 4.
(15) T. L. Brown, *J. Amer. Chem. Soc.*, 80, 6489 (1958); *Chem. Rev.*, 58, 581 (1958).
(16) R. Filler and R. M. Schure, *J. Org. Chem.*, 32, 1217 (1967).
(17) Melting points and boiling points are uncorrected. Microanalyses were performed by the Microanalytical Services Section of this laboratory, under the direction of Dr. W. C. Alford.
(18) M. Geiger, E. Usteri, and C. Gränacher, *Helv. Chim. Acta*, 34, 1335 (1951).

propargyl alcohol, bp 112° (1 mm), was prepared by borohydride reduction of phenylpropargyl aldehyde.[19] 3,5-Dinitrobenzyl alcohol was obtained by reduction of 3,5-dinitrobenzoic acid with diborane in tetrahydrofuran. The crude product was chromatographed on silica gel (chloroform–methanol, 95:5) and recrystallized from chloroform, mp 78–81°.

Anal. Calcd for $C_7H_6N_2O_5$: C, 42.42; H, 3.05; N, 14.14. Found: C, 42.60; H, 3.25; N, 14.19.

Esters.—All esters of 3-phenylpropionic acid were prepared by a modification of the trifluoroacetic anhydride method previously described.[8c] A mixture of trifluoroacetic anhydride (210 g, 1 mol) and 3-phenylpropionic acid (150 g, 1 mol) was stored at 40° for 2 hr. Following removal of trifluoroacetic acid under reduced pressure, a residual oil (220 g) was obtained, consisting mainly of the mixed anhydride. Although the latter could be purified by distillation [bp 67° (0.3 mm)], the crude material was used for further work. To 12.5 g of the mixed anhydride, at 0°, was added 0.05 mol of alcohol, and the mixture stored at ambient temperature overnight. The reaction mixture was poured into 3% sodium bicarbonate and the ester separated by filtration or ether extraction. The esters were purified by distillation under reduced pressure or recrystallization (Table III). Yields varied from 60 to 90%. In the case of *tert*-butyl alcohol, the components were mixed at −20° and stored at 0° for 2 days.

Infrared Spectra.—Spectra were measured on solutions of esters in carbon tetrachloride (0.012–0.025 *M*) using a Perkin-Elmer Model 521 spectrophotometer, whose monochromator and source compartments were flushed continuously with dry nitrogen. The carbonyl region was scanned slowly (15 sec/cm^{-1}) and spectra were recorded in duplicate, at a chart speed of 5 cm^{-1}/cm. Intervals were marked with frequency counter-synchronized pips, whose positions were calibrated against standard water vapor lines, recorded under the same conditions. The transmittance minima given in Tables I and II are the averages of six readings (on duplicate runs) and have been corrected by calibration against water vapor. In general, readings agreed to better than ±0.2 cm^{-1}.

Acknowledgment.—We are indebted to Dr. S. Milstien for assistance in computer calculation, to Dr. I. Levin for assistance in recording of spectra, and to Dr. H. A. Saroff for valuable discussion.

(19) H. H. Guest, *J. Amer. Chem. Soc.*, **47**, 860 (1925).

Substituent Effects in the Reaction Rates of 2-Arylhexafluoroisopropyl Glycidyl Ethers with Dibutylamine

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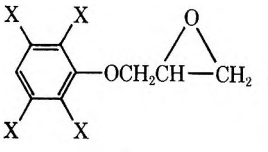
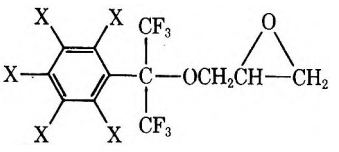
The effects of ring fluorine substituents upon the reactivity of compounds of structure $ArC(CF_3)_2OCH_2\overline{CHCH_2}O$ (**2**) with dibutylamine in alcohol have been studied. It was found that *o*-fluorine atoms exert a pronounced activating influence upon the rate of epoxide ring opening, whereas *m*- and *p*-fluorines exert a deactivating influence. These effects are not generally additive, however, in compounds containing several ring fluorine atoms. In addition, an *o*-bromine atom was found to accelerate the amine–epoxide reaction, while *o*-methyl groups had an opposite effect. Second-order rate constants are presented for each of the reactions studied, and a mechanism consistent with the observed substituent effects is proposed.

In a recent study[1] we observed that tetrafluorophenyl glycidyl ether[2] (**1b**) reacts more slowly with dibutylamine in alcohol than does phenyl glycidyl ether (**1a**), whereas the glycidyl ether of 2-pentafluorophenylhexafluoropropanol-2 (**2b**) under identical conditions reacts nearly twice as fast as does its non-ring-fluorinated analog **2a**. Furthermore, it was found that meta CF_3 groups deactivate both parent compounds by comparable amounts.



1a, X = H
b, X = F



2a, X = H
b, X = F

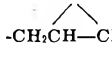
Since both F and CF_3 substituents deactivate the epoxide ring of **1a**, and meta CF_3 groups also deactivate **2a**, the activation of compound **2b** over **2a** seemed quite unusual. In order to determine the factors responsible for this behavior, it was desirable to study the rates of reaction of amines with compounds similar to **2b**. We therefore undertook an investigation of the amine reactivity of molecules of structure **2** containing various patterns of fluorine substitution on the aromatic ring. In addition, two compounds containing ring substituents other than fluorine were synthesized and studied.

Results and Discussion

Synthesis of the Glycidyl Ethers.—Table I presents structures and physical properties of the compounds, all of which are new to the literature, used for kinetic studies. Syntheses were achieved *via* the addition of Grignard or aryllithium reagents to hexafluoroacetone, followed by reaction of the tertiary alcohols with epichlorohydrin and base (*e.g.*, Scheme I). Table I lists nmr data for the compounds.

Several aspects of the synthetic work appear to be noteworthy. The reaction of 1,2,4,5-tetrafluorobenzene with stoichiometric amounts of butyllithium and hexafluoroacetone in tetrahydrofuran produced a 1:1 mixture of mono- and disubstituted products, rather than favoring monoaddition as expected.[3] However, by using diethyl ether as the solvent the ratio of mono- to disubstitution could be increased to 100:1 (Scheme II). This pronounced solvent shift is presumably due to the weaker solvating ability of the diethyl ether for the dilitho derivative.[3,4]

(1) S. A. Reines, J. R. Griffith, and J. G. O'Rear, *J. Org. Chem.*, **35**, 2772 (1970).

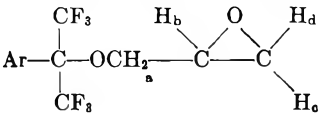
(2) The term "glycidyl" is used to denote the structure 

(3) R. J. Harper, E. J. Soloski, and C. Tamborski, *J. Org. Chem.*, **29**, 2385 (1964).

(4) R. J. Harper and C. Tamborski, *Chem. Ind. (London)*, 1824 (1962).

TABLE I

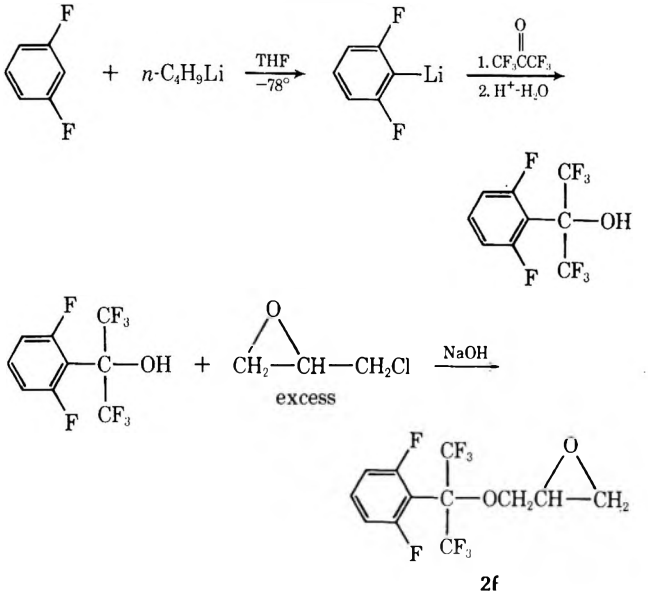
STRUCTURES AND PROPERTIES OF COMPOUNDS 2c–j



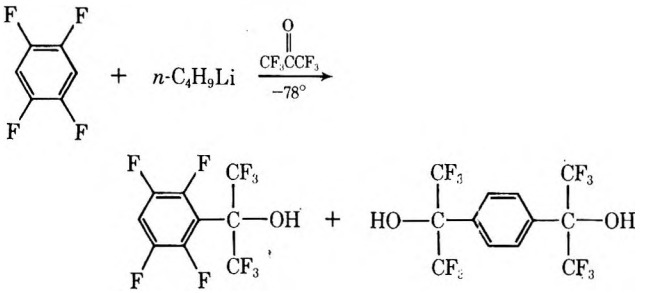
Compd[a]	Ar	Yield, %[b]	$n^{20}D$	Bp, °C (10 mm)	Nmr data[e,f] $H_{aromatic}$	H_a[g]	H_b	H_c	H_d	CH_3
					7.67 (1)					
2c	2-FC_6H_4	50	1.4373	113	7.43 (1)	3.80	3.19	2.77	2.59	
					7.2–7.0 (2)	3.54				
2d	3-FC_6H_4	44	1.4355	107	7.5–7.0 (4)	3.90	3.18	2.76	2.63	
						3.53				
2e	4-FC_6H_4	40	1.4308	105	7.62 (2)	3.88	3.19	2.78	2.64	
					7.14 (2)	3.49				
2f	2,6-$F_2C_6H_3$	82	1.4292	124	7.48 (1)	3.63	3.19	2.74	2.50	
					7.01 (2)					
2g	3,5-$F_2C_6H_3$	53	1.4190	100	7.21 (2)	3.93	3.18	2.79	2.64	
					6.93 (1)	3.56				
2h	2,3,5,6-F_4C_6H	76	1.4164	119	7.33[i]	3.65	3.21	2.79	2.53	
					7.76 (1)					
2i	2-BrC_6H_4	40	1.4770	128[c]	7.60 (1)	3.65	3.32	2.76	2.54	
					7.5–7.1 (2)					
2j	2,6-$(CH_3)_2C_6H_3$	62	*d*	134	7.06 (3)	3.62	3.14	*h*	*h*	2.67 (3)[j]
						3.37				2.45 (3)[k]

[a] Satisfactory analytical data have been obtained for all of the compounds listed. [b] Per cent conversion from corresponding hydroxy compounds. [c] Boiling point at 5.0 mm. [d] Solid, mp 53–54°. [e] Parts per million downfield from tetramethylsilane in CCl_4 solution. [f] Assignment of epoxide protons is based on that made for monosubstituted epoxides by P. A. Cruickshank and M. Fishman, *J. Org. Chem.*, **34**, 4060 (1969). [g] Listing of dual signal indicates chemical nonequivalence of the geminal protons. [h] Obscured by CH_3 absorption. [i] Quintet. [j] Singlet. [k] Multiplet.

SCHEME I

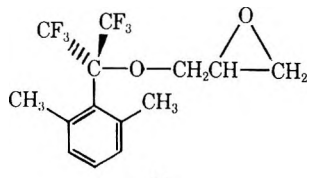


SCHEME II



THF 1:1
ether 100:1

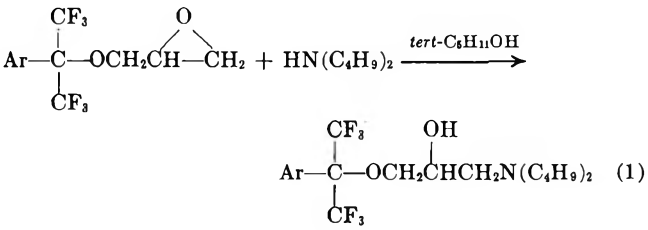
Compound **2j** is of interest because of the extreme hindrance, created by the *o*-methyl groups, to rotation



2j

of the aromatic ring around the Ar–$C(CF_3)_2$ bond. The nmr spectrum of this compound at room temperature exhibits two distinct methyl absorptions (Table I), indicating that the ring is essentially prevented from rotating. Models indicate only one possible conformation for the molecule, that in which the CF_3 groups are perpendicular to the plane of the ring, and the ether oxygen is jammed into one of the methyl groups.

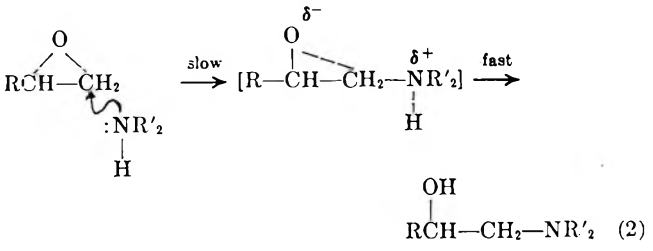
Amine–Epoxide Reaction.—The reaction of compounds of type **2** with dibutylamine in alcohol proceeds *via* nucleophilic attack at the terminal epoxide carbon atom to form a β-amino secondary alcohol. No evidence of attack by the amine at the substituted ring position has been found for this system,[1] presum-



(1)

ably because steric hindrance prohibits that mode of reaction.

In protic solvents, formation of the C–N bond with simultaneous cleavage of the epoxide C–O bond is believed to be the slow step of amine–epoxide reactions. This rate-limiting step is then followed by rapid proton transfer to the incipient hydroxyl group.[5–7] In agreement with this SN2 mechanism, reaction 1 has been found to obey second-order kinetics when dilute (0.2 *M*) solutions of the reactants are employed.[1]



$$\text{RCH(O)CH}_2 + :\text{NR}'_2\text{H} \xrightarrow{\text{slow}} [\text{R—CH(O}^{\delta-}\text{)—CH}_2\text{—NR}'_2\text{H}^{\delta+}] \xrightarrow{\text{fast}} \text{RCH(OH)—CH}_2\text{—NR}'_2 \quad (2)$$

Fluorine Substituent Effects.—In order to isolate the factors responsible for the high reactivity of **2b,** rates of reaction of the mono- and disubstituted compounds **2c–g** with dibutylamine were measured. Compound **2h** was also studied, because of its direct analogy to **1b.** Disappearance of the reactants was followed by gas chromatographic analysis. Figure 1 depicts the straight-line plots obtained by graphing glycidyl ether concentration as a function of time, for the reaction of equimolar quantities of amine and epoxide. Under these conditions the slope of each line represents an individual rate constant.

$$\frac{1}{[\text{glycidyl ether}]_t} = -k_2 t + [\text{glycidyl ether}]_{t_0}$$

It is clear from Figure 1 that *m*- and *p*-fluorine atoms deactivate the epoxide ring toward nucleophilic attack by dibutylamine.[8] The magnitude of deactivation appears to be very similar for both ring positions. In addition, the effects appear to be roughly additive, since two meta F atoms decrease the rate constant of 2a by about twice as much as does a single *m*-fluorine substituent. CF_3 groups in the meta positions exhibit identical behavior.[1]

Figure 1 shows that *o*-fluorine atoms exert an opposite, activating influence upon amine–epoxide reactivity. All compounds containing ortho F atoms were activated relative to **2a,** in spite of "deactivating" substituents on other ring positions. That the *o*-fluorine effects are not additive with those of the meta or para positions can be seen by comparing the slope of **2h** or **2b** with that of **2f.** The combination of two *o*- and two *m*-fluorines is expected to make compound **2h** considerably less reactive than **2f,** which contains only "activating" *o*-fluorines. Likewise, **2b,** which contains three "deactivating" and two "activating" fluorines, should be the least reactive of these three compounds. However, all three produced similar rate constants when treated with dibutylamine, and, in fact, **2b** reacted

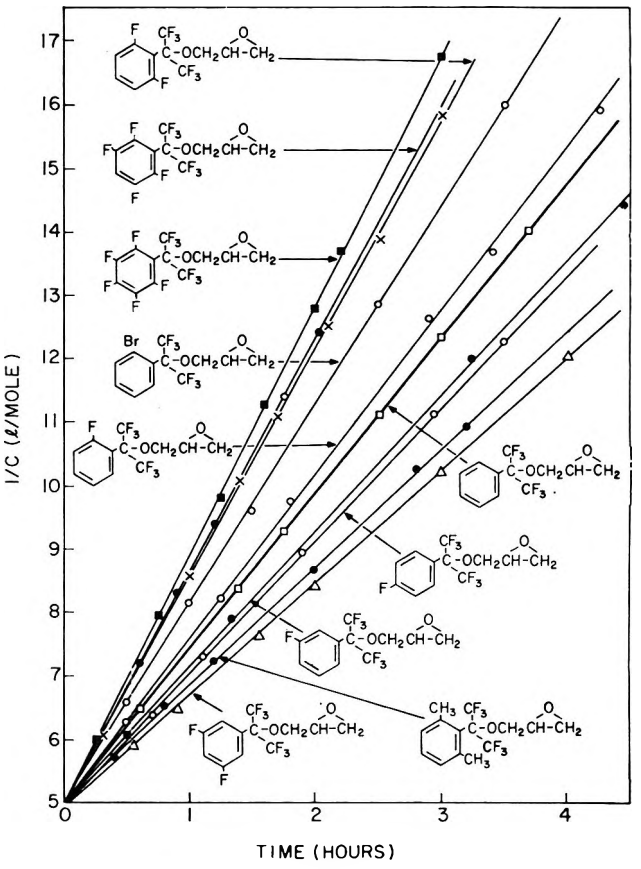


Figure 1.—Reaction of dibutylamine with various glycidyl ethers using equimolar amounts of reactants in *tert*-amyl alcohol (T = 60°). Reciprocal concentration of the glycidyl ether is plotted as a function of time.

slightly faster than the others. The presence of fluorine in both ortho positions seems to cancel the effect of *m*- or *p*-fluorines and defines the molecule's reactivity somewhat independently of these more distant substituents.

A comparison of the reactivity of **2c** to that of **2f** reveals the pronounced change associated with the addition of a second *o*-fluorine atom to the singly substituted compound **2c.** A single *o*-fluorine produces only slight activation relative to the unsubstituted parent compound **2a.** This slight effect is magnified by a factor of 8 however, when the remaining *o*-hydrogen is replaced by fluorine.

Rate constants illustrating these phenomena are presented in Table II. The activation energy of the reac-

TABLE II

RATE CONSTANTS FOR THE REACTION OF COMPOUNDS OF TYPE 2 WITH DIBUTYLAMINE IN *tert*-AMYL ALCOHOL

Compd	$10^4 k_2$[a] (T = 51°)	$10^4 k_2$ (T = 60°)
2a	4.88	7.03
2b	7.71	11.14
2c	5.24	7.43
2d		6.0
2e		5.98
2f	7.13	10.27
2g	3.36	5.12
2h	6.99	10.25
2i		9.03
2j	3.44	5.32

[a] k_2 in l. mol^{-1} sec^{-1}.

(5) N. B. Chapman, N. S. Isaacs, and R. E. Parker, *J. Chem. Soc.*, 1925 (1959).

(6) L. Schecter, J. Wynstra, and R. P. Kurkjy, *Ind. Eng. Chem.*, **48**, 94 (1956).

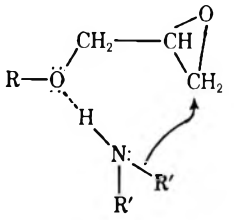
(7) N. S. Isaacs and R. E. Parker, *J. Chem. Soc.*, 3497 (1959).

(8) The rate curves for compounds **2a,b,** taken from ref 1, have been redrawn in this paper for the purpose of comparison.

tion of dibutylamine with compounds of type 2 in *tert*-amyl alcohol is about 10–11 kcal/mol, and the entropy of activation[9] is about −43 eu.[1]

Effects of Other Ortho Substituents.—In order to determine the influence of some ortho substituents other than fluorine, compounds **2i** and **2j** were synthesized. As can be seen from Table II, these two compounds differ widely in their reactivity with dibutylamine. An *o*-bromine atom exerts an activating influence, whereas *o*-methyl groups cause significant deactivation relative to unsubstituted **2a**.

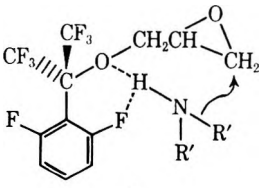
Mechanistic Interpretation.—We have shown[1] that the mechanism of glycidyl ether–amine reactions in alcohol appears to involve a hydrogen-bonded intermediate such as **3**. In the case of compounds of type



3

1 (R = Ar), electron-withdrawing groups on the aromatic ring deactivate the epoxide ring toward attack by the amine. This deactivation presumably results from decreased electron density around the ether oxygen[10] and consequent reduction of its ability to associate with the amino hydrogen atom. The deactivation of compounds of type **2** (R = $ArC(CF_3)_2$–) by electron-withdrawing substituents in meta or para positions is believed to occur for this same reason.

According to this theory, compounds of type **2** which contain *o*-fluorine atoms should also be deactivated. Since these compounds instead show increased reactivity with dibutylamine, it would appear that *o*-fluorines exert a special influence. We believe that the influence results from an intermediate such as **4**, in



4

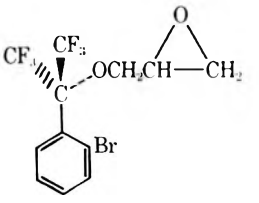
which *o*-fluorine atoms contribute to the hydrogen bond formed with the amino hydrogen.[11] Models indicate that in compounds containing two ortho F atoms the *gem*-CF_3 groups are somewhat constrained in the conformation shown. This constraint forces the glycidyl ether oxygen to lie very close to an ortho F atom, which should then allow a hydrogen bonded complex such as **4** to form. This effect appears to outweigh the expected deactivation resulting from electron-withdrawing substituents and produces an activated epoxide ring.

In compound **2c**, which contains only one ortho F atom, the rotation of the benzylic carbon atom appears to be hindered only slightly. The glycidyl ether oxygen atom is not held in position near the *o*-fluorine, and therefore a complex such as **4** should be relatively unimportant. In accordance with this reasoning, compound **2c** shows only slight activation relative to the parent compound **2a**.

The *o*-fluorine atoms in compound **1b** are not in close proximity to the glycidyl ether oxygen, as they are in similarly ring-substituted compounds of type **2**. The deactivating inductive effect of the ring fluorines upon the glycidyl ether oxygen appears to be the determining factor in the reactivity of **1b** with dibutylamine. No special activating influence seems to operate in compounds of this structure.

As further evidence for the existence of an intermediate of type **3** or **4**, the diminished reactivity of compound **2j** may be cited. In this molecule the glycidyl ether oxygen is buried beneath one of the *o*-methyl groups and the *gem*-CF_3 groups, and should be barely accessible for hydrogen bonding to the amine. Decreased reactivity is therefore predicted for this compound and is also observed.

The predicted reactivity of compound **2i**, which contains an *o*-bromine atom, is somewhat ambiguous. The bromine substituent provides considerable steric hindrance to rotation around the Ar–$C(CF_3)_2$ bond, and one of the two preferred conformations (**5**) places it against



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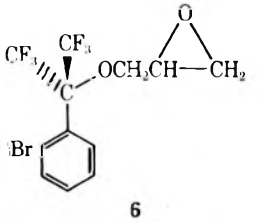

6

the ether oxygen atom. It is not clear, however, whether the bromine atom would participate in hydrogen bonding with an amino hydrogen.[12,13] In any case, the reaction rate of **2i** is considerably greater than that of **2a**, or even **2c**, which contains a single *o*-fluorine atom. This observation leads us to believe that the bromine atom may, in fact, participate in a complex such as **4**, when the molecule is in conformation **5**.

Experimental Section

Nuclear magnetic resonance spectra were obtained at 24° as 10–20% solutions in CCl_4 on a Varian HA-100 spectrometer, using tetramethylsilane as an internal standard. Infrared spectra were run as smears of the neat liquids between salt plates on a Perkin-Elmer Model 457 grating spectrophotometer. All glycidyl ethers were fractionated on a Nester-Faust auto annular teflon spinning-band still at reduced pressure, prior to use in kinetic experiments. Analytical samples of the glycidyl ethers were used for all kinetic runs. Elemental analyses were performed at the Schwarzkopf Laboratories, Woodside, N. Y.

Materials.—Purification of the dibutylamine and *tert*-amyl alcohol used for kinetic studies has been described previously.[1] Starting materials including *m*-difluorobenzene, 1,2,3,4-tetrafluorobenzene, 2-bromo-*m*-xylene, and *o*-, *m*-, and *p*-fluoro-

(9) Calculated at 300°K according to J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 71.

(10) It can be seen that the ring substituents are "insulated" from the ether oxygen by the $-C(CF_3)_2-$ group. However, studies of ring-substituted phenylacetic acid show that substituent effects are transmitted with nearly 50% efficiency through an "insulating" carbon atom.

(11) This intermediate was tentatively suggested by us in ref 1, to account for the high reactivity of compound **2b**.

(12) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience, New York, N. Y., 1967, p 215.

(13) P. A. Cruickshank and M. Fishman, *J. Org. Chem.*, **34**, 4060 (1969).

bromobenzene were obtained from the Aldrich Chemical Co. and used as received.

2-(2,6-Difluorophenyl)hexafluoro-2-propanol.—To a predried 500-ml flask equipped with N_2 atmosphere, Dry Ice condenser, and mechanical stirrer were added 250 ml of dry THF and 56 ml (0.15 mol) of 22% C_6H_8Li in hexane. The solution was cooled to −78°, and 17 g (0.15 mol) of *m*-difluorobenzene in 30 ml of THF was added over a period of 10 min.[14] The clear solution was stirred at −78° for 2 hr, after which time 30 g (0.18 mol) of hexafluoroacetone was distilled from a Dry Ice trap into the flask. After 2 hr more the solution was allowed to warm to room temperature. Most of the THF was then distilled from the flask before hydrolysis of the lithium complex in order to avoid formation of a THF–product azeotrope. HCl (2 *N*, 200 ml) was then added to the residue, followed by 150 ml of ether. The two-phased mixture was transferred to a separatory funnel, and the ethereal layer was separated, washed twice with H_2O and twice with saturated aqueous NaCl, and dried over Na_2SO_4. Clear, colorless material (22 g, 82%), bp 98–100° (41 mm), was collected after distillation through a 6-in. Vigreux column. The infrared spectrum of this product showed a sharp OH absorption at 3620 cm^{-1}, strong C–F bands at 1300–1100 cm^{-1}, and characteristic aromatic bands at 1630, 1580, and 1470 cm^{-1}. Its nmr spectrum displayed signals centered at 7.45 (m, 1, Ar H), 6.98 (m, 2, Ar H), and 4.78 (s, broad, 1, OH).

2-(3,5-Difluorophenyl)hexafluoro-2-propanol.—2,4-Difluoroaniline was converted to 3,5-difluorobromobenzene by published procedure.[15] The Grignard reagent was prepared from 40 g (0.2 mol) of this product in 200 ml of Et_2O, using a few drops of MeI to initiate the reaction. Hexafluoroacetone was introduced at room temperature, followed by gentle heating for 1 hr. The magnesium complex was then hydrolyzed with 2 *N* HCl, and work-up was carried out as described above. Distillation of the ethereal solution yielded an azeotrope, bp 160° (760 mm), composed of Et_2O and about 30 g (52% yield) of the desired product. The nmr spectrum of a pure product sample (collected by glc) displayed signals at δ 7.27 (d, 2, Ar H), 6.93 (triplet of triplets, 1, Ar H), and 4.26 (s, 1, OH), and the infrared spectrum revealed a characteristic hydroxyl band at 3600 cm^{-1}.

2-(2,3,5,6-Tetrafluorophenyl)hexafluoro-2-propanol.—To 15 g (0.1 mol) of 1,2,4,5-tetrafluorobenzene at −78°, under a nitrogen atmosphere, were added 250 ml of anhydrous Et_2O and 27.7 g (0.1 mol) of 23.1% butyllithium in hexane. The solution was stirred for 2 hr and then 16.6 g (0.1 mol) of hexafluoroacetone was added. After warming to room temperature, the stirred solution was treated with 200 ml of 2 *N* HCl. The usual work-up, followed by distillation on a 6-in. Vigreux column, led to 23 g (73%) of the desired prouct: bp 90–91° (40 mm); nmr δ 7.21 (quintet, 1, Ar H) and 4.13 (s, 1, OH); ir 3620 cm^{-1} (OH).

Use of THF as the solvent in this reaction produced 1,4-di(2-hydroxyhexafluoro-2-propyl)tetrafluorobenzene in about 30% yield, along with a 30% yield of the above-named product. The disubstituted compound had mp 99–101° and was characterized by its mass spectrum, which showed a parent ion at *m/e* 482 (calcd 482) and a consistent fragmentation pattern. Its nmr spectrum had a single, broad absorption at δ 4.17, and an ir spectrum of the solid on NaCl plates displayed a very sharp OH stretch at 3590 cm^{-1}.

2-(2,6-Dimethylphenyl)hexafluoro-2-propanol.—Into a three-neck flask equipped with magnetic stirrer, Dry Ice condenser, and N_2 atmosphere were placed 400 ml of anhydrous Et_2O and 30 g (0.16 mol) of 2-bromo-*m*-xylene. An excess of *n*-C_4H_9Li in hexane was added slowly, causing a white suspension to form. The reaction mixture was heated to reflux and held there for 2 hr, after which time glc analysis revealed little remaining starting material. Excess hexafluoroacetone was added, causing the suspension to disappear. The clear solution was hydrolyzed with 2 *N* HCl, and after work-up and distillation 16 g (36%) of product, bp 130° (40 mm), was obtained: nmr δ 7.04 (m, 3, ArH), 3.25 (s, 1, OH), 2.62 (s, 3, CH_3), and 2.47 (m, 3, CH_3); ir 3600 (OH), 2750 (aliphatic CH), 1590, and 1460 cm^{-1} (aromatic).

2-Fluorophenylhexafluoro-2-propanol.—The ortho, meta, and para isomers were made from the Grignard reagent of the corresponding bromofluorobenzene and hexafluoroacetone, using ether as a solvent. These materials were not isolated as pure compounds but were reacted without extensive purification to form the corresponding glycidyl ethers. The Grignard reagent of *o*-bromofluorobenzene was produced in the presence of hexafluoroacetone and gave rise to the desired product in 30% yield.

2-Bromophenylhexafluoro-2-propanol.—In addition to producing the expected 2-fluorophenylhexafluoro-2-propanol, the Grignard reaction of *o*-bromofluorobenzene with hexafluoroacetone led to the formation of 2-bromophenylhexafluoropropanol-2 in variable yield.[16] It was necessary to add the hexafluoroacetone to the ethereal solution of starting material as soon as reaction with magnesium had begun, to minimize the formation of benzyne products.

o-Bromofluorobenzene (25 g) treated with Mg and hexafluoroacetone as described above, produced about 10 g of white solid. This material formed nearly colorless crystals, mp 37–40°, when recrystallized carefully from hexane. Its ir spectrum showed a strong band at 3500 cm^{-1} (OH), bands at 1595, 1570, and 1480 (aromatic), 1060, 1030, 760 cm^{-1} (ortho-substituted aromatic), and broad absorption around 1200 cm^{-1} (CF). Mass spectral analysis indicated the presence of bromine (parent peak at *m/e* 322 and P + 2 = 98% P) and showed strong peaks at 253, 255 (loss of CF_3) and 184, 186 (loss of $2CF_3$). The nmr contained signals centered at δ 7.66 (m, 2, Ar H), 7.28 (m, 2, Ar H), and 5.20 (s, 1, OH).

Preparation of the Glycidyl Ethers.—These compounds were synthesized and purified according to published procedure[1] from the intermediate alcohols described above. Table I presents the physical properties of the glycidyl ethers.

Rate Measurements.—The kinetic procedure employed has been described previously.[1] Rate constants have been shown to be reproducible to within 1% in a typical case and to within 3% in the least favorable case.

Registry No.—**2a,** 25056-11-5; **2b,** 25080-58-4; **2c,** 28180-36-1; **2d,** 28180-37-2; **2e,** 28180-38-3; **2f,** 28180-39-4; **2g,** 28292-00-4; **2h,** 28180-40-7; **2i,** 28180-41-8; **2j,** 28180-42-9; dibutylamine, 111-92-2; 2-(2,6-difluorophenyl)hexafluoro-2-propanol, 28180-43-0; 2-(3,5-difluorophenyl)hexafluoro-2-propanol, 28180-44-1; 2-(2,3,5,6-tetrafluorophenyl)hexafluoro-2-propanol, 13732-54-2; 1,4-di(2-hydroxyhexafluoro-2-propyl)tetrafluorobenzene, 13732-55-3; 2-(2,6-dimethylphenyl)hexafluoro-2-propanol, 28180-47-4; 2-bromophenylhexafluoro-2-propanol, 28180-48-5.

Acknowledgment.—We wish to thank Dr. Fred Saalfeld for the mass spectral analyses.

(14) A. M. Roe, R. A. Burton, and D. R. Reavill, *Chem. Commun.*, **22**, 582 (1965).

(15) A. Roe and W. F. Little, *J. Org. Chem.*, **20**, 1577 (1955).

(16) An analogous product has been reported in very low yield in the original study of the Grignard reaction of *o*-bromofluorobenzene: G. Wittig and L. Pohmer, *Ber.*, **89**, 1334 (1956).

Kinetics of Inhibition of Hydrocarbon Autoxidation by 1,1′-Bis(*N*-phenyl-2-naphthylamine)

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The kinetics of inhibition of cumene autoxidation at 60° by 1,1′-bis(*N*-phenyl-2-naphthylamine), a sterically hindered amine, are reported. The stoichiometry of inhibition indicates consumption of two peroxy radicals per amino group. The deuterium isotope effect [k_5(H)/k_5(D)] is 3.6 in the rate-determining hydrogen transfer step. This hydrogen transfer is unusually slow (k_5 = 1320 M^{-1} sec^{-1}), and the kinetics suggest an abnormally fast reverse reaction. Experiments with inhibited autoxidations of tetralin indicate that the inhibitor radicals abstract hydrogen atoms from the hydrocarbon. The failure of steric hindrance about the amino group to reduce hydrogen abstraction reactions by inhibitor radicals stands in strong contrast to experience with hindered phenols.

1,1′-Bis(*N*-phenyl-2-naphthylamine) (bis-PBN) is formed by the coupling of amino radicals during oxidation of *N*-phenyl-2-naphthylamine (PBN).[1] As an oxidation inhibitor this compound is of interest for several reasons. Naphthylamines with substituents on the naphthyl moiety are not commonly used as antioxidants, and the effect of such substitution on the inhibition kinetics is unknown. Bis-PBN is formed as an intermediate[2] during inhibition by *N*-phenyl-2-naphthylamine and, as such, may be kinetically significant as a secondary inhibitor during high temperature antioxidation by PBN. Bis-PBN is one of the few examples of a highly hindered amine antioxidant. Ingold and coworkers have reported results for the highly hindered 2,4,6-tri-*tert*-butylaniline.[3] They have subsequently shown, however, that primary aromatic amines are anomalous in their behavior toward peroxy radicals[4] and are not representative of the diarylamines commonly used as antioxidants in practice.

Results and Discussion

Reactions which must be considered during the inhibition of hydrocarbon autoxidation are shown below,[5] where RH is hydrocarbon, RO_2H is hydroperoxide, AH is the inhibitor, and I is the initiator, 2,2′-azobis(2-methylpropionitrile). Various kinetic expressions have been derived,[5-10] using all or part of eq 1–8. The apparent kinetic orders in [I], [RH], and [AH] generally indicate which reactions can be neglected. Rates of oxidation of tetralin at 60° inhibited by bis-PBN exhibited nonintegral kinetic orders in all reactants. The

$$\mathrm{I} \xrightarrow{2ek_1} 2\mathrm{R}\cdot \quad (1)$$

$$\mathrm{R}\cdot + \mathrm{O_2} \xrightarrow{k_2} \mathrm{RO_2}\cdot \quad (2)$$

$$\mathrm{RO_2}\cdot + \mathrm{RH} \xrightarrow{k_3} \mathrm{RO_2H} + \mathrm{R}\cdot \quad (3)$$

$$2\mathrm{RO_2}\cdot \xrightarrow{k_4} \mathrm{O_2} + \text{inert products} \quad (4)$$

$$\mathrm{RO_2}\cdot + \mathrm{AH} \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \mathrm{RO_2H} + \mathrm{A}\cdot \quad (5)$$

$$\mathrm{A}\cdot + \mathrm{RO_2}\cdot \xrightarrow{k_6} \text{inert products} \quad (6)$$

$$2\mathrm{A}\cdot \xrightarrow{k_7} \text{inert products} \quad (7)$$

$$\mathrm{A}\cdot + \mathrm{RH} \xrightarrow{k_8} \mathrm{AH} + \mathrm{R}\cdot \quad (8)$$

$$-\frac{\mathrm{d}[\mathrm{O_2}]}{\mathrm{d}t} = R_0 \propto \frac{[\mathrm{I}]^{0.8}[\mathrm{RH}]^{1.5}}{[\mathrm{AH}]^{0.7}}$$

three-halves order in tetralin is taken as a definite indication of hydrogen transfer from hydrocarbon to inhibitor radical (reaction 8).[8] Inhibited oxidations of cumene resulted in first-order dependence on hydrocarbon concentration. The nonintegral orders in [I]

$$R_0 \propto \frac{[\mathrm{I}]^{0.9}[\mathrm{RH}]^{1.0}}{[\mathrm{AH}]^{0.7}}$$

and [AH] suggest that reaction −5 is important. This was confirmed by an apparent kinetic order in hydroperoxide of about 0.5 (see below), indicating applicability of the following kinetic expression[6,7] in cumene.

$$R_0 = \frac{k_3[\mathrm{RH}]ek_1[\mathrm{I}]}{2k_5[\mathrm{AH}]}\left[1 + \left\{1 + \frac{4k_5k_{-5}[\mathrm{AH}][\mathrm{RO_2H}]}{k_6ek_1[\mathrm{I}]}\right\}^{1/2}\right] \quad (9)$$

Although cumene is not generally the hydrocarbon of choice because of its low value of k_3, it is well suited to the present study because k_8 vanishes, and k_5 is small enough that oxidation rates are large enough to measure conveniently.

The stoichiometry of inhibition and deuterium isotope effect were examined as criteria of normal antioxidant behavior. The stoichiometries of inhibition of bis-PBN and 1,1′-bis(di-2-naphthylamine) were determined by the inhibition period method,[11] with the results summarized in Table I. Each amine stopped four kinetic chains per molecule, equivalent to two peroxy radicals per amino group, as anticipated by the results of Thomas and Tolman with diphenylamine.[12]

(1) (a) R. F. Bridger, D. A. Law, D. F. Bowman, B. S. Middleton, and K. U. Ingold, *J. Org. Chem.*, **33**, 4329 (1968); (b) R. F. Bridger, *ibid.*, **35**, 1746 (1970).

(2) D. F. Bowman, B. S. Middleton, and K. U. Ingold, *ibid.*, **34**, 3456 (1969).

(3) D. V. Gardner, J. A. Howard, and K. U. Ingold, *Can. J. Chem.*, **42**, 2847 (1964).

(4) K. Adamic and K. U. Ingold, *ibid.*, **47**, 295 (1969).

(5) L. R. Mahoney, *Angew. Chem., Int. Ed. Engl.*, **8**, 547 (1969); *J. Amer. Chem. Soc.*, **89**, 1895 (1967).

(6) J. R. Thomas, *ibid.*, **85**, 2166 (1963); **86**, 4807 (1964).

(7) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **42**, 2324, 2724 (1964).

(8) L. R. Mahoney and F. C. Ferris, *J. Amer. Chem. Soc.*, **85**, 2346 (1963).

(9) A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.* 2215 (1956); 2217 (1957).

(10) W. A. Waters and C. Wickham-Jones, *ibid.*, 812 (1951).

(11) C. E. Boozer, G. S. Hammond, C. E. Hamilton, and J. N. Sen, *J. Amer. Chem. Soc.*, **77**, 3233 (1955).

(12) J. R. Thomas and C. A. Tolman, *ibid.*, **84**, 2930 (1962).

TABLE I

STOICHIOMETRY OF INHIBITION OF 3.46 *M* CUMENE AUTOXIDATION AT 60°

Inhibitor,[a] 4 × 10^{-4} *M*	Initiator concn, *M*	*t*,[b] min	*n*[c]
1,1′-Bis(*N*-phenyl-2-naphthylamine)	0.05	38	3.9
1,1′-Bis(*N*-phenyl-2-naphthylamine)	0.05	40	4.1
1,1′-Bis(*N*-phenyl-2-naphthylamine)	0.10	23	4.8[d]
1,1′-Bis(di-2-naphthylamine)	0.05	37	3.8
1,1′-Bis(di-2-naphthylamine)	0.10	19	3.9

[a] Chlorobenzene was used as solvent. [b] Inhibition period. [c] $n = 2ek_i[I]t/[AH]$ = number of radicals generated during the inhibition period/number of inhibitor molecules. [d] This run was too weakly inhibited for accurate interpolation of the inhibition period.

The deuterium isotope effect for inhibition by bis-PBN was determined by measuring rates in the presence of H_2O and D_2O (Figure 1).[13] Dividing[14] $R_0(D_2O)$ by $R_0(H_2O)$ yielded a value for $k_5(H)/k_5(D)$ of 3.6. This compares with values of 3.0 to 4.0 for several typical diarylamine antioxidants determined by Brownlie and Ingold[15] (Table II) and establishes

TABLE II

DEUTERIUM ISOTOPE EFFECTS FOR HYDROGEN TRANSFER REACTIONS OF AMINE INHIBITORS

Inhibitor	$k_5(H)/k_5(D)$
Diphenylamine	3.0[a]
N-Phenyl-2-naphthylamine	3.0[a]
N-Phenyl-1-naphthylamine	4.0[a]
1,1′-Bis(*N*-phenyl-2-naphthylamine)	3.6[b]

[a] Styrene at 65°, ref 15. [b] Cumene at 60°.

hydrogen transfer from the N–H bond (reaction 5) as the rate-determining step of inhibition.

Kinetic investigations utilizing electron spin resonance[4,12,16] have shown eq 5–8 to be insufficient for description of inhibition by diphenylamine and its derivatives because of the contribution of diaryl nitroxide radicals. *N*-Arylnaphthylamines, however, exhibit negligible nitroxide contribution,[4] and the kinetics[15] and termination products[2] of inhibition by PBN are consistent with eq 1–7. Since inhibition by bis-PBN yields only marginally more nitroxide radicals than PBN,[4] the contribution of nitroxide has been neglected in the kinetics treatment.

The application of eq 9 to the autoxidation of cumene inhibited by bis-PBN is summarized in Figure 2. From the observed value of 5.87 × 10^{-4} for k_3/k_5, a value for k_5 of 1320 M^{-1} sec^{-1} is calculated using Hendry's value[17] of 0.78 M^{-1} sec^{-1} for k_3 at 60°.[18] The value of k_5 is unusually low for an amine antioxidant, as seen by comparison with similar data for various inhibitors in Table III.

Molecular models suggest that the preferred conformations of 1,1′-bis(*N*-phenyl-2-naphthylamine) and

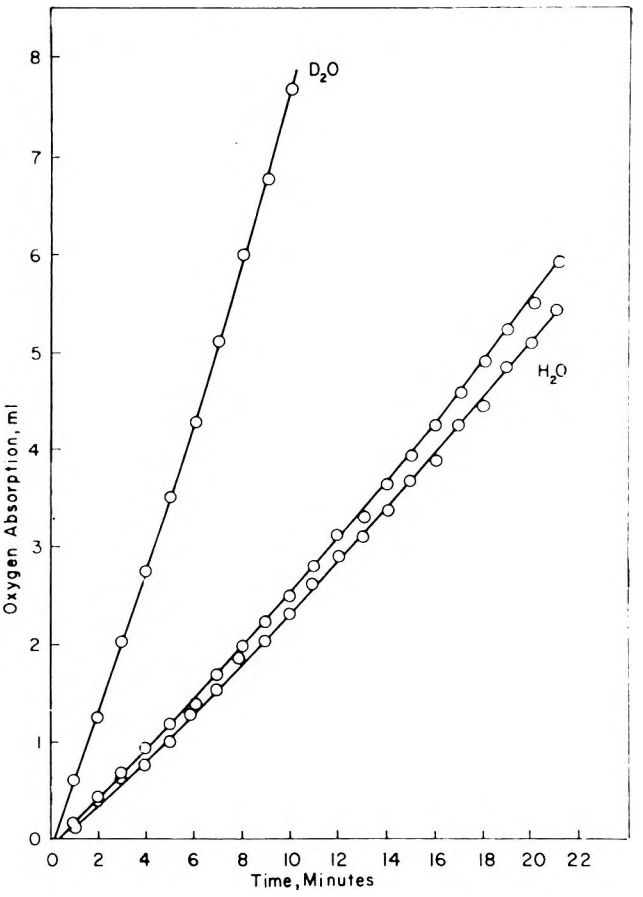
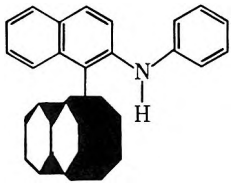
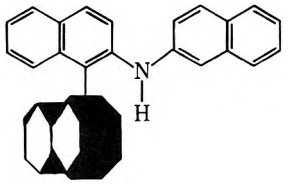


Figure 1.—Inhibition of cumene autoxidation by 1,1′-bis-PBN. Deuterium isotope effect: [AH] = 3.86 × 10^{-4} *M*, [ABN] = 0.05 *M*, [RH] = 3.46 *M* in chlorobenzene at 60°, 100 ml of solution.

1,1′-bis(di-2-naphthylamine) place the N–H bonds approximately parallel to the opposing naphthyl groups, as illustrated below. (One arylamino group has been omitted from each structure for clarity.) This not only makes the NH bond relatively inaccessible to



k_5 = 1320 M^{-1} sec^{-1}



k_5 = 12.000 M^{-1} sec^{-1}

the attacking peroxy radical but interferes with delocalization of the incipient amino radical into the naphthyl group of bis-PBN during attainment of the transition state. As a consequence of steric hindrance to radical attack and loss of overlap with the naphthyl moiety, bis-PBN is only one-fifteenth as efficient as diphenylamine.

(13) K. U. Ingold and J. A. Howard, *Nature*, **195**, 280 (1962).

(14) By substituting typical values of concentrations and rate constants in eq 9, it can be shown that this approximation leads to a maximum error of 5% in $k_5(H)/k_5(D)$.

(15) (a) I. T. Brownlie and K. U. Ingold, *Can. J. Chem.*, **44**, 861 (1966); (b) I. T. Brownlie and K. U. Ingold, *ibid.*, **45**, 2419 (1967).

(16) K. Adamic, M. Dunn, and K. U. Ingold, *ibid.*, **47**, 287 (1969).

(17) D. G. Hendry, *J. Amer. Chem. Soc.*, **89**, 5433 (1967).

(18) This value of k_5 is *per molecule*; an approximate value of k_5 *per NH bond* may be obtained by dividing by two.

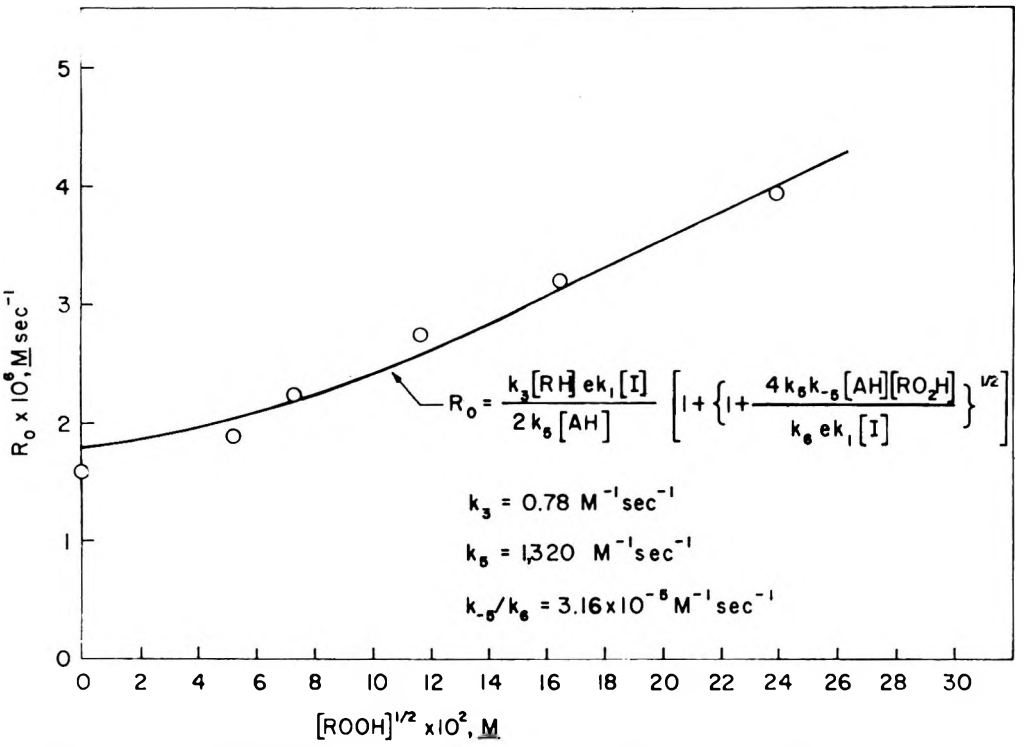


Figure 2.—Inhibition of cumene autoxidation by 1,1′-bis(*N*-phenyl-2-naphthylamine): 0.05 *M* [I], 3.86 × 10^{-4} *M* [AH], 3.46 *M* [RH].

TABLE III

COMPARISON OF RATE CONSTANTS FOR VARIOUS INHIBITORS

Inhibitor	$k_5 \times 10^{-3}$ M^{-1} sec^{-1}	$k_{-5}/k_6 \times 10^7$
Diphenylamine[a]	20	44
N-Phenyl-2-naphthylamine[a]	50	29
N-Phenyl-1-naphthylamine[a]	70	3.6
Di-2-naphthylamine[a]	90	16
2,6-Di-*tert*-butyl-4-methylphenol[a]	17.8	
Phenol[a]	4.9	130
1,1′-Bis(*N*-phenyl-2-naphthylamine)[b]	1.32	316
1,1′-Bis(di-2-naphthylamine)[b]	12	*c*

[a] Styrene, 65°, ref 15. [b] Cumene, 60°, this work. [c] Not determined.

Much more surprising, however, is the extraordinarily high value of k_{-5}/k_6. This implies either a very slow termination (k_6) or a high value of k_{-5}. A distinction cannot be made without more detailed information on the termination processes. In view of the observed hydrogen transfer from tetralin, however, we believe that the reversibility of reaction 5 must be quite high, reflecting enhanced reactivity of the amino radical due to the reduced delocalization described above.

The present results are similar to those of Gardner, Howard, and Ingold, who observed chain transfer of the 2,4,6-tri-*tert*-butylanilino radical with both hydroperoxide and styrene.[3] These observations with hindered amines contrast strongly with the beneficial effects of bulky substituents on phenols for which reactions −5 and 8 can be virtually eliminated.[3,5,7] The anomalous behavior of amines may be due to their degradation chemistry, which is quite complex. Despite several recent studies,[2,4,19] this area is in need of more attention.

(19) R. Okazaki, T. Hosogai, M. Hashimoto, and N. Inamoto, *Bull. Chem. Soc. Jap.*, **42**, 3559 (1969).

Experimental Section

Hydrocarbons, hydroperoxides, and initiator were purified by standard methods. Preparations of the inhibitors have been described.[1]

Initial rates of oxidation were measured in a previously described apparatus,[20] using 100 ml of solution and dropping a glass bucket[15a] containing initiator into the previously thermostated solution. Rates were independent of oxygen pressure and rate of stirring. Oxidation rates have been corrected for nitrogen evolution and oxygen consumption by initiator fragments. The efficiency[21] of 2,2′-azobis(2-methylpropionitrile) at 60° was taken as 0.60 and the specific rate constant of decomposition[22] as 1.15 × 10^{-5} sec^{-1}. Equation 9 was fitted by computer.[23] Representative data are summarized in Table IV.

TABLE IV

KINETIC DATA FOR INHIBITION OF CUMENE AUTOXIDATION BY 1,1′-BIS(*N*-PHENYL-2-NAPHTHYLAMINE) AT 60°

[ROOH] × 10^3 *M*[a]	$R_0 \times 10^6$ *M* sec^{-1} Expt	Calcd[b]	Difference × 10^6	Difference, %
0.00	1.59	1.81	+0.22	+13.8
2.75	1.89	2.02	+0.13	+6.9
5.45	2.24	2.20	−0.04	−1.8
13.63	2.75	2.62	−0.13	−4.7
27.3	3.22	3.15	−0.07	−2.2
57.8	3.93	4.03	+0.10	+2.5

[a] Other reagents include 0.05 *M* [I], 3.86 × 10^{-4} *M* [AH], 3.46 *M* [RH]; chlorobenzene was used as solvent. [b] Calculated from eq 9 using k_3, 0.78 M^{-1} sec^{-1}; k_5, 1320 M^{-1} sec^{-1}; and k_{-5}/k_6, 3.16 × 10^{-5}.

Registry No.—Bis-PBN, 17704-02-8; 1,1′-bis(di-2-naphthylamine), 4488-22-6; cumene, 98-82-8.

(20) R. F. Bridger, A. L. Williams, and L. J. McCabe, *Ind. Eng. Chem., Prod. Res. Develop.*, **5**, 226 (1966).

(21) G. S. Hammond, J. N. Sen, and C. E. Boozer, *J. Amer. Chem. Soc.*, **77**, 3244 (1955).

(22) G. A. Russell, *ibid.*, **79**, 3871 (1957).

(23) We are grateful to E. B. Peterson for writing the program for eq 9.

Quaternary Benzylammonium Ion Rearrangements with Organolithium Compounds. V. Reaction of *N*,*N*-Dimethyl-*N*-benzylanilinium Halides[1a,b]

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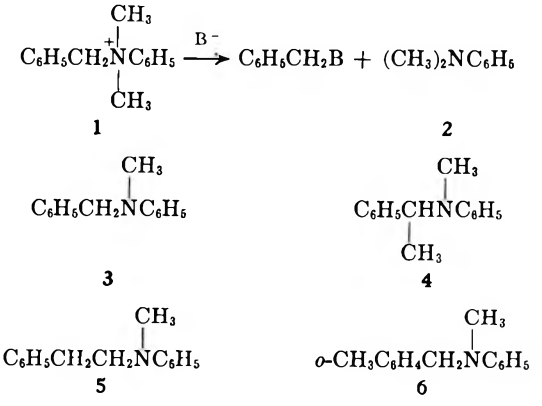
Received March 28, 1969

A new rearrangement product, *N*-methyl-*N*-(α-phenethyl)aniline (**4**), and a new cleavage product, *N*-methyl-*N*-benzylaniline (**3**), have been observed in reactions of *N*,*N*-dimethyl-*N*-benzylanilinium ion (**1**) with organolithium bases. *N*-Methyl-*N*-(β-phenyl)aniline (**5**) was directly isolated from reaction mixtures, whereas it is destroyed by sodium amide. The Sommelet rearrangement product, *N*-methyl-*N*-(*o*-xylyl)aniline (**6**), was observed in very small quantities because of the benzylation of its *o*-Li precursor by the starting salt, to give a dimeric product. Cleavage reactions of the quaternary benzylanilinium salt with potassium hydroxide and sodium ethoxide in refluxing ethanol also gave **3** in addition to the principal products, *N*,*N*-dimethylaniline (**2**) and ethyl benzyl ether. Analogous cleavage products were observed with organolithium reagents plus significant amounts of *trans*-stilbene (**8**). The effects of concentration, ether–hexane solvent mixtures, and anion of the salt on the ratios of rearrangement and cleavage products were studied for *n*-butyllithium reactions and are interpreted in terms of dianion and radical pair mechanisms.

N,*N*-Dimethyl-*N*-benzylanilinium chloride is known[2-4] to undergo ortho substitution rearrangement (Sommelet) on treatment with sodium amide in liquid ammonia. In the most comprehensive study of this reaction,[4] indirect evidence of a 1,2 shift (Stevens) was also observed. The latter type of reaction generally occurs readily[1a,5-7] on treatment of benzylic quaternary ammonium salts with organolithium reagents; the effect of base on the distribution of the competing rearrangement processes has been compared for *N*-benzyltrimethylammonium ion.[8]

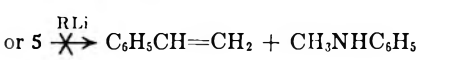
We have now observed that the *N*,*N*-dimethyl-*N*-benzylanilinium ion (**1**), when treated with organolithium reagents, produces *N*,*N*-dimethylaniline (**2**), *N*-methyl-*N*-benzylaniline (**3**), *N*-methyl-*N*-(α-phenethyl)aniline (**4**), *N*-methyl-*N*-(β-phenethyl)aniline (**5**), *N*-methyl-*N*-(*o*-xylyl)aniline (**6**), a dimeric amine (**7**), and *trans*-stilbene (**8**). Hot ethanolic hydroxide or ethoxide caused displacement of substituents on quaternary nitrogen of **1** Cl^- with **2**, **3**, and benzyl ethyl ether formation (Table I, expt 1 and 2). Lower yields



1 **2** **3** **4** **5** **6**

of **2** and **3** resulted with the lithium reagents in aprotic media, but significant amounts of the rearrangement products **4**, **5**, and **6** were obtained with 1,2 shifts predominating (Table I, expt 3–7). In addition to the effect of halide and solvent on the 1,2-shift ratio of **4**/**5** (Table II), the ratio was 0.8 in a 2:1 v/v solution of ether–hexane with *n*-butyllithium. The best mass balance, 90% obtained when a 2.2:1 mixture of *n*-butyllithium:**1** Br^- reacted in hexane, gave 47% **2**, 7.4% **3**, 11.3% **4**, 14.4% **5**, 1.5% **6**, 8.5% **7**, 18% **8**, and 3.4% *n*-pentylbenzene.

We did not observe *N*-methylaniline or styrene, evidence of cleavage in the β-phenethyl product,[4] even when pure **5** was treated with *n*-butyllithium. Ethyl-



benzene was absent in experiments with methyllithium; toluene may be present in several cases, but we were unable to collect an adequate sample from gas chromatography (gc) for characterization. Separation characteristics and physical properties of separately synthesized materials were determined[9] (Table III) and used in product identification and analysis.

Discussion

General trends due to base, solvent, and halide ion may best be considered in reference to earlier studies on this and related rearrangements. The reaction conditions certainly have a distinct effect. Earlier sodium amide rearrangements[2-4] were at temperatures 50–60° below the current ambient organolithium experiments or as much as 110° below our reactions in refluxing ethanol. Hauser and coworkers[10] noted that benzylammonium salt reactions in related Stevens rearrangement predominate at high temperatures and Sommelet migration is almost exclusive at low temperatures. These rearrangements are very base and solvent dependant as well and, for benzyltrimethylammonium ion at least, almost exclusive ortho migration can be observed within the temperature range currently used.[1a,8,11] The low ortho conversions ob-

(1) (a) Part IV: A. R. Lepley and T. A. Brodof, *J. Org. Chem.*, **32**, 3234 (1967). (b) This investigation was supported in part by U. S. Public Health Service Grant GM-09136 from the National Institute of General Medical Sciences and was presented in part before the X Congresso Nazionale della Societa Chimica Italiana, Padova, Italy, June 1968. (c) To whom reprint requests should be sent, Marshall University. (d) Fulbright student, State University of New York at Stony Brook, 1962–1964.

(2) E. J. Gaugham, *Diss. Abstr.*, **22**, 1827 (1961).

(3) L. P. A. Fery, *Bull. Soc. Chim. Belges*, **71**, 376 (1962).

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(5) A. R. Lepley and A. G. Giumanini, *ibid.*, **32**, 1706 (1967).

(6) K. P. Klein, D. N. Van Enam, and C. R. Hauser, *ibid.*, **32**, 1155 (1967).

(7) G. Wittig, *Angew. Chem.*, **63**, 15 (1951).

(8) A. R. Lepley and R. H. Becker, *J. Org. Chem.*, **30**, 3888 (1965).

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(10) C. R. Hauser, R. M. Manyik, W. R. Brasen, and P. L. Bayless, *ibid.*, **20**, 1119 (1955).

(11) K. P. Klein and C. R. Hauser, *ibid.*, **31**, 4276 (1966).

TABLE I

REACTIONS OF *N,N*-DIMETHYL-*N*-BENZYLANILINIUM (1) CHLORIDE WITH SEVERAL BASES

Expt no.	1	2	3	4	5	6	7
Base concn (*M*)	KOH, 1.3	NaOEt, 1.9	MeLi, 0.8	C_6H_5Li, 0.6	*n*-BuLi, 0.3	*n*-BuLi, 1.1	*n*-BuLi, 0.5
Molar ratio of base/1	2.1:1	3.2:1	3.3:1	1.4:1	0.4:1	4.4:1	1.9:1
Solvent	EtOH	EtOH	C_6H_{14}	C_6H_{14}–C_6H_6–Et_2O, 7:3:1	C_6H_{14}	C_6H_{14}	C_6H_{14}
Time (hr), temp	24, reflux	12, reflux	24, ambient	14, ambient	24, ambient	24, ambient	24, ambient
Products							
Amines							
N,N-Dimethylaniline (2)	42	59	22	39.5	10.3	4.9	29
N-Methyl-*N*-benzylaniline (3)	5.8	5.3	2.2	4.0	3.1	9.7[a]	5.3
N-Methyl-*N*-(α-phenethyl)aniline (4)	[b]	[b]	39.5	30	6.2	2.7	2.4
N-Methyl-*N*-(β-phenethyl)aniline (5)	[b]	[b]	8.4	3.9	8.7	14.8	12.7
N-Methyl-*N*-(*o*-xylyl)aniline (6)	[b]	[b]	[b]	[b]	[b]	2.5[c]	2.1
Neutral compd							
$C_6H_5CH_2B$ (B = radical from base)	45[d]	63	[b]	0.9	[e]	0.6	2.1
trans-Stilbene (8)	[e]	[b]	[e]	10.1	[e]	[a]	>10
Overall[f]	51	69	72	82	28	33	60[g]
Ratios							
4/5 (α/β rearrangement)			4.7	7.7	0.7	0.2	0.2
2/3 (benzyl/methyl loss)	7.0	11.1	9.7	9.9	3.3	0.5	5.5

[a] Probably a mixture of 3 and 8, but calculated as pure 3. [b] Not observed. [c] At 60 hr, this material was not detected in 24-hr sample. [d] Ethyl benzyl ether. [e] Not determined. [f] Calculated on the basis of C_6H_5N or $C_6H_5CH_2$ groups accounted for depending on which was the greatest. [g] Includes 8.3% of the dimeric material 7.

TABLE II

HALIDE ANION EFFECTS ON STEVENS REARRANGEMENT PRODUCTS FROM *N,N*-DIMETHYL-*N*-BENZYLANILINIUM (1) CATION WITH ORGANOLITHIUM BASES

Base–solvent	Base:1 ratio	Anion, X^-	α/β product ratio, 4/5
C_6H_5Li–7:3:1 hexane: benzene:ether	1.4:1	Cl	7.7
		Br	7.2
n-BuLi–5.5:1 ether:hexane	1:1	Cl	1.3
		Br	1.6
		I	1.0
n-BuLi–hexane	1.9:1	Cl	0.2
		Br	0.8
n-BuLi–hexane	0.4:1	Cl	0.7
		Br	1.3

TABLE III

GAS CHROMATOGRAPHIC RETENTION RATIOS OF SOME NEUTRAL AND BASIC COMPOUNDS RELATED TO THE FRAGMENTATION AND DISPLACEMENT REACTIONS OF *N,N*-DIMETHYL-*N*-BENZYLANILINIUM (1) HALIDES

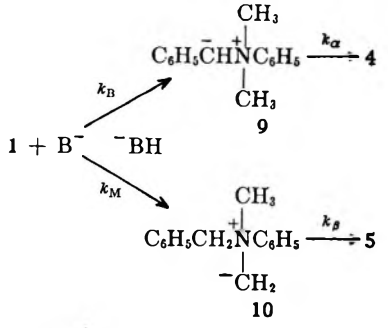
Compd	Retention ratio: GE-SF96[a]	Retention ratio: Carbowax, KOH[b]
Toluene		0.129
Ethylbenzene		0.178
Styrene		0.280
N,N-Dimethylbenzylamine	0.659	0.445
Ethyl benzyl ether	0.827	0.627
N-Methylaniline	0.907	
N,N-Dimethylaniline[c] (2)	1.00	1.000
n-Pentylbenzene	1.27	0.635
N,N-Dimethyl-β-phenethylamine (5)	1.51	0.920

[a] A 0.25 in. × 5 ft column of 20% GE-SF96 on 60–80 mesh Chromosorb W at 122°, 62 ml/min He flow; ratios are ±0.005. [b] A 0.25 in. × 5 ft column of 20% Carbowax 20M plus 5% KOH, on 40–60 mesh firebrick at 115°, 42 ml/min He flow; ratios are ±0.002. [c] On GE-SF96, retention time for calibration standard 19.3 ± 0.6 min, peak width at half-height 1.6 ± 0.1 min; on Carbowax–KOH, 44.0 ± 0.7 min and 3.3 ± 0.2 min, respectively.

served are, therefore, not totally attributable to temperature effects; *vide infra*.

Base and solvent effects were not completely distinct. The cleavage observed in ethanolic hydroxide (Table I) was accompanied by 27% rearrangement with 5.8 4/5, between that of methyl- and phenyllithium, when 1 Cl was heated with solid KOH at 100°.[12] No ortho migration product was evident in any of these reactions until a solvent change to hexane with *n*-butyllithium as base gave detectable 6.

Both cleavage and rearrangement products show comparable trends with base variation. If proton abstraction giving ylides 9 and 10, as evident in the

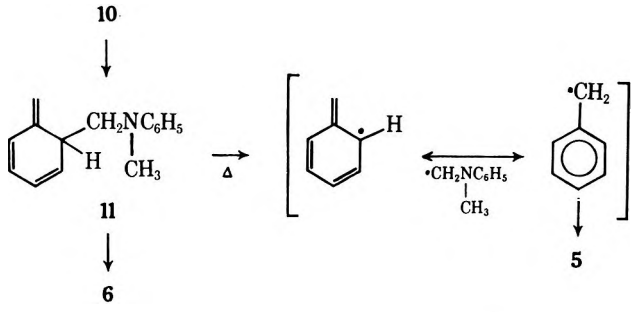


α/β rearrangement ratio 4/5, was the controlling factor ($k_\alpha \gg k_B$, $k_\beta \gg k_M$), then less discrimination was evident with increasing base strength. However, the α/β ratio was lower than the statistical minimum of 2/6 in the butyllithium reaction where it reached 1/5. Butyllithium induced rearrangements of benzyltrimethylammonium ion also exceed statistical distributions.[8] These data seem to preclude a prerearrangement equilibrium, 9 ⇌ 10,[13] unless one assumes the reverse of benzyl > methyl acidity or unless $k_\beta \gg k_\alpha \sim k_{9-10}$. The α/β ratios paralleled the α/ortho order for the benzyltrimethylammonium system;[8] *i.e.*, for the lithium bases, RLi, the R group effect was

(12) A. G. Giumanini, *Chem. Ind. (London)*, 1140 (1967).

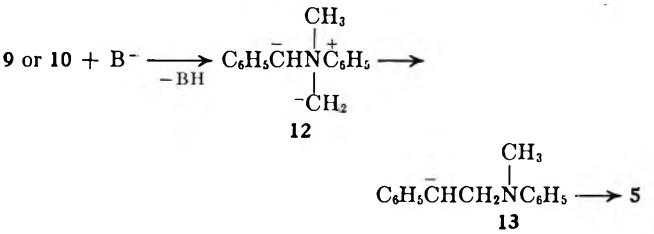
(13) In aprotic media even slow return to 1, k_{-B} or k_{-M}, does not furnish an equilibration path but exchange with 1, 1 + 9 ⇌ 10 + 1, gives an alternate path.

phenyl > methyl > *n*-butyl. Such comparable changes could indicate a relationship between **5** and **6** and detectable amounts of **6** only appear when **5** increases. Baldwin and Brown[14] suggest that β products are actually formed by a thermal Hauser rearrangement of the *exo*-methylenecyclohexadiene intermediate which precedes a Sommelet product. Thus a concerted [3,2]



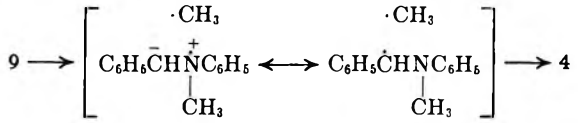
sigmatropic migration in **10** would give **11** which undergoes proton loss to base yielding **6** on water quenching[15] or which thermally breaks a C–C bond homolytically and collapses into **5**. Carbonyl stabilized nitrogen ylides do not rearrange by a combination of concerted and radical pair mechanisms.[16] The sulfur angular methyl analog of **11** also thermally forms a β-phenyl product *via* a radical pair.[17] In the instance of **11** → **5**, only resonance stabilization of the benzyl radical is possible since the aniline fragment electron redistribution structures involve pentavalent nitrogen. Although the higher temperatures than in liquid ammonia, *vide supra*, drive the reaction to **5** rather than **6**, the condition for the observed thermal rearrangements were in excess of 100°.[14,17]

Greater proton abstraction at high base concentrations would tend to trap more **11** as **6**, but **6** was not seen until after **4** and **5** buildup ceased. Furthermore, Pine has found that high base concentrations cause RLi addition to intermediates like **11**.[18] Thus **5** and **6** should decrease at very high base–salt ratios rather than increasing at the apparent expense of **4** (*cf.* Table I, expt 5–7). Another pathway to **5** and **6** are dianions of the type proposed by Hauser[6] to account for effects in the presence of excess base. The most probable dianion, **12**, could rearrange to anionic precursors of **4**, **5**,



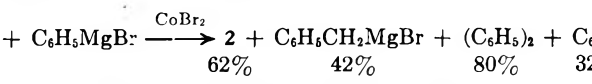
or **6** by homolytic or heterolytic benzyl CN cleavages.[19] However, the only rearranged anion with resonance stabilization is **13**. Thus as seen in Tables I and II, as the base–salt ratio increases the **4**/**5** value decreases supporting the **9** → **12** → **13** → **5** route. Dianions with aromatic ring deprotonation, either benzyl[20] or *N*-phenyl[21] as with tertiary amines, may also account for the destruction of **1** but none of these species has been trapped as has the benzyl ylide of benzyltrimethylammonium,[22] *cf.* **9**, or isolated as have several phenacyl nitrogen ylides.[23] A number of other ion pair and carbene pathways could participate in the rearrangements of **1** but have been extensively discussed elsewhere.[19] Therefore only the radical pair mechanisms based on the analogous benzyne amine reactions,[9] Stevens rearrangements with CIDNP,[16,17,25–27] and product evidence[28] are specifically applied to **1** → **4**.

Although the CIDNP producing rearrangements include sulfonium[17,25] and aminimide[16,26,27] results as well as ammonium salts,[23,24] all the reactions invoke a caged radical pair state. In terms of the current system the conversion of **9** to **4** would involve homolytic



CH_3–N bond breaking and subsequent collapse of the radical pair after electron redistribution to the more stable neutral resonance contributor. This is exactly the same step as that which gave CIDNP in the benzyne formation of **4**.[9] Unfortunately, the heterogeneous reactions of **1** could not be accelerated to produce **4** under conditions for the direct observation of this phenomena. However, the close analogy with the other Stevens 1,2 shifts providing evidence for radical pairs is compelling. Since some escape from the cage might be anticipated,[9] the cleavage product **3** would be expected to increase as **4** decreases as appears to be qualitatively true in the organolithium reactions (Table I).

A case for free-radical participation in cleavage reactions was presented when Kharasch, Williams, and Nudenberg[29] used cobalt salts to catalyze the reaction of **1** with phenylmagnesium bromide. The Grignard reagent in the absence of catalyst formed only 4%



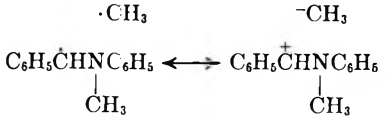
of **2**. This radical participation in reactions of a number of other quaternary ammonium salts was also shown,[29] but investigators have not specifically tested such mechanisms with other bases.

(14) J. E. Baldwin and J. E. Brown, *J. Amer. Chem. Soc.*, **91**, 3647 (1969).
(15) The analogous [1,3] sigmatropic shift is forbidden.
(16) J. E. Baldwin, J. E. Brown, and R. W. Cordell, *Chem. Commun.*, 31 (1970).
(17) J. E. Baldwin, W. F. Erickson, R. E. Hackler, and R. M. Scott, *ibid.*, 576 (1970).
(18) S. H. Pine, *Org. React.*, **18** (1970); S. H. Pine and B. L. Sanchez, *Tetrahedron Lett.*, 1319 (1969).
(19) A. R. Lepley and A. G. Giumanini, in "Mechanisms of Molecular Migrations," Vol. 3, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1971.
(20) W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **86**, 1394 (1964).
(21) A. R. Lepley, W. A. Khan, A. B. Giumanini, and A. G. Giumanini, *J. Org. Chem.*, **31**, 2047 (1966).
(22) W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **86**, 1105 (1964).
(23) R. W. Jemison, S. Mageswaran, W. D. Ollis, S. E. Potter, A. J. Pretty, and I. O. Sutherland, *Chem. Commun.*, 1201 (1970).
(24) U. Schöllkopf, U. Ludwig, G. Osterman, and M. Patsch, *Tetrahedron Lett.*, 3415 (1969).
(25) U. Schöllkopf, G. Ostermann, and J. Schossig, *ibid.*, 2619 (1969); U. Schöllkopf, J. Schossig, and G. Osterman, *Justus Liebigs Ann. Chem.*, **737**, 158 (1970).
(26) R. W. Jemison and D. G. Morris, *Chem. Commun.*, 1226 (1969); D. G. Morris, *ibid.*, 1345 (1969).
(27) H. P. Benecke and J. Wikel, private communication.
(28) G. F. Hennion and M. J. Shoemaker, *J. Amer. Chem. Soc.*, **92**, 1769 (1970).
(29) M. S. Kharasch, G. H. Williams, and W. Nudenberg, *J. Org. Chem.*, **20**, 937 (1955).

Although this last route might contribute to the current reactions, all the cleavage products observed are reasonable for direct displacement. Alternative pathways for the production of **8** were previously discussed.[5]

Displacements and rearrangements of **1** with hydroxide and phenoxide at high temperatures were first observed by Michler and Gradmann.[30] Benzyl alcohol and **2** were obtained by codistillation of sodium hydroxide and **1** until high temperatures were reached (220–230°); then higher molecular weight products, thought to be ring benzyl derivatives of **2** or methyl derivatives of **3**, were observed. These latter rearrangements products were probably the compounds recently identified[12] as **4** and **5**. Sodium phenoxide and **1** at 300°,[30] however, gave only **2** and benzyl phenyl ether. Ethyl benzyl ether was observed with **2** when **1** was "reduced" with sodium in ethanol.[31] Only **2** and no ether was mentioned in a later work with sodium ethoxide,[32] while reduction[33] with platinium–barium sulfate or platinium oxide gave toluene, **2**, and other more highly saturated products. Sodium derivatives of ethyl malonate and related compounds were also benzylated with **1** in good yields.[34] In addition, **2**[3,4] and **8**[4] were observed as cleavage products of **1** with sodium amide. This latter base also caused product breakdown to *N*-methylaniline[3,4] and styrene.[4]

No single reaction pathway for rearrangement or cleavage products allows the *a priori* prediction of the exact products which will be formed, let alone their quantitative distribution. Therefore, the suggestion made previously[8] that two or more different types of intermediates are involved in the benzylammonium salt reaction is particularly applicable to the current case. The new products identified in the reaction of **1** support an ylide precursor **9** which rearranges *via* a radical pair to **4**. To accommodate known substituent effects in Stevens 1,2 shifts and the exchange properties of radical pairs,[35] a facile one-electron transfer process may occur for the caged pair. In addition, a



dianion is apparent in the production of **5**, but the intermediate interconversion of **12** to **13** needs further clarification.

Experimental Section[36]

Chemicals.—Mono-free *N*,*N*-dimethylaniline from Fisher was dried over potassium hydroxide and vacuum distilled before use. Iodomethane, α-chloro- and α-bromotoluene, β-bromoethylbenzene, and hexamethylphosphoramide were obtained from Eastman. Deuterium oxide (99.5+%) was from Matheson Coleman and Bell. Hexane solutions of *n*-butyllithium and methyllithium and ether–benzene solution of phenyllithium were from Foote Mineral. *N*,*N*-Dimethyl-β-phenethylamine[37] and *n*-pentylbenzene[5] were available from previous work. Other compounds are described in ref 9.

Ethyl Benzyl Ether.—Sodium wire (7.5 g, 0.33 g-atom) was dissolved in 100 ml of absolute ethanol and 38 ml (0.33 mol) of α-chlorotoluene was very slowly added to the mixture at 60° with stirring. Sodium chloride separated from the bright yellow solution which was refluxed for 3 hr. After addition of 200 ml of water and 5 g of sodium chloride to the cooled reaction mixture, a deep red oil separated. The product was dried over potassium hydroxide and distilled to give a 65% yield (29 g) of a colorless oil, bp 83.5–84° (17 mm) [lit.[38] 70° (15 mm)], n^{25}D 1.4903 (lit.[39] n^{25}D 1.4934).

***N*-Methyl-*N*-(β-phenethyl)aniline (5).**[40]—*N*-Methylaniline (36 ml, 0.33 mol) and 47 ml (0.33 mol) of β-bromoethylbenzene were mixed and heated on a steam bath for 24 hr. The brownish glass obtained was decomposed with warm (30°) concentrated potassium hydroxide solution (40 ml of water and 19 g KOH). The oily insoluble amine was dissolved in ether; the ether solution was separated, dried over potassium hydroxide, decanted, and distilled. The white crystalline product (58 g, 84% yield) was collected at 195–197° (24 mm) [lit.[40] 198–199° (18 mm)], mp 43.5–44° (lit.[40] 44°). An additional 7.5 g, 11%, of product was obtained on heating the distillation forerun (1:1 mixture of starting material, gc) for an additional 15 hr on a steam bath.

The infrared spectrum had bands at 3040 w, 2940 w, 2880 w, 2810 vw, 1605 s, 1503 s*, 1448 w, 1374 m, 1355 m, 1275 vw, 1250 w, 1222 w, 1190 w, 1160 vw, 1114 w, 1078 vw, 1034 w, 992 w, 956 vw, 906 vw, 860 vw, 751 s, and 690–700 m cm^{-1}. Gc and pmr data on this material are given elsewhere.[9]

Attempted Cleavage of *N*-Methyl-*N*-(β-phenethyl)aniline (5) with *n*-Butyllithium.—The amine **5** (2.1 g, 10 mmol), dissolved in 10 ml of dry hexane, was added to 20 ml of 1.5 *M* (30 mmol) *n*-butyllithium in hexane at room temperature. The solution was clear and remained clear for the period of observation, 2 days. Gc analysis of quenched samples from the initial solution and at several intervals up to 48 hr showed that **5** concentration remained constant, within experimental error. No *N*-methylaniline was observed.

Preparation of *N*,*N*-Dimethyl-*N*-benzylanilinium (1) Halides. A. Chloride.—Equimolar amounts[30,31,41] of *N*,*N*-dimethylaniline (255 ml, 2.0 mol) and of α-chlorotoluene (230 ml, 2.0 mol) were stored in the dark in a dessicator containing anhydrous magnesium sulfate for a month. The quantitatively produced solid was washed repeatedly with dry hexane to give a salt, mp 108°. Recrystallization from hot absolute ethanol raised the melting point to 110° (lit. 110°,[30,42] 116°[31]); the material was then vacuum dried for 2 hr at 75°, mp 150° for the colorless crystals.

Anal. Calcd for $C_{15}H_{18}NCl$: C, 72.72; H, 7.32; N, 5.65; Cl, 14.31. Found: C, 72.41; H, 7.45; N, 5.40; Cl, 14.06.

The infrared spectrum of the dried recrystallized product had bands at 3400–3300 m, 3070 w, 2985 m, 2960 m, 2982 m, 1630 vw, 1590 w, 1490 s, 1450 s, 1400 m, 1380 m, 1225 m, 1120 w, 1085 vw, 1030 w, 1000 m, 970 m, 935 w, 890 s, 845 m, 775, s, 760 s*, 710 s, and 700 s cm^{-1}. An additional 24 hr of vacuum drying at 75° had no appreciable effect on this spectrum. However, the initial drying period had caused a very large decrease (*ca.* fourfold) in the OH stretch, intensity at 3400–3300 cm^{-1}, an inversion of the intensity ratios for the weak 1630 and 1590 cm^{-1} bands, an increase in intensity of the weak 1400 and 1380 cm^{-1} bands, and a doubling in width of the strong bands at 775 and 760 cm^{-1}. The pmr spectrum of this salt in D_2O was comparable to the spectrum given for the bromide; *vide infra*.

B. Bromide.—An equimolecular mixture[43] of *N*,*N*-dimethylaniline (38.2 ml, 0.3 mol) and of α-bromotoluene (35.7 ml, 0.3 mol) was heated on a steam bath overnight. Colorless crystals were slowly formed from the solution, which rapidly turned bright blue. The crude product was quantitatively recovered, washed with dry acetone, dissolved in a minimum quantity of absolute alcohol, and reprecipitated with anhydrous ether. The colorless

(30) W. Michler and A. Gradmann, *Ber.*, **10**, 2078 (1877).
(31) H. Emde, *Arch. Pharm.* (*Weinheim*), **249**, 108 (1911).
(32) D. Vorlander and E. Spreckels, *Ber.*, **52**, 309 (1919).
(33) H. Emde and H. Kull, *Arch. Pharm.* (*Weinheim*), **274**, 173 (1936).
(34) H. R. Snyder, C. W. Smith, and J. M. Stewart, *J. Amer. Chem. Soc.*, **66**, 200 (1944).
(35) C. Walling, H. P. Waits, J. Milovanovic, and C. G. Pappiaonnou, *ibid.*, **92**, 4927 (1970).
(36) The data used in product separations and identification are described in Table III and ref 9. Melting points and boiling points are uncorrected.
(37) A. R. Lepley and R. H. Becker, *Tetrahedron*, **21**, 2365 (1965).
(38) M. J. Murray and F. F. Cleveland, *J. Chem. Phys.*, **9**, 129 (1941).
(39) P. P. T. Sah and H.-H. Lei, *Sci. Rep. Nat. Tsing Hau Univ., Ser. A*, **1**, 193 (1932); *Beilstein*, III, 1454 (1966).
(40) J. von Braun, *Ber.*, **43**, 3213 (1910).
(41) Similar combinations of reagents were used by ref 32, 33, and 42.
(42) D. E. Ryan, *Can. J. Chem.*, **34**, 1383 (1956).
(43) Related reaction procedures and literature references reporting product melting points of 98, 129, 145, and 203° have been summarized by ref 4.

solid had mp 148–149° which increased to 153° (lit.[4] mp 145–146°) after vacuum drying for 12 hr at 75–85°. The solid, and especially its solutions in protic solvents, were lacrimatory[44] even after repeated purification of the solid. Both the solid and its solutions develop a bright blue color on standing in contact with moist air.

Anal. Calcd for $C_{15}H_{18}NBr$: C, 61.65; H, 6.21; N, 4.79; Br, 27.35. Found: C, 61.38; H, 6.15; N, 4.82; Br, 27.14.

The pmr spectrum was measured in D_2O, using the water impurity at δ 4.52 ppm as a standard, and in hexamethylphosphoramide (HMPA) or in dimethyl sulfoxide (DMSO), using a tetramethylsilane standard (Table IV). The anion, chloride, bromide,

TABLE IV

SOLVENT EFFECTS ON PMR CHEMICAL SHIFTS OF *N,N*-DIMETHYLBENZYLANILINIUM (1) BROMIDE

Protons of group	Multiplicity	Relative integral	Chemical shifts, δ (ppm) D_2O[a]	DMSO[b]	HMPA[b]
CH_3	Singlet	6	3.50	3.70	3.98
CH_2	Singlet	2	4.82	5.32	5.75
Ar	Multiplets	5	7.19	7.28[c]	7.31[d]
		3	7.49[e]	7.62[f]	7.60[g]
		2	7.49[e]	8.03[f]	8.43[g]

[a] Relative to H_2O impurity at 4.52 ppm. [b] Relative to TMS. [c] Center of integral of broad multiplet *ca.* 25 cps wide. [d] Broad singlet, width at half-height *ca.* 3 cps. [e] Center of integral of broad multiplet *ca.* 40 cps wide. [f] Centers of integrals of two well-separated multiplets *ca.* 13 cps wide. [g] As in footnote *f* but *ca.* 15 cps wide.

or iodide, had no appreciable effect on the pmr spectra. The ir spectrum of this salt had the same major peaks as given for the chloride above.

C. Iodide.—*N*-Methyl-*N*-benzylaniline (51.7 g, 0.27 mol) and 19 ml (0.3 mol) of iodomethane were warmed gently as described by Jones.[45] The salt was recrystallized twice from methanol, mp 147° (lit. 165°,[45] 155°[46]).

The infrared spectrum contained no bands in the OH stretch region, indicating the absence of hydroxylic solvents. The spectra, ir and pmr, had bands comparable to those given above. The solid and especially its solutions were lacrimatory.[47]

Reaction of *N,N*-Dimethylbenzylanilinium (1) Halides with *n*-Butyllithium.—Tables I and II summarize the results and variables in reactions with either chloride or bromide salts and *n*-butyllithium. A particular example, including product identification, is given here in some detail (*cf.* Table I, expt 7).

n-Butyllithium (0.30 *M* in 200 ml of hexane) was rapidly added to a vigorously magnet-stirred suspension of 40.0 g (0.16 mol) of finely powered, vacuum dried 1 chloride in 100 ml of sodium-dried hexane. The three-necked reaction flask, equipped with calcium chloride drying tube, was flame dried and then swept with dry nitrogen during the butyllithium addition and kept at 30 ± 2° for 36 hr before 50 ml of water was slowly added. The reaction was exothermic and an initial greenish-yellow color of the solution disappeared after 2 hr. The organic layer was separated and all materials boiling up to 100° were distilled off. The undistilled liquid was cooled to 0° and filtered, giving colorless crystals, which were washed with 5 ml of methanol, 2.9 g, mp 121–123°. The ir spectrum of the solid **8** in CS_2 was identical with that of *trans*-stilbene (yield 10.1%).

The liquid product mixture was then distilled; fractions were collected from 165 to 205° (1 atm), 58 to 130°, 133 to 190°, and 190 to 215° (1.5 mm). The first of these fractions contained predominantly two materials observed by gc analysis at 122°. The ir spectra in CS_2 of preparative gc samples were comparable with **2** (yield 29%) and *n*-pentylbenzene (2.1%).

The second and third distillation fractions both showed the same four gc peaks. Analysis of retention ratios and ir and pmr spectra gave the product yields: 5.3% **3**, 2.4% **4**, 12.7% **5**, and 2.1% **6**.

The last fraction, 3.5 g, was essentially pure **7** (8.3% yield based on *N*-methyl-*N*-[*o*-(β-phenethyl)benzyl]aniline[4]) and was further purified (>99%) by preparative gc. The yellow oil had bp 200–204° (1.0 mm) [lit.[4] 199–203° (1.10 mm)], $n^{25}D$ 1.6037, $n^{30}D$ 1.6018.

Anal. Calcd for $C_{22}H_{23}N$: C, 87.66; H, 7.69; N, 4.65. Found: C, 87.39; H, 7.99; N, 4.82.

The ir spectrum of a liquid film had bands at 3015 w, 2890 w, 1590 s, 1500 s*, 1445 w, 1370 w, 1340 w, 1255 w, 1210–1190 w, 1155 vw, 1115 w, 1035 w, 990 w, 953 vw, 860 vw, 752 m, and 695 m cm^{-1}. The pmr spectrum had absorption in three regions, centered near 2.5, at 4.12, and centered near 6.9 ppm with the relative integral intensities of 5.8:1.0:13.8, respectively. The first of these multiplets was composed of four distinguishable bands with peaks at 2.28, 2.45, 2.53, and 2.72 ppm but only the last two of these being of sufficient intensity to qualify as a CH_3 singlet attached to aromatic nitrogen; the remainder might be accounted for by an A_2B_2 link between two aromatic rings in the assigned structure. The singlet at 4.12 ppm would then be a benzylic methylene attached to aromatic nitrogen in the assigned structure, but its intensity was only half that required. The third region, that of the aromatic proton multiplet, was between 6.35 and 7.20 ppm with a broad singlet at 6.95 ppm accounting for more than two-thirds of the region's integrated area.

Reaction of *N,N*-Dimethylbenzylanilinium Bromide with Phenyllithium.—Results of a comparable reaction with the chloride are given in Table II. A solution of 40 ml of 1.7 *M* phenyllithium (0.68 mol) in 3:1 v/v benzene–ether was added to vigorously stirred suspension of 14.6 (50 mmol) of the finely powdered quaternary bromide at room temperature. The solution turned yellow and became warm in 25 min. After 14 hr, 20 ml of water was added slowly. The organic layer was reduced in volume to 29 ml by distillation and this product mixture was extracted with concentrated hydrochloric acid. The remaining organic phase had gc peaks at 168° with ir spectra for hydrocarbon product **8** and biphenyl present in the original phenyllithium solution. Diphenylmethane was not observed.

The acidic aqueous extract of the original organic layer was washed with ether and then made strongly alkaline with potassium hydroxide. The oil was collected by washing twice with 20-ml portions of ether. The extracts were evaporated and analyzed. *N,N*-Dimethylbenzylamine was used as a standard for analysis at 115° on a 20M Carbowax–KOH column after determining the absence of conflicting peaks. The single basic product observed on this column was **2** in 37% yield with a retention ratio of 2.20 relative to the standard used. The higher boiling amines were determined by analysis relative to *N,N*-dimethylbenzhydrylamine at 168° as previously described.[9] Only three product peaks were observed, retention ratios 1.49, 1.80, 2.28; these peaks were assigned to **3** (1.3%), **4** (23%), and **5** (3.9%), respectively. Products detected accounted for 65% of the starting salt.

Reaction of *N,N*-Dimethylbenzylanilinium (1) Chloride with Ethanolic Potassium Hydroxide.—Powdered 1 chloride (23.6 g, 95 mmol) was added to a solution of 11.2 g (0.2 mol) of potassium hydroxide in 150 ml of absolute ethanol. The mixture was refluxed for 24 hr, and then, after cooling, 200 ml of water was added. The separated organic layer and an ether extract of the aqueous solution were combined and dried over potassium hydroxide. Gc analysis at 135° on an 18-ft 20M Carbowax–KOH column[37] gave two peaks which had retention ratios of 4.75 and 7.75 relative to toluene at 1.00 (retention time 4.0 min), and at 122° on a GE-SF96 column these two peaks had retention ratios of 0.546 and 0.660 relative to *N,N*-dimethyl-β-phenethylamine. Ir analysis on a preparative gc sample containing both products gave a spectrum which was a composite of ethyl benzyl ether (45%, gc) and **2** (42%, gc).

A single peak with a retention ratio of 1.48 relative to *N,N*-dimethylbenzhydrylamine at 1.00 was observed in gc analysis at 168° on a GE-SF96 column. No trace of **8** was apparent in the ir of a preparative gc sample which was identical with that of commercial **3**, 5.8% yield.

Reaction of *N,N*-Dimethylbenzylanilinium (1) Chloride with Sodium Ethoxide.—The quaternary chloride (10.0 g, 40 mmol) was added to a solution which had been prepared by reacting 3.0 g (0.13 g-atom) of sodium with 70 ml of absolute ethanol. The solution was stirred at reflux for 24 hr. After cooling, 250 ml of water was added, and the solution was salted out with 10 g of sodium chloride and extracted with 20 ml of ether. The organic layer and a subsequent 50-ml ether extract were combined, dried over potassium hydroxide, and evaporated to 44 ml before analysis. The same three products and their characteristic gc retention ratios

(44) E. Wedekind, *Ber.*, **39**, 481 (1906).
(45) H. O. Jones, *J. Chem. Soc.*, **83**, 1400 (1903).
(46) W. Steinkopf and R. Bessaritsch, *J. Prakt. Chem.*, **109**, 244 (1925).
(47) H. O. Jones and J. R. Hill, *J. Chem. Soc.*, **91**, 2083 (1907).

were observed as in the preceding experiment: ethyl benzyl ether 63%, 2 59%, 3 5.3%. The neutral product structure was confirmed by ir analysis of the crude product distillate, bp 98–180° (1 atm), after acid washing and drying over calcium chloride. Gc characterization showed only a single peak for this material; its ir spectrum for a carbon disulfide solution with peaks at 3020 w, 2960 m, 2860 s, 1365 m, 1345 m, 1300 vw, 1265 vw, 1250 vw, 1200 w, 1165 w, 1145 w, 1110–1100 s*, 1070 m, 1030 w, 1015 w, 905 vw, 890 vw, 850 vw, 735 s, and 695 s cm^{-1}, was identical with that of the previously synthesized ether.

Rearrangement Product Ratios from the *n*-Butyllithium Reactions with *N,N*-Dimethylbenzylanilinium (1) Halides.—In this series of reactions, 15 ml of 1.5 *M* (23 mmol) *n*-butyllithium in hexane was rapidly added to a vigorously stirred suspension of 20 mmol of 1 halide in 85 ml of anhydrous ethyl ether. After 24 hr stirring at room temperature, 25 ml of water was added. The organic phase which separated was dried over potassium carbonate and analyzed directly at 168° on the GE-SF96 column. In no case was a peak or shoulder on an adjacent peak evident for an *o*-xylyl product. Therefore, the relative yields of rearrangement of α- and β-phenethyl products 4 and 5 were calculated directly from the areas of their respective gc peaks.

Registry No.—1 chloride, 3204-68-0; 1 bromide, 23145-45-1; 1 iodide, 25458-36-0; 5, 28059-49-6; 7, 28059-50-9; KOH, 1310-58-3; NaOEt, 141-52-6; MeLi, 917-54-4; C_6H_5Li, 591-51-5; *n*-BuLi, 109-72-8.

Benzyne Addition to *N,N*-Dimethylbenzylamine[1a]

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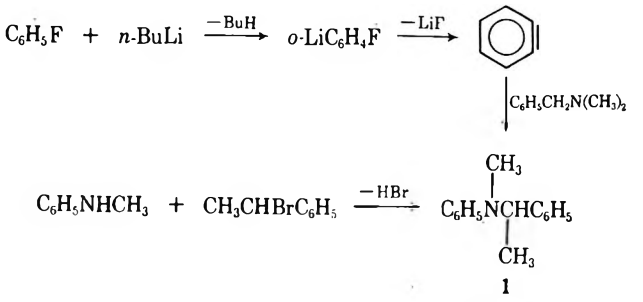
N-Methyl-*N*-(α-phenethyl)aniline (1) was obtained as the principal amine addition–rearrangement product when benzyne was generated by the attack of organolithium compounds on fluoro-, chloro-, or bromobenzene in *N,N*-dimethylbenzylamine. Small amounts of *N*-methyl-*N*-benzylaniline (2) and *N*-methyl-*N*-(β-phenethyl)-aniline (3) were also formed. Considerable variation in yields were observed with base and halobenzene variation. Fluorobenzene reaction with the metalated product from room temperature reaction of *N,N*-dimethylbenzylamine gave the same principal product plus a small amount of *N,N*-dimethyl-*o*-phenylbenzylamine (4). Proton magnetic resonance studies of the fluorobenzene, *n*-butyllithium, dimethylbenzylamine reaction show stimulated emission and enhanced adsorption in the chemical shift for the benzylic protons of the product. These data are interpreted as evidence for an ortho betaine from benzyne–amine addition which undergoes a proton shift to a benzyl ylide and subsequent free-radical pair methyl migration to the major product.

Although extensive studies of benzyne reactions have been reported,[2,3] relatively little work has been directed toward the addition of neutral, lone pair, electron donors to the active aromatic sites.[4,5] Several examples of this type of reaction involving tertiary aliphatic amine additions have been carried out by Wittig and coworkers[6–9] and by Hellmann's group[10–13] using Grignard generated benzyne, while benzyne *vs.* displacement reactions of strong bases on halobenzenes have been characterized with aniline derivatives.[14,15]

Since this last method, the action of organolithium compounds on monohalobenzenes, provides a method of generating intermediates comparable to those of several quaternary ammonium salt rearrangements, we have carried out this study on the addition of benzyne to *N,N*-dimethylbenzylamine. Where feasible, this work paralleled the organolithium rearrangements of the *N,N*-dimethyl-*N*-benzylanilinium ion.[16]

Results and Discussion

The principal addition–rearrangement product, *N*-methyl-*N*-(α-phenethyl)aniline (1), was obtained in 35% yield from the reaction of *n*-butyllithium and fluorobenzene in a 1:3:1 v/v solution of *N,N*-dimethylbenzylamine, anhydrous ether, and *n*-hexane. Identification of this product was based on the identity of proton magnetic resonance (pmr) and infrared (ir)



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spectra for material from a preparative scale reaction[17] and for the authentic compound synthesized by the reaction[18] of *N*-methylaniline and α-bromoethylbenzene. The formation of 1 was smooth reaching three-

(1) (a) This investigation was supported by U. S. Public Health Service Grant GM-09136 from the National Institute of General Medical Sciences and was presented in part before the Division of Organic Chemistry, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, Abstracts, 5Q. (b) To whom reprint requests should be sent, Marshall University. (c) Fulbright student, State University of New York at Stony Brook, 1962–1964.

(2) For reviews of aryne chemistry, see E. F. Jenny, M. C. Caserio, and J. D. Roberts, *Experientia*, **14**, 349 (1958); R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960); R. Huisgen, "Organometallic Chemistry," H. Zeiss, Ed., Reinhold, New York, N. Y., 1960, pp 75–87; J. F. Bunnett, *J. Chem. Educ.*, **38**, 278 (1961); H. Heaney, *Chem. Rev.*, **62**, 81 (1962); G. Wittig, *Angew. Chem., Int. Ed. Engl.*, **4**, 731 (1965).

(3) R. W. Hoffman, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967.

(4) A. R. Lepley, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14**, C43 (1969).

(5) Reference 3, pp 164–179.

(6) G. Wittig and W. Merkle, *Chem. Ber.*, **76**, 109 (1943).

(7) G. Wittig, *Angew. Chem.*, **63**, 16 (1951).

(8) G. Wittig and R. Polster, *Justus Liebigs Ann. Chem.*, **599**, 13 (1956); **612**, 103 (1958).

(9) G. Wittig and E. Benz, *Chem. Ber.*, **92**, 1999 (1959).

(10) H. Hellmann and W. Unseld, *Justus Liebigs Ann. Chem.*, **631**, 82 (1960).

(11) H. Hellmann and W. Unseld, *ibid.*, **631**, 89 (1960).

(12) H. Hellmann and W. Unseld, *ibid.*, **631**, 95 (1960).

(13) H. Hellmann and G. M. Scheytt, *ibid.*, **642**, 22 (1961).

(14) A. R. Lepley, A. G. Giumanini, A. B. Giumanini, and W. A. Khan, *J. Org. Chem.*, **31**, 2051 (1966).

(15) H. Heaney and T. J. Ward, *Chem. Commun.*, 810 (1969).

(16) A. R. Lepley and A. G. Giumanini, *J. Org. Chem.*, **36**, 1217 (1971).

(17) A. G. Giumanini and A. R. Lepley, *Bull. Chem. Soc. Jap.*, **42**, 2359 (1969).

(18) A. H. Wagg, T. S. Stevens, and D. M. Ostle, *J. Chem. Soc.*, 4057 (1958).

fourths of the maximum yield after 9 hr at constant temperature. Changes in base or halobenzene (Table I) all resulted in decreased yields of **1**. Phenyllithium and chlorobenzene gave approximately one-half the production of **1** as was formed with *n*-butyllithium and the same halobenzene. Fluoro-, chloro-, and bromobenzene, in that order, gave decreasing amounts of **1**. The *in situ* generation of benzyne[19] from anthranilic acid and *n*-butyl nitrite gave a maximum yield of 3% **1** on reaction with dimethylbenzylamine. An equal amount of *N*-methyl-*N*-benzylaniline (**2**) was formed in the latter reaction.

TABLE I

N-METHYL-*N*-(α-PHENETHYL)ANILINE (**1**) PRODUCED IN THE ADDITION OF DIMETHYLBENZYLAMINE[a] TO BENZYNE

Benzyne source	Yield of **1**, %
1 *o*-$NH_2C_6H_4CO_2H$ + 1 *n*-BuONO	3
1 C_6H_5Br + 2 C_6H_5Li	4
1 C_6H_5Cl + 2 C_6H_5Li	10
1 C_6H_5Cl + 1 *n*-BuLi	14
1 C_6H_5Cl + 2 *n*-BuLi	18
1 *o*-FC_6H_4Br + 1 Mg	21[b]
1 C_6H_5F + 2 *n*-BuLi	33

[a] Six- to eightfold excess used. [b] Equimolar amount of amine, ref 10.

This same material, **2**, was also detected in small amounts, 1.0 and 0.2% yields, respectively, from chloro- and fluorobenzene reactions with *n*-butyllithium in dimethylbenzylamine. *N*-Methyl-*N*-(β-phenethyl)aniline (**3**) was formed in 1.0 and 0.5% in these same reactions. In general, the reactions were slower and yields of secondary productions, **2** and **3**, were higher with changes in the halobenzene from fluoro to chloro to bromo. The pmr (Table II) and gas chromatographic (Table III) data for these compounds and a number of related isomeric compounds were used in confirming structures.

Since the amine reactant in these studies has been reported[20] to rapidly convert to species lithiated in the α and ortho positions, *N,N*-dimethylbenzylamine was treated with *n*-butyllithium for 24 hr at room temperature before addition of fluorobenzene. In this case, **1** was the principal product, 17%, and small amounts of three other compounds were detected. Compounds with the gc and organolectic characteristics of benzaldehyde and *N,N*-dimethylaniline were present in trace amounts relative to the starting amine. The third compound, *N,N*-dimethyl-*o*-phenylbenzylamine (**4**), was formed in 1.0% yield.

Benzyne is generated by the action of a strong base on a haloaromatic compound in two steps:[2] (1) ortho proton abstraction by the base, and (2) loss of metal halide from the metalated haloaromatic formed in step 1. Although the equilibrium characteristics of the first step have been studied,[21] the use of *n*-butyl- or phenyllithium effectively eliminated reversibility in the metalation reaction. Benzyne formation or reaction with this species thus became the subsequent routes in conversion of the ortho halo metal compound. The halide reactivity order F > Cl > Br for benzyne formation was the same as that previous observed.[2,3]

The benzyne generated acts as an electrophilic reagent in subsequent reactions. The base itself can react with benzyne if present in an excess if step 1 is rate controlling. Although biphenyl and/or metalated diphenyl were present in the phenyllithium solution used, additional amounts of this material may also have been formed by a side reaction of phenyllithium with benzyne. *n*-Butylbenzene was not sought in the current experiments; however, it has been reported[2] when benzyne is generated with *n*-butyllithium. Other related species could form from the addition of the ortho halo metal intermediate to benzyne.

Metalation of *N,N*-dimethylbenzylamine occurs in the ortho position.[20] The benzyne adduct of this metalated species gives **4**, an isomer of **1**, on reaction

$$C_6H_5CH_2N(CH_3)_2 + n\text{-BuLi} \xrightarrow{-\text{BuH}} o\text{-}LiC_6H_4CH_2N(CH_3)_2$$

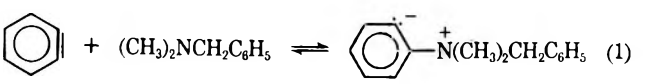
$$\downarrow C_6H_4$$

$$o\text{-}C_6H_5C_6H_4CH_2N(CH_3)_2 \xleftarrow{H_2O} o\text{-}(o'\text{-}LiC_6H_4)C_6H_4CH_2N(CH_3)_2$$

4

with water. Neither **4** nor benzhydryldimethylamine (**5**), a potential product *via* methylene metalation of dimethylbenzylamine, was observed in direct reactions of an organolithium reagent with halobenzene in amine. However, when the amine was allowed to react with *n*-butyllithium prior to fluorobenzene addition, a small amount of **4** was observed. These observations may be interpreted in any of several fashions; either metalation of the amine was relatively slow under the reaction conditions and/or amounts of metalated amine were very small and/or the addition of these metalated species to benzyne is relatively inefficient. The first of these possibilities is favored, although not necessarily to the exclusion of the others by the premetalation reaction results and by the observed very slow change in integrated nmr proton ratios for mixtures of the tertiary amine and *n*-butyllithium.

The equilibrium addition[22] of the less basic, neutral nitrogen lone pair to benzyne (eq 1) is favored by



(1)

high amine concentrations. Since low aryne concentrations mitigate against further benzyne addition to the betaine, SNi-sigmatropic shifts[23] of the betaine are proposed to account for final aniline-containing products in the aprotic media. A pseudo-Sommelet [3,3] shift of the betaine to an *exo*-methylenecyclohexadiene

(19) Method of L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **85**, 1549 (1963); *J. Org. Chem.*, **34**, 3089 (1969).

(20) W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **85**, 2467 (1963).

(21) J. F. Bunnett and D. A. R. Happer, *J. Org. Chem.*, **31**, 2369 (1966).

(22) Evidence for equilibrium is the formation of products attributable to benzyne generation in base attack on quaternary anilinium salts: F. Weygand, A. Schroll, and H. Daniel, *Chem. Ber.*, **97**, 857 (1964); A. G. Giumanini, *Chem. Ind. (London)*, 1140 (1967).

(23) Although no stereochemistry distinguishing between the inversion of a nucleophilic displacement and the retention of a sigmatropic shift is possible in these reactions, we have used the more descriptive reaction orders as defined by A. R. Lepley and A. G. Giumanini in "Mechanisms of Molecular Migration," Vol. 3, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1970.

Table II

Proton Magnetic Resonance Spectra of Reaction Products and Other Compounds Related to the Benzyne Addition to Dimethylbenzylamine and to the Rearrangement of Dimethylbenzylanilinium Salts[a]

	Chemical shift[b]										
	CH₃				CH₂					CH	H
Compd	C	NC	Ar	NAr	C, Ar	NC, Ar	Cr, NAr	Ar, Ar	NAr, Ar	N, Ar, Ar	C, Ar, NAr	Ar
N,*N*-Dimethylaniline				2.78 s (6)								6.60 m (3), 7.08 m (2)
N,*N*-Dimethylbenzhydrylamine (**5**)		2.11 s (6)								4.00 s (1)		7.23 m (10)
N,*N*-Dimethylbenzylamine		2.13 s (6)				3.31 s (2)						7.20 m (5)
N,*N*-Dimethyl-*o*-benzylaniline (**7**)				2.57 s (6)				4.01 s (2)				7.01 m (9)
N,*N*-Dimethyl-*o*-phenylamine (**4**)		2.08 s (6)				3.23 s (2)						7.29 m (9)
N-Ethyl-*N*-benzylaniline	1.12 t (3)						3.35 q (2)		4.34 s (2)			6.67 m (3), 7.16 m (7)
N-Methyl-*N*-benzylaniline (**2**)				2.86 s (3)					4.36 s (2)			6.63 m (3), 7.15 m (7)
N-Methyl-*N*-benzyl-*o*-toluidine (**6**)			2.34 s (3)	2.50 s (3)					3.92 s (2)			6.99 m (4), 7.23 m (5)
N-Methyldibenzylamine (**10**)		2.08 s (3)				3.41 s (4)						7.22 m (10)
N-Methyl-*N*-(α-phenethyl)aniline (**1**)	1.46 d (3)			2.56 s (3)							5.03 q (1)	6.71 m (3), 7.18 m (7)
N-Methyl-*N*-(β-phenethyl)aniline (**3**)				2.74 s (3)[c]	2.77 m (2)[c,d]		3.44 m (2)[d]					6.60 m (3), 7.11 m (7)
N-Methyl-*N*-(*o*-xylyl)-aniline			2.21 s (3)	2.86 s (3)					4.32 s (2)			6.62 m (3), 7.03 m (6)

[a] Reference 16. [b] All peaks are relative to tetramethylsilane as δ values in parts per million (ppm); splitting, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; *J* values are 7.0 ± 0.1 cps unless otherwise indicated; values in parentheses are relative integrated peak ratios in compound. [c] Overlapping singlet and multiplet, center of multiplet determined from integral and singlet peak maximum. [d] Centers of respective parts of A_2X_2 multiplet.

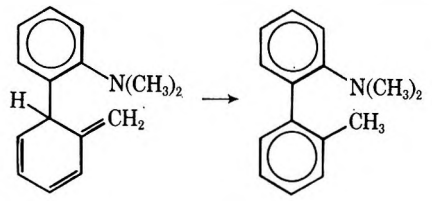
Table III

Gas Chromatographic Retention Ratios of Compounds Related to the Benzyne Addition of Dimethylbenzylamine

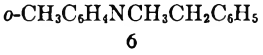
	Retention ratio by column			
	20% 20M Carbowax	20% GE-SF96[b]		20% Apiezon
Compd	plus 5% KOH[a]	168°[c]	200°[d]	H[e]
N,*N*-Dimethyl-*o*-phenylbenzylamine (**4**)	0.896	1.00		0.855
N,*N*-Dimethylbenzhydrylamine[f] (**5**)	1.00	1.00	1.00	1.00
N,*N*-Dimethyl-*o*-benzylaniline (**7**)	1.29	1.22	1.23	1.08
N-Methyl-*N*-benzyl-*o*-toluidine[g] (**6**)	1.34	1.29	1.27	1.20
N-Methyldibenzylamine (**10**)	1.37	1.28	1.28	1.28
N-Methyl-*N*-benzylaniline (**2**)	2.17	1.45	1.40	1.65
N-Ethyl-*N*-benzylaniline		1.73		
N-Methyl-*N*-(α-phenethyl)aniline (**1**)	2.21	1.76	1.62	1.86
N-Methyl-*N*-(*o*-xylyl)aniline	2.91	2.18	1.88	
N-Methyl-*N*-(β-phenethyl)aniline (**3**)	3.13	2.29	2.02	

[a] 0.25 in. × 12 ft column, 190°, 150 ml/min He flow; ratios are ±0.01. [b] 0.25 in. × 5 ft column. [c] 72 ml/min He flow; ratios are ±0.01. [d] 26 ml/min He flow; ratios are ±0.02. [e] 1/8 in. × 5 ft column, 195°, 30 ml/min N_2 flow; ratios are ±0.005. [f] Retention ratio standard. [g] Used as internal standard for quantitative analysis.

and subsequent [1,3] proton migration would form the biphenyl product of eq 2, but no product was


(2)

detected with the properties of this compound. [1,3] shifts from betaine nitrogen to the ortho aniline position by methyl or benzyl groups would produce *N*-methyl-*N*-benzyl-*o*-toluidine (6) or *N,N*-dimethyl-*o*-benzylaniline (7), respectively. Although such a direct in-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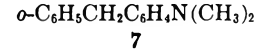
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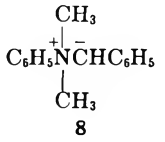
ternal displacement of an ethyl group in the benzyne addition of triethylamine was suggested,[6] it was later shown[9] that the product observed came from an α rearrangement. Absence of 6 and 7 in the current reactions supports the forbidden nature of [1,3] processes since the intermolecular displacement products *N,N*-dimethylaniline and 2 were observed.

Proton migrations [1,4] from either benzyl or methyl groups of the betaine give the respective ylides 8 and 9. The subsequent conversion of 8 and 9 to 1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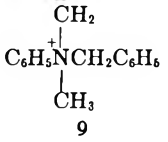
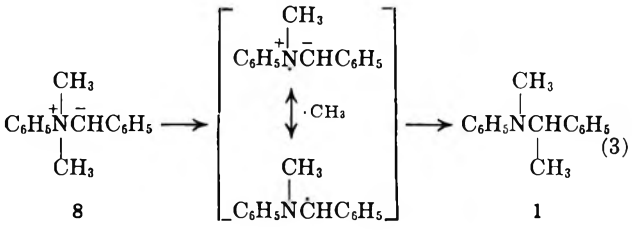

9

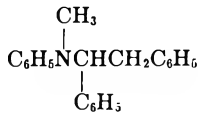
and 2 is the same as discussed for rearrangements of the *N,N*-dimethyl-*N*-benzylanilinium ion.[16] The ammonium salt rearrangement to 1 was favored by low strength in the attacking base. In the betaine, the proton-abstracting power of the ortho anion is probably less than that of any of the organolithium bases studied. The benzyl proton migration, favored by phenyllithium attack on the salt, was even more viable with the ortho betaine. The contrast of phenyllithium and butyllithium as benzyne-generating agents indicates that the stronger base was rapidly consumed so that internal benzyl proton migration was betaine controlled. The slower phenyllithium generation of benzyne thus provided a stronger base which was still present to modulate the methyl ylide formation and increase the relative production of the β-phenethyl product, 3. Although ylides are generated by comparable bases from two different starting points, the Stevens rearrangement *via* α methyl migration from 8 to form 1 predominates in both cases. Therefore, it is possible to extrapolate the following detailed evidence from the benzyne reaction to the quaternary salt rearrangement.

The definition of the pathway from 8 to 1 is based on proton magnetic resonance (pmr) measurements during the benzyne addition reaction. When reaction is complete within 30 min, the pmr spectrum of the reaction mixture gives a $-0.9:-4.9:5.6:1.1$ peak intensity ratio for the methyne quartet of 1 at δ 5.01 ppm. Since the intensity ratio differs from the normal 0.9:3.0:3.0:1.1 observed in pure 1 (Table II), chemically induced dynamic nuclear polarization (CIDNP)[24] giving a multiplet effect[25] was evident.[26] CIDNP multiplet effects with downfield emission and upfield absorption occur when singlet radical pairs are direct product precursors.[27] Thus a radical pair compatible with homolytic cleavage of the single bond must precede 1. The caged singlet state, however, does not produce a multiplet effect except when some spin sorting takes place by conversion to a triplet pair and subsequent separation of the radical pair. A loss of $\cdot CH_3$ from the cage of eq 3 would give 2 if the re-


(3)

maining radical abstracted hydrogen; the related dimers were not sought. Absence of CIDNP effects in 2 do not effect this interpretation since multiplet effects are self-cancelling in singlets.[28] If the ratio of 1:2, $>30:<1$, indicates the amount of 1 contributing to the multiplet effect, then (a) trapping within the cage of eq 3 is very efficient; (b) most of the production of 1 is by some other route; or (c) major amounts of dimeric and other unidentified materials are present. While we have not yet distinguished between these possibilities, we favor a. However, we can demonstrate that the conditions for CIDNP measurements do not greatly change the reaction chemistry.

In order to accelerate the reaction from 9–24 hr to <30 min, concentrations and temperature were increased and catalyst was added to speed metalation by depolymerization of the *n*-butyllithium hexamer.[29] The elimination of diluents, heating to 60°, and addition of very small amounts of *N,N,N,N*-tetramethylethylenediamine (TMEDA) are adequate to give a strong e/a multiplet in the *N,N*-dimethylbenzylamine reaction. The quantitative variation in the reaction of *N*-methyldibenzylamine (10) with fluorobenzene and *n*-butyllithium and the resulting effect on yields of *N*-methyl-*N*-(1,2-diphenylethyl)aniline (11) and *N*-methyl-*N*-benzyl-*o*-phenylbenzylamine (12) are shown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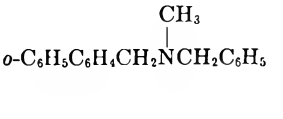
12

in Table IV.[30] CIDNP effect pmr spectra were attained from both the methyne and methylene protons of 11[26] but only when 11 was formed in high yields *and* reaction completion was rapid. Since comparable results are obtained both in slow and fast reactions and the catalyst is known to accelerate the first reaction

(24) For a recent review, see H. R. Ward, *Accounts Chem. Res.*, **4**, in press.
(25) A. R. Lepley, *J. Amer. Chem. Soc.*, **91**, 749 (1969).
(26) A. R. Lepley, *ibid.*, **91**, 1237 (1969); *Chem. Commun.*, 1460 (1969).
(27) G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **91**, 4550 (1969).
(28) Decoupling experiments on the pmr multiplet effect spectra in RLi + R'I reactions confirm this conclusion: A. R. Lepley, unpublished work.
(29) J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969).
(30) A. R. Lepley and P. M. Cook, unpublished work.

TABLE IV

EFFECT OF REAGENTS ON PRODUCT DISTRIBUTIONS IN BENZYNE ADDITION TO *N*-METHYLDIBENZYLAMINE (10)

Molar ratio *n*-BuLi[a]:10:C_6H_5F	Time, hr	% yield 11	% yield 12
1:1:1	24	8.3	6.0
1:5:1	24	24.9	4.0
1:1:1[b]	0.5	1.8	3.6
1:5:1[b]	0.5	24.6[c]	2.8

[a] *n*-BuLi (1.5 *M*) in hexane. [b] Plus 0.01 mol ratio TMEDA. [c] CIDNP in pmr spectrum during reaction.

step, the subsequent steps are essentially unchanged under CIDNP conditions.

The generalized radical pair pathway of eq 3 offers a reasonable explanation for the observations. These and the related results discussed for ammonium salts[16] furnish a strong basis for future tests of rearrangement mechanisms.

Experimental Section[31]

Gas Chromatography (Table II).—Separations were accomplished on an Aerograph A-90P using the nonpolar substrate GE-SF96. The polar 20M Carbowax plus KOH column was used on an F & M Model 500. Several compounds, inadequately separated on the preceding columns, were characterized on an Apiezon H column using an Aerograph A-600 with flame ionization detector. Quantitative analyses were carried out on the Carbowax and GE-SF96 columns.

Chemicals.—Bromo-, chloro-, and fluorobenzene, α-chlorotoluene, α-bromo-*o*-xylene, (α-bromoethyl)benzene, *N*-methyl-*o*-toluidine, *N*-methylaniline, *N*-methyl-*N*-benzylaniline, *N*-ethyl-*N*-benzylaniline, *n*-butyl nitrite, and anthranilic acid were purchased from Eastman. *N*,*N*-Dimethylbenzylamine and *N*-methyldibenzylamine (10) were obtained from Miles Chemical. *o*-Nitrobenzyl chloride and aminodiphenylmethane were from Aldrich, and *o*-aminobiphenyl was a Pfister product. Foote Mineral Co. 15% *n*-butyllithium in hexane and 20% phenyllithium in 3:1 v/v benzene–ether were titrated to determine active lithium content[32] before use. *N*-Methyl-*N*-(β-phenethyl)aniline (3)[16] and *n*-pentylbenzene[33] were available from related studies.

2-Cyanobiphenyl.—*o*-Aminobiphenyl (100 g, 0.59 mol) was mixed with 150 ml (1.8 mol) of concentrated hydrochloric acid. The salt slurry formed was cooled to 0° by addition of crushed ice and an ice-cold solution of 42 g (0.61 mol) of sodium nitrite in 100 ml of water was added at such a rate that the temperature did not rise above 5°.[34] The mixture was neutralized with solid sodium carbonate. Cuprous cyanide[35] (65 g, 0.75 mol) was suspended in 450 ml of water and 82 g (1.25 mol) of potassium cyanide was added to effect solution. The cyanide solution was cooled to 0° by addition of ice, mixed with 200 ml of toluene, and slowly added to the diazonium solution with vigorous stirring while maintaining the temperature below 5°. The tarry mixture was allowed to gradually warm to room temperature and then was heated to 50°. On cooling the oily layer was separated. Toluene extracts were combined with the previous organic layer and washed with dilute (6 *F*) hydrochloric acid, sodium bicarbonate solution, and then water, dried with sodium sulfate, and distilled. The product, 45 g, 43% yield, was obtained as a colorless oil boiling at 170–171° (15 mm) [lit.[36] 163° (14 mm)], $n^{25}D$ 1.6147. The infrared spectrum had bands at 3030 w, 2220 w, 1590 w, 1555 vw, 1470 m, 1445 w, 1425 w, 1265 vw, 1185 vw, 1160 vw, 1075 vw, 1010 w, 920 vw, 845 vw, 780 w, 762 s, 738 s, and 700 s* cm^{-1}.

***N*,*N*-Dimethyl-*o*-phenylbenzylamine (4).**—2-Cyanobiphenyl (44 g, 0.25 mol) in 200 ml of anhydrous ether was reduced with a suspension of lithium aluminum hydride[37] in 500 ml of anhydrous ether. After removing excess hydride with 20% NaOH and water, and decanting, the ether was stripped from the solution to give crude primary amine.[38] Formic acid (90% solution, 1.25 mol) and then 0.55 mol of formaldehyde[39] were added with cooling to the crude amine. The mixture was refluxed for 16 hr. Hydrochloric acid (12 *N*, 0.44 mol) was added and the mixture was vacuum evaporated to half its volume. The solution was made strongly basic by slow addition of solid sodium hydroxide and was then extracted with ether. The ether layer was dried over solid potassium hydroxide. Distillation of the ether solution gave 26 g, 50% yield, of the gas chromatographically pure product, bp 162–164° (21 mm), $n^{25}D$ 1.5759, d^{20}_4 1.003. The infrared spectrum had bands at 3060 w, 2940 m, 2820 m, 2770 s, 1685 vw, 1590 w, 1475 m, 1450 m, 1360 m, 1300 vw, 1282 vw, 1260–1245 w, 1173 w, 1147 vw, 1097 w, 1075 vw, 1045 m, 1030 m, 1011 m, 946 vw, 915 vw, 880 vw, 852 w, 776 m, 754 s*, 724 w, and 703 s cm^{-1}.

Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.43; H, 8.05; N, 6.45.

o-Nitrodiphenylmethane.—Aluminum chloride (51 g, 0.38 mol) was slowly added at 0° with vigorous stirring to an anhydrous solution of 39 g (0.23 mol) of *o*-nitrobenzyl chloride[40] in 500 ml of benzene and reacted as previously described.[41] After washing and drying, vacuum distillation gave 21 g, 43% yield, of the product boiling at 204–207° (21 mm) [lit.[41] 183–184° (10 mm)]. The product had infrared peaks at 3070 w, 2930 vw, 2857 vw, 1608 w, 1530 s*, 1495 m, 1452 w, 1355 s, 1183 vw, 1112 w, 1078 vw, 1033 vw, 1019 vw, 864 w, 819 vw, 790 w, 745–735 m, and 704 m cm^{-1}.

o-Benzylaniline.—Five grams of 10% palladium on powdered charcoal was added to a stirred boiling solution of 20 g (94 mmol) of *o*-nitrodiphenylmethane in 400 ml of 95% ethanol. Hydrazine hydrate (37 ml) was slowly added and the solution was refluxed until evolution of gas ceased. The solution was filtered and distilled giving 13.5 g, 79% yield, of product, bp 171–172° (12 mm) [lit.[41] 172–173° (13 mm)], with infrared peaks at 3450 w, 3370 m, 3225 w, 3020 m, 2910 w, 2850 vw, 1620 s*, 1510 s, 1485 s, 1450 m, 1275 m, 1180 w, 1075 w, 1040 w, 838 w, 783 w, 754 s, 731 s, and 698 s cm^{-1}.

***N*,*N*-Dimethyl-*o*-benzylaniline (7).**—*o*-Benzylaniline (4.5 g, 24 mmol) was mixed with 6.8 g (49 mmol) of trimethyl phosphate and heated gently in a 1-l. flask until a fine mist appeared. The heat was removed until the initial reaction ceased and then the solution was gently refluxed for 2 hr. A solution of 20 g of sodium hydroxide in 150 ml of water was slowly added to the cooled reaction mixture. Then 200 ml of water was added and the amine was extracted with ether. The ether solution was dried over sodium hydroxide pellets, decanted, and vacuum distilled to give 1.8 g, 35% yield, of the tertiary amine, bp 93–95° (0.01 mm), $n^{23}D$ 1.5799.

Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.11; H, 8.23; N, 6.80.

The product had infrared peaks at 3020 m, 2940 m, 2860 w, 2830 w, 2780 w, 1675 w, 1600 m, 1490 s*, 1450 s, 1315 w, 1180 w, 1157 w, 1094 w, 1064 w, 1050 w, 1034 w, 950 w, 769 m, 750 m, 731 m, and 700 s cm^{-1}.

***N*-Methyl-*N*-benzyl-*o*-toluidine (6).**[42]—*N*-Methyl-*o*-toluidine (22 ml, 166 mmol) and 19 ml (166 mmol) of α-chlorotoluene were heated at 100° for 5 hr. The crystalline product was triturated with four 50-ml portions of ether and the remaining solid was mixed with 50 ml of 6 *N* sodium hydroxide. The oil which resulted was extracted with ether. The ether layer was washed with 6 *N* sodium hydroxide and water, dried over anhydrous silica gel, decanted, and distilled. A 57% yield, 20 g, of product

(31) (a) Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. (b) Physical constants were measured and are reported as previously described: A. R. Lepley, V. C. Dohm, and A. G. Giumanini, *J. Org. Chem.*, **34**, 3042 (1969); A. R. Lepley and R. H. Becker, *Tetrahedron*, **21**, 2365 (1965).

(32) H. Gilman and F. K. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964); D. E. Applequist and D. F. O'Brien, *J. Amer. Chem. Soc.*, **85**, 743 (1963); H. Gilman and A. H. Haubein, *ibid.*, **66**, 1515 (1944).

(33) A. R. Lepley and A. G. Giumanini, *J. Org. Chem.*, **32**, 1706 (1967).

(34) *Cf.* H. T. Clarke and R. R. Read, *Org. Syn.*, **1**, 514 (1941).

(35) H. J. Barber, *J. Chem. Soc.*, 79 (1943).

(36) J. von Braun and G. Manz, *Justus Liebigs Ann. Chem.*, **468**, 258 (1929).

(37) General nitrile reduction method of L. Amundsen and L. Nelson, *J. Amer. Chem. Soc.*, **73**, 242 (1951).

(38) This primary amine has previously been prepared by other methods: T. A. Geissman and R. W. Tess, *ibid.*, **62**, 514 (1940); *cf.* ref 36.

(39) General methylation method of H. T. Clark, H. B. Gillespie, and S. Z. Weisshaus, *ibid.*, **55**, 4571 (1933).

(40) Recrystallized from petroleum ether, (bp 35–60°), prior to use, mp 48–49°.

(41) P. Carré, *C. R. Acad. Sci.*, **148**, 101 (1909).

(42) E. Wedekind and F. Oberheide, *Ber.*, **37**, 3898 (1904).

was obtained boiling at 158–159° (12 mm) [lit.[42] 167° (13 mm)], n^{23}D 1.5742, d^{20}_4 1.019. The infrared spectrum had bands at 3060 w, 2970 w, 2870 w, 2825 w, 1610 m, 1495 s*, 1460 m, 1368 m, 1334 w, 1300 vw, 1230 m, 1177 w, 1123 w, 1099 m, 1078 w, 1058 w, 1033 w, 990 vw, 910 vw, 818 vw, 768 s, 750 w, 726 s, and 699 m cm^{-1}.

***N*-Methyl-*N*-(α-phenethyl)aniline** (1).—*N*-Methylaniline (25 ml, 0.23 mol) was added to an excess (50 ml, 0.35 mol) of α-bromoethylbenzene. After the initial reaction subsided, the mixture was heated for 2 hr on a steam bath. The mixture, which solidified on cooling, was washed with cold acetone which left a readily filtered, white crystalline powder. The solid was dissolved in water and solid potassium hydroxide was added until strongly basic. The insoluble oily amine was extracted with ether, and the ether solution was dried over potassium hydroxide, decanted, and distilled. A 49% yield, 24 g, of product was obtained boiling at 188–189° (23 mm) [lit. 158–165° (7 mm),[18] 166–168° (14 mm)[43]], n^{25}D 1.5946 [lit.[43] n^{23}D 1.5967], d^{20}_4 1.033. Infrared analysis showed bands at 3030 w, 2970 w, 2870 w, 2800 vw, 1605 s, 1510 s*, 1450 m, 1370 m, 1315 m, 1208 w, 1185 w, 1162 vw, 1103 m, 1031 m, 997 w, 909 vw, 787 w, 751 s, 723 w, and 965 s cm^{-1}.

***N*-Methyl-*N*-(*o*-xylyl)aniline.**[44]—*N*-Methylaniline (18 ml, 166 mmol) and 22 ml (166 mmol) of α-bromo-*o*-xylene were treated as in the preparation of *N*-methyl-*N*-benzyl-*o*-toluidine. A 40% yield, 14 g, of product was obtained which boiled at 165–170° (13 mm) [lit.[44] 200° (35 mm)], n^{23}D 1.5998, d^{20}_4 1.057, with infrared peaks at 3060 w, 2940 m, 1610 s, 1515 s*, 1470 m, 1385 m, 1355 m, 1265 m, 1222 m, 1213 m, 1162 w, 1125 w, 1108 w, 1055 vw, 1040 w, 1008 w, 994 w, 957 w, 930 w, 868 vw, 751 s, and 694 m cm^{-1}.

***N,N*-Dimethylbenzhydrylamine** (5).—α-Aminodiphenylmethane (47 ml, 0.27 mol) was mixed with 50 ml of 36% formaldehyde and 52 ml of 95% formic acid. Reaction and work-up were as in the preparation of 4. Evaporation of the final dried ether solution gave a crude solid, mp 55, which when recrystallized from absolute ethanol gave 21 g, 37% yield, of white crystalline product, mp 69–70° (lit.[45] 68.5–70.5°).

Benzyne Additions of Benzyldimethylamine. General Procedure Using Organolithium Compounds.—The halobenzene (20 mmol) was added to a rapidly stirred mixture of 40 mmol of the organolithium compound, 20 ml of *N,N*-dimethylbenzylamine, and 80 ml of anhydrous ether under a dry nitrogen atmosphere. After 24 hr at room temperature, 15 ml of water and then 100 ml of 6 *N* hydrochloric acid were added. The aqueous layer was separated and made strongly alkaline with solid sodium hydroxide. The products were recrovered by ether extraction of the basic aqueous solution. The ether was evaporated and basic products were determined by gc.

The back extraction procedure was shown to be generally unnecessary by gc. Satisfactory gc analysis were obtained merely by adding water to the reaction mixture and separating the ether layer which contains the products. This procedure was used for yield *vs.* time studies as described in the following examples.

Reaction of Chlorobenzene with *n*-Butyllithium in *N,N*-Dimethylbenzylamine.—*n*-Butyllithium (15 ml of 1.5 *M*, 23 mmol) in hexane was rapidly added to a solution of 1.9 ml (20 mmol) of chlorobenzene, 80 ml of anhydrous ether, and 20 ml (135 mmol) of *N,N*-dimethylbenzylamine and reacted as described in the general procedure. The solution immediately became bright yellow and 1 hr later a white precipitate began to form. Gc of the separated amines at 200° on GE-SF96 indicated the presence of three peaks with relative areas of 6, 87, and 7%. The first and third peaks had retention ratios of 0.86 and 1.24 with respect to the second. The principal component (second peak) was comparable to the material obtained in the large scale reaction with fluorobenzene.[17] The absolute yield of this compound, *N*-methyl-*N*-(α-phenethyl)aniline (1), was 14%. The third peak was found to be compatible with assignment of *N*-methyl-*N*-(β-phenethyl)aniline (3) by peak enhancement. Stilbene was not detected in the neutral extracts of this or other halobenzene reactions.

The replacement of chlorobenzene with a comparable quantity of fluorobenzene gave a basic extract with the same three gc peaks in the relative ratio 0.5:98:1.5%.

Reactions Conditions Giving CIDNP.—The anhydrous tertiary amine, 0.25 cc of *N,N*-dimethylbenzylamine (or 10 for reactions producing CIDNP in 11), was added to 0.625 cc of 1.5 *M* *n*-butyllithium in hexane inside an over-dried, thin-wall, 5-mm nmr tube. The solution rapidly changes color to yellow orange and a small amount of precipitate formed. The external lock pmr spectrometer was tuned on the sample at 40° using the $-CH_2Li$ group at δ −0.8 ppm. The sample was removed and the probe was heated to 60°. Fluorobenzene (150 μl) was added to the solution at ambient temperature, rapidly followed by 6 μl of TMEDA. The tube was quickly but firmly capped, thoroughly shaken, and inserted in the nmr probe. Spectra were recorded within 15 sec of mixing and scans repeated for 5 to 10 min.

Reaction of Fluorobenzene with Lithiated *N,N*-Dimethylbenzylamine.—The addition of 70 ml of 1.5 *M* (115 mmol) *n*-butyllithium in hexane to 17 ml (115 mmol) of *N,N*-dimethylbenzylamine gave a bright orange solution for the slightly exothermic reaction. After 24 hr at room temperature, large colorless crystals separated from the solution. Fluorobenzene (9.4 ml, 100 mmol) was then added dropwise with rapid stirring. Water (25 ml) was carefully added after an additional 24 hr. Two gc peaks for products were observed at 168° on GE-SF96. The first of these had a gc retention ratio of 0.57 with respect to the second. Preparative gc gave a material for the second peak with refractive index of n^{25}D 1.5948 and an ir spectrum identical with that of 1, 17.3% yield. Distillation gave a fraction boiling at 125–138° (1 mm) which had a pmr spectrum identical with the α-phenethyl compound except for a trace peak at δ 2.08 ppm. This pmr peak was due to the first of the high boiling gc peaks, for which the ir spectrum on a preparative gc sample was comparable with that of 4, 1.0% yield.

A low boiling fraction [<40° (1 mm)] for the distillation showed two trace peaks in gc analysis at 122° on GE-SF96.[16] The ir spectra of preparative gc samples were comparable with those of commercial benzaldehyde and *N,N*-dimethylaniline.

Reactions of *N,N*-Dimethylbenzylamine, Butyl Nitrite, and Anthranilic Acid.—*N,N*-Dimethylbenzylamine (20 ml, 135 mmol) in 25 ml of methylene chloride was mixed with a solution of 4.6 ml (40 mmol) of *n*-butyl nitrite. This solution was heated to reflux and a solution of 5.5 g (40 mmol) of anthranilic acid in 30 ml of methylene chloride and 5 ml of dimethylbenzylamine was added with stirring over 30 min. The gc peak with a retention ratio of 1.75 on GE-SF96 at 168° slowly increased to a maximum of 3% yield (calculated as 1) after 2–3 hr.

A similar reaction used 100 ml of benzene as the solvent and 11 ml (0.1 mol) of *n*-butyl nitrite added in four equal portions at 30-min intervals to the refluxing solution. A mixture of 55 ml (0.4 mol) of dimethylbenzylamine and 13.7 g (0.1 mol) of anthranilic acid in 80 ml of benzene was added dropwise over a 2-hr period. After addition was complete, the mixture was cooled and extracted with 20% potassium hydroxide solution and then with concentrated hydrochloric acid. The acid extracts were made basic with 20% potassium hydroxide solution and the amines were removed by ether extraction. Evaporation of the ether solution and gc of the remaining oil showed peaks of retention ratio 1.45 and 1.76 with the relative areas 7:6, respectively. The total yield of both components was <6%.

Registry No.—**1**, 6299-04-3; **2**, 614-30-2; **3**, 28059-49-6; **4**, 20292-22-2; **5**, 5336-72-1; **6**, 28059-58-7; **7**, 28059-59-8; **10**, 102-05-6; benzyne, 462-80-6; 2-cyanobiphenyl, 24973-49-7; *o*-nitrodiphenylmethane, 5840-40-4; *o*-benzylaniline, 28059-64-5; *N*-methyl-*N*-(*o*-xylyl)aniline, 28059-65-6; *N,N*-dimethylaniline, 121-69-7; *N,N*-dimethylbenzylamine, 103-83-3; *N*-ethyl-*N*-benzylaniline, 92-59-1.

(43) D. A. Archer, H. Booth, and P. C. Crisp, *J. Chem. Soc.*, 249 (1964).
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(45) M. Sommelet, *C. R. Acad. Sci.*, **175**, 1149 (1922).

Purine N-Oxides. XXXIV. Synthesis of Purine 3-Oxide, 6-Methylpurine 3-Oxide, and Related Derivatives[1]

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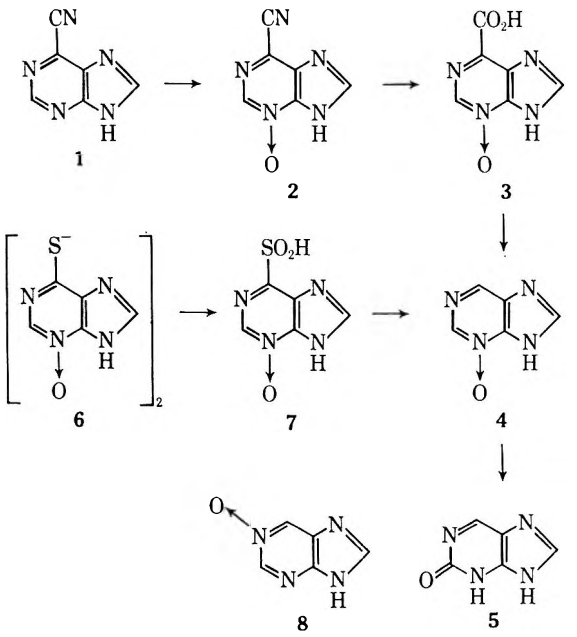
In the first examples of N-oxidation of a purine to more than a single *N*-oxide derivative, 6-methylpurine and purine have been oxidized to mixtures of their isomeric 1- and 3-oxides. 6-Cyanopurine has been oxidized to its 3-oxide derivative, which was demonstrated by hydrolysis of the latter to purine-6-carboxylic acid 3-oxide, followed by decarboxylation to purine 3-oxide. Reductive hydrolysis of purine-6-sulfinic acid 3-oxide provided an unambiguous synthesis of purine 3-oxide. Ultraviolet irradiation of the 3-oxides of purine and 6-methylpurine led to 2-hydroxypurine and 2-hydroxy-6-methylpurine, respectively. The differences in chemical and photochemical reactivities and physical properties of the isomeric 1- and 3-oxides are discussed. 6-Methylpurine 1-oxide was oxidized to purine-6-carboxaldehyde 1-oxide, and thence to purine-6-carboxylic acid 1-oxide, which yielded only purine upon heating. Several other 6-substituted purine 1-oxides derived from 6-methylpurine 1-oxide gave 1-hydroxyhypoxanthine upon further oxidation.

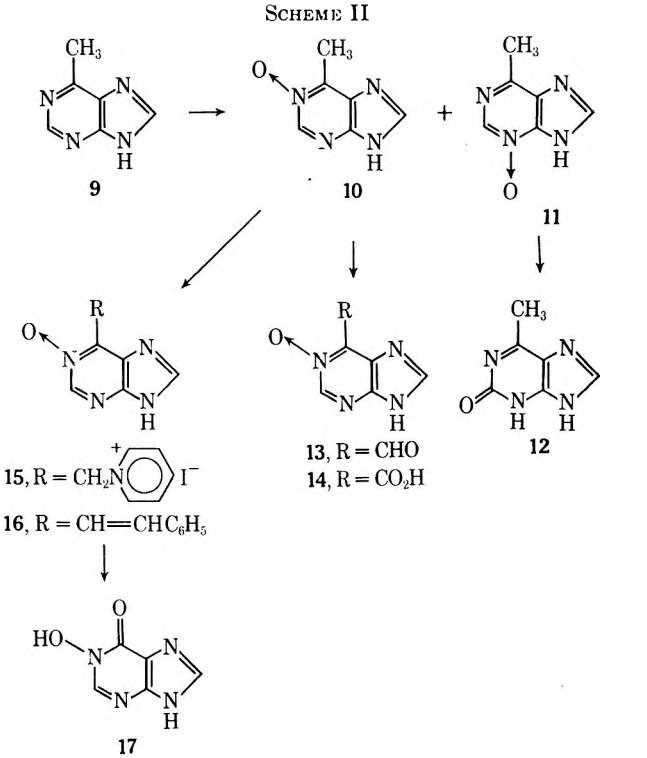
In studies of purine *N*-oxides for evaluation in chemotherapy[2] and oncogenesis assays,[2,3] 6-cyanopurine[4] (**1**) was oxidized with peroxyacetic and *m*-chloroperoxybenzoic acids to produce a single *N*-oxide derivative. To determine the position of oxidation, the cyanopurine *N*-oxide (**2**) was converted to the corresponding 6-carboxylic acid *N*-oxide (**3**), which was then decarboxylated to a purine *N*-oxide (Scheme I). This purine *N*-oxide (**4**) was not identical with purine 1-oxide (**8**) prepared earlier[5] by direct oxidation of purine with peroxyacetic or peroxybenzoic acids. It was previously noted[6] that N-oxidation of purines occurs preferentially at the 3-nitrogen when the substituent at the 6 position exerts a negative inductive effect (*e.g.*, 6-chloro, 6-methoxy). By analogy, 6-cyanopurine (**1**) might be expected to be oxidized at the 3 position. For structure determination purine 3-oxide (**4**) was prepared unambiguously by reaction of purine-6-sulfinic acid[6a,7] (**7**) with 90% formic acid, the reagent used in the conversion of purine-6-sulfinic acid to purine.[8] This sample of **4** and that prepared from the oxidation product of 6-cyanopurine were identical and verified that oxidation occurs at N-3 of 6-cyanopurine.

SCHEME I



In a related study, the oxidation of 6-methylpurine (**9**) with *m*-chloroperoxybenzoic acid, two *N*-oxides **10** and **11** were obtained (Scheme II). One was 6-methyl-

SCHEME II



(1) This investigation was supported in part by funds from the National Cancer Institute (Grant No. CA 08748), the Atomic Energy Commission (Contract No. AT(30-1)-910), and the American Cancer Society (Grants No. T-128F and P-295). Paper XXXIII in this series is *Science*, **167**, 1622 (1970).

(2) G. B. Brown, "Antagonists and Nucleic Acids," M. E. Balis, Ed., North-Holland Publishing Co., Amsterdam, 1968, Chapter 9, p 237.

(3) K. Sugiura, M. N. Teller, J. C. Parham, and G. B. Brown, *Cancer Res.*, **30**, 184 (1970).

(4) (a) L. B. Mackay and G. H. Hitchings, *J. Amer. Chem. Soc.*, **78**, 3511 (1956); (b) A. Giner-Sorolla, *Chem. Ber.*, **101**, 611 (1968).

(5) M. A. Stevens, A. Giner-Sorolla, H. W. Smith, and G. B. Brown, *J. Org. Chem.*, **27**, 567 (1962).

(6) (a) I. Scheinfeld, J. C. Parham, S. Murphy, and G. B. Brown, *ibid.*, **34**, 2153 (1969); (b) A. Giner-Sorolla, C. Gryte, A. Bendich, and G. B Brown, *ibid.*, **34**, 2157 (1969).

(7) Two alternative methods are described for the preparation of purine-6-sulfinic acid 3-oxide (**7**).

(8) I. L. Doerr, I. Wempen, D. A. Clarke, and J. J. Fox, *ibid.*, **26**, 3401 (1961).

purine 1-oxide (**10**), which had previously been isolated as the sole product from the oxidation of **9** with peroxyacetic acid.[5] The second had uv spectral properties similar to purine 3-oxide (**4**) and could be reduced to **9**. To confirm the assignment of structure as 6-methylpurine 3-oxide (**11**), it was treated with acetic anhydride. *N*-Oxides of purines, when reacted with acetic anhydride, have been shown to undergo either a rearrangement of the *N*-oxide oxygen to the adjacent carbon[5,9] or, in the case of some purine 3-oxides, a rearrangement to the 8-carbon.[9] However, treatment of **11** or **4** with acetic anhydride caused decomposition and no product could be isolated.[10]

Proof of the structures of **4** and **11** was possible through their photochemical behaviors. When exposed to uv light, 6-substituted purine 1-oxides in solution have been reported to undergo both deoxygenation and rearrangement of the *N*-oxide oxygen to the adjacent carbon.[11] The uv irradiation of an aqueous solution of 6-methylpurine 3-oxide (**11**) produced a rapid and nearly quantitative conversion of **11** to 6-methyl-2-hydroxypurine (**12**).[12a] Small amounts of two additional products, neither of which was 6-methylpurine (**9**), could be detected by chromatography. Purine 3-oxide (**4**) underwent a similar rapid and nearly quantitative photochemical rearrangement to 2-hydroxypurine[12,13] (**5**). These reactions support the assignments of 3-oxide structures to both **4** and **11**. The absence of photochemically induced deoxygenation and the high yield of the rearrangement products from these purine 3-oxides is in contrast to the photochemical behavior of purine 1-oxides. Irradiation of either adenine 1-oxide or **10** in solution was shown to yield approximately equal amounts of deoxygenation and rearrangement products.[11b]

A reinvestigation of the oxidation of purine with peracids revealed that both 1- and 3-oxides of purine could be produced. Yields from most oxidation conditions were low and consisted of complex mixtures that could be resolved only by ion exchange chromatography. Peroxyacetic acid favored N-1 oxidation almost exclusively, while *m*-chloroperoxybenzoic acid in ether favored oxidation at N-3 to give **4** with only traces of **8**. In methanol, *m*-chloroperoxybenzoic acid afforded a mixture of about equal amounts of **4** and **8**. Purine 1-oxide (**8**) proved unstable under all conditions used in attempts to isolate it from column eluates.

While isolation of isomeric *N*-oxides from peroxy acid oxidation of methylpyridazines[14] and of 4-methylpyrimidine[15] has been reported, these are the first instances of two isomeric *N*-oxides being characterized from such oxidations in the purine series. The ratio of "ortho/para" oxidation products in this case is in agreement with the observation that the methyl group favors oxidation at an adjacent nitrogen.[16] However, it is also evident from the oxidations of purine that the oxidizing medium can exert an influence.

Several attempts were made to synthesize quantities of **8**. Selenium dioxide treatment[4b] of **10** gave purine-6-carboxaldehyde 1-oxide (**13**) which could be reduced to the known purine-6-carboxaldehyde.[17] Oxidation of **13** with $KMnO_4$ gave crude purine-6-carboxylic acid 1-oxide (**14**), which produced hypoxanthine upon treatment with Raney nickel. Hydrazine reduced **14** to purine-6-carboxylic acid.[4a] Reaction of **10** with the Ortoleva–King[18] and Knoevenagel[19] reagents produced the 1-oxides of purine-6-methylenepyridinium iodide (**15**) and 6-styrylpurine (**16**), respectively. Oxidation of either compound gave only 1-hydroxyhypoxanthine[20] (**17**).

The availability of purine 3-oxide and the 1- and 3-oxides of 6-methylpurine permits a comparison of the physical properties of the 1- and 3-oxide isomers. 6-Methylpurine 1-oxide (**10**) shows marked spectral and pK differences from the 3-oxides, **4** and **11** (Table I). The 3-oxides are weaker bases than **10**, as shown by the lower pK of ionization ($\sim$6.4), compared to that of **10** (7.5), and a decrease in the pK of protonation from 1.1 to ~ -0.5, relative to **10**. A significantly lower intensity of the high extinction band near 230 nm is associated with the protonation of **10**. From this, it is deduced that protonation occurs on the *N*-oxide function of **10**, as it does for the 1-oxides of adenine and adenosine.[21] The 3-oxides (**4** and **11**) show a band near 225 nm of lower intensity than the 230-nm band in the 1-oxides. This absorption at 225 nm disappears in acid, suggesting that protonation also occurs on the *N*-oxide function in **4** and **11**; similar behavior is observed with 6-methoxypurine 3-oxide.[6a]

Experimental Section

The uv spectra were obtained with a Cary Model 11 or a Unicam SP800A recording spectrophotometer, the infrared data with a Perkin-Elmer Model 137B Infracord spectrophotometer (KBr pellet), and the nmr data with a Varian A-60 spectrometer. Melting points were determined with a Thomas-Hoover apparatus and were corrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

The pK_a values were determined spectrophotometrically with a Beckman DU spectrophotometer by methods described,[22] with 0.01 *M* buffers[23] at 20 to 23° or electrometrically with 0.01 *M* solutions.

Ascending chromatograms were developed on Whatman No. 1 paper in the following solvents: (A) *i*-PrOH–H_2O–28% NH_4OH (7:2:1 v/v); (B) *n*-BuOH–H_2O–AcOH (2:1:1); (C) EtOH–1 *M* NH_4OAc (2:1); (D) CH_3CN–H_2O (3:1).

6-Cyanopurine 3-Oxide (2). Method A.—6-Cyanopurine[4] (1, 2.7 g, 18 mmol) in glacial AcOH (15 ml) and 30% H_2O_2 (2.7 ml) was heated to 80° for 4 hr; additional 30% H_2O_2 (2.1 ml) was added. The solution was kept at 80° for 8 hr and then at 25°

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TABLE I

SPECTRAL DATA AND pK_a's

pH	Charge	λ_{max}, nm ($\epsilon \times 10^{-3}$)	pK_a
		6-Cyanopurine 3-Oxide (2)	
5	0	231 (14.3), 300[a] (6.2), 326 (9.0)	
			6.63 ± 0.05
9	−	231 (15.6), 307[a] (5.3), 335 (6.1)	
		Purine-6-carboxylic Acid 3-Oxide (3)	
0	0	234 (11.5), 303[a] (6.7), 327 (9.1)	
			2.20 ± 0.03
5	−	228 (14.0), 298[a] (7.2), 316 (9.0)	
			7.82 ± 0.1
9	2−	224 (18.7), 300–315 (6.2)	
		Purine 3-Oxide (4)[c]	
3	0	224 (17.6), 295 (8.4)	
			E[b] 6.36 ± 0.02
14	−	225 (25.4), 300 (7.1)	
		6-Methylpurine 3-Oxide (11)[c]	
3	0	220 (21.2), 290 (8.8)	
			E[b] 6.48 ± 0.05
14	−	226 (26.4), 297 (7.3)	
		6-Methylpurine 1-Oxide (10)	
−1.0	+	275 (5.2), 311 (2.2)	
			1.18 ± 0.07
6	0	230 (16.3), 260 (4.6), 312 (5.7)	
			7.51 ± 0.02
10	−	232 (20.0), 309 (6.3)	
		Purine-6-carboxaldehyde 1-Oxide (13)[d]	
3	0	236.5 (16.0), 272 (4.8), 325 (7.0)	
			E[b] 7.75 ± 0.02
10	−	232 (18.1), 321 (6.2)	
		Purine-6-methylenepyridinium Iodide 1-Oxide (15)	
1		224 (26.9), 258[a] (8.0), 333 (4.3)	
6.8		225 (32.8), 248[a] (18.0), 332 (6.2)	
14		229 (29.4), 248[a] (16.4), 332 (5.9)	

[a] Shoulder. [b] Determinated electrometrically with 0.01 *M* solutions. [c] The protonation p*K* is estimated to be ~−0.5 from isosbestic spectra taken at pH values from +2 to −2. [d] The p*K* of protonation is estimated to be near 1.0 from isosbestic spectra.

overnight. After evaporation of the solvent *in vacuo*, H_2O was added and evaporated. The residue was washed with cold H_2O (10 ml), collected, and dried to yield 1.65 g (50%) of crude crystalline product, mp 305–310° dec. Repeated recrystallization from 50% aqueous EtOH was required to yield hexagonal plates, mp 316–318° dec.

Anal. Calcd for $C_6H_3N_5O \cdot H_2O$: C, 40.22; H, 2.81; N, 39.09. Found: C, 40.24; H, 2.93; N, 39.12.

Method B.—A solution of 1 (0.90 g), ether (100 ml), and *m*-chloroperoxybenzoic acid (9 g) was kept at 25° for 10 days. The resulting precipitate was collected, washed with ether, boiled three times with benzene (70 ml), and filtered each time when hot, to yield 0.46 g (44%) of crude **2**, mp 295–298°, which after recrystallization from 50% aqueous EtOH gave a product identical with that obtained by method **A**.

Purine-6-carboxylic Acid 3-Oxide (3).—6-Cyanopurine 3-oxide (**2**, 0.15 g, 0.8 mmol) in 2 *N* NaOH (1 ml) was refluxed for 1 hr. The solution was cooled, treated with charcoal, and filtered. The filtrate was acidified with concentrated HCl to pH 2. The white crystalline precipitate was collected and dried to yield microneedles (0.070 g, 46%), mp 285–287° dec.

Anal. Calcd for $C_6H_4N_4O_3 \cdot {}^1/_8H_2O$: C, 39.51; H, 2.34; N, 30.72. Found: C, 39.64; H, 2.81; N, 31.08.

Refluxing a solution of **3** (10 mg) in water (2 ml) with Raney nickel (30 mg) for 1 hr produced a compound whose uv spectrum and R_f values were indistinguishable from those of purine-6-carboxylic acid.[4]

Purine 3-Oxide (4). Method A.—Purine-6-carboxylic acid 3-oxide (**3**, 0.30 g, 1.6 mmol) was heated at 10 mm and 280–285° in a sublimation apparatus to yield white needles (60 mg, 26%), mp 288–290° dec.

Anal. Calcd for $C_5H_4N_4O$: C, 44.11; H, 2.93; N, 41.16. Found: C, 44.26; H, 3.06; N, 41.20.

Method B.—Purine-6-sulfinic acid 3-oxide Na salt (**7**, 3.0 g, 13.5 mmol) in 88% formic acid (30 ml) was heated at 70–80° for 30 min, treated with charcoal, filtered, and evaporated to dryness *in vacuo*. The residue was suspended in 70% cold EtOH (50 ml) and filtered to yield 1.3 g (71%) of pink, short prisms, mp ~282° dec. A sample was recrystallized from 70% EtOH to yield colorless needles, mp 288–290° dec.

Anal. Calcd for $C_5H_4N_4O$: C, 44.11; H, 2.93; N, 41.16. Found: C, 43.91; H, 2.95; N, 41.08.

The products obtained by using methods A and B showed identical uv and ir spectra and R_f values, and a mixture gave no depression of the melting point.

Hydrogenation of Purine 3-Oxide.—A solution of purine 3-oxide (**4**, 8.2 mg) in H_2O with Raney nickel (10 mg) was shaken with hydrogen at 1 atm for 5 hr. The nickel was collected and washed with H_2O, and the combined filtrates were evaporated to dryness *in vacuo* at 60°. The product (4.0 mg, 55%), mp 198–200°, showed uv spectra and R_f's indistinguishable from those of an authentic sample of purine.

Purine-6-sulfinic Acid 3-Oxide Sodium Salt (7). Method A.—A suspension of 6-mercaptopurine 3-oxide[24] (1 g, 6 mmol) in H_2O (100 ml) containing $NaHCO_3$ (2 g) was heated to 50°, the solution was cooled to 25°, and active MnO_2[25] (4.0 g) was added. The mixture was stirred for 5 hr and filtered, and the MnO_2 was washed twice with hot H_2O. The combined filtrates were adjusted to pH 5 with glacial AcOH, treated with charcoal, filtered, and evaporated to dryness *in vacuo*. The residue was suspended in 70% cold EtOH (30 ml), and the precipitate was collected to give 1.1 g (83%) of a product identical with an authentic sample of **7**.[6a]

Method B.—Active MnO_2 (1.2 g) was added to 6-mercaptopurine 3-oxide disulfide[6] (**6**, 0.30 g, 1.8 mmol) in H_2O (30 ml) containing $NaHCO_3$ (0.60), stirred for 5 hr, and filtered through Celite; the pH was adjusted to 5 with glacial AcOH, and 0.33 g (82%) of a product identical with **7**[6a] was isolated as described above.

6-Methylpurine 3-Oxide (11).—To a suspension of 6-methylpurine (6 g, 0.045 mol) in ether (400 ml) was added *m*-chloroperoxybenzoic acid (60 g, 0.38 mol) and the mixture was stirred at 25°. After 2 days the reaction mixture became too thick to permit mechanical stirring. The mixture was shaken occasionally for 5 additional days. The precipitate was collected and washed with Et_2O, benzene, and then Et_2O to yield a white product (5.9 g), mp 235°, consisting of a mixture of **10** and **11**. The product was dissolved in hot 90% EtOH (75 ml), treated with charcoal, filtered, and kept overnight at 25°. The precipitate was 6-methylpurine 3-oxide (**11**). Concentration of the filtrate gave two additional crops of **11**, total yield 1.3 g (19%), mp 240° dec.

Anal. Calcd for $C_6H_6N_4O$: C, 47.99; H, 4.03; N, 37.31. Found: C, 48.05; H, 4.01; N, 37.26.

From the mother liquor after further concentration, 6-methylpurine 1-oxide (**10**) was obtained (2.2 g, 32%). On paper chromatography **10** and **11** had the same R_f; the 3-oxide (**11**) showed absorption while the 1-oxide (**10**) was fluorescent when viewed under uv light (253.7 nm). Treatment of **11** with the Ortoleva–King or Knoevenagel reagents, as described below for **10**, resulted in its complete decomposition. Sublimation of **11** at 250° and 10 mm gave only 6-methylpurine.

Reduction of 11.—A solution of 6-methylpurine 3-oxide (**11**) (10 mg) in H_2O (5 ml) and Raney nickel (50 mg) was boiled for 1 hr. The product showed uv spectra and R_f values identical with those of **9**.[13]

Irradiation of 6-Methylpurine 3-Oxide (11).—A stirred 250-ml H_2O solution of **11** was irradiated in a quartz flask with a Black Light Eastern Corp. R-51 low-pressure Hg lamp (90% emission at 253.7 nm). Aliquots were removed periodically and the reaction progress was followed by monitoring the uv spectrum until

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no further change occurred (30 min). The changing spectra taken during the irradiation showed clear isosbestic points at 219.5, 239, 250.5, and 308 nm, and the spectrum of the final solution was virtually identical with that of 2-hydroxy-6-methylpurine (12) at three pH's.[12b] Paper chromatography confirmed that the predominant product was 12, with a trace of a second component.

Development of a heavily loaded chromatogram in CH_3CN–H_2O–28% NH_4OH (7:2:1 v/v) resolved the second component into two bands at R_f 0.51 and 0.56 (12 at R_f 0.21). The first showed uv absorption at 284 nm in neutral and alkaline and 230 nm in acidic solution. The second compound had uv absorption bands at 283 and 213 nm in H_2O. The addition of acid modified this compound so that it lost long wavelength absorption and showed uv bands only at 211 nm in acid and 208 nm in base.

Irradiation of Purine 3-Oxide (4).—A sample of 4 was irradiated as described. Spectra taken of aliquots during the irradiation showed isosbestic points at 218.5, 239.5, 255, and 313 nm. Reaction was complete in 30 min, and the spectrum after irradiation was nearly identical with that of 2-hydroxypurine (5) at three pH's.[12b] Paper chromatography confirmed the major product was 5 and revealed a small amount of a second compound. The uv spectrum of a sample of this by-product eluted from a paper chromatogram developed in CH_3CN–H_2O–28% NH_4OH (7:2:1 v/v) showed very little change with changes in pH and showed absorption at 214, 245 sh, 252, and 270 sh nm.[26]

Oxidation of Purine.—Purine (0.5–1 g) was oxidized as described below, and the reaction progress was followed by chromatographing aliquots from the reaction media over Dowex-50 (H^+), X8, 200–400 mesh, column (1 × 15 cm) and monitoring the eluates with an ISCO UA-2 uv analyzer. Purine 3-oxide was eluted with H_2O, while purine 1-oxide, which preceded purine, required 1 *N* HCl. All oxidations yielded complex mixtures, were accompanied by the loss of uv absorbing components, and had to be stopped with some unreacted purine still present. Evaporation under reduced pressure of the HCl from the purine 1-oxide eluates caused decomposition of 8. Neutralization with NaOH prior to evaporation of the solvent afforded 8 contaminated with salt, but attempts to isolate 8 in pure form resulted in its decomposition. Purine 1-oxide was identified by uv spectra taken at several pH's, which agreed with those reported[5] for 8. They also showed a strong similarity to those of 10 (Table I). The approximate ratio of 8 and 4 produced under the various experimental conditions could be estimated from the ISCO uv recording.

Oxidations were carried out at 25°, except as noted, and the reagent quantities and yields are expressed per gram of purine.

(a) Oxidation with AcOH (6 ml) and 30% H_2O_2 (4 ml) gave optimum results after 5 days and afforded mainly 8 with a small amount (~20 mg) of 4. Although successful in some cases in reducing the amount of ring oxidation, oxidation at 0° did not alter significantly the ratio of oxidation products but proceeded more slowly.

(b) Oxidation with *m*-chloroperoxybenzoic acid (8 g) in Et_2O (250 ml) was slower than other conditions and required at least a month. It yielded ~250 mg of purine 3-oxide that was identical with synthetic samples and a small quantity of 8.

(c) Oxidation with *m*-chloroperoxybenzoic acid (6 g) in MeOH (100 ml) yielded about equal quantities of 4 and 8 in 1 week. Before chromatography over Dowex 50-X8 (H^+), the MeOH was removed under reduced pressure, H_2O (10 ml) was added to the solid, and the solution was extracted with Et_2O to remove the *m*-chlorobenzoic acid.

Purine-6-carboxaldehyde 1-Oxide (13).—Freshly prepared selenium dioxide (2.0 g, 18 mmol) was added at 25° with stirring to a suspension of 6-methylpurine 1-oxide[5] (10, 2.0 g, 13 mmol) in dry DMF (25 ml). The solution turned yellow and after 30 min a red precipitate of selenium appeared. The reaction mixture was stirred at 25° for 21 hr and then filtered. The selenium precipitate was washed twice by suspension in H_2O (10 ml), and the washings were added to the above filtrate. After standing at 5° for 30 min, a precipitate formed which was collected, yield 1.2 g of a brown solid, mp 165° dec. The selenium precipitate was washed twice more with H_2O (10 ml), and these washings were combined with the above mother liquor. This solution was treated with charcoal and concentrated *in vacuo* to yield tan crystals (0.4 g), overall yield 1.6 g (73%). Two recrystallizations from MeOH gave white crystals, 165° dec.

Anal. Calcd for $C_6H_4N_4O_2 \cdot CH_3OH$: C, 42.86; H, 4.11; N, 28.56. Found: C, 42.44; H, 4.08; N, 28.47.

The presence of 1 mol of MeOH as shown by analysis and the absence of carbonyl absorption in the ir indicate the hemiacetal of 13 was formed during recrystallization.

Reaction of 13 (25 mg) with Raney nickel (50 mg) in H_2O (5 ml) for 30 min at 100°, filtering the solution, and evaporating the filtrate gave purine-6-carboxaldehyde (21 mg, 93%),[17] identified by its uv spectrum.

Oxidation of Purine-6-carboxaldehyde 1-Oxide (13).—A solution of $KMnO_4$ (0.125 g) in H_2O (3 ml) was added dropwise to a suspension of 13 (0.35 g, 2 mmol) in 10% H_2SO_4 (3.5 ml) at 0° with stirring until a brown color persisted. The solution was decolorized by the addition of 1 drop of 30% H_2O_2. After rapid filtration and cooling at 5° for 30 min, a light yellow crystalline product, mp 260° (effervescence) (0.1 g, 30%), was collected. The residue in the capillary tube after melting showed a uv spectrum identical with that of purine.

Treatment with Raney nickel resulted in the formation of hypoxanthine. By boiling 14 (25 mg) in 10% aqueous hydrazine for 30 min, a solution was obtained which had uv spectra and R_f values identical with those of purine-6-carboxylic acid.[4a]

When heated at 240° at 0.05 mm pressure, the crude purine-6-carboxylic acid 1-oxide gave a sublimation product consisting of unchanged 14 and a small amount of purine.

Purine-6-methylenepyridinium Iodide 1-Oxide (15).—To 6-methylpurine 1-oxide[5] (10, 0.45 g, 3 mmol) in pyridine (8 ml), a solution of iodine (0.38, 3 mmol) in pyridine (4 ml) was added and the mixture heated with stirring at 100° for 6 hr and cooled. A brown precipitate was collected, washed with benzene (5 ml), and dried to yield 0.80 g (76%), mp 198° dec, which was recrystallized from 95% aqueous EtOH to yield colorless prisms, mp 205° dec.

Anal. Calcd for $C_{11}H_{10}N_5OI$: C, 37.20; H, 2.84; N, 19.72; I, 35.73. Found: C, 37.28; H, 2.84; N, 19.80; I, 36.04.

6-Styrylpurine 1-Oxide (16).—6-Methylpurine 1-oxide (10) (1.2 g) was suspended in benzaldehyde (40 ml) at 175° and a stream of dry HCl was passed through for 10 min. A yellow precipitate formed. The suspension was cooled, benzene was added (40 ml), and the precipitate was collected and washed with benzene (15 ml) to yield a yellow product. Recrystallization from 50% EtOH gave yellow needles: 1.75 g (90%); mp 212–214° dec; pH 5 (H_2O), λ_{max} 235 and 343 nm.

Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.51. Found: C, 65.85; H, 4.44; N, 24.03.

1-Hydroxyhypoxanthine (17). Method A.—Purine-6-methylenepyridinium iodide 1-oxide (15) (2.0 g, 2.8 mmol) was dissolved in H_2O (10 ml) and cooled to 0°. A solution of $KMnO_4$ (1.8 g) in H_2O (30 ml) was added dropwise, and the mixture was stirred at 0° for 30 min and at 25° for 2 hr. The suspension was adjusted to pH 10 with 2 *N* NaOH. The precipitate was collected and extracted twice with hot H_2O (20 ml each), and the combined filtrates were acidified to pH 3 with 2 *N* HCl. After concentration *in vacuo* a crystalline precipitate was obtained which after recrystallization from H_2O gave 20 mg of colorless needles, mp 340–345° dec, identical with 1-hydroxyhypoxanthine (17).[20]

Method B.—6-Styrylpurine 1-oxide (16, 1.5 g, 6.3 mmol) was suspended in H_2O (20 ml) and cooled to 0°. A solution of $KMnO_4$ (5.2 g, 0.032 mol) in H_2O (80 ml) was added slowly with stirring. After addition the suspension was stirred at 0° for 2 hr and at 25° for 2 hr and then adjusted to pH 10 with 2 *N* NaOH and filtered. The precipitate was extracted twice with hot H_2O (30 ml), and the combined filtrates were adjusted to pH 3 with 2 *N* HCl and then concentrated *in vacuo*. The crystalline precipitate was dried, washed with 70% EtOH, and recrystallized from H_2O to give 15 mg of 17 as colorless needles, mp 340–345° dec.

Registry No.—2, 28199-53-3; 3, 28199-54-4; 4, 28199-55-5; 10, 28199-56-6; 11, 28199-57-7; 13, 28199-58-8; 15, 28199-59-9; 16, 28267-46-1; 17, 5193-34-0.

(26) The small quantity of by-products observed in these irradiations may arise either from chemical or from photochemical rearrangement of the oxaziranе intermediate postulated in the N to C rearrangement of an *N*-oxide oxygen. Examples of additional pathways of reaction of photochemically generated oxaziranes have appeared recently: C. Kaneko, I. Yokoe, S. Yamada, and M. Ishikawa, *Chem. Pharm. Bull.*, 17, 1290, 1294 (1969).

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Synthesis of Indoles from 4-Oxo-4,5,6,7-tetrahydroindoles. II.[1] Introduction of Substituents into the 4 and 5 Positions

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A new general method for the synthesis of indoles is described. In this method 4-oxo-4,5,6,7-tetrahydroindoles, which have suitable blocking groups on the nitrogen, are substituted at the 5 position by groups such as alkyl, phenyl, alkylthio, bromo, and cyano. Most of these transformations (except bromination) were effected by the use of a 5-hydroxymethylene substituent. Heterocyclic rings, such as isoxazole and aminothiazole, could be fused to the 4,5 positions. Other substituents were introduced at the 4 position by reaction of the carbonyl group with Grignard, Reformatsky, and Wittig reagents. Certain of the novel substituted 4-oxotetrahydroindoles and 6,7-dihydroindoles prepared by these reactions were then dehydrogenated to the fully aromatic indoles. In order to obtain indoles unsubstituted on nitrogen, various removable blocking groups were examined. Of these groups, benzyl and benzoyl were the most useful.

In a previous communication[1a] we suggested that a versatile new method of indole synthesis was available based upon transformations of 4-oxotetrahydroindoles. Since then, we have expanded the method to include a wide variety of substituents at the 4 and 5 positions. The present article describes the introduction of these substituents, considers the use of blocking groups on nitrogen to further extend the method, and points out important limitations in the method.

The most generally useful method for the preparation of 4-oxotetrahydroindoles is due to Stetter and Lauterbach.[3] In this method 1,3-cyclohexanediones (**1**), including those substituted at the 6 position, are alkylated with α-halo ketones and the resulting triones **3** are condensed with ammonia or primary amines. Products with a variety of alkyl and aryl groups at 1, 2, 3, and 6 are obtained. A useful variant of this procedure is based upon alkylation of 1,3-cyclohexanedione with ethyl bromopyruvate. Treatment of the resulting 4-oxotetrahydrobenzofuran-3-carboxylic acid (**2**) with ammonia at 153° gives the parent 4-oxotetrahydroindole **5**.[3] There are also three other known methods for the preparation of 4-oxotetrahydroindole derivatives.[4-7]

The usefulness of 4-oxotetrahydroindoles in indole synthesis is determined by two factors inherent in their structures. One of these factors is the conjugation between the pyrrole nitrogen and the carbonyl group (which deactivates both functions). Thus the carbonyl group is less reactive than normal carbonyl groups toward nucleophiles, and the pyrrole ring is less susceptible to electrophilic attack (and consequently more stable in acid) than ordinary pyrroles. Physical evidence for this conjugation is provided by the ir spectra of the 4-oxotetrahydroindoles. In the N-alkyl derivatives the carbonyl stretch is at 6.38 μ and in N-H derivatives it is at 6.25 μ (KBr disks). Chemical evidence for this deactivation is found in the failure of **5** to undergo reaction with sodium bisulfite, potassium cyanide in acetic acid, or pyrrolidine and p-toluenesulfonic acid. However, the carbonyl group of **5** does retain sufficient ketonic character to allow oxime and hydrazone formation. As discussed below, 4-oxotetrahydroindoles blocked on nitrogen also react with certain Grignard and Wittig reagents.

The second important feature of 4-oxotetrahydroindoles which determines their usefulness in indole synthesis is the relatively acidic hydrogen possessed by those derivatives unsubstituted on nitrogen. Treatment of these compounds (*e.g.*, **5**) with bases affords a pyrrolyl-type anion which recieves additional stabilization due to conjugation with the carbonyl group. This conjugation decreases the reactivity of the carbonyl group to a level where it is unreactive toward carbanions. Furthermore, the methylene group adjacent to this carbonyl group does not participate in base-catalyzed condensations.[8] However, if the nitrogen is substituted with an alkyl or benzyl group, both of these reaction types can be effected.

We have examined several different types of substituents, including removable blocking groups, for the nitrogen of 4-oxotetrahydroindoles. The ethyl group was particularly important in the synthesis of indoloquinone analogs of the mitomycin antibiotics. This

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(7) J. M. Bobbitt and C. P. Dutta, *Chem. Commun.*, 1429 (1968).

(8) This aspect of the chemistry of 4-oxotetrahydroindoles was first investigated by F. J. McEvoy, J. M. Smith, Jr., and D. S. Allen, Jr., U. S. Patent 3,404,157 (1968); see *Chem. Abstr.*, **65**, 20134c (1966).

work has been reported previously.[9] Additional indole syntheses with *N*-ethyl compounds were based upon the preparation of 5-hydroxymethylene derivatives **6a** and **6b**, by formylation of **4a** and **4b** with ethyl formate in the presence of sodium methoxide.[10] These hydroxymethylene derivatives afford the means for introduction of various substituents into the 5 position, as well as for the fusion of an additional ring to the 4,5 positions. For example, **6a** was converted into the corresponding nitrile **10a** upon treatment with bis-*O*,*N*-trifluoroacetylhydroxylamine.[11] Under mild conditions, **6b** and hydroxylamine afforded the 4,5-dihydroisoxazolo[5,4-*e*]indole **11**. However, prolonged heating of the reaction mixture resulted in opening of the isoxazole ring of **11**, affording nitrile **10b**.[8] The pyrroloindazole system was obtained by treatment of **6b** and **10b** with a variety of hydrazine derivatives.[8] The hydroxymethylene groups of **6a** and **6b** were also useful for the introduction of 5-methyl groups. Products **9a** and **9b** were obtained in good yields by treatment of these compounds with methyl iodide and potassium carbonate followed by methoxide-catalyzed deformylation (Scheme I).

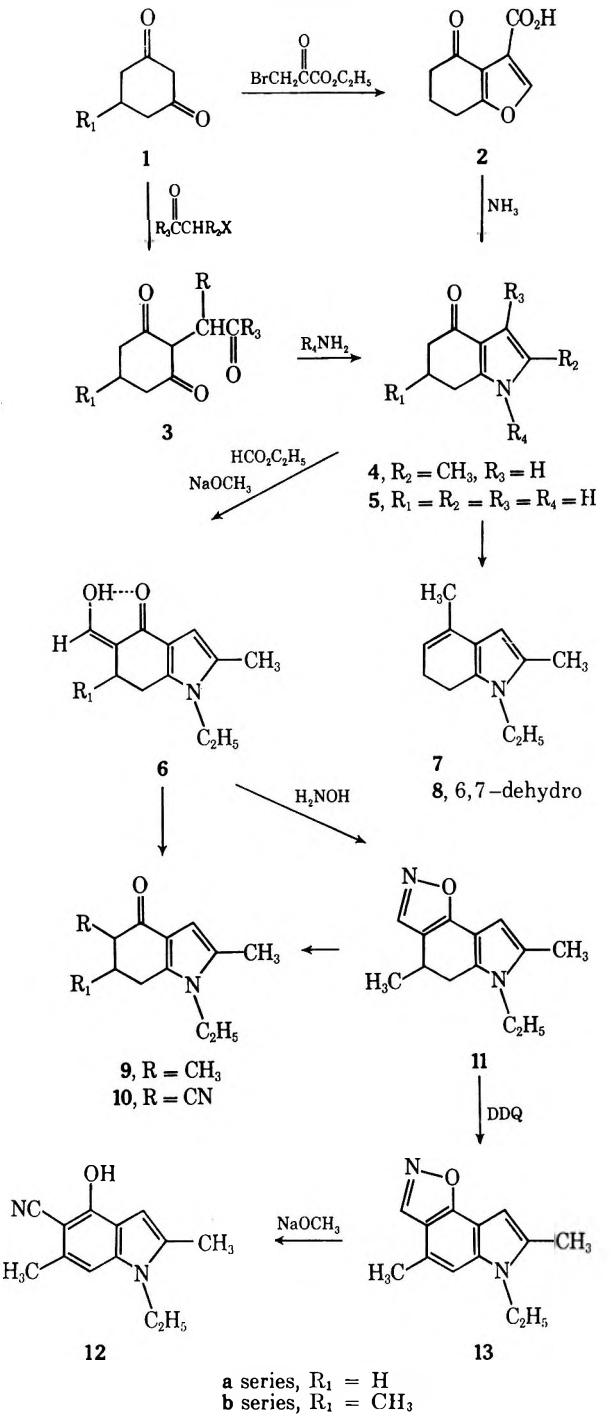
The *N*-benzyl blocking group can be introduced in the formation of the 4-oxotetrahydroindole[3] or, alternatively, it can be introducted by alkylation with benzyl chloride of the anion formed by the action of base on the N-unsubstituted 4-oxotetrahydroindole. The most satisfactory method for this alkylation was treatment of the 4-oxotetrahydroindole with 1 equiv of methylsulfinyl carbanion in dimethyl sulfoxide[12] followed by benzyl chloride. As noted below, the benzyl blocking group was readily removed from the ultimate indole product by reduction with sodium in ammonia.[8]

The 1-benzyl compound **17** was converted into its 5-hydroxymethyl derivative **21**, which was further transformed into 5-methyl derivative **20**. The carbonyl groups of 4-oxotetrahydroindoles blocked on nitrogen are reactive toward certain Wittig reagents. Thus treatment of **20** with triphenylmethylene phosphorane afforded a mixture of the 5-methyl-4-methylenetetrahydroindole **25** and the isomeric 4,5-dimethyl-6,7-dihydroindole **22** in approximately equal amounts, as shown by the nmr spectrum of this mixture (Experimental Section). Observations of isomers in the products of Wittig reactions are extremely rare,[13] and the reasons for their occurrence in the present example (and that of **4** noted below) are not apparent. Excess base was present, but this is true in many Wittig reactions.

Isomerization was also noted in the reaction of **4** with triphenylmethylene phosphorane. In this case the only product isolated was the isomeric 4-methyl-6,7-dihydroindole **7**. Treatment of **4** with methylmagnesium iodide also afforded **7**.

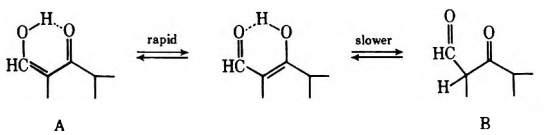
Hydroxymethylene derivative **21** was also useful for the introduction of a 5-phenyl substituent. When it was treated with potassium *tert*-butoxide and diphenyliodonium chloride, followed by deformylation with methanolic sodium methoxide,[14] a good yield of the 5-phenyl-4-oxotetrahydroindole **19** was obtained.

SCHEME I



(9) (a) W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, **88**, 804 (1966); (b) R. H. Roth, W. A. Remers, and M. J. Weiss, *J. Org. Chem.*, **31**, 1012 (1966).

(10) In the case of the 6-unsubstituted compound **6a**, two tautomeric forms could be isolated. In methylene chloride, the lower melting monocarbonyl form A (6.03 μ) predominated in the ratio 9:1 according to the nmr spectrum of this solution (see Experimental Section) and A could be obtained upon concentration of this solution. However, when A was carefully crystallized from methanol, the higher melting decarbonyl form B (6.05, 6.15 μ) was obtained.



(11) Method of J. H. Pomeroy and C. A. Craig, *J. Amer. Chem. Soc.*, **81**, 6340 (1959).

(12) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(13) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, p 134.

(14) F. M. Beringer and S. A. Galton, *J. Org. Chem.*, **28**, 3417 (1963); J. F. Poletto, G. R. Allen, Jr., and M. J. Weiss, *J. Med. Chem.*, **10**, 106 (1967).

Attempts to reduce the carbonyl group of **5** with sodium borohydride were unsuccessful, probably because of salt formation due to the acidic NH group of this compound.[15] In contrast, *N*-benzyl derivative **19** could be reduced with this reagent under vigorous conditions. The product was not the anticipated alcohol. Rather, it was the corresponding tetrahydroindole **16** in which the carbonyl group was reduced to a methylene group.[16] This same product was obtained by treatment of **19** with lithium aluminum hydride in ether.

The carbonyl group of a 4-oxotetrahydroindole can also be reduced to a methylene group by the Wolff–Kishner method (*e.g.*, **17** was converted into **15**).[17] However, in this example it was necessary to isolate the intermediate hydrazone prior to heating with potassium hydroxide. Otherwise the only product found was the azine **14**.

Finally, the methylthio group was introduced into the 5 position by treating hydroxymethylene derivative **21** with methyl thiotosylate[18] in ethanolic sodium ethoxide. Under these conditions the carboxaldehyde group was cleaved directly and work-up afforded the 5-methylthio-4-oxotetrahydroindole **18** (Scheme II).

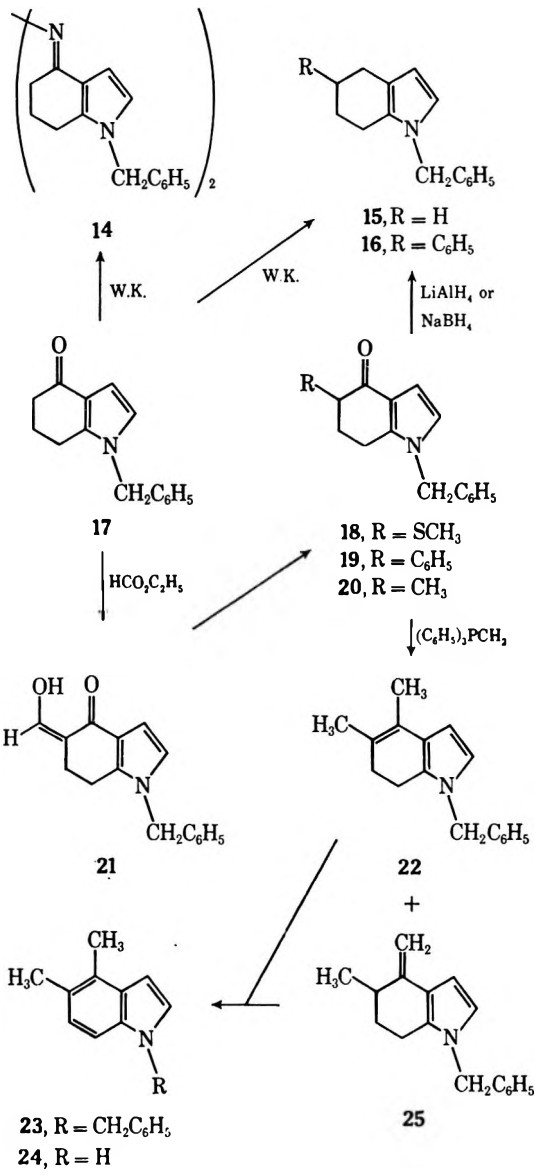
The foregoing results demonstrate the wide range of substituents which have been introduced into the 4 and 5 positions when the nitrogen is substituted. As described below, certain of the resulting compounds afford the corresponding fully aromatic indoles upon dehydrogenation. However, the versatility of these procedures is limited by the difficulty in removing the substituent from nitrogen. In several examples, one of which is discussed below, the benzyl group was removed by reduction with sodium in ammonia.[8] Unfortunately, this method is limited to compounds which are compatible with such a vigorous reductive cleavage. Therefore, we examined several more labile blocking groups.

The 1-benzenesulfonyl derivative **28** was readily prepared and it could be hydrolyzed back to **5** by heating with potassium hydroxide in methanol. Although stable under midly acidic conditions, the benzenesulfonyl group of **28** proved too readily cleaved by bases to allow preparation of a 5-hydroxymethylene derivative. However, a Reformatsky reaction with ethyl bromoacetate and zinc afforded the anticipated 4-carbethoxymethyl-4-hydroxy derivative **26** in nearly quantitative yield. Upon storage at room temperature **26** gradually underwent dehydration to the corresponding 4-carboxymethylene derivative **27**. This assignment of the double bond to the exocyclic position is supported by its nmr spectrum, which shows no significant splitting of the peak for the vinyl hydrogen (δ 5.88 ppm).

The benzenesulfonyl group of **28** was ideally suited to the introduction of bromine at C_5. In the absence of an electron-withdrawing substituent on nitrogen (*e.g.*, compound **5**), bromination, even with selective reagents such as phenyltrimethylammonium tribromide, takes place preferentially in the pyrrole ring.[19,20] However, the benzenesulfonyl group so deactivates the pyrrole ring (and presumably activates the carbonyl group by inhibiting electron release to it) that bromination adjacent to the carbonyl group is favored. Thus, treatment of **28** with phenyltrimethylammonium tribromide in tetrahydrofuran afforded the bromo ketone **29** in 59% yield.

Our initial attempt to convert bromo ketone **29** into the aminothiazole derivative **37**, by heating it with thiourea and triethylamine in ethanol, afforded the bromine-containing carbonyl derivative **34**. However, an attempted recrystallization of **34** from methanol induced its cyclization to **36**. Repetition of the experiment with methanol instead of ethanol led to the direct isolation of **36**. It is known that in the presence of dilute acid carbonyl derivatives such as **34** are some-

SCHEME II



(15) As anticipated, the carbonyl group of **5b** was readily reduced by diborane (ir evidence); however, only amorphous solid was obtained from this reduction.

(16) Related reductions of 1-tetralone derivatives to the corresponding tetrahydronaphthalenes fiy sodium borohydride were reported by K. H. Bell, *Aust. J. Chem.*, **22**, 601 (1969).

(17) The Wolff–Kishner reduction of 4-oxotetrahydroindoles has been reported by Kost, Ovseneva, and Shuvaeva (ref 4).

(18) We wish to thank Dr. M. L. Scheinbaum for sending us a detailed procedure for the preparation of potassium thiotosylate from his Ph.D. dissertation, Harvard University, 1965 [*Dissertation Abstr.*, **26**, 713 (1965)]. Methyl thiotosylate was prepared from it by the method of D. T. Gibson, *J. Chem. Soc.*, 2637 (1931).

(19) W. A. Remers and M. J. Weiss, *J. Org. Chem.*, **36**, 1241 (1971).

(20) Introduction of bromine at C_5 by way of the hydroxymethylene derivative appeared to be an attractive method; however, treatment of **6a** with bromine and sodium acetate afforded extensive decomposition.

times isolated in attempts to form aminothiazoles.[21] However, the excess triethylamine present in our experiment should have effectively scavenged any traces of liberated HBr. We are unable to offer a reason for the unusual difference in solvent effect between ethanol and methanol.

Despite the facile hydrolysis of the benzenesulfonyl group of **28**, it was difficult to remove this blocking group from **36**. Acid hydrolysis or alkaline hydrolysis under mild conditions was unsuccessful and strong alkaline conditions destroyed the molecule. Lithium-in-ammonia reduction also decomposed **36**. Rather than pursue these experiments further, we decided to change blocking groups.

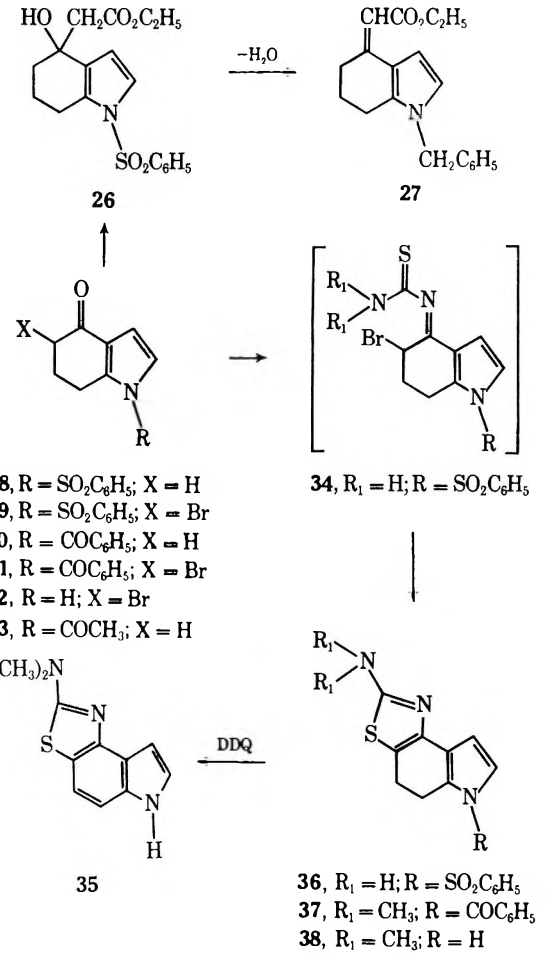
The benzoyl group offered an attractive possibility since it appeared sufficiently electron withdrawing to direct bromination at C_5 and more labile to hydrolysis than the benzenesulfonyl group. Preparation of 1-benzoyl-4-oxotetrahydroindole **30** was straightforward, and it was readily brominated at C_5 by phenyltrimethylammonium tribromide or pyridinium bromide perbromide. The resulting 5-bromo derivative **31** was hydrolyzed to 5-bromo-4-oxo-4,5,6,7-tetrahydroindole (**32**) by brief treatment with methanolic sodium hydroxide. Attempted condensations of the bromo ketones **31** and **32** with thiourea were fruitless since extensive decomposition occurred in both cases. On the supposition that the successful reaction with benzenesulfonyl derivative **29**, but failure with benzoyl derivative **31**, was due to rapid methanolysis of the latter compound under the experimental conditions, a less reactive solvent was sought for the aminothiazole synthesis. Tetrahydrofuran was a good solvent for **31** but not for thiourea. However, it readily dissolved substituted thioureas such as 1,1-dimethylthiourea. When a solution of this thiourea derivative, bromo ketone **31**, and triethylamine in tetrahydrofuran was heated at reflux temperature, the desired aminothiazole derivative **37** formed in good yield. Treatment of **37** with 1 equiv of sodium hydroxide in methanol then furnished the corresponding debenzoylated compound **38** (Scheme III).

The acetyl group was briefly investigated as a potential blocking group for 4-oxotetrahydroindoles, but it proved too labile for general use. For example, the 1-acetyl derivative **33**, prepared by heating **5** with acetic anhydride and sodium acetate, reverted to **5** upon attempted recrystallization from methanol.

To complete the synthesis of indoles, it was necessary to find suitable means for the dehydrogenation and the removal (where required) of certain blocking groups from nitrogen of the intermediates described above. In some cases dehydrogenation was facile, but in other cases it could not be accomplished. These difficulties in dehydrogenation impose important limitations upon this general method of indole synthesis.

Catalytic dehydrogenation, with palladium on charcoal in an aromatic hydrocarbon solvent[22] such as cumene, was a useful method for conversion of 4-oxotetrahydroindoles to the corresponding 4-hydroxyindoles except when a 5 substituent was present. As shown in Table I the yields for a series of methyl-

SCHEME III



substituted 4-oxotetrahydroindoles were acceptable (although not high) for the compounds unsubstituted at the 5 and 6 positions, or substituted only at the 6 position, but the yields were decreased when a 5 substituent was present.[23,24] 4-Oxotetrahydroindoles with 5-phenyl and 5-methylthio substituents (*e.g.*, **19** and **18**) also failed to undergo catalytic dehydrogenation. Steric inhibition of enolization is probably important in at least some of these 5-substituted compounds.

Dehydrogenation of the parent 4-oxotetrahydroindole (**5**) was attempted with palladium on charcoal in cumene, but repeated attempts afforded only low yields of the 4-hydroxyindole. Since our initial communication[1] on this method, Plieninger and Klinga reported the dehydrogenation of **5** in high yield using the same type of catalyst in mesitylene.[25] We repeated this experiment and confirmed their result, except that our product was contaminated with a small amount of starting material. As catalytic dehydrogenation is quite sensitive to the catalyst, it is probable that our particular sample of catalyst was inferior in activity.

The two 6,7-dihydroindoles with alkyl substituents, **7** and **22**, were readily dehydrogenated to the corresponding indoles **8** and **23**, respectively, by palladium on charcoal (Table II). In the case of **22** the 5-methyl

(21) J. M. Sprague and A. H. Land, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 579.

(22) Method of E. C. Horning, M. G. Horning, and G. N. Walker, *J. Amer. Chem. Soc.*, **71**, 169 (1949).

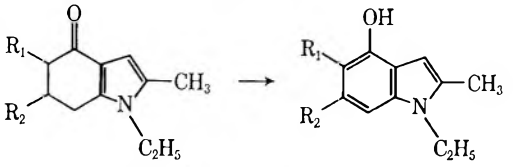
(23) Extensive efforts to obtain optimum yields were not made.

(24) Catalytic dehydrogenation of ten different 3-alkyl- and 2,3-dialkyl-4-oxotetrahydroindoles in yields of 26–65% was reported by S. Hauptmann, G. Blume, G. Hartmann, D. Haendel, and P. Franke, *Z. Chem.*, **6**, 183 (1966).

(25) H. Plieninger and K. Klinga, *Chem. Ber.*, **101**, 2605 (1968).

TABLE I[a]

DEHYDROGENATION OF 4-OXO-4,5,6,7-TETRAHYDROINDOLES



39

Compd	Product	R_1	R_2	R_3	Method	Yield, %	Mp,[b] °C
4a	39a	H	H	H	Pd/C	38	98–102
4b	39b	H	CH_3	H	Pd/C	20–45	141–143
9a	39c	CH_3	H	CH_3	Pd/C	13	110–112
9b	39d	CH_3	CH_3	CH_3	Pd/C	0[c]	
6a	39e	=CHOH	H	CHO	DDQ	12	95–96
6b	39f	=CHOH	CH_3	CHO	DDQ	51	129–131

[a] Satisfactory analytical values (±0.35% in C, H, and N) were reported for all compounds in the table: Ed. [b] Recrystallized from hexane. [c] For a successful preparation from 6, see ref 9b.

TABLE II[a]

DEHYDROGENATION OF 6,7-DIHYDROINDOLES

Compd	Product	Method	Yield, %	Mp, °C
7	8	Pd/C	42	Oil
22 + 25	23	Pd/C	60	87
11	13	DDQ	40	148–153
38	35	DDQ	15	255 dec

[a] Satisfactory analytical values (±0.35% in C, H, and N) were reported for all compounds in the table: Ed.

group did not inhibit the dehydrogenation as it did in the related 4-oxo compounds.

We attempted dehydrogenation of certain of the above 4-oxotetrahydroindoles by 5,6-dichloro-2,3-dicyanobenzoquinone[26] (DDQ), but we obtained only polymeric products. It seems likely that dehydrogenation occurred, but the products were unstable in the presence of DDQ. In contrast, when the product indoles were stabilized by the carboxaldehyde group at C_5 or a heterocyclic ring fused to the 4 and 5 positions, DDQ generally afforded crystalline products. Thus 5-hydroxymethylene-4-oxotetrahydroindoles **6a** and **6b** were converted to the corresponding 4-hydroxyindole-5-carboxaldehydes **39e** and **39f** (Table I), and the 6,7-dihydroindoles substituted with isoxazole and aminothiazole rings (**11** and **38**, respectively) afforded the fully aromatic tricyclic systems **13** and **35** (Table II). An attempt to dehydrogenate **11** by palladium on charcoal had given only the 5-cyano-4-oxotetrahydroindole **10**.

Certain 4-oxotetrahydroindoles proved resistant to dehydrogenation by both catalytic and quinone methods. They were subjected to a variety of their dehydrogenating agents such as diphenyl picryl hydrazyl, trityl perchlorate, selenium dioxide, and sulfur without success. No method was found for dehydrogenation of the 5-phenyl derivative **19** or the related 5-phenyltetrahydroindole **16**. Dehydrogenation of the 5-methylthio derivative **18** was also unsuccessful, except that when heated with sulfur it gave a very small amount of 1-benzyl-4-hydroxyindole. In several examples 5-substituted 4-hydroxyindoles, which could not be prepared directly from the 4-oxotetrahydroindoles, were obtained by transformation of other dehydrogenation products. Thus the 5-cyano-4-hydroxyindole **12** was formed by base-catalyzed ring opening of isoxazole **13**, and catalytic hydrogenation of the carboxaldehyde group of **6b** afforded the desired 5,6-dimethyl-4-hydroxyindole **39d**.[9b]

Finally, the removal of blocking groups must be considered. The benzoyl group of the aminothiazole derivative **37** was removed prior to dehydrogenation since, at least with DDQ, it prevented this process. In the synthesis of 4,5-dimethylindole (**24**)[27] it was desirable to dehydrogenate the isomeric dihydroindoles **22** and **25** prior to cleavage of the benzyl group. This cleavage was effected in good yield by sodium in liquid ammonia.[28]

In this paper we have partially outlined the potential scope of indole synthesis from the 4-oxotetrahydroindoles by describing the introduction of a variety of substituents including fused heterocycles[8] into the 4 and 5 positions. In the accompanying publication we extend this scope by electrophilic substitution of the pyrrole ring and the α-methylenecarbonyl system of the 4-oxotetrahydroindole.[19]

Experimental Section

General.—Melting points were determined on a Mel-Temp apparatus and are corrected. Ultraviolet spectra were determined in methanol using a Cary recording spectrophotometer. Infrared spectra were determined in potassium bromide disks or as films between salt plates on a Perkin-Elmer spectrophotometer (Model 21). Nuclear magnetic resonance spectra were determined in deuteriochloroform on a Varian A-60 spectrometer with tetramethylsilane as an internal standard. Solutions were dried over magnesium sulfate and concentrated under reduced pressure on a rotary evaporator.

4-Oxo-4,5,6,7-tetrahydroindole Oxime.—A mixture of 2.70 g (20 mmol) of **5**,[3] 5 ml of ethanol, 5 ml of pyridine, and 1.39 g (20 mmol) of hydroxylamine hydrochloride was heated on a steam bath for 2 hr. The mixture was concentrated and the residue was treated with brine and ethyl acetate. The organic layer was concentrated to a viscous oil which crystallized on standing. Two recrystallizations from acetone gave a low yield of colorless prisms, mp 174–179°.

(26) E. A. Braude, A. G. Brooke, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954); J. A. Edwards, J. C. Orr, and A. Bowers, *J. Org. Chem.*, **27**, 3378 (1962).

(27) 4,5-Dimethylindole is a new compound, one of the three isomeric dimethylindoles not reported by L. Marion and C. W. Oldfield, *Can. J. Chem.*, **25**, 1 (1947), in their systematic attempt to prepare all of the possible dimethylindoles.

(28) M. Julia, P. Manoury, and J. Igolen, *C. R. Acad. Sci., Paris*, **251**, 294 (1960).

Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.95; H, 6.90; N, 18.45.

A superior procedure was the following. A solution of 18 g of **5** in 150 ml of hot water was treated with a solution of 45 g (excess) of hydroxylamine hydrochloride in 180 ml of 10% sodium hydroxide, and the mixture was heated on a steam bath for 30 min. At this time crystals began to appear. Just enough ethanol was added to dissolve them and the hot solution was filtered. Upon cooling, the filtrate gave 18.9 g of crystals. Recrystallization from ethanol–water gave 12.4 g (62%) of colorless needles, mp 168.5–170.5°. This product was sufficiently pure for use in subsequent preparations.

1-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydroindole (4a).—This compound was prepared by a procedure analogous to that utilized by Stetter and Lauterbach for the corresponding 1,2-dimethyl compound,[3] with the additional feature of washing a methylene chloride solution of the crude product two times with 5% sodium hydroxide solution. In this manner we obtained from 33 g of 2-acetonyl-1,3-cyclohexanedione and 2 g of anhydrous ethylamine, after recrystallization from cyclohexane, 18.8 g (54%) of **4a** as white prisms: mp 74–75°; λ_{max} 6.10 μ, 252 mμ (ϵ 10,500) 284 mμ (7200).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.20; H, 8.80; N, 8.02.

2,6-Dimethyl-1-ethyl-4-oxo-4,5,6,7-tetrahydroindole (4b).—This compound was prepared by a procedure analogous to that used by Stetter and Lauterbach[3] for the corresponding 1,2-dimethyl compound. From 87.4 g (0.47 mol) of 2-acetonyl-5-methyl-1,3-cyclohexanedione[3] and 68.8 g of anhydrous ethylamine, after adsorption chromatography on a column of 1 kg of magnesia–silica gel 60/100 with methylene chloride as the eluent, 52.76 g (58.7%) of product was obtained. This material was recrystallized from cyclohexane to give white needles: mp 77–79°; λ_{max} 6.08 μ, 252 mμ (ϵ 10,400), 285 mμ (7200).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.30. Found: 74.80; H, 9.05; N, 7.17.

2,4-Dimethyl-1-ethylindole (8).—To a suspension of 9.40 g (25 mmol) of methyltriphenylphosphonium bromide in 80 ml of hexane was added 2.8 g (25 mmol) of potassium *tert*-butoxide. This mixture was stirred 30 min and treated with a suspension of 885 mg (5 mmol) of **4a** in 10 ml of ether. The mixture was stirred 16 hr and poured into water, and the organic layer was separated. The aqueous layer was extracted with methylene chloride and the combined organic layers were dried and concentrated. A benzene solution of the residue was passed through a silica gel column. Concentration of the eluate (50 ml) afforded 620 mg of **7**, an amber oil that had λ_{max} 13.2 μ, 231 mμ, 270 mμ, identical in infrared absorption spectrum with a sample prepared by treatment of **4a** with methylmagnesium bromide (see below).

A solution of 20 mmol of methylmagnesium iodide in 25 ml of ether was treated with a suspension of 3.54 g (20 mmol) of **4a** in 30 ml of ether, and the mixture was stirred 16 hr and treated with water and ammonium chloride solution. The ether layer was dried and concentrated to afford 2.08 g of **7**, identical in ir and uv absorption spectra with the sample described above. The ir spectrum had absorptions(s) at 13.2 μ characteristic of a trisubstituted double bond but had no absorptions in the regions 3.2–3.3 and 10.9–11.1 μ characteristic of terminal olefins. Without further purification this sample was converted to the corresponding indole **8**.

A mixture of 2.08 g of **7**, 8 ml of cumene, and 500 mg of 10% palladium on charcoal was heated at reflux temperature for 3 hr, cooled, and filtered. Concentration of the filtrate gave 850 mg of **8** as brownish oil: bp 84° (0.5 mm); λ_{max} 236 mμ (ϵ 28,000) 278 (5820), 282 (5820), 294 (4800); nmr δ 7.0 (three-proton multiplet, benzene-ring protons), 6.22 (singlet, C-3 proton), 3.95 (two-proton quartet, CH_2CH_3), 2.47 (three protons, 4-methyl), 2.33 (three protons, 2-methyl), 1.2 ppm (three-proton triplet, CH_2CH_3). The analytical data are given in Table II.

1-Ethyl-5-hydroxymethylene-2-methyl-4-oxo-4,5,6,7-tetrahydroindole (6a).—An ice-cooled suspension of 1.08 g (20 mmol) of sodium methoxide in 10 ml of dry benzene, under nitrogen, was treated with a solution of 1.48 g (20 mmol) of ethyl formate in 5 ml of benzene and a solution of 885 mg (5 mmol) of **4a** in 10 ml of benzene. The mixture was stirred at room temperature overnight, and was then cooled in an ice bath and treated with 20 ml of 5% sodium hydroxide solution. The combined alkaline extracts were cooled in an ice bath, layered with 20 ml of benzene, and acidified with 6 *N* hydrochloric acid. A pale yellow solid separated. This solid (230 mg) had λ_{max} 6.05, 6.15 μ, indicating that it was **6a** in a dicarbonyl form. When a methylene chloride solution of this solid was concentrated, it afforded **6a** as the monocarbonyl form, λ_{max} 6.03 μ.

Concentration of the benzene layer, from which the above yellow solid had separated, gave a pale yellow oil that crystallized on standing, affording an additional 400 mg of monocarbonyl form, mp 65–70°. Thus, the total yield of product was 670 mg (65%). Recrystallization from methanol afforded white prisms: mp 82–90°; λ_{max} 6.05, 6.15 μ (dicarbonyl form), 265 (ϵ 7770) mμ, 281 mμ (7800), 329 mμ (10,600); nmr δ 10.08 (5% HC(=O)CHC(=O)), 7.80 ppm (95% HC(OH)=CC(=O) $\rightleftarrows$ HC(=O)C=C(OH)) (in CH_2Cl_2).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.71; H, 7.75; N, 6.63.

On a 10-g scale this reaction afforded a 70% yield of **6a**, mp 91–95° (from ether).

2,6-Dimethyl-1-ethyl-5-hydroxymethylene-4-oxo-4,5,6,7-tetrahydroindole (6b).—This compound was prepared by the procedure described for **6a**. When 65.67 g (34 mmol) of **4b** was treated with 64.8 g of sodium methoxide and 88.8 g of ethylformate in dried benzene under nitrogen, 70.2 g (96.1%) of **6b** was obtained as a tan solid which was of sufficient purity to be used in subsequent reactions. Recrystallization from petroleum ether gave gray-tinged needles: mp 71–74°; λ_{max} 6.16 μ, 221 mμ (ϵ 10,400), 203 mμ (7700), 283 mμ (7800), 330 mμ (10,600); nmr 2.20 ppm (HC(OH)=CC(=O) $\rightleftarrows$ HC(=O)C=C(OH)).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.38; H, 7.86; N, 6.48.

2,5-Dimethyl-1-ethyl-4-oxo-4,5,6,7-tetrahydroindole (9a).—A mixture of 1.0 g of **6a**, 3.0 g of powdered potassium carbonate, 30 ml of acetone, and 4 ml of methyl iodide was stirred at room temperature overnight. It was then concentrated and the residue was treated with water and methylene chloride. The organic layer was washed with 1% sodium hydroxide solution and brine, dried, and concentrated, affording a pale yellow oil: λ_{max} 5.8 μ, 6.1 μ, 285 mμ. Without further purification this oil was converted to the deformylated product by heating it with 270 mg of sodium methoxide in 20 ml of methanol at reflux temperature for 2 hr. The resulting solution was concentrated and the residue was treated with water and methylene chloride. The organic layer was washed with water, dried, and concentrated, and the residue was purified by adsorption chromatography on silica gel with ether as eluent. Concentration of the eluate gave **9a** as white crystals: mp 44–47°; λ_{max} 6.08 μ, 255 mμ (ϵ 10,500), 285 mμ (ϵ 7200).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.39; H, 8.68; N, 7.29.

1-Ethyl-4-oxo-2,5,6-trimethyl-4,5,6,7-tetrahydroindole (9b).—This compound was prepared by the procedure described for **9a**, with the intermediate 5-carboxaldehyde being converted directly to **9b**. From treatment of 2.19 g of **6b** with potassium carbonate and methyl iodide in aetone, followed by treatment of the intermediate with methanol and sodium methoxide, and subsequent purification by adsorption chromatography on magnesia–silica gel, 1.18 g (57.5%) of **9b** was obtained as off-white solid. A 425-mg sample of this product was recrystallized from 10 ml of hexane to give 228 mg of pale tan needles: mp 97–99.5°; λ_{max} 6.09 μ, 210 mμ (ϵ 12,200), 252 mμ (9300), 285 mμ (6600).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.72; H, 9.35; N, 6.77.

1-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolecarbonitrile (10a).—A mixture of 1.03 g (5 mmol) of **6a**, 1.13 g (5 mmol) of *O*,*N*-bistrifluoroacetylhydroxylamine,[11] 0.79 g (10 mmol) of pyridine, and 10 ml of benzene was heated at reflux temperature for 20 min and then left at room temperature for 18 hr. It was treated with water, and the benzene phase was washed with water and sodium bicarbonate solution, dried, and concentrated to a brown solid. Two recrystallizations of this solid from acetone–hexane afforded 360 mg (35%) of **10a** as white prisms: mp 141–145°; λ_{max} 4.4 μ, 6.05 μ, 255 mμ (ϵ 11,000), 291 mμ (7300).

Anal. Calcd for $C_{12}H_{14}NO$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.20; H, 6.89; N, 14.03.

2,6-Dimethyl-1-ethyl-4-oxo-4,5,6,7-tetrahydro-5-indolecarbonitrile (10b).—A mixture of 2.19 g (10 mmol) of **6b**, 765 mg (10 mmol) of hydroxylamine hydrochloride, and 50 ml of ethanol was refluxed for 18 hr. The resulting dark brown solution was filtered and concentrated to give 2.59 g of a dark brown semisolid which was dissolved in methylene chloride and chromatographed on 30 g of magnesia–silica gel. A total of 1.04 g (48%) of **10b** (tan solid)

was obtained. A 170-mg sample of this solid was recrystallized from boiling methanol (3 ml) to give 107 mg of white solid: mp 140–143°; λ_{max} 4.45 μ, 6.03 μ, 210 mμ (ε 13,300), 255 mμ (10,800), 289 mμ (6500).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.69; H, 7.43; N, 13.48.

When a mixture of 2 g of isoxazoloindole **11**, 0.5 g of 10% palladium on charcoal, and 10 ml of cumene was heated at reflux for 4 hr and then filtered and cooled, crystals of **10b** separated from the filtrate. They had mp 141–144°, undepressed upon admixture with the sample described above.

4,5-Dihydro-4,7-dimethyl-6-ethyl-6*H*-isoxazolo[5,4-*e*]indole (11).—A solution of 16.9 g (77 mmol) of **6b** in 100 ml of warm ethanol was treated with a solution of 5.37 g (77 mmol) of hydroxylamine hydrochloride in 15 ml of water. Within a few minutes crystals of the product appeared. The mixture was cooled and filtered, and the crystals were washed with aqueous ethanol. This procedure gave 14.8 g (88%) of **11** as a nearly white product which had mp 135–138° after recrystallization from ethanol–water: λ_{max} 234 mμ (ε 8100), 380 mμ (12,400).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.65; H, 7.92; N, 12.95.

2,6-Dimethyl-1-ethyl-4-hydroxy-5-indolecarbonitrile (12.)—To an ice-cooled suspension of 0.38 g (7 mmol) of sodium methoxide in 10 ml of dry benzene, under nitrogen, was added a solution of 1.51 g (7 mmol) of **13** in 50 ml of benzene. The mixture was stirred for 4 hr and then treated with 5% NaOH solution. The benzene layer was extracted with additional 5% NaOH and the combined alkaline solutions were acidified to pH 2 with HCl, whereupon the product precipitated. It was washed with water and dried under vacuum. A yield of 0.6 g (40%) of **12** as white solid with mp 230–243° was obtained. Recrystallization from acetonitrile gave needles: mp 243–248°; λ_{max} 3.1 μ (OH), 4.5 (CN).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.38; H, 6.21; N, 12.96.

1-Benzyl-4-oxo-4,5,6,7-tetrahydroindole (17).—A solution of 0.133 mol of methylsulfinyl carbanion in dimethyl sulfoxide,[12] prepared from 5.8 g of 55% sodium hydride in mineral oil and 50 ml of dimethyl sulfoxide, was cooled to 18° and treated with a solution of 16.4 g (0.12 mol) of **5**[3] in 50 ml of dimethyl sulfoxide. The mixture was stirred under nitrogen for 2 hr and then treated with 15.4 g (0.12 mol) of benzyl chloride. The resulting solution was stirred at room temperature for 17 hr and then diluted gradually with water. The white crystals which separated were washed with water and dissolved in methylene chloride, and this solution was washed with water, dried, filtered, and concentrated on a steam bath as hexane was added. When most of the methylene chloride had boiled off the solution was cooled. This procedure gave 20.8 g (76%) of **17** as white prisms, mp 80–81.5°.

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.57; H, 6.63; N, 6.14.

This preparation could also be carried out with potassium *tert*-butoxide as the base, but the yields were variable and sometimes the product was difficult to separate from starting material.

1-Benzyl-4,5,6,7-tetrahydroindole (15).—A mixture of 5.62 g of **17**, 18 ml of hydrazine hydrate, and 200 ml of benzene was heated in a Dean–Stark apparatus for 21 hr and then was concentrated. The residue (hydrazone) was treated for 1 hr at 100° with 5 g of powdered potassium hydroxide and 3 ml of hydrazine hydrate in 150 ml of diethylene glycol. The temperature was then increased until the mixture began to distil. After 50 ml of water and solvent were removed, the remaining solution was heated at reflux temperature for 5 hr. It was then cooled and extracted with benzene. This extract was washed with water and brine and concentrated. Distillation of the residual oil (5.38 g) afforded 4.35 g (83%) of **15** as a colorless oil, bp 185–188° (8 mm).

Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 84.37; H, 8.06; N, 7.03.

When the Wolff–Kishner reduction was run without isolation of the intermediate hydrazone, the product (1.35 g, 25%) was bis[4-(1-benzyl-4,5,6,7-tetrahydroindole)] azine (**14**), mp 221.5–224.5°.

Anal. Calcd for $C_{30}H_{30}N_4$: C, 80.68; H, 6.77; N, 12.55. Found: C, 80.22; H, 6.86; N, 12.25.

1-Benzyl-5-hydroxymethylene-4-oxo-4,5,6,7-tetrahydroindole (21).—This compound was prepared by the procedure described for **6a**. However, no indication of the tautomeric equilibrium noted for **6a** was found. From 20 g of **17** was obtained 18.0 g (80%) of white prisms, mp 45–48°.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.53; H, 5.72; N, 5.59.

1-Benzyl-5-methylthio-4-oxo-4,5,6,7-tetrahydroindole (18).—To a solution of 115 mg (5 mmol) of sodium in 5 ml of ethanol was added, under nitrogen, 1.265 g (5 mmol) of **21**. The mixture was stirred 20 min and then treated with 1.10 g (5 mmol) of methyl thiotosylate.[18] After 16 hr the mixture was neutralized with 5 mmol of acetic acid and concentrated under reduced pressure. The residual solid was treated with methylene chloride and 2.5% sodium hydroxide solution. The resulting organic layer was washed with brine, dried, and concentrated. Recrystallization of the residual solid from methanol gave 604 mg (45%) of **18** as colorless prisms, mp 94–96°. An analytical sample, recrystallized once more from methanol, had mp 95–97°, λ_{max} 6.08 μ.

Anal. Calcd for $C_{16}H_{17}NOS$: 70.83; H, 6.32; N, 5.16; S, 11.79. Found: C, 71.09; H, 6.46; N, 5.19; S, 11.83.

In larger scale experiments, yields of **18** up to 83% were obtained.

1-Benzyl-4-oxo-5-phenyl-4,5,6,7-tetrahydroindole (19).—To a solution of sodium *tert*-butoxide in *tert*-butyl alcohol (made from 0.69 g(30 mg-atoms) of sodium and 250 ml of *tert*-butyl alcohol) was added 6.76 g (30 mmol) of **21**. To the resulting solution was added 9.50 g (30 mmol) of diphenyliodonium chloride and the mixture was stirred at reflux temperature under nitrogen for 22 hr. It was then concentrated and the residue was treated with dilute hydrochloric acid and methylene chloride. The organic layer was washed with brine, dried, and concentrated. A solution of the residual brown liquid in 250 ml of methanol was treated with 4.0 g of sodium methoxide at reflux temperature for 2 hr. After concentration of the resulting solution, the residue was treated with water and methylene chloride. The organic layer was washed with brine, dried, and concentrated. Trituration of the residue with ether afforded 4.33 g (54%) of **19** with mp 92–98°. Recrystallizations from ether–methylene chloride and from methanol–water gave an analytical sample with mp 109–111°.

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.32; N, 4.65. Found: C, 83.18; H, 6.45; N, 4.85.

1-Benzyl-5-phenyl-4,5,6,7-tetrahydroindole (16).—A suspension of 6.0 g of **19** in 400 ml of ether was treated with 1.0 g of lithium aluminum hydride. The mixture was stirred for 21 hr and then treated with 6.5 ml of saturated potassium sodium tartrate solution. It was filtered and the filtrate was dried and concentrated. The residual oil was further concentrated under higher vacuum (1 mm) until became glassy. Trituration with ether then afforded **16** as white solid (5.4 g, 94%) with mp 63–72°. Recrystallization from methanol gave white crystals, mp 70–72°.

Anal. Calcd for $C_{21}H_{21}N$: C, 87.76; H, 7.36; N, 4.88. Found: C, 87.33; H, 7.39; N, 4.80.

Reduction of 602 mg of **19** with 380 mg of sodium borohydride in 10 ml of ethanol at reflux temperature for 4 hr gave 483 mg of **16** identical in ir spectrum (no carbonyl group remained) with the sample described above.

1-Benzyl-5-methyl-4-oxo-4,5,6,7-tetrahydroindole (20).—This compound was prepared by the procedure described for **9a**. From 16.0 g of **21** was obtained 12.4 g (82%) of **20** as an amber oil which solidified upon storage at 5°. Recrystallization from ether–hexane gave white plates, mp 57–58°.

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.25; H, 6.87; N, 6.12.

1-Benzyl-4,5-dimethylindole (23).—To a suspension of 18.0 g (47.5 mmol) of methyltriphenylphosphonium bromide in 150 ml of hexane was added 5.3 g (47.5 mmol) of potassium *tert*-butoxide. The mixture was stirred 30 min and then treated with a solution of 2.3 g (9.5 mmol) of **20** in 10 ml of benzene and 10 ml of ether. The mixture was stirred under nitrogen for 16 hr and treated with water and methylene chloride, and the organic layer was dried and concentrated. Treatment of the residue with ether induced crystallization of the phosphine oxides. The mixture was filtered and the filtrate was concentrated. Extraction of the residue with hexane, followed by concentration of this extract, gave 1.27 g of a mixture of **1-benzyl-4-methylene-5-methyl-4,5,6,-7-tetrahydroindole (25)** and **1-benzyl-4,5,dimethyl-6,7-dihydroindole (22)** in a ratio of approximately 1:1, as indicated by its nmr spectrum: five protons 7.6–6.2 (phenyl), 5.25 and 5.04 (one-half proton each, $=CH_2$), 4.95 (two protons, benzyl CH), 2.46 and 2.33 (one and one-half proton each, methyl groups on

double bond), 1.78 (one and one-half proton doublet, J = 8 Hz, methyl group of **25**), aliphatic protons 2.65–1.67 ppm. This mixture of isomers was treated directly with 300 mg of 10% palladium on charcoal and 10 ml of cumene at reflux temperature for 3 hr. The resulting mixture was cooled, filtered, and concentrated, and the residual oil was purified by adsorption chromatography on Florisil with methylene chloride as eluent. Concentration of the eluate gave a colorless oil which crystallized upon cooling. Recrystallization from hexane gave 750 mg (34% from 20) of **23** as waxy white prisms, mp 87°. The analytical data are given in Table II.

4,5-Dimethylindole (24).—To a solution of 2.04 g of sodium in 250 ml of liquid ammonia was added a solution of 3.48 g of **23** in 60 ml of ether. The mixture was stirred 5 min and then decolorized with ammonium chloride. After evaporation of the solvents, the residue was treated with water and methylene chloride. The organic layer was washed with water, dried, concentrated, and heated under vacuum to remove toluene. The white solid product (1.50 g, 69%) had, upon recrystallization from hexane, mp 106.5–108°: λ_{max} 222 mμ (ε 29,000), 269 (7110), 284 (5010), 296 (3420).

Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.57; H, 7.54; N, 9.78.

1-Benzenesulfonyl-4-oxo-4,5,6,7-tetrahydroindole (28).—Potassium *tert*-butoxide was freshly prepared from 7.8 g (0.2 g-atom) of potassium and 400 ml of *tert*-butyl alcohol. The excess *tert*-butyl alcohol was removed under reduced pressure and benzene was added to the residue and removed under reduced pressure to further decrease the adhering *tert*-butyl alcohol. The residual solid was suspended in 300 ml of dry benzene and treated with a suspension of 27.0 g (0.2 mol) of **5** in 100 ml of benzene. An atmosphere of nitrogen was introduced and the mixture was stirred for 1 hr at reflux temperature. It was then cooled and treated with a solution of 35.3 g (0.2 mol) of benzenesulfonyl chloride. The resulting mixture was stirred at room temperature under nitrogen for 16 hr and then stirred at reflux temperature for 4 hr. It was cooled and treated with water, and the layers were separated. The aqueous layer was extracted with methylene chloride and the combined organic layers were washed with water, and concentrated. Recrystallization of the residual solid from 250 ml of methanol gave 40.3 g (73%) of **28** as nearly white prisms, mp 117–118.5°.

Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.06; H, 4.76; N, 5.09; S, 11.65. Found: C, 60.75; H, 4.95; N, 5.16; S, 11.51.

1-Benzenesulfonyl-4-carbethoxymethylene-4-hydroxy-4,5,6,7-tetrahydroindole (26).—A mixture of 7.25 g (30 mmol) of **28**, 12.0 g (72 mmol) of ethyl bromoactate, 4.80 g (72 mg-atom) of zinc dust, and 69 ml of dry benzene was heated at reflux temperature for 45 min, cooled, and poured into ice water containing dilute sulfuric acid. The organic layer was washed with sodium bicarbonate solution, dried, and concentrated. Recrystallization of the residue from methanol–water afforded 10.1 g of **26** as white solid, mp 79–80.5°.

Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.50; H, 5.82; S, 8.82. Found: C, 59.36; H, 5.78; S, 8.84.

1-Benzenesulfonyl-4-carbethoxymethylene-4,5,6,7-tetrahydroindole (27).—Upon prolonged storage the above-described sample of **26** was completely converted by spontaneous dehydration into **27**, which after recrystallization from ether–hexane had mp 89–92°: λ_{max} 293 mμ (ε 19,000), 275 (16,400), 268 (16,000); nmr δ 5.88 (vinyl), 4.12 (quartet, OCH_2CH_3), 2.84 (4-proton multiplet, C-5 and C-7 protons), 1.77 (2-proton multiplet, C-6 protons), 1.22 ppm (triplet, OCH_2CH_3).

Anal. Calcd for $C_{18}H_{19}NO_4S$ (345.41): C, 62.60; H, 5.55; N, 4.06; S, 9.27. Found: C, 62.40; H, 5.57; N, 4.08; S, 9.49.

If either **26** or **27** was heated with 10% palladium on charcoal in refluxing cumene, a low yield of an oily product was obtained. This oil had an uv spectrum typical for the corresponding fully aromatic indole [λ_{max} 292 mμ (ε 4200), 283 (4400), 252 (18,000)]. However, it was not possible to repeat this preparation on a usful scale and an analytical sample was not obtained.

1-Benzenesulfonyl-5-bromo-4-oxo-4,5,6,7-tetrahydroindole (29).—A solution of 550 mg (2 mmol) of **28** in 6 ml of tetrahydrofuran was treated with a solution of 752 mg (2 mmol) of phenyltrimethylammonium tribromide in 2 ml of tetrahydrofuran. After 30 min the mixture was filtered and the filtrate was concentrated under reduced pressure. A methylene chloride solution of the concentrate was washed with sodium bicarbonate and brine, dried, and concentrated. The residual syrup, upon trituration with ether, afforded 416 mg (59%) of **29** as white crystals, mp 85–88°. Recrystallization from tetrahydrofuran–hexane gave needles with mp 94–96°: λ_{max} 5.98 μ; nmr δ 8.2–7.7 (five protons, phenyl) ppm, 7.52 (d, 2 proton), 6.66 (d, 3 proton), 4.80 (dd, 4 proton), 3.18 (two-proton multiplet, 7 protons), 2.45 (DMSO + 6 protons).

Anal. Calcd for $C_{14}H_{12}BrNO_3S$: C, 47.46; H, 3.42; N, 3.96; Br, 22.56. Found: C, 47.86; H, 3.43; N, 3.99; Br, 22.06.

2-Amino-6-benzenesulfonyl-4,5-dihydro-6*H*-pyrrolo[3,2-*e*]benzothiazole (36).—A mixture of 708 mg (2 mmol) of **29**, 304 mg (4 mmol) of thiourea, 404 mg (4 mmol) of triethylamine, and 30 ml of ethanol was heated at reflux temperature for 18 hr (tlc showed no **29** present). It was then concentrated and the syrupy residue was treated with water. The light grey solid (600 mg) that separated was recrystallized from dimethyl sulfoxide–water. This procedure afforded white crystals of impure **34**, mp 203–205°.

Anal. Calcd for $C_{15}H_{13}N_3O_2S_2$: N, 9.98; S, 15.53; Br, 17.88. Found: N, 10.19; S, 15.55; Br, 19.38.

Attempted recrystallization from methanol afforded 317 mg of benzothiazole **36** (48% from **29**) as yellow needles, mp 215–219°.

Anal. Calcd for $C_{15}H_{13}N_3O_2S_2$: C, 54.37; H, 3.96; N, 12.69; S, 9.34. Found: C, 54.80; H, 3.99; N, 12.61; S, 19.62.

When this preparation was repeated with methanol as the solvent, **36** was isolated directly from the concentrate. A 63% yield of crystals with mp 215–219° was obtained after recrystallization from methanol.

1-Benzoyl-4-oxo-4,5,6,7-tetrahydroindole (30).—A mixture of 13.5 g (0.1 mol) of **5**, 11.2 g (0.1 mol) of potassium *tert*-butoxide, and 200 ml of dry benzene was stirred at reflux temperature for 1 hr. It was then cooled and treated gradually with 14.06 g (0.1 mol) of benzoyl chloride in 25 ml of benzene. The mixture was stirred for 2 hr and then treated with 200 ml of water and 150 ml of methylene chloride. The organic layer was washed with sodium bicarbonate solution, dried, and concentrated to a yellowish solid. This solid was washed with hexane and then recrystallized from acetone–hexane (charcoal). A yield of 14.98 g (63%) of **30** as colorless prisms, mp 120–123°, was obtained in two crops. Recrystallization from acetone gave mp 122–123°.

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.18; H, 5.51; N, 5.83.

1-Benzoyl-5-bromo-4-oxo-4,5,6,7-tetrahydroindole (31).—This compound was prepared by the procedure described for **29**. From 478 mg of **30** and 752 mg of phenyltrimethylammonium tribromide was obtained 433 mg (68%) of white crystals, mp 129–130°. The nmr spectrum showed two pyrrole protons at δ 6.92 and 6.58 ppm.

Anal. Calcd for $C_{15}H_{12}BrNO_2$: C, 56.62; H, 3.80; N, 4.40; Br, 25.11. Found: C, 57.05; H, 4.01; N, 4.59; Br, 24.62.

Larger scale preparations of **31** involved pyridinium bromide perbromide as the brominating agent in the same type of procedure. Yields were in the range of 71–83% on a 0.1-mol scale.

5-Bromo-4-oxo-4,5,6,7-tetrahydroindole (32).—A suspension of 636 mg (2 mmol) of **31** in 15 ml of methanol was treated with 2 mmol of 5 *N* NaOH. After 1 hr the resulting solution was neutralized with HCl and concentrated to dryness. A methylene chloride solution of the residue was washed with sodium bicarbonate solution, dried, and concentrated. Recrystallization of the white solid residue from methanol gave 351 mg (82%) of **32** as white prisms, mp 167–169°. Another recrystallization gave mp 170–173°.

Anal. Calcd for C_8H_8BrNO: C, 44.89; H, 3.77; N, 6.55; Br, 37.34. Found: C, 45.32; H, 3.91; N, 6.84; Br, 36.89.

6-Benzoyl-4,5-dihydro-2-dimethylamino-6*H*-pyrrolo[3,2-*e*]benzothiazole (37).—A mixture of 318 mg (1 mmol) of **31**, 104 mg (1 mmol) of 1,1-dimethylthiourea, 101 mg (1 mmol) of triethylamine, and 10 ml of tetrahydrofuran was warmed at reflux temperature for 20 hr and then filtered. The filtrate was concentrated to an oily residue which crystallized upon trituration with ether. Recrystallization from methanol afforded **37** as yellow needles, mp 117–120°.

Anal. Calcd for $C_{18}H_{17}N_3OS$: C, 66.86; H, 5.30; S, 9.92. Found: C, 66.48; N, 5.51; S, 9.49.

When this experiment was repeated on a 5.0-g scale, the yield of **37** was 3.8 g (75%).

4,5-Dihydro-2-methylamino-6*H*-pyrrolo[3,2-*e*]benzothiazole (38).—A suspension of 3.8 g (11.8 mmol) of **37** in 75 ml of methanol was treated with 11.8 mmol of 5 *N* NaOH. Within 10 min this yellow solid had dissolved and pale yellow crystals of product had formed. The product was washed well with methanol and

dried in air. A 2.15-g (80%) yield of crystals with mp 244–245° was obtained. Recrystallization from methanol afforded **38** as pale yellow needles, mp 246–248°.

Anal. Calcd for $C_{11}H_{11}N_3S$: C, 60.25; H, 5.98; N, 19.15; S, 14.62. Found: C, 59.98; H, 5.99; N, 19.02; S, 14.33.

1-Acetyl-4-oxo-4,5,6,7-tetrahydroindole (33).—A mixture of 10.3 g of **5**, 7.5 g of potassium acetate, and 75 ml of acetic anhydride was heated at reflux temperature for 16 hr and then concentrated. The residue was extracted with 150 ml of acetone. This extract was filtered and concentrated on a steam bath as hexane was added. When the first crystals appeared, the mixture was cooled. This procedure gave 12.1 g (90%) of **33** as white prisms, mp 85–93°. Recrystallization from acetone–hexane gave crystals with mp 98.5–99.5°: λ_{max} 5.75 μ ($COCH_3$), 6.00 μ (4-carbonyl), 275 mμ (ϵ 5200), 235 mμ (16,000).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.64; H, 5.50; N, 8.04.

Upon attempted recrystallization from methanol, **33** was hydrolyzed back to **5**, as indicated by identity of ir absorption spectra.

Dehydrogenation with Palladium on Charcoal.—A mixture of 10.0 g of the 4-oxo-4,5,6,7-tetrahydroindole or 6,7-dihydroindole, 2.5 g of 10% palladium on charcoal, and 50 ml of cumene was stirred at reflux temperature for 3 hr, cooled, and filtered. When a hydroxyindole was the product, the filtrate was extracted with 100 ml of 5% NaOH and this extract was layered with methylene chloride and carefully neutalized with acetic acid. The organic layer was washed with sodium bicarbonate, dried, and concentrated, and the residue was extracted with 500 mg of boiling *n*-hexane. White crystals of the product indole formed on cooling. Melting points and analytical data are given in Tables I and II.

Dehydrogenation with 5,6-Dichloro-2,3-dicyanobenzoquinone.—Equimolar portions of the 4-oxotetrahydroindole or 6,7-dihydroindole and 2,3-dichloro-5,6-dicyanobenzoquinone, each dissolved in the minimum volume of dioxane, were combined. After 1 hr the mixture was filtered to remove the hydroquinone and the filtrate was concentrated under reduced pressure. Residues were worked up as follows. For **39e** and **39f** the residual solids were extracted with boiling hexane and crystals formed upon cooling this extract. The products were recrystallized from hexane. For **35** the residue was extracted with dilute HCl and then the free base was literated by neutralization with NaOH. The best procedure for **13** was to dilute the dioxane filtrate with water until the product crystallized. Recrystallization was from ethanol. The yields, melting points, and analytical data for these compounds are given in Tables I and II.

4-Hydroxyindole.—A mixture of 1.35 g of **5**,[3] 0.50 g of 10% palladium on charcoal, and 75 ml of cumene was heated at reflux temperature for 4 hr and filtered, and the solid cake was washed with methylene chloride. The combined filtrate and wash was concentrated, and the residue was extracted with 10% sodium hydroxide solution containing a little sodium hydrosulfite. This extract was acidified with acetic acid and extracted with methylene chloride. The organic extract was dried and concentrated. The greenish residue was extracted with boiling cyclohexane. Upon cooling this extract gave 274 mg (21%) of a white solid: mp 101–102° (lit.[29] mp 98°); λ_{max} 222 mμ (ϵ 30,000), 264 (9700), 282 (5600), 292 (5400); one spot on tlc.

When the dehydrogenation of **5** was effected in mesitylene according to the procedure of Plieninger and Klinga,[25] a 48% yield of 4-hydroxyindole was obtained. It had mp 88–91° after recrystallization from water. The presence of a small amount of **5** was shown by tlc and its nmr spectrum.

1-Benzyl-4-hydroxyindole.—A mixture of 213 mg (0.79 mmol) of **18** and 25 mg (0.79 mmol) of sulfur was heated at 220–240° for 30 min, cooled, and extracted with methylene chloride. This extract was concentrated and the residue was purified by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methanol system. The main peak absorbing at 300 mμ (sixth holdback volume) afforded 56 mg of a viscous, colorless oil upon concentration. This oil crystallized on standing. After washing with ether it had mp 90–92°.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.55; H, 6.00; N, 6.30.

Registry No.—**4a**, 4674-52-6; **4b**, 4583-63-5; **5** oxime, 27866-27-9; **6a**, 4657-85-6; **6b**, 4657-86-7; **8**, 4657-73-2; **9a**, 4660-04-2; **9b**, 4657-71-0; **10a**, 4660-05-3; **10b**, 4657-72-1; **11**, 27866-35-9; **12**, 27866-36-0; **13**, 27866-37-1; **14**, 27866-38-2; **15**, 27866-39-3; **16**, 27866-40-6; **17**, 13671-74-4; **18**, 27866-42-8; **19**, 27866-43-9; **20**, 27866-44-0; **21**, 27866-45-1; **23**, 27866-46-2; **24**, 27866-47-3; **26**, 27866-48-4; **27**, 27866-49-5; **28**, 18518-46-2; **29**, 27866-51-9; **30**, 27866-52-0; **31**, 27866-53-1; **32**, 27866-54-2; **33**, 27866-55-3; **35**, 27866-56-4; **36**, 27928-70-7; **37**, 27866-57-5; **38**, 27866-58-6; **39a**, 4657-80-1; **39b**, 4657-81-2; **39c**, 4657-82-3; **39e**, 4624-36-6; **39f**, 4657-84-5; 1-benzyl-4-hydroxyindole, 27866-64-4.

Acknowledgment.—We thank Mr. W. Fulmor and staff for spectra, Mr. L. Brancone and staff for microanalyses, and Mr. C. Pidacks and staff for chromatographic separations.

(29) R. J. S. Beer, K. Clarke, H. G. Khorana, and A. Robertson, *J. Chem. Soc.*, 1605 (1948).

Synthesis of Indoles from 4-Oxo-4,5,6,7-tetrahydroindoles. III.[1a] Introduction of Substituents by Electrophilic Substitution

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The general method of indole synthesis by way of 4-oxo-4,5,6,7-tetrahydroindoles has been extended by a variety of electrophilic substitution reactions, including bromination, nitration, acylation, and formylation. An order of selective substitution was established as follows: $C_2 > C_3 > C_5$, except in certain Vilsmeier–Haack formylations of 2-substituted compounds. When the pyrrole ring of a 4-oxo-4,5,6,7-tetrahydroindole was substituted with a strong electron-withdrawing group, electrophilic substitution was diverted to C_5. Most of the 6,7-dihydroindoles prepared in this investigation could be dehydrogenated to the fully aromatic indoles, but many of the new 4-oxo-4,5,6,7-tetrahydroindoles were resistant to dehydrogenation. Vilsmeier–Haack formylation of certain 4-oxo-4,5,6,7-tetrahydroindoles led directly to fully aromatic indoles which had a 4-chloro-5-(dimethylaminomethyl) pattern of substitution.

Discussion

A general approach to the synthesis of indoles from 4-oxo-4,5,6,7-tetrahydroindoles was outlined in the preceding article in this series.[1] The present article is concerned with extending this approach by a variety of electrophilic substitution reactions of 4-oxo-4,5,6,7-tetrahydroindoles and conversion of the resulting products into novel indoles.

There are three possible sites for electrophilic substitution of **3a**, the parent 4-oxo-4,5,6,7-tetrahydroindole. Two of these sites, C_2 and C_3 are in the pyrrole ring, and the third, C_5, is provided by enolization of the carbonyl group. The relative rates of substitution in the pyrrole ring and at C_5 will obviously be influenced by the rate and extent of this enolization. Important conjugation between the carbonyl group and pyrrole nitrogen[1] affects this factor, and others, in the electrophilic substitutions.

In a preliminary experiment, the acid-catalyzed deuterium exchange of **3a** in CD_3OD was determined. This experiment (Table I) revealed no appreciable difference in the rates of exchange of the C_2 and C_3 protons, but their exchange rates were approximately double those of C_5 protons. Although this experiment afforded no basis for the prediction of selective reactivity between C_2 and C_3, LCAO–MO calculations for the relative π energies of hypothetical pyrrolenine cation intermediates for electrophilic substitution at these positions indicated a preference for substitution at C_2 (the α-pyrrole position).[2]

TABLE I

ACID-CATALYZED DEUTERIUM EXCHANGE IN 4-OXO-4,5,6,7-TETRAHYDROINDOLE (**3a**)[a]

	% exchange at times, hr				
Proton	0[b]	1	2	7	26[c]
2	33	75	86	86	87
3	33	75	86	86	87
5,5	17	50	71	83	83

[a] A 12% solution of **3a** in CD_3OD in an nmr tube was treated with one small drop of DCl and the solution was kept at 25° between measurements. [b] The short time between preparation of the sample and completion of the nmr spectrum caused the indicated exchanges. [c] The figures in this column represent the maximum possible exchange, since four exchangeable protons were present in starting **3a**.

The group of experiments described in the sequel have established that, as anticipated above, C_2 is the preferred site of electrophilic substitution in **3a**. Thus, Vilsmeier–Haack formylation[3] of **3a** afforded, as the only isolable product, a 2-formyl derivative **4a** in which the 4-oxo substituent had been replaced by a vinyl chloride function. The location of the formyl group at C_2 was established by dehydrogenation (DDQ) of **4a** to 4-chloroindole-2-carboxaldehyde which differed from the known 4-chloroindole-3-carboxaldehyde[4] in infrared and ultraviolet spectra, melting point, and mixture melting point (Experimental Section). Treatment of **3a** with 1 equiv of 70% perchloric acid in acetic anhydride gave the crystalline perchlorate salt of the 2-acetyl derivative **7**.[5] The free base formed when this salt was dissolved in water. Assignment of the acetyl substituent to C_2 follows from the ultraviolet spectrum of **7**, which is significantly different from that of the 3-

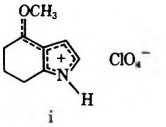
(1) (a) For part II, see W. A. Remers, R. H. Roth, G. J. Gibs, and M. J. Weiss, *J. Org. Chem.*, **36**, 1232 (1971). A portion of this work has been previously communicated: W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, **87**, 5262 (1965); also M. J. Weiss, G. R. Allen, Jr., G. J. Gibs, J. F. Poletto, and W. A. Remers, "Topics in Heterocyclic Chemistry," R. C. Castle, Ed., Wiley-Interscience, New York, N. Y., 1963. (b) To whom inquiries should be addressed at the Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Ind. 47907.

(2) These calculations were based upon the parameters $\alpha_N{}^+ = \alpha_C + 2.0\beta$, $\alpha_O = \alpha_C + 1.5\beta$. The total π-electron energies for the pyrrolenine cations corresponding to electrophilic substitution at C_2 and C_3 were 11.93 and 11.82β, respectively. Thus C_2 substitution is favored by *ca.* 2 kcal/mol if it is assumed that β = 18 kcal/mol.

(3) Recent reviews of the Vilsmeier–Haack reaction include the following: G. Hazebroucq, *Ann. Pharm. Fr.*, **24**, 793 (1966); M. R. deMaheas, *Bull. Soc. Chim. Fr.*, 1989 (1962).

(4) B. A. Whittle and E. H. Young, *J. Med. Chem.*, **6**, 378 (1963).

(5) Treatment of **3a** with 70% perchloric acid in excess methyl orthoformate afforded *O*-methyl perchlorate i (see Experimental Section). This



i

type of O-alkylation is related to the O-alkylations of enamino ketones reported by A. I. Meyers, A. H. Reine, and R. Gault, *Tetrahedron Lett.*, 4049 (1967); however, in contrast to enamino ketones, **3a** does not react with a weak electrophile like methyl iodide.

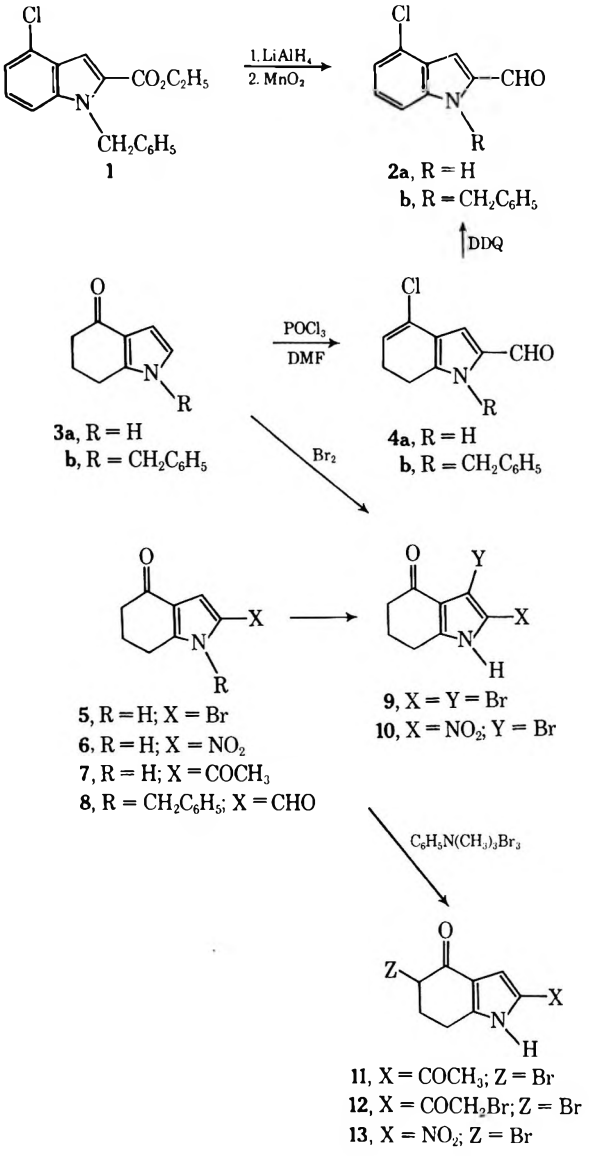
acetyl-4-oxo derivative **17**.[6] A similar line of reasoning supports the conclusion that the product **6** obtained from nitration of **3a** is substituted at C_2, since its ultraviolet spectrum is unlike that of **16**, which must bear the nitro group at C_3.

The products isolated from bromination of **3a** depended upon the nature of the brominating agent. Thus bromine in acetic acid afforded mainly the 2,3-dibromo derivative **9**, whereas the more selective phenyltrimethylammonium tribromide furnished a single monobromo derivative **5** in good yield. The location of the bromine atom at C_2 (rather than C_3) of **5** has not been confirmed; however, this is the most probable position by analogy to the other electrophilic substitutions.

The presence of a benzyl substituent on the nitrogen of a 4-oxo-4,5,6,7-tetrahydroindole (*e.g.*, **3b**) apparently did not change the preferred site of formylation from C_2, since the product **4b** of the Vilsmeier–Haack reaction with **3b** in three of four experiments was of the same type as that obtained from **3a**. In one of these four experiments, conducted as nearly as possible under conditions identical with those of the other three, the product isolated (**8**) had undergone formylation (probably at C_2), but it retained the 4-oxo group. It is possible that **8** is an intermediate the formation of **4b**, but this point was not investigated further. Location of the formyl group of **4b** at C_2 was established by dehydrogenation to indole derivative **2b**, which was identical in infrared spectrum, melting point, and mixture melting point with a sample of **2b** prepared by an unequivocal route from methyl 1-benzyl-4-chloroindole-2-carboxylate (**1** → **2b**). The ultraviolet absorption spectrum of **2b** was nearly identical with that of 4-chloroindole-2-carboxaldehyde (**2a**) (Scheme I).

When substituents were present at the 2 position of a 4-oxo-4,5,6,7-tetrahydroindole, electrophilic substitution generally occurred at the 3 position. Thus bromination and nitration of the 1-ethyl-2-methyl derivative **14c** afforded the corresponding 3-bromo and 3-nitro derivatives **15** and **16**, respectively.[7] Furthermore, treatment of 2,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindole **14b** with acetic anhydride and perchloric acid gave the 3-acetyl derivative **17**. Vilsmeier–Haack formylation of **14c** and **14a** appeared to afford exceptions to this generalization, since only the corresponding 4-chloro-

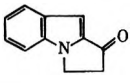
SCHEME I



5-carboxaldehydes **19b** and **19a** were isolated when the former compounds were warmed with 1 equiv of phosphorus oxychloride in excess dimethylformamide. However, the yields of isolated products were very low in both examples (6 and 2.5%, respectively), with much tar formation. Even if these products represent the main course of electrophilic substitution of **14c** and **14a**, it is not certain that this means a preference for C_5 over C_3. In the presence of phosphorus oxychloride these compounds might have been converted first into the corresponding 4-chloro-6,7-dihydroindoles and then formylation of the resulting vinyl pyrrole system might have been preferred at C_5.[8]

When either **14c** or its 6-methyl homolog **14d** were warmed with 2 equiv of phosphorus oxychloride in dimethylformamide, an unexpected result was obtained. In each case there were two products, one neutral and the other basic. The neutral products were shown (Experimental Section) to be the 4-chloro-3,5-dicarboxaldehydes **20a** and **20b**, resulting from the anticipated formylations at both C_3 and C_5. However, the basic products **21b** and **21c** had fully aromatic indole

(6) In making this assignment it is necessary to rule out the possibility that in the 2,3-disubstituted compound **17** steric inhibition forces the acetyl group out of the plane of the pyrrole ring and thus distorts the chromophore. There are several pertinent model compounds which demonstrate that this is not an important factor at the 2 and 3 positions of indole derivatives. Thus 2-acetyl-3-methylindole [W. E. Noland and R. J. Sunderberg, *J. Org. Chem.*, **28**, 884 (1963)] has an uv chromophore nearly identical with that of

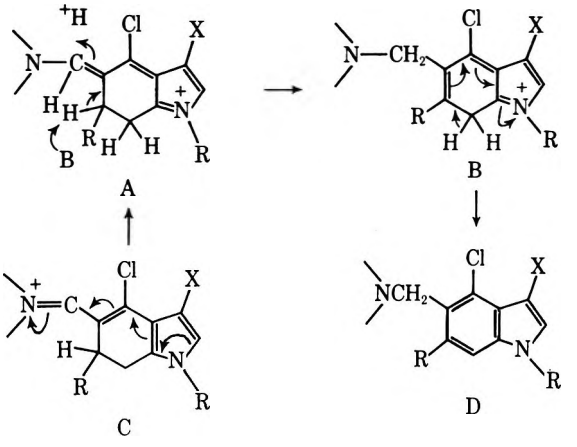


in which the carbonyl group is held in the plane of the pyrrole ring: W. A. Remers and M. J. Weiss, *J. Med. Chem.*, **8**, 700 (1965). In contrast, the uv chromophore of 3-acetylindole differs widely from that of these compounds. Furthermore, the uv spectra of all compounds in the group including indole-2-carboxylic acid and its 1-methyl, 3-methyl, and 5-methyl derivatives are nearly identical: R. Andrisano and T. Vitali, *Gazz. Chim. Ital.*, **87**, 949 (1957). Steric inhibition does distort uv chromophores at certain other indole positions, for example, in 1-acylindolines: A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, New York, N. Y., 1964.

(7) Preparation of 2-bromo-3-methyl-4-oxo-4,5,6,7-tetrahydroindole from bromine and the corresponding 2-unsubstituted compound has been reported: Belgian Patent 670,797 (1965); *Chem. Abstr.*, **65**, 12174*b* (1966).

(8) Formylation of vinyl-substituted aromatic compounds readily occurs (ref 3).

systems and instead of a 5-formyl group they had a 5-dimethylaminomethyl group. The genesis of these basic products is uncertain, but one hypothetical pathway involves the interaction of the dihydroindole and immonium[9] systems as shown in C → D. In these



structures X represents either hydrogen or a group which is precursor to the 3-carboxaldehyde function.

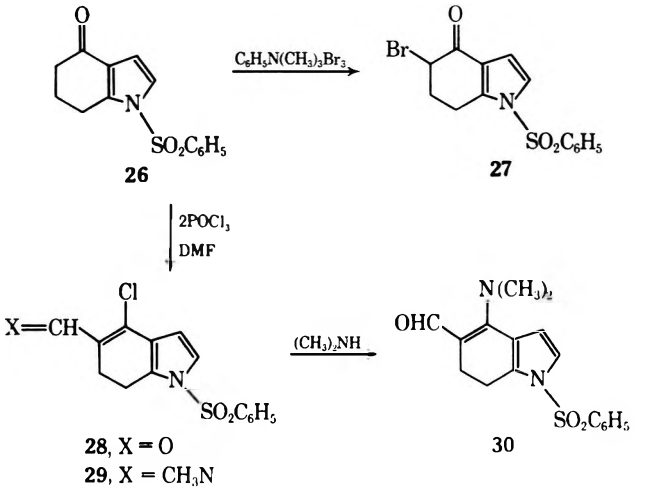
Treatment of **14a** with 2 equiv of phosphorus oxychloride in dimethylformamide also gave a 5-dimethylaminomethyl-substituted indole **21a**, but in extremely low yield.

When Vilsmeier–Haack formylation of 1-ethyl-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindole (**14e**) was conducted under the same conditions as described above (2 equiv of phosphorus oxychloride), the product **18** differed from **14e** only by a 3-formyl substituent. No reaction of the 5-methylene-4-oxo system was apparent, which suggests important hindrance of the 5 position by the *gem*-dimethyl groups at C_6 (Scheme II).

The presence of an electron-withdrawing substituent in the pyrrole ring of a 4-oxo-4,5,6,7-tetrahydroindole has a pronounced effect upon the relative ease of electrophilic substitution in the remaining positions. If this substituent is only weakly electron withdrawing (*e.g.*, bromine), the electrophilic substitution can take place in the pyrrole ring. However, a strong electron-withdrawing group such as acetyl or benzenesulfonyl so deactivates the pyrrole ring that electrophilic substitution is favored at C_5. Thus treatment of 2-bromo-4-oxo-4,5,6,7-tetrahydroindole (**5**) with phenyltrimethylammonium tribromide afforded the 2,3-dibromo derivative **9**, whereas this same reagent converted the corresponding 2-acetyl analog **7** into a mixture which contained the 5-bromo derivatives **11** and **12**. No 3-bromo derivatives were found in this mixture. Similar bromination of 1-benzenesulfonyl-4-oxo-4,5,6,7-tetrahydroindole (**26**) gave the 5-bromo derivative **27**.[10] Only 4-chloro-5-carboxaldehyde **28** was obtained upon Vilsmeier–Haack formylation of **26**, even when 2 equiv of phosphorus oxychloride was present.

An interesting variation in the selectivity of bromination was encountered with 2-nitro-4-oxo-4,5,6,7-tetrahydroindole (**6**). When this compound was treated with phenyltrimethylammonium tribromide in tetrahydrofuran, the product was the 5-bromo derivative **13**. In contrast, bromination with this same reagent in dimethylformamide afforded only the 3-bromo isomer **10**. We do not know whether this difference in site of substitution is due to specific solvent effects or merely to dimethylformamide scavenging the HBr needed to promote enolization of the 4-carbonyl group.

Thus far, the electrophilic substitution reactions of a variety of 4-oxo-4,5,6,7-tetrahydroindoles have been described. In order to utilize the products of these reactions for indole synthesis, it was necessary to do certain further chemical transformations and to dehydrogenate to the fully aromatic indoles. The 4-chloro-6,7-dihydro-5-carboxaldehyde system of compounds such as **20a** and **28** provided a convenient entry for new substituents into the 4 position by way of addition–elimination type sequences. Thus the chlorine of **20a** was replaced by a methoxyl group (affording **22**) when it was treated with sodium methoxide. In similar fashion, dimethylamine replaced the chlorine of **28** to give **30**. Unfortunately, this type of transformation was not applicable in all cases. An amine such as methylamine which could react irreversibly with an aldehyde carbonyl tended to do so in preference to displacing the chlorine. For example, methylamine converted **28** into imine **29**.



Dehydrogenation of most of the 6,7-dihydroindoles described above was readily produced by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[11] in dioxane. The conversions of **4a** and **2a** to **4b** and **2b**, respectively have already been mentioned. Additional examples are the dehydrogenations of **20a** and **22** to **23** and **24**, respectively. Recrystallization of the 3,5-dicarboxaldehyde **23** from methanol afforded an acetal derivative **25** in which the 5-formyl group, but not the 3-formyl group, had reacted with the methanol. The structure of this derivative was inferred from comparisons of its ultraviolet absorption spectrum with those of related indole-3- and -5-carboxaldehydes (Experimental Section).

In contrast to 4-oxo-4,5,6,7-tetrahydroindoles substituted with alkyl groups,[1,12] most of the 4-oxo-4,5,6,7-tetrahydroindoles substituted with electron-withdrawing groups could not be dehydrogenated by heating with

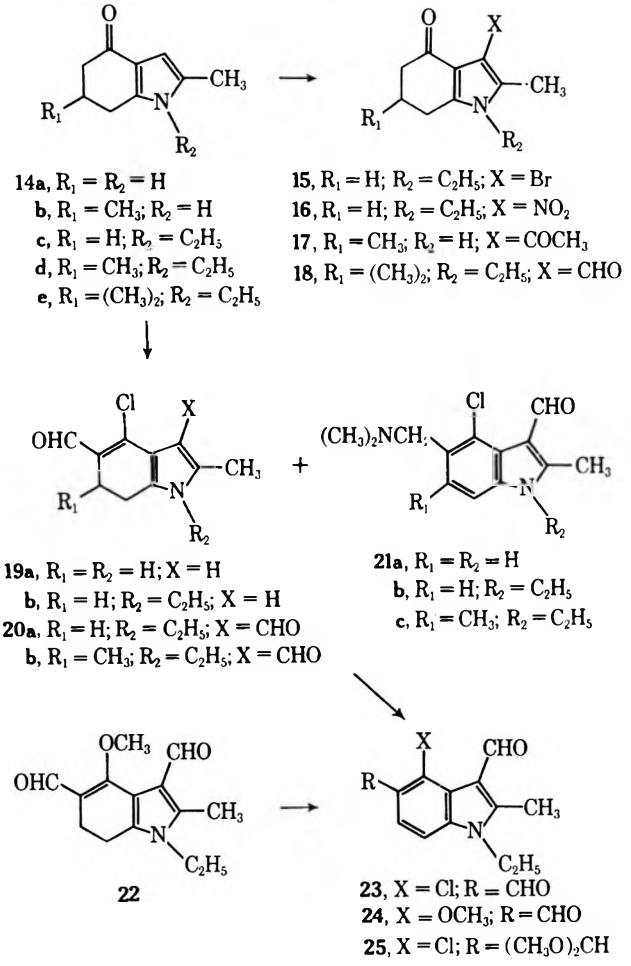
(9) The identification of indole bearing this type of immonium group at C_3 from a Vilsemeier–Haack formylation was reported by G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(10) These 5-bromo-4-oxotetrahedroindoles are important to the preparation of indole derivatives containing heterocycles such as aminothiazole fused to the 4,5 positions (ref 1).

(11) E. A. Braude, A. G. Brooke, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).

(12) S. Hauptmann, H. Blume, G. Hartmann, D. Haendel, and P. Francke, *Z. Chem.*, **6**, 183 (1966).

SCHEME II



palladium on charcoal.[13] They were also resistant to dehydrogenation by DDQ. Thus important limitations are imposed upon the generality of this approach to the synthesis of novel indoles. Although the dehydrobromination of 5-bromo-4-oxo-4,5,6,7-tetrahydroindoles was generally an unsatisfactory procedure, we were able to obtain a small amount of the corresponding 4-hydroxyindole from **27**.[1] Finally, we note that, whereas dehydrogenation of 1-benzyl-4-chloro-6,7-indole-2-carboxaldehyde (**4b**) by DDQ furnished the corresponding 4-chloroindole **2b**, treatment of **4b** with palladium on charcoal in refluxing cumene afforded the related dechlorinated compound, 1-benzylindole-2-carboxaldehyde.

Experimental Section[14a]

4-Chloro-6,7-dihydroindole-2-carboxaldehyde (4a).[14b]—A solution of formylating complex was prepared by dropwise addition of 6.13 g (40 mmol) of phosphorus oxychloride to 30 ml of stirred, ice-cooled *N*,*N*-dimethylformamide (drying tube on apparatus). This complex was then treated with a solution of 5.40 g (40 mmol) of **3a**[15] in 30 ml of *N*,*N*-dimethylformamide. The resulting orange solution was heated on a steam bath for 1 hr,[16] cooled, and poured onto crushed ice. It was then made distinctly basic with 10 *N* NaOH and extracted with methylene chloride (150 ml). This extract was washed with water, dried, and concentrated. The residue was purified by adsorption chromatography on magnesia–silica gel with methylene chloride as solvent. Concentration of the yellow eluate gave, after washing with ether, 1.82 g (25%) of **4a** as pale yellow needles which decomposed above 130°. The decomposition point was unchanged after recrystallization from methylene chloride–hexane: ir 3.05 (NH), 3.53 and 6.05 μ (CHO); uv max 224 mμ (ε 11,000), 257 (8800), 332 (3100); nmr ($CDCl_3$) δ 9.37 (s, CHO), 6.90 (s, pyrrole ring), 5.83 (t, *J* = 4.5 Hz, $CH_2CH{=}C$), 3.0–2.0 ppm (m, 4, CH_2CH_2).

Anal. Calcd for C_9H_8ClNO: C, 59.51; H, 4.44; N, 7.71. Found: C, 59.78; H, 4.33; N, 7.41.

4-Chloroindole-2-carboxaldehyde (2a).—A solution of 908 mg (5 mmol) of **4a** in 20 ml of dioxane was treated portionwise with a solution of 1.35 g (5 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 10 ml of dioxane. After 3 hr the resulting mixture was filtered, the filtrate was concentrated, and the residue was treated with ether. The crude crystalline product was purified by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methanol solvent system.[17] Concentration of eluate corresponding to the major peak detected at 310 mμ afforded 192 mg (21%) of **2a** as pale yellow solid, which had mp 189–192° after recrystallization from CH_2Cl_2–petroleum ether: ir 3.05 (NH), 3.50, 5.95 μ (CHO); uv max 238 mμ (ε 17,400), 307 (22,600); nmr ($CDCl_3$) δ 11.2 (NH), 9.90 (s, CHO), 7.6–7.1 ppm (m, 4, aromatic).

Anal. Calcd for C_9H_6ClNO: C, 60.17; H, 3.37; Cl, 19.73; N, 7.80. Found: C, 60.04; H, 3.46; Cl, 20.24; N, 7.50.

The mixture melting point with authentic 4-chloroindole-3-carboxaldehyde[4] (mp 175–178°) was at 135–143° (droplets 120°). The ir and uv spectra of the two compounds differed; for the 3-carboxaldehyde isomer the uv max were 215 mμ (ε 34,000), 245 (12,100), 267 (7700), 308 (9900).

2-Bromo-4-oxo-4,5,6,7-tetrahydroindole (5).—A solution of 270 mg (2 mmol) of **3a** in 5 ml of tetrahydrofuran was treated dropwise with a solution of 752 mg (2 mmol) of phenyltrimethylammonium tribromide[6] in 3 ml of tetrahydrofuran. After 2 hr the mixture was filtered and the filtrate was concentrated. The residue was treated with CH_2Cl_2 and 5% sodium bicarbonate solution. The organic layer was washed with saline solution, dried, and concentrated, and the residual solid was crystallized from methanol–water. This procedure gave 210 mg (49%) of a white solid: mp 175° dec; ir 3.15 (NH), 6.12 μ (C=O); uv max 213 mμ (ε 32,000), 235 (14,400), 281 (12,300); nmr (DMSO-d_6) δ 11.9 (NH), 6.30 (s, pyrrole), 2.9–1.7 ppm (m, 6, aliphatic).

Anal. Calcd for C_8H_8BrNO: C, 44.89; H, 3.77; Br, 37.34; N, 6.55. Found: C, 44.41; H, 3.66; Br, 37.79; N, 6.52.

2-Acetyl-4-oxo-4,5,6,7-tetrahydroindole (7).—To a stirred, ice-cooled suspension of 405 mg (3 mmol) of **3a** in 10 ml of acetic anhydride was added 0.43 ml (3 mmol) of 70% perchloric acid. An orange solution formed initially, but crystallization then occurred. The crystals of **7** perchlorate (yield 650 mg) were washed with acetic anhydride and ether and dried under vacuum.

Anal. Calcd for $C_{10}H_{12}NO_2 \cdot HClO_4$: C, 43.25; H, 4.36; Cl, 12.77; N, 5.05. Found: C, 43.55; H, 4.73; Cl, 12.61; N, 4.79.

When this crystalline perchlorate was dissolved in water the free base rapidly crystallized. Recrystallization from boiling water gave **7** as pale yellow plates: mp 185–188°; ir 3.25 (NH), 6.02–6.20 μ (broad, two C=O); uv max 224 mμ (ε 15,100), 262 (6300), 297 (14,800); nmr ($CDCl_3$) δ 10.8 (NH), 7.33 (d, *J* = 4.5 Hz, pyrrole), 2.99 (t, 2, CH_2CO), 2.17 ppm (s, 3, CH_3).

When this preparation was repeated on a 4.05-g scale, a 2.05-g (39%) yield of **7**, mp 187–189°, was obtained. The uv spectrum of **7** differs widely from that of the 3-acetyl analog **17**.

6,7-Dihydro-4-methoxy-5*H*-indole Perchlorate (i).[5]—An ice-cooled suspension of 405 mg (3 mmol) of **3a** in 3 ml of methyl orthoformate was treated with 0.43 ml (3 mmol) of 70% perchloric acid. A solution formed immediately and then crystallization occurred. The colorless crystals of i were washed well with ether and dried under vacuum. They then had mp 121–125°: ir 3.1–3.25 (NH), 6.25 (w, C=C?), 8.8, 9.0, and 9.25 μ (all s, ClO_4); nmr (CD_3CN) δ 7.05 (m, pyrrole), 6.74 (m, pyrrole), 4.42 (s, 3, OCH_3), 3.1–2.0 ppm (m, 6, aliphatic).

(13) Hauptmann also noted that 4-oxo-4,5,6,7-tetrahydroindoles substituted with an electron-withdrawing group (carbethoxy) could not be dehydrogenated by palladium on charcoal (ref 12).

(14) (a) General procedures are given in ref 1a; (b) this experiment was first performed by R. H. Roth.

(15) H. Stetter and R. Lauterbach, *Justus Liebigs Ann. Chem.*, **655**, 20 (1962).

(16) Indoles and pyrroles substituted with electron-withdrawing groups require higher temperatures for formylation than do the corresponding unsubstituted compounds; see W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Amer. Chem. Soc.*, **86**, 402 (1964).

(17) For a detailed description of this chromatography procedure (developed by C. Pidacks), see M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

Anal. Calcd for $C_9H_{12}NO \cdot ClO_4$: C, 43.30; H, 4.84; Cl, 14.20; N, 5.61. Found: C, 43.43; H, 4.83; Cl, 14.02; N, 5.52.

2,3-Dibromo-4-oxo-4,5,6,7-tetrahydroindole (9). A. From 3a.—A solution of 270 mg (2 mmol) of **3a** in 3 ml of warm acetic acid was treated dropwise with 320 mg (2 mmol) of bromine. Decolorization was instantaneous. Dilution of the resulting mixture with 7 ml of water caused white crystals to separate. Recrystallization from ethanol–water gave 182 mg (31%) of **9** as white prisms, mp 162–163° dec. Successive recrystallization from CH_2Cl_2–hexane (two times) and methanol gave mp 175° dec: ir 3.1–3.3 (NH), 6.10 μ (C=O); uv max 213 mμ (ε 32,000), 243 (16,000), 282 (8900); nmr (DMSO-d_6) no pyrrole protons, 2.9–1.9 ppm (m, 6, aliphatic).

Anal. Calcd for $C_8H_7Br_2NO$: C, 32.79; H, 2.41; Br, 54.66; N, 4.78. Found: C, 32.74; H, 2.26; Br, 54.72; N, 4.64.

B. From 5.—This preparation was done according to the method described for **5**. From 214 mg of **5** and 376 mg of phenyltrimethylammonium tribromide was obtained 146 mg of a white solid, mp 173° dec, undepressed upon admixture of **9** prepared as described above. The ir spectra of these samples were superimposable.

2-Acetyl-5-bromo-4-oxo-4,5,6,7-tetrahydroindole (11) and 5-Bromo-2-bromoacetyl-4-oxo-4,5,6,7-tetrahydroindole (12).—This preparation was conducted as described for **5**. From 354 mg of **5** and 752 mg of phenyltrimethylammonium tribromide was obtained a viscous oil which was resolved into its components by liquid–liquid partition chromatography on diatomaceous earth with a heptane–ethyl acetate–methanol–water system (70:30:17:4) and recording spectrophotometer set at 300 mμ.[17] Two major and two minor peaks were observed in that order. Concentration of the eluate from the first peak gave 43 mg of **12** as pale yellow solid: mp 183–184° dec after recrystallization from CH_2Cl_2–hexane; ir 3.05 (NH), 5.85 and 6.05 μ (C=O); uv max 235 mμ (ε 8400), 312 (12,300); nmr (DMSO-d_6) δ 12.5 (NH), 7.51 (d, J = 4.5 Hz, pyrrole), 4.80 (t, J = 12 Hz, $COCHBrCH_2$), 4.65 (s, 2, $COCH_2Br$), 3.1–2.7 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{10}H_9Br_2NO_2$: C, 35.85; H, 2.68; N, 4.18. Found: C, 36.32; H, 2.66; N, 4.30.

Concentration of the eluate from the second peak gave, after recrystallization from CH_2Cl_2–hexane, 41 mg of **11** as yellow solid with mp 157–159°: ir 3.05 (NH), 5.85, 6.05 μ (C=O); uv max 230 mμ (ε 13,500), 265 sh (8700), 303 (16,400); nmr (DMSO-d_6) δ 12.0 (NH), 7.29 (d, J = 4.5 Hz, pyrrole), 4.75 (t, J = 12.0 Hz, $COCHBrCH_2$), 3.0–2.4 (m, 4, CH_2CH_2), 2.38 ppm (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.89; H, 3.93; Br, 31.20; N, 5.47. Found: C, 47.13; H, 3.94; Br, 31.09; N, 5.21.

From the third peak was obtained 10 mg of yellow solid, mp 176–177° after recrystallization from CH_2Cl_2–hexane. This solid appeared to be 2-bromoacetyl-4-oxo-4,5,6,7-tetrahydroindole by nmr [(DMSO-d_6) δ 7.39 (d, J = 4.5 Hz, pyrrole), 4.59 (s, 2, $COCH_2Br$), 3.0–2.0 ppm (m, 6, aliphatic)], but it could not be fully characterized. The fourth peak afforded 14 mg of starting material.

2-Nitro-4-oxo-4,5,6,7-tetrahydroindole (6).—A mixture of 540 mg (4 mmol) of **3a** and 3 ml of concentrated sulfuric acid was cooled in an ice–salt mixture and treated portionwise with 340 mg (4 mmol) of sodium nitrate in 3 ml of concentrated sulfuric acid. After this addition was completed, the mixture was stirred for 10 min and then poured onto ice. The product separated as pale tan crystals which were dried in air and recrystallized from methanol–water. This procedure gave 170 mg (24%) of **6** as pale yellow needles: mp 217–272° dec; ir 3.2–3.5 (NH), 6.05 (C=O), 6.65 and 7.40 μ (CNO_2); uv max 221 mμ (ε 12,500), 334 (12,100); nmr (DMSO-d_6) 13.3 (NH), 7.20 (s, pyrrole), 2.81 (t, 2, J = 14 Hz, $COCH_2CH_2$), 2.3–1.9 ppm (m, 4, $COCH_2CH_2CH_2$).

The uv spectra of this **6** differed considerably from that of the 3-nitro analog **16**. In larger scale preparation of **6** yields up to 32% were obtained.

3-Bromo-2-nitro-4-oxo-4,5,6,7-tetrahydroindole (10).—To a solution of 180 mg (1 mmol) of **6** in 2 ml of *N*,*N*-dimethylformamide was added dropwise a solution of 376 mg (1 mmol) of phenyltrimethylammonium tribromide in 0.5 ml of *N*,*N*-dimethylformamide. After 2 hr the resulting solution was diluted with water which caused crystallization of **10** as a white product (180 mg, 69% after it was washed with water and dried under vacuum) that did not melt below 360°. The analytical sample was recrystallized from *N*,*N*-dimethylformamide–water: ir 3.2–3.6 (NH), 6.05 (C=O), 6.65 and 7.40 μ (NO_2); uv max 233 mμ (ε 16,000), 338 (13,000); nmr (DMSO-d_6) δ 13.7 (NH), no pyrrole protons, 2.87 (t, 2, J = 14 Hz, $COCH_2$), 2.6–2.0 ppm (m, 4, $COCH_2CH_2CH_2$).

Anal. Calcd for $C_8H_7BrN_2O_3$: C, 37.10; H, 2.72; N, 10.81. Found: C, 37.44; H, 2.78; N, 10.82.

5-Bromo-2-nitro-4-oxo-4,5,6,7-tetrahydroindole (13).—A solution of 420 mg (2.33 mmol) of **6** in 35 ml of tetrahydrofuran was treated dropwise with a solution of 876 mg (2.33 mmol) of phenyltrimethylammonium tribromide in 3 ml of tetrahydrofuran. After 2 hr the mixture was filtered and the filtrate was concentrated under reduced pressure. The residual solid was washed well with water and ether and dried in air. This procedure gave 550 mg (91%) of **13** as a white solid, which had mp 215° dec after recrystallization from acetone–hexane: ir 3.10 (NH), 5.96 (C=O), 6.65 and 7.40 μ (NO_2); uv max 228 mμ (ε 12,000), 335 ε13,000); nmr (DMSO-d_6) δ 13.7 (NH), 7.35 (s, pyrrole), 4.83 (t, 2, J = 10 Hz, $COCHBrCH_2$), 3.1–2.4 ppm (m, 4, aliphatic).

Anal. Calcd $C_8H_7BrN_2O_3$: C, 37.10; H, 2.72; N, 10.81. Found: C, 36.90; H, 2.36; N, 10.28.

1-Benzyl-4-chloro-6,7-dihydroindole-2-carboxaldehyde (4b).—This compound was prepared by the procedure described for **4a**, except that 2 equiv of phosphorus oxychloride was used. From 4.5 g of **3b**[1] and 3.06 g of phosphorus oxychloride in 21 ml (total) of *N*,*N*-dimethylformamide was obtained 4.76 (88%) of **4b** as a tan solid which had mp 116–119° after recrystallization from ether: ir 3.50 and 6.10 μ (CHO); uv max 251 mμ (ε 10,500), 275 sh (8700), 330 (3000); nmr ($CDCl_3$) ε 9.35 (s, CHO), 7.4–7.0 (m, 5, phenyl), 6.85 (s, pyrrole), 5.60 (t, J = 4.5 Hz, CH_2-$CH{=}CCl$), 5.5 (s, 2, benzylic), 2.8–2.5 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.71; H, 5.19; Cl, 13.05; N, 5.15. Found: C, 70.76; H, 5.71; Cl, 13.06; N, 5.40.

1-Benzyl-4-oxo-4,5,6,7-tetrahydroindole-2-carboxaldehyde (8).—In one of four attempts to prepare **4b** from **3b**, a different product **8** was obtained upon work-up of the reaction mixtures. From 9.0 g of **3b** and 12.2 g of phosphorus oxychloride was obtained 6.71 g (66%) of **8** as a pale yellow crystals, mp 110–114°. Recrystallization from CH_2Cl_2–hexane gave mp 114–116°: ir 6.05 μ (C=O); uv max 234 mμ (ε 15,000), 260 inflection (7100), 298 (12,000); nmr (DMSO-d_6) δ 9.59 (s, CHO), 7.40 (s, pyrrole), 7.3–6.9 (m, 5, phenyl), 5.61 (s, 2, benzylic), 2.75 (t, 2, J = 14 Hz, $COCH_2$), 2.5–1.9 ppm (m, 4, aliphatic).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; N, 5.97. Found: C, 75.66; H, 6.14.

1-Benzyl-4-chlorindole-2-carboxaldehyde (2b). A. From 4b.—Solutions of 554 mg (2 mmol) of **4b** in 8 ml of dioxane and 455 mg (2 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 4 ml of dioxane were combined. After 30 min the mixture was filtered and the filtrate was concentrated. The residual solid was extracted with ether–hexane. Upon concentration, this extract gave pale yellow crystals, mp 85–92°, which were nearly identical in ir spectra with **2b** prepared below. Purification by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methanol solvent system and recording spectrophotometer set at 300 mμ gave, after concentration of the eluate from the main peak, pale yellow crystals, mp 94–96°, undepressed upon admixture of **2b** prepared as described below. The ir spectra of these two samples were superimposable.

B. From 1.—To a suspension of 860 mg (7.5 mmol) of potassium *tert*-butoxide in 30 ml of dry benzene was added a slurry of 1.57 g (7.5 mmol) of methyl 4-chloroindole-2-carboxylate. The mixture was stirred at reflux temperature for 1 hr, cooled, and treated with 950 mg (7.5 mmol) of benzyl chloride. This mixture was heated 16 hr at reflux temperature, cooled, and poured into water. The benzene layer was washed with water, dried, and concentrated to a viscous oil which gave white crystals of starting material upon trituration with ether. The ether phase was decanted and concentrated to a colorless oil. This oil, after purification by adsorption chromatography on magenesia–silica gel, weighed 1.2 g and showed no NH stretch in the ir.

Without further purification, this sample of **1** was dissolved in 5 ml of ether and treated with 150 mg of lithium aluminum hydride, added in small portions. After 1 hr the mixture was treated with water and the ether layer was washed with water, dried, and concentrated. Recrystallization of the residual solid from ether–hexane gave 398 mg (37% from **1**) of the corresponding alcohol as white prisms: mp 95–97°; ir 2.9 μ (OH), no carbonyl; nmr (DMSO-d_6) ε 7.5–6.8 (m, 8, phenyl and indole benzene ring), 6.50 (s, pyrrole), 5.50 (s, 2, benzylic), 5.41 (t, J = 6 Hz, CH_2OH), 4.63 ppm (d, 2, J = 6 Hz, CH_2OH).

Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.71; H, 5.19; Cl, 13.05; N, 5.15. Found: C, 70.77; H, 5.10; Cl, 13.32; N, 5.44.

A solution of 50 mg of this alcohol in 10 ml of ether was stirred with 300 mg of manganese dioxide for 16 hr. The mixture was filtered and the filtrate was concentrated, affording a viscous oil that crystallized upon scratching. Two recrystallizations from ether–hexane gave **2b** as pale yellow prisms: mp 93–96°; ir 3.50, 6.0 μ (CHO); uv max 239 mμ (ε 17,000), 307 (21,000), 340 (5700) inflection; nmr (DMSO-d_6) δ 10.0 (s, CHO), 7.59 (s, pyrrole), 7.4–7.0 (m, 8, phenyl and indole benzene ring), 5.87 ppm (s, 3, benzylic), no aliphatic protons.

Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.49; Cl, 13.14; N, 5.19. Found: C, 70.65; H, 4.49; Cl, 13.36; N, 5.51.

3-Bromo-1-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydroindole (15).—This compound was prepared by the procedure described for **5**. From 885 mg of **14c**[18] was obtained 810 mg (64%) of **15** as white needles: mp 96–98° after recrystallization from hexane; ir 6.0 μ (C=O); uv max 254 mμ (ε 11,000), 284 (4600); nmr ($CDCl_3$) showed no pyrrole hydrogen.

Anal. Calcd for $C_{11}H_{14}BrNO$: C, 51.58; H, 5.51; N, 5.47. Found: C, 51.83; H, 5.49; N, 5.45.

1-Ethyl-2-methyl-3-nitro-4-oxo-4,5,6,7-tetrahydroindole (16).—This compound was prepared by the procedure described for **6**. From 1.06 g of **14c**[18a] was obtained 1.01 g (76%) of **16** as a tan solid, mp 125–127°. Recrystallization from methanol gave yellow needles: mp 140–142°; ir 5.95 (C=O), 6.65 and 7.40 μ (NO_2); uv max 215 mμ (ε 18,700), 245 (6700), 279 (5800), 320 (4700); nmr (DMSO-d_6) showed no pyrrole proton.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.44; H, 6.50; N, 12.52.

4-Chloro-1-ethyl-6,7-dihydro-2-methylindole-5-carboxaldehyde (19b).—This compound was prepared by the procedure described for **4a**. From 1.77 g of **14c** was obtained a dark semisolid which was purified by adsorption chromatography on magnesia–silica gel with CH_2Cl_2 as solvent. Concentration of the yellow eluate gave **19b** as a yellow solid which was recrystallized from ether–hexane. It then weighed 124 mg (6%) and had mp 105–107°: ir 3.50, 6.15 μ (OCHC=C); uv max 237 mμ (ε 8100), 250 (6300), 310 (6000), 390 (15,000); nmr ($CDCl_3$) δ 10.2 (s, CHO), 6.25 (s, pyrrole), 3.90 (q, 2, J = 16 Hz, NCH_2CH_3), 2.82 (broad s, 4, CH_2CH_2), 2.25 (s, 3, C=CCH_3), 1.27 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.42; N, 6.31; Cl, 15.85; N, 6.25. Found: C, 64.70; H, 6.35; Cl, 15.73; N, 6.06.

4-Chloro-5-(dimethylaminomethyl)-1-ethyl-2-methylindole-3-carboxaldehyde (21b) and 4-Chloro-1-ethyl-6,7-dihydro-2-methylindole-3,5-dicarboxaldehyde (20a).—These compounds were prepared by the procedure described for **4b**. From 10.62 g of **14c** and 12 ml of phosphorus oxychloride was obtained, following the sodium hydroxide treatment, a mixture which was extracted with 300 ml of CH_2Cl_2. This extract was shaken with 150 ml of water containing 15 ml of 3 *N* HCl. The layers were separated and the acidic layer was basified with NaOH and extracted with CH_2Cl_2. This extract was washed with saline, dried, and concentrated. Recrystallization of the residue from methanol afforded 4.69 g (28%) of **21b** as white prisms: mp 95–96°; ir 3.50, 6.08 μ (CHO); uv max 222 mμ (ε 34,000), 248 (10,500), 274 (7400), 315 (1100); nmr ($CDCl_3$) 11.2 (s, CHO), 7.23 (d, J = 8 Hz, ortho aromatic), 7.10 (d, J = 8 Hz, ortho aromatic), 4.73 (q, 2, J = 16 Hz, NCH_2CH_3), 3.65 (s, 2, HCH_2C=C), 2.86 (s, 3, C=CCH_3), 2.23 (s, 6, $N(CH_3)_2$), 1.39 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{15}H_{19}ClN_2O$: C, 63.31; H, 6.85; Cl, 12.72; N, 10.05. Found: C, 63.94; H, 6.89; Cl, 12.81; N, 9.81

The organic layer from the HCl treatment was washed with dilute sodum bicarbonate solution, dried, and concentrated, and the residue was purified by absorption chromatography on magnesia–silica gel with CH_2Cl_2 as solvent. The yellow eluate was concentrated and the residual solid was recrystallized from methanol. This procedure gave 2.10 g (14%) of **20a** as yellow prisms: mp 128–135°; ir 3.50, 6.10 μ (CHO); uv max 228 mμ (ε 28,000), 306 (9000), 375 (15,000); nmr ($CDCl_3$ δ 10.7 (s, CHO), 10.4 (s, CHO), 4.03 (q, 2, J = 16 Hz, NCH_2CH_3), 2.80 (broad s, 4, CH_2CH_2), 2.65 (s, 3, C=CCH), 1.35 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.04; H, 5.21; Cl, 14.09; N, 5.57. Found: C, 61.61; H, 5.51; Cl, 14.50; N, 5.72.

4-Chloro-5-(dimethylaminomethyl)-1-ethyl-2,6-dimethylindole-3-carboxaldehyde (21c) and 4-Chloro-1-ethyl-6,7-dihydro-2,6-dimethylindole-3,5-dicarboxaldehyde (20b).—These compounds were prepared by the procedure described for **21b** and **20a**. From 11.46 g of **14c** and 12 ml of phosphorus oxychloride was obtained from the acidic extract, after recrystallization from methanol, 5.37 g (31%) of **21c** as white prisms: mp 108–110°; ir and uv spectra closely related to **21b**; nmr differed from **21b** only by replacement by CH_3 (s, ε 2.45 ppm) of the hydrogen at C_6. The proton at C_7 was now s, δ 7.7 ppm.

Anal. Calcd for $C_{16}H_{21}ClNO_2$: C, 65.63; H, 7.23; Cl, 12.11; N, 9.57. Found: C, 65.47; H, 7.43; Cl, 12.51; N, 9.35.

From the neutral extract was obtained 1.78 g (11%) of **20b** as yellow plates, mp 110–113°. Recrystallization from CH_2Cl_2–ether–hexane gave mp 120–122°: ir and uv spectra closely related to **20a**; nmr differed from **20a** only by replacement by CH_3 (d, J = 8 Hz at δ 1.00 ppm) of one hydrogen at C_6. The remaining hydrogen at C_6 was now a multiplet at δ 3.30 ppm.

Anal. Calcd for $C_{14}H_{16}ClNO_2$: C, 63.27; H, 6.07; Cl, 13.35; N, 5.27. Found: C, 63.59; H, 6.36; Cl, 13.60; N, 5.27.

4-Chloro-1-ethyl-2-methylindole-3,5-dicarboxaldehyde (23).—This compound was prepared by the procedure described for **2b** from **4b**. From 103 mg of **20a** was obtained 318 mg (70%) of **23** as white crystals, mp 157–159°. Recrystallization from hexane gave mp 160°: ir 3.35, 3.50, 5.9, 6.05 μ (CHO); uv max 253 mμ (ε 32,000), 307 (11,000), 331 (6600); nmr ($CDCl_3$) δ 10.9 (s, CHO), 10.5 (s, CHO), 7.79 (d, J = 8 Hz, ortho aromatic) 7.37 (d, J = 8 Hz, ortho aromatic), 4.25 (q, 2, J = 16 Hz, NCH_2CH_3), 2.87 (s, 3, C=CCH_3), 1.41 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.52; H, 4.84; N, 5.61. Found: C, 62.19; H, 4.41; N, 5.39.

1-Ethyl-6,7-dihydro-4-methoxy-2-methylindole-3,5-dicarboxaldehyde (22).—A mixture of 300 mg (1.2 mmol) of **20a**, 84 mg (1.5 mmol) of sodium methoxide, and 15 ml of methanol was kept at room temperature for 3 days and concentrated, and the residue was treated with CH_2Cl_2 and water. The organic layer was washed with water, dried, and concentrated, whereupon the residue crystallized. Recrystallization from methanol–water gave 137 mg (45%) of **22** as white plates: mp 110–120°; ir 3.4, 3.5, 6.1 μ (CHO); uv max 235 mμ (ε 24,000), 300 (10,500), 368 (21,000).

Anal. Calcd for $C_{14}H_{17}NO_3 \cdot H_2O$: C, 63.38; H,7.22; N, 5.28. Found: C, 63.86; H, 7.60; N, 5.73.

1-Ethyl-4-methoxy-2-methylindole-3,5-dicarboxaldehyde (24).—This compound was prepared by the procedure described for **2a**. From 103 mg of **22** was obtained 62 mg of a white solid, mp 168–176°. This solid was purified by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methanol system and recording spectrophotometer set at 305 mμ.[17] Concentration of the eluate from the major (second) peak gave 25 mg (25%) of **24** as white prisms: mp 186–190°; ir 3.3, 3.5, 5.95, 6.00 μ (CHO); uv max 251 mμ (ε 33,000), 305 (6900), 337 (4900); nmr ($CDCl_3$) δ 10.5 (s, CHO), 10.4 (s, CHO), 7.71 (d, J = 8 Hz, ortho aromatic), 7.20 (d, J = 8 Hz, ortho aromatic), 4.25 (q, 2, J = 16 Hz, NCH_2CH_3), 4.03 (s, 3, OCH_3), 2.87 (s, 3, C=CCH_3), 1.41 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.52; H, 5.89; N, 5.80.

2-Acetonyl-5,5-dimethylcyclohexane-1,3-dione.—A suspension of 70 g (0.5 mol) of dimedone in 175 ml of methanol was treated with a solution of 28 g (0.5 mol) of potassium hydroxide in 50 ml of water. The resulting solution was cooled in an ice bath and treated with 46.3 g (0.5 mol) of chloroacetone. After 3 days the mixture was filtered and the filtrate was concentrated. The residual solid was dissolved in sodium hydroxide solution (pH 10), washed two times with CH_2Cl_2, and acidified (pH 2). The precipitated solid was dissolved in 300 ml of CH_2Cl_2 and this solution was dried and concentrated on a steam bath as hexane was added. Cooling when the first crystals appeared afforded 62 g (63%) of white crystals, mp 134°.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.08; H, 8.17.

1-Ethyl-2,6,6-trimethyl-4-oxo-4,5,6-tetrahydroindole (14e).—A mixture of 39.2 g of 2-acetonyl-5,5-dimethylcyclohexane-1,3-dione, 36.0 g of ethylamine, and 150 ml of methanol was heated in a steel pressure vessel at 150° for 2 hr, cooled, and concentrated under reduced pressure, whereupon partial crystallization ensued. The crystals were filtered free of adhering dark viscous liquid and recrystallized two times from cyclohexane. Re-

(18) (a) W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, **88**, 804 (1966); (b) R. H. Roth, W. A. Remers, and M. J. Weiss, *J. Org. Chem.*, **31**, 1012 (1966).

crystallization of the resulting material (low yield, mp 94–100°) from methanol–water gave **14e** as white crystals: mp 97–103°; ir 6.07 μ (C=O); uv max 254 mμ (ε 9200), 290 (6300).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.11; H, 9.11; N, 6.81.

1-Ethyl-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindole-3-carboxaldehyde (18).—This compound was prepared by the procedure for **4b**. From 6.15 g of **14e** and 6 ml of phosphorus oxychloride was obtained, after adsorption chromatography on magnesia–silica gel with CH_2Cl_2 as solvent and recrystallization from CH_2Cl_2–ether–hexane, 1.57 g (27%) of **18** as yellow crystals, mp 138–141°. Another such recrystallization gave mp 147–149.5°: ir 3.5, 6.0, 6.05 μ (CHO and C=O); uv max 218 mμ (ε 21,500), 244 (6800), 279 (8000), 303 (8300).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.75; H, 8.17; N, 6.09.

3-Acetyl-2,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindole (17).—An ice-cooled suspension of 401 mg (2.5 mmol) of **14b**[15] in 4 ml of acetic anhydride was treated with 0.36 ml (2.5 mmol) of 70% perchloric acid. A clear solution formed, but the perchlorate salt not be induced to crystallize from it. The mixture was poured into ice water, where crystallization resulted following hydrolysis of the acetic anhydride. The white crystals were dried in air and recrystallized from 10 ml of methanol to give 270 mg (525) of **17** with mp 201–207°. Another recrystallization gave mp 203–206°: ir 3.1–3.4 (NH), 6.0, 6.1 μ (C=O); uv max 239 mμ (ε 6000), 268 (7500), 293 (8700); nmr (DMSO-d_6) δ no pyrrole proton, 2.41 (s, 3, CH_3), 2.25 (s, 3, CH_3), 2.8–2.0 (m, 5, $CH_2CH_2CH_2$), 1.17 ppm (d, 3, J = 12 Hz, $CHCH_3$).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.65; H, 7.42; N, 6.67.

4-Chloro-6,7-dihydro-2-methylindole-5-carboxaldehyde (19a).—This compound was prepared by the procedure described for **4a**. From 5.96 g of **14a**[15] and 6.12 g of phosphorus oxychloride was obtained 1.07 g of an amber oil. Purification of this oil by liquid–liquid partiton chromatography on diatomaceous earth with a heptane–ethyl acetate–methanol–water system (70:30:17:4) and recroding spectrophotometer set at 296 mμ gave upon concentration of the eluate from the second major peak (holdback volume 1.0–2.0) 205 mg of **19a** as a yellow solid. This product had mp 122–124° dec after two recrystallizations from methanol–water: ir 3.05 (NH), 3.4, 3.5, 6.15 μ (OHCC=C); uv max 233 mμ (ε 12,000), 302 (6500), 387 (13,500).

Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.38; H, 5.15; Cl, 18.12; N, 7.16. Found: C, 61.85; H, 5.47; Cl, 18.05; N, 6.96.

4-Chloro-5-(dimethylaminomethyl)-2-methylindole-3-carboxaldehyde (21a).—This compound was prepared by the procedure described for **23a** and **24a**. From 745 mg of **14a**[15] was obtained, following work-up of the acid extract and two recrystallizations from methanol, 30 mg (2.4%) of **21a** as white plates: mp 164–164.5°; ir 3.15 (NH), 3.55, 3.60, 6.07 μ (CHO); uv max 222 mμ (ε 22,000), 247 (12,500), 272 (9400), 310 (11,000).

Anal. Calcd for $C_{13}H_{15}ClN_2O$: C, 62.27; H, 6.03; Cl, 14.15. Found: C, 61.82; H, 6.39; Cl, 14.33.

From the neutral fraction was obtained 2 mg of yellow solid that decomposed above 180° and had an uv spectrum [235 mμ (ε 13,200), 302 (8000), 375 (8800)] which closely resembled that of **20a**; however, complete characterization was not possible.

1-Benzenesulfonyl-4-chloro-6,7-dihydroindole-5-carboxaldehyde (28).—This compound was prepared by the procedure described for **4b**. From 11.0 g of **26**[15a] and 12.3 g of phosphorus oxychloride was obtained 5.8 g (45%) of **28** as a nearly white solid, mp 150–154°. Recrystallization from acetone–hexane gave colorless prisms: mp 150–154°; ir 3.5 6.02 μ (CHO); uv max 228 mμ (ε 18,000), 265 sh (7200), 346 (9800); nmr ($CDCl_3$) δ 10.0 (s, CHO), 7.25 (d, J = 4 Hz, pyrrole), 6.50 (d, J = 4 Hz, pyrrole), 3.2–2.2 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{15}H_{12}ClNO_3S$: C, 56.01; H, 3.76; Cl, 11.02; N, 4.35; S, 9.96. Found: C, 56.31; H, 3.66; Cl, 11.18; N, 4.31; S, 10.01.

1-Benzenesulfonyl-4-(dimethylamino)-6,7-dihydroindole-5-carboxaldehyde (30).—A solution of 324 mg of **28** in 20 ml of tetrahydrofuran was saturated with dimethylamine. After 20 hr the mixture was filtered and the filtrate was diluted with CH_2Cl_2 and shaken with water. The organic layer was dried and concentrated to an oil which crystallized upon trituration with ether. These crystals weighed 166 mg (50%) and had mp 113–117°. Two recrystallizations from CH_2Cl_2–hexane gave **30** as yellow prisms: mp 138–139°; ir 3.5, 6.25 μ (OHCC=CN); uv max 252 mμ (ε 8200), 318 (6400), 405 (14,000); nmr ($CDCl_3$); nmr ($CDCl_3$) δ 9.69 (s, CHO), 8.0–7.5 (m, 5, phenyl), 7.29 (d, J = 4 Hz, pyrrole), 6.45 (d, J = 4 Hz, pyrrole), 3.21 (s, 6, $N(CH_3)_2$), 2.70 ppm (broad s, 4, CH_2CH_2).

Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.79; H, 5.49; N, 8.48; S, 9.71. Found: C, 61.89; H, 5.69; N, 8.10; S, 9.70.

1-Benzenesulfonyl-4-chloro-6,7-dihydro-5-(*N*-methylformididoyl)indole (29).—A solution of 324 mg of **28** in 15 ml of methanol was treated with excess methylamine. After 2 days the mixture was filtered and the tan crystalline product, 225 mg (69%), mp 158–159°, was recrystallized from CH_2Cl_2–hexane. This procedure gave **29** as yellow prisms: mp 158–159°; ir 3.5, 6.2 μ (N=CHC=C); uv max 227 mμ (ε 14,000), 265 sh (5300), 330 (8400).

Anal. Calcd for $C_{16}H_{15}ClN_2O_2S$: C, 57.40; H, 4.52; N, 8.37; S, 9.58. Found: C, 57.48; H, 4.89; N, 8.54; S, 9.45.

4-Chloro-1-ethyl-2-methylindole-3,5-dicarboxaldehyde-5-(dimethylacetal) (25).—In one experiment **23** was prepared from **20a** as described above; however, the crude product was recrystallized from hot methanol. This procedure gave the corresponding 5-dimethylacetal **25** as white needles: mp 141–143°; ir 3.5, 6.12 μ (CHO); uv max 224 mμ (ε 34,000), 247 (16,500), 275 (10,000), 315 (12,000); nmr ($CDCl_3$) δ 11.1 (CHO), 7.67 (d, J = 8 Hz, ortho aromatic), 7.37 (d, J = 8 Hz, ortho aromatic), 5.91 (s, $CH(OCH_3)_2$), 4.19 (q, 2, J = 16 Hz, NCH_2CH_3), 3.50 (s, 6, $(OCH_3)_2$), 2.87 (s, 3, CH_3), 1.40 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{15}H_{18}ClNO_3$: C, 60.92; H, 6.13; Cl, 11.99. Found: C, 61.27; H, 6.61; Cl, 12.59.

The uv spectrum of **25** closely resembled that of **21b** but differed considerably from that of 1-ethyl-4-hydroxy-2-methylindole-5-carboxaldehyde[1a] [uv max 245 mμ sh (ε 24,500), 261 (36,500), 290 (11,000), 305 (15,000)] which suggests that the acetal was formed selectively by the 5-carboxaldehyde.

1-Benzylindole-2-carboxaldehyde 2,4-Dinitrophenylhydrazone.—A mixture of 544 mg of **4b**, 125 mg of 10% palladium on charcoal, and 8 ml of cumene was stirred 2 hr at reflux temperature, cooled, filtered, and concentrated under reduce pressure. The oily residue (370 mg) gave a negative Beilstein test. A 312-mg portion of it was dissolved in 30 ml of hot ethanol and treated with 264 mg of 2,4-dinitrophenylhydrazine in 0.3 ml of concentrated HCl. The mixture was boiled for 5 min and cooled, and the brick-red solid product was washed with cold ethanol. Recrystallization from methanol–pyridine gave dark red prisms: mp 237–249°; uv max 315 mμ (ε 12,000), 405 (31,000); nmr (DMF-d_7) 10.2 (s, NH), 9.03 (s, C=CCHN), 8.91 (s, J = 3 Hz), 8.25 (dd, J = 3, J = 8 Hz), 7.67 (d, J = 8 Hz, protons on dinitrophenylhydrazinyl benzene ring), 7.29 (m, 10, protons on indolyl and phenyl rings), 6.11 ppm (s, 2, benzylic).

Anal. Calcd for $C_{22}H_{17}N_5O_4$: C, 63.61; H, 4.13; N, 16.86. Found: C, 63.06; H, 4.27; N, 16.90.

Registry No.—**2a,** 27932-08-7; **2b,** 18603-30-0; **4a,** 18518-43-9; **4b,** 4657-77-6; **5,** 27784-79-8; **6,** 27784-80-1; **7,** 27784-81-2; **7** perchlorate, 27784-82-3; **8,** 27784-83-4; **9,** 24836-93-9; **10,** 27784-85-6; **11,** 27784-86-7; **12,** 27784-87-8; **13,** 27784-88-9; **14e,** 27784-89-0; **15,** 27784-90-3; **16,** 27784-91-4; **17,** 27784-92-5; **18,** 27784-93-6; **19a,** 18518-54-2; **19b,** 4657-74-3; **20a,** 4657-75-4; **20b,** 18518-60-0; **21a,** 27784-98-1; **21b,** 4657-76-5; **21c,** 27932-10-1; **22,** 4657-78-7; **23,** 4583-54-4; **24,** 4660-03-1; **25,** 27787-33-3; **28,** 4583-62-4; **29,** 18518-56-4; **30,** 4657-79-8; i, 27787-37-7; alcohol melting at 95–97°, 27787-38-8; 2-acetonyl-5,5-dimethylcyclohexane-1,3-dione, 13148-87-3; 1-benzylindole-2-carboxaldehyde 2,4-DNP, 27787-40-2.

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Quinazolines and 1,4-Benzodiazepines. L.[1] The Ring Contraction of 4-Hydroxy-5-phenyltetrahydro-1,4-benzodiazepines to Tetrahydroquinoxalines

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4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines have been shown to dehydrate to the corresponding 2,3-dihydro derivatives or to ring contract to 1,2,3,4-tetrahydroquinoxalines. The extent of dehydration *vs.* ring contraction depends on the reagents used and on the substituents on the benzodiazepine nucleus. These effects and possible mechanisms are discussed.

In connection with other work, we were able to show that, by generating a carbanion at the 5 position of 4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines[2] with base, imine formation occurs with elimination of hydroxyl ion to give the corresponding 2,3-dihydrobenzodiazepines[3] in good yield. In an attempt to effect this dehydration with other reagents, *e.g.*, the phosphorus halides and thionyl chloride, we observed cleavage of the hydroxylamine and rearrangement. Two products were isolated from the reaction mixture and were identified as benzaldehyde and 1,2,3,4-tetrahydroquinoxaline.

This ring contraction was applied to the preparation of a few unsymmetrically substituted racemic tetrahydroquinoxalines, compounds **3a–d**. The starting hydroxylamines **1**, of unknown stereochemistry, were obtained by reduction of the corresponding 1,4-benzodiazepin-2-one 4-oxides **9a–d** with lithium aluminum hydride. These compounds were prepared in turn by alkylating the 3-sodio derivative of the known compound **9b**[4] with the appropriate alkyl halide.

This reaction constitutes another novel C to N migration[5] and may be considered to be an extension of a Stieglitz-type of rearrangement.[6] A plausible mechanism is given in Scheme I, in which the first step is shown as esterification of the 4-hydroxy group. This would result in an increase in the electron deficiency of the 4-nitrogen. Rupture of the N–O bond with concerted migration of the C_5–C_{11} bond would generate the carbonium ion A stabilized through the corresponding immonium ion C. The existence of the intermediate ions B or C was confirmed by the isolation of the 4-benzyltetrahydroquinoxaline **4** from a reductive work-up of the reaction mixture. Hydrolytic work-up led to the tetrahydroquinoxaline **3** and benzaldehyde.

Interestingly, the electron-releasing aniline nitrogen is necessary for the success of this rearrangement. When 1-acetyl-7-chloro-4-hydroxy-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**6**) (Scheme II) was treated with phosphorus oxychloride, only dehydration was observed and compound **7** was isolated.

This fact may help explain the different extent of dehydration observed with compound **1a** *vs.* **1b** upon reaction with thionyl chloride. Chlorosulfination of the aniline nitrogen of **1a** would decrease its electron-donating capacity, thus favoring elimination rather than rearrangement. Chlorosulfination of the aniline nitrogen is not possible with **1b** and accordingly the amount of dehydration product observed is negligible.

The same ring contraction along with some dehydration could also be effected by phenyl isocyanate. When compound **1b** was refluxed in toluene with an excess of phenyl isocyanate, the urea derivative **8** was the major product obtained. A possible mechanism for this example is given in Scheme III.

Experimental Section

Melting points were determined microscopically on a hot stage. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer; nmr spectra were recorded with a Varian A-60 instrument. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–325 mesh) was used for chromatography. Petroleum ether refers to a fraction of bp 30–60°.

7-Chloro-1,3-dihydro-1,3-dimethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (9c).—Potassium *tert*-butoxide (23 g, 0.2 mol) was added to a solution of 50 g (0.167 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**9b**)[4] in 250 ml of dry dimethylformamide cooled to 0°. The mixture was stirred for 5 min in a nitrogen atmosphere, 12.5 ml (28.6 g or 0.2 mol) of methyl iodide was added, and stirring was continued for 10 min without cooling. The reaction mixture was diluted with ice–water. The precipitated crystals were collected, washed with water, and recrystallized from ethanol to yield 38.6 g (73%) of product with mp 185–188°: nmr ($CDCl_3$) δ 1.68 (d, 3, J = 6.5 Hz, C_3CH_3), 3.50 (s, 3, NCH_3), 4.43 (q, 1, J = 6.5 Hz, C_3H); ir ($CHCl_3$) 1680 cm^{-1} (C=O); uv max 237 mμ (ϵ 30,000), 311 (11,200).

Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.77; H, 4.85; N, 8.86.

3-Benzyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (9d).—A solution of 60 g (0.2 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**9b**)[4] in 400 ml of dimethylformamide was cooled to −20°. Potassium *tert*-butoxide (28 g, 0.25 mol) was added with stirring under nitrogen. The mixture was stirred for 10 min and then cooled to −40° when 31.6 g (0.25 mol) of benzyl chloride was added. The temperature was allowed to rise to room temperature. After stirring for 2 hr, the reaction mixture was quenched with ice–water. The precipitate was collected, washed with water, and dissolved in methylene chloride. The solution was dried over sodium sulfate, filtered, and evaporated. Crystallization of the residue from ether yielded 46 g (59%) of product. The analytical sample was recrystallized from methanol and melted at 180–182°: nmr ($CDCl_3$) δ 3.46 (s, 3, NCH_3), 4.48 (t, 1, J = 6.5 Hz, C_3H).

Anal. Calcd for $C_{23}H_{19}ClN_2O_2$: C, 70.68; H, 4.90; N, 7.17. Found: C, 70.47; H, 5.09; N, 7.19.

7-Chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (1b).—7-Chloro-1,3-dihydro-1-methyl-5-

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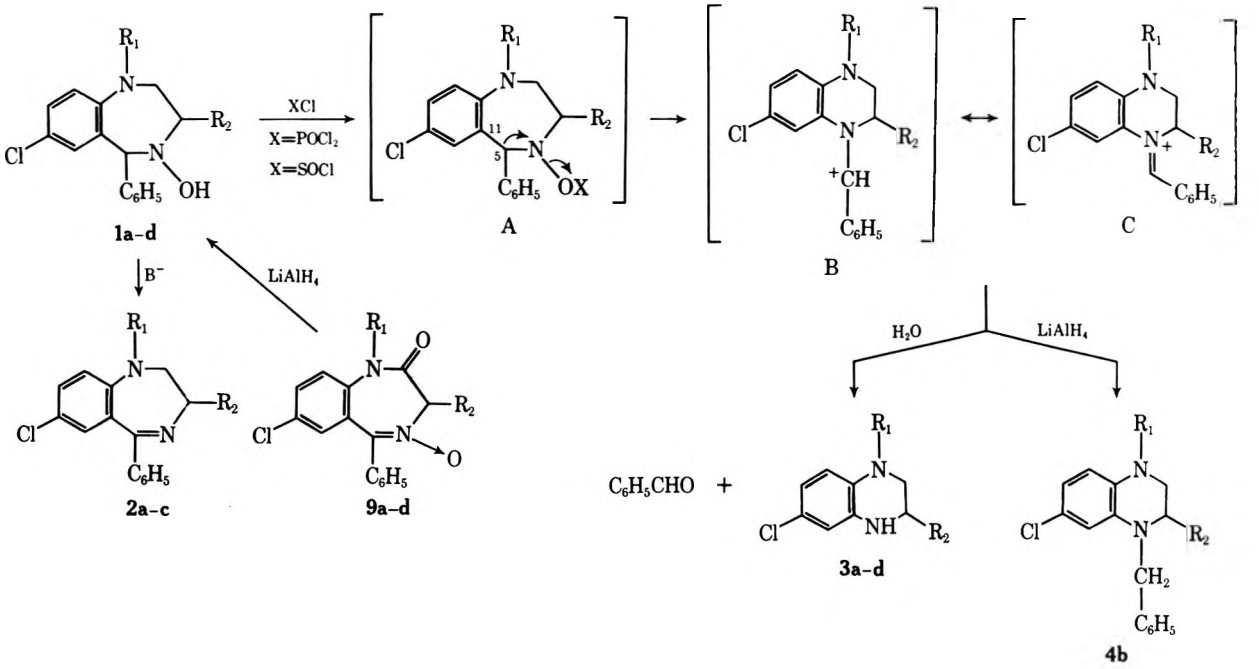
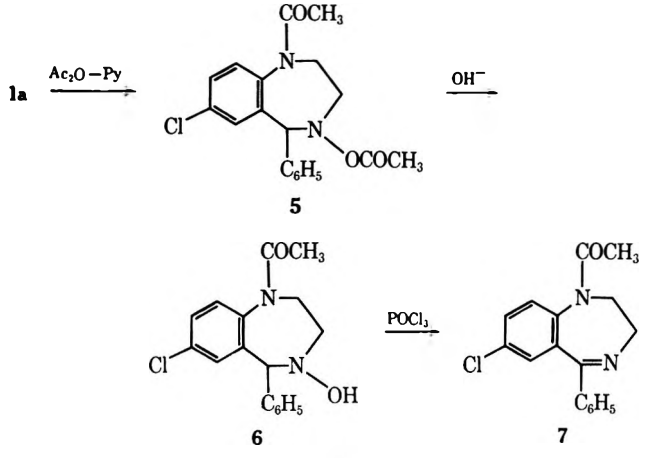
SCHEME I

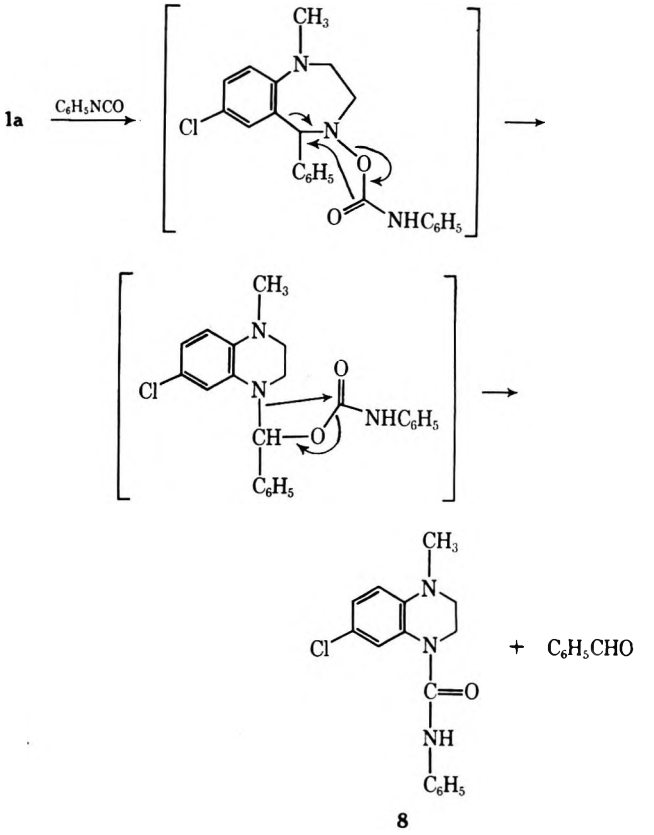


a, $R_1, R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1, R_2 = CH_3$
d, $R_1 = CH_3$; $R_2 = CH_2C_6H_5$

SCHEME II



SCHEME III



phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (9b)[4] (20 g, 0.066 mol) was added in portions to a suspension of 6 g of lithium aluminum hydride in 250 ml of ether. After addition, the mixture was refluxed for 4 hr and hydrolyzed by the careful addition of 30 ml of water. The inorganic material was filtered off and washed well with benzene. The filtrate was evaporated and the residue was crystallized from methanol with seeding to yield 10 g (52%) of product with mp 138–140°. Seeds were obtained by chromatographic purification of part of the crude product on a 30-fold amount of silica gel using 10% (v/v) ethyl acetate in methylene chloride for elution. Recrystallization from methanol raised the mp 141–143°.

Anal. Calcd for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.28; H, 5.88; N, 9.63.

7-Chloro-1,3-dimethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (1c).—7-Chloro-1,3-dihydro-1,3-dimethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (9c) (50 g, 0.16 mol) was reduced as above with 17 g of lithium aluminum hydride in 800 ml of ether. The usual work-up followed by crystallization from ether–petroleum ether yielded 36 g (75%) of the hydroxylamine: mp 135–136°; nmr ($CDCl_3$) δ 1.14 (d, 3, J = 6 Hz, C_3 CH_3), 2.89 (s, 3, NCH_3), 4.87 (broad s, 1, OH), 5.46 (s, 1, C_5 H); uv max 265 mμ (ϵ 10,800), inflection 300 (2300).

Anal. Calcd for $C_{17}H_{19}ClN_2O$: C, 67.43; H, 6.32; N, 9.25. Found: C, 67.44; H, 6.41; N, 9.42.

3-Benzyl-7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (1d).—3-Benzyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (9d) (39 g, 0.1 mol) was added to a suspension of 20 g (0.5 mol) of lithium aluminum hydride in 500 ml of ether. The mixture was

refluxed for 2 hr. Regular work-up followed by crystallization from methylene chloride–hexane gave 30.6 g (81%) of product with mp 140–143°: nmr ($CDCl_3$) δ 2.83 (s, 3, NCH_3), 4.97 (s, 1, OH), 5.47 (s, 1, C_5 H).

Anal. Calcd for $C_{23}H_{23}ClN_2O$: C, 72.91; H, 6.12; N, 7.39. Found: C, 72.90; H, 6.11; N, 7.59.

6-Chloro-1,2,3,4-tetrahydroquinoxaline (3a).[7] 1.—A mixture of 2.75 g (0.01 mol) of 7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1a**),[2] 40 ml of methylene chloride, and 2 ml (0.028 mol) of thionyl chloride was allowed to stand at room temperature for 1 hr. Water (100 ml) and 100 ml of hexane were added. The two phases were well agitated for 10 min. The aqueous layer was separated and washed with ether. The organic phase was extracted twice with 1 *N* hydrochloric acid. The aqueous layer was combined with the acid extracts which were then made alkaline with sodium hydroxide and extracted with benzene. The extracts were dried over sodium sulfate and evaporated to give 2.1 g of residue which was chromatographed on 60 g of silica gel with solvent mixtures (v/v) of methylene chloride–ethyl acetate (1:1) followed by ethyl acetate–ethanol (9:1).

Thin layer chromatographically pure fractions eluted with the first solvent system were combined and evaporated. Crystallization from methylene chloride–hexane yielded 0.24 g (14%) of 6-chloro-1,2,3,4-tetrahydroquinoxaline, mp 112–114°.[7]

The pure fractions eluted with ethyl acetate–ethanol were also combined and evaporated. The crystalline residue was recrystallized from methylene chloride–hexane to give 0.9 g (35%) of 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (**2a**), mp 170–172°.[3]

2.—Phosphorus oxychloride (3.3 ml or 0.03 mol) was added to an ice-cooled solution of 2.75 g of 7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1a**) in 80 ml of methylene chloride. The mixture was stirred for 3 hr at room temperature and worked up as above. The solid residue obtained was recrystallized twice from benzene–hexane to yield 0.9 g (53%) of 6-chloro-1,2,3,4-tetrahydroquinoxaline. A small amount of **2a** was present in the mother liquors as determined by thin layer chromatography.

6-Chloro-1-methyl-1,2,3,4-tetrahydroquinoxaline (3b). 1.—A mixture of 2.9 g (0.01 mol) of 7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1b**), 1 ml (0.014 mol) of thionyl chloride, and 30 ml of methylene chloride was stirred at room temperature for 15 min. The dark purple reaction mixture was worked up as described above. The base obtained as a yellow oil (1.4 g) was short path distilled under high vacuum to yield 1.15 g (63%) of distillate which solidified. Recrystallization from ether–petroleum ether gave the pure product: mp 51–53°; nmr ($CDCl_3$) δ 2.80 (broad s, 3, NCH_3), 3.0–4.0 (m, 5, NH, C_2 H, C_3 H): uv max 227–228 mμ (ε 33,300), 268–273 (5700), 320–324 (5250).

Anal. Calcd for $C_9H_{11}ClN_2$: C, 59.20; H, 6.07; N, 15.34. Found: C, 59.13; H, 6.14; N, 15.44.

The benzaldehyde present in the original organic layer was isolated and identified as the 2,4-dinitrophenylhydrazone derivative.

2.—Phosphorus oxychloride (20 ml, 0.22 mol) was added to a solution of 29 g (0.1 mol) of 7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1b**) in 300 ml of methylene chloride cooled to −20°. The temperature was allowed to reach 10° within 30 min. After addition of 300 ml of ether and 300 ml of water, the mixture was stirred vigorously for 15 min. Extraction, short-path distillation under high vacuum, and crystallization from ether–petroleum ether yielded 8.2 g (45%) of **3b**. The benzoyl derivative of **3b**, mp 128–130°, was also prepared and analyzed.

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; N, 9.77. Found: C, 67.15; H, 5.24; N, 9.68.

6-Chloro-1,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (3c).—A solution of 9 g (0.03 mol) of 7-chloro-1,3-dimethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1c**) in 100 ml of methylene chloride was cooled to −20°. Phosphorus oxychloride (6 ml, 0.065 mol) was added and the temperature was allowed to rise to 20° within 1.5 hr. The usual hydrolytic work-up followed by short-path distillation of the bases yielded 2.8 g (47%) of a light yellow oil which was crystallized from petroleum ether to give the pure product: mp 35–37°; nmr ($CDCl_3$) δ 1.13 (d, 3, *J* = 6.5 Hz, C_3 CH_3), 2.80 (broad s, 3, NCH_3), 6.2–6.8 (m, 3, aromatic H); uv max 226–227 mμ (ε 33,250), 272–273 (5800), 320–322 (5370).

Anal. Calcd for $C_{10}H_{13}ClN_2$: C, 61.07; H, 6.66; N, 14.24. Found: C, 61.05; H, 6.66; N, 14.35.

The *p*-chlorobenzoyl derivative (mp 124–128°) obtained under Schotten–Baumann conditions was crystallized from methanol: nmr ($CDCl_3$) δ 1.18 (d, 3, *J* = 6.5 Hz, C_3 CH_3), 2.98 (s, 3, NCH_3), 4.9 (m, 1, C_3 H); uv max 224–225 mμ (ε 27,200), 254–257 (16,000), 338–342 (4400); ir ($CHCl_3$) 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{16}Cl_2N_2O$: C, 60.91; H, 4.81; N, 8.36. Found: C, 61.12; H, 4.78; N, 8.46.

3-Benzyl-6-chloro-1-methyl-1,2,3,4-tetrahydroquinoxaline (3d).—A mixture of 15 g (0.04 mol) of 3-benzyl-7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1d**), 30 ml of phosphorus oxychloride, and 100 ml of chloroform was refluxed for 20 min. The solvent and excess reagent were evaporated under reduced pressure and the residue was distributed between methanol–1 *N* hydrochloric acid (1:1) and ether–hexane (1:1) v/v. The aqueous phase was separated, made alkaline with sodium hydroxide, and extracted with ether. The combined extracts were dried and evaporated. The residue (9.8 g) was chromatographed over 200 g of silica gel with benzene. Homogeneous fractions were combined and evaporated. Crystallization of the residue from ether–hexane yielded 4.6 g (42%) of product with mp 67–69°: nmr ($CDCl_3$) δ 2.5–4.0 (m, 6, NH, C_2 H, C_3 H, $CH_2C_6H_5$), 2.8 (s, 3, NCH_3), 6.25–6.7 (m, 3, C_5H, C_7H, C_8H), 7.7–5 (m, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{17}ClN_2$: C, 70.45; H, 6.28; N, 10.27. Found: C, 70.50; H, 6.48; N, 10.37.

The monohydrochloride (mp 135–145° dec) was prepared and recrystallized from 2-propanol–methylene chloride.

Anal. Calcd for $C_{16}H_{17}ClN_2 \cdot HCl$: C, 62.14; H, 5.82; N, 9.06. Found: C, 62.25; H, 6.12; N, 9.06.

4-Benzyl-6-chloro-1-methyl-1,2,3,4-tetrahydroquinoxaline (4b).—A mixture of 2.9 g (0.01 mol) of 7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1b**), 1 ml (0.014 mol) of thionyl chloride, and 40 ml of methylene chloride was stirred at room temperature for 15 min. The solvent was removed under reduced pressure and the dark purple residue was dissolved in 40 ml of dry tetrahydrofuran. This solution was added to a suspension of 1 g of lithium aluminum hydride in 40 ml of tetrahydrofuran whereupon immediate decolorization was observed. The reaction mixture was hydrolyzed by addition of 5 ml of water. The inorganic material was filtered and washed with ether. The filtrate was dried and evaporated to leave 2.7 g of residue which was chromatographed on 60 g of silica gel with benzene, followed by benzene–ether (1:1, v/v). Evaporation of the fractions eluted with benzene and crystallization of the residue from methylene chloride–hexane yielded 1.33 g (49%) of product: mp 122–124°; nmr ($CDCl_3$) δ 2.78 (s, 3, NCH_3), 3–3.5 (m, 4, C_2 H, C_3 H), 4.37 (s, 2, $NCH_2C_6H_5$), 6.25–6.7 (m, 3, C_5 H, C_7 H, C_8 H), 7.21 (s, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{17}ClN_2$: C, 70.44; H, 6.28; N, 10.26. Found: C, 70.16; H, 6.27; N, 10.23.

The fractions eluted with benzene–ether (1:1) left 0.2 g of oily 5-chloro-1-methyl-1,2,3,4-tetrahydroquinoxaline (**3b**).

Compound **4b** was also prepared by heating 6-chloro-1-methyl-1,2,3,4-tetrahydroquinoxaline with benzyl chloride.

1-Acetyl-4-acetoxy-7-chloro-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5).—A mixture of 8.25 g (0.03 mol) of 7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1a**), 100 ml of methylene chloride, 15 ml of acetic anhydride, and 20 ml of pyridine was allowed to stand at room temperature for 3 hr. The reaction mixture was washed twice with water, dried over sodium sulfate, and evaporated. The residue was crystallized from ether–hexane to give 7.3 g (68%) of product: mp 134–136°; ir ($CHCl_3$) 1750 (OC=O), 1645 cm^{-1} (NC=O); uv max 237–238 mμ (ε 8820), inflection 280 (530).

Anal. Calcd for $C_{19}H_{19}ClN_2O_3$: C, 63.60; H, 5.34; N, 7.81. Found: C, 63.62; H, 5.45; N, 7.78.

1-Acetyl-7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (6).[2]—A solution of 7.2 g (0.02 mol) of the diacetate **5** in 100 ml of warm methanol was treated with 40 ml of 1 *N* sodium hydroxide and the mixture was stirred for 15 min at 40–50°. The crystals which precipitated upon the addition of ice were collected, washed with water, and dissolved in methylene chloride. The solution was dried and evaporated. Crystallization of the residue from ethyl acetate–hexane yielded 4.9 g (77%) of the known **6**, mp 160–162°.

(7) J. C. Cavagnol and F. Y. Wiselogle, *J. Amer. Chem. Soc.*, **69**, 795 (1947).

1-Acetyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (7).[2]—A mixture of 3.2 g (0.01 mol) of 1-acetyl-7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine, 60 ml of methylene chloride, and 4 ml of (0.044 mol) of phosphorus oxychloride was stirred at room temperature for 3 hr. The usual hydrolytic work-up left 2.7 g of residue which was chromatographed on 90 g of silica gel with ethyl acetate. Crystallization of the evaporated clean fractions from ethyl acetate–hexane yielded 1.4 g (47%) of product, mp 164–166° (some starting material was eluated first).

6-Chloro-1-methyl-4-phenylcarbamoyl-1,2,3,4-tetrahydroquinoxaline (8).—A mixture of 2.9 g (0.01 mol) of 7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1b**), 1.5 g (0.0125 mol) of phenyl isocyanate, and 40 ml of toluene was refluxed for 24 hr. The crystals which separated from the cooled reaction mixture were collected by filtration and recrystallized twice from ethyl acetate–ethanol to yield 1.2 g (40%) of **8**: mp 190–192°; nmr (DMSO-*d*) δ 2.89 (s, 3, NCH_3), 3.1–4 (m, 4, C_2 H, C_3 H), 8.85 (s, 1, NH); uv max 227–228 mμ (ε 24,300), 244–246 (20,800), 273–274 (17,900); ir (KBr) 3250 (NH), 1640 cm^{-1} (NC=O).

Anal. Calcd for $C_{16}H_{16}ClN_3O$: C, 63.68; H, 5.34; N, 13.92. Found: C, 63.48; H, 5.39; N, 14.01.

The original filtrate was extracted three times with 1 *N* hydrochloric acid. The combined extracts were made alkaline with ammonia and extracted with benzene. The dried and evaporated extracts left a yellow oil which was chromatographed on 40 g of silica gel with ethyl acetate. The known 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (0.18 g, 6.6%) was obtained, melting point and mixture melting point with an authentic sample,[3] 97–99°.

7-Chloro-2,3-dihydro-1,3-dimethyl-5-phenyl-1*H*-1,4-benzodiazepine (2c).—A mixture of 5 g (0.0165 mol) of 7-chloro-1,3-dimethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1c**), 2.5 g (0.045 mol) of potassium hydroxide, and 50 ml of ethanol was refluxed for 24 hr. The solvent was removed under reduced pressure and the residue was distributed between benzene and water. The organic layer was dried over sodium sulfate and evaporated. Crystallization of the residue from methylene chloride–petroleum ether gave 3.1 g (66%) of product, mp 102–104°.

Anal. Calcd for $C_{17}H_{17}ClN_2$: C, 71.70; H, 6.02. Found: C, 71.90; H, 6.24.

By the same procedure the known compounds **2a**[3] and **2b**[3] were obtained from **1a**[2] and **1b** in 93 and 72% yield, respectively.

Registry No.—**1b**, 28121-71-3; **1c**, 28199-16-8; **1d**, 28199-17-9; **2c**, 28199-18-0; **3b**, 28199-19-1; **3b** benzoyl, 28199-20-4; **3c**, 28199-21-5; **3c** *p*-chlorobenzoyl, 28199-22-6; **3d**, 28199-23-7; **3d** HCl, 28199-24-8; **4b**, 28199-25-9; **5**, 28199-26-0; **6**, 1803-97-0; **7**, 1803-95-8; **8**, 28199-28-2; **9c**, 28199-29-3; **9d**, 28199-30-6.

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Pyrimidines. XI. The Conversion of 5-Hydroxyuracils into 6-Alkyluracils *via* Claisen Rearrangements[1]

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Approaches to the synthesis of 6-carbon-substituted pyrimidine nucleosides from 5-hydroxypyrimidine nucleosides have been investigated using N-alkylated 5-hydroxyuracils as model compounds. 5-Allyl ethers of hydroxyuracils readily undergo Claisen rearrangement at ~120° to give the 6-allyl-5-hydroxyuracils in very high yield. These rearrangements proceed by a normal intramolecular Claisen mechanism. Under more drastic conditions (207°), 5-allylamino-1,3-dimethyluracil undergoes an amino-Claisen rearrangement to 6-allyl-5-amino-1,3-dimethyluracil. 5-Benzyloxy-1,3-dimethyluracil undergoes a different type of rearrangement at 207° to give 6-benzyl-1,3-dimethyl-5-hydroxyuracil. Direct electrophilic attack at C-6 of 5-hydroxyuracils is demonstrated with the hydroxymethylation of 1-methyl-5-hydroxyuracil. Two methods for removal of a pyrimidine 5-hydroxyl group are given. Thus hydrogenolysis of the 5-tetrazolyl ether of 1,3-dimethyl-6-propyl-5-hydroxyuracil and treatment of 1,3-dimethyl-5-mesyloxy-6-propyldihydrouracil with 1,5-diazobicyclo[5.4.0]-undecene-5 (DBU) both afford 1,3-dimethyl-6-propyluracil. The synthesis of 5-allyloxyuridine and subsequent Claisen rearrangement to give 6-allyl-5-hydroxyuridine is described.

Orotidylic acid (the 5′-phosphate ester of 6-carboxyuridine) plays an important role in the biosynthesis of the nucleotide components of ribonucleic acid. Synthetic pyrimidine nucleosides bearing a carbon substituent at C-6 are of interest because of their structural similarity to orotidylic acid, and it is possible that compounds of this class may interfere with nucleic acid metabolism. However, 6-carbon-substituted nucleosides are not easily prepared and the first examples of synthetic compounds of this type were described only recently.[2,3] These compounds, the 6-methyl and 5,6-dimethyl analogs of uridine and cytidine, were prepared in low yield by use of conventional procedures involving the initial condensation of suitable 6-methylcytosines with halogeno sugars.

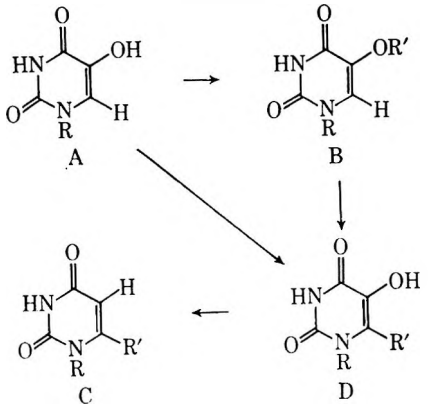
An alternative approach to the synthesis of 6-substituted nucleosides, namely substitution of C-6 of a *preformed* nucleoside, is shown in Scheme I, which illustrates two possible methods for converting a 5-hydroxyuracil A into a 6-carbon substituted uracil C. One route involves the rearrangement of suitable 5-hydroxyuracil ethers B to give the isomeric 6-substituted 5-hydroxyuracils D. The other route involves the formation of compounds D by direct attack of a carbon electrophile at C-6 of A. Removal of the 5-hydroxyl group of D would then effect an overall synthesis of C from A. We have now investigated these general approaches and the results obtained using N-alkylated 5-hydroxyuracils as models form the subject of this paper.

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08478), and by a Postdoctoral Fellowship (to A. T.) from the Westchester Division of the American Cancer Society.

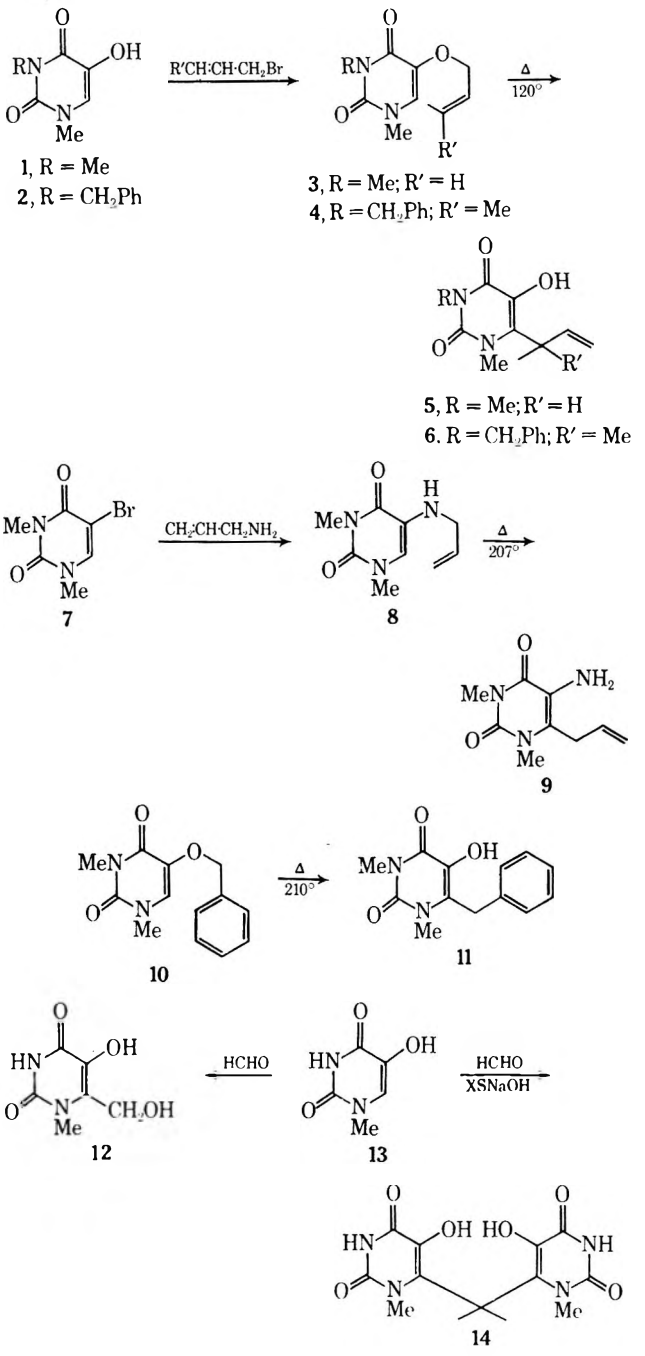
(2) M. W. Winkley and R. K. Robins, *J. Org. Chem.*, **33**, 2822 (1968).

(3) M. Prystaš and F. Šorm, *Collect. Czech. Chem. Commun.*, **34**, 2316 (1968).

SCHEME I



SCHEME II



An obvious choice for the reaction B → D in Scheme I is the Claisen rearrangement of a 5-allyloxyuracil.[4] Such a compound (**3**, Scheme II) was easily prepared by treatment of the sodium salt of 1,3-dimethyl-5-hydroxyuracil (**1**) with allyl bromide in methanol. Rearrangement of the allyl ether **3** occurred readily at 120°. Moreover, the product **5** was formed in quantitative yield within a 10-min period. The structure of **5** was evident from the uv spectrum, and from the nmr spectrum, which shows absence of a C-6 proton but presence of the 5-hydroxyl and 6-allyl protons. The 5-crotyloxy ether **4** was prepared from **2** and rearranged at 125° to test for the inversion of the allyl group that is characteristic of the ortho-Claisen rearrangement. The nmr spectrum of the product **6** shows the presence of the 6-methylallyl group, thereby confirming that inversion had taken place. Pyrolysis of a mixture of ethers **3** and **4** afforded only **5** and **6**; the absence of crossover products means that these reactions proceed by the normal intramolecular mechanism established for the ortho-Claisen rearrangement.[5]

It is clear from examination of the experimental conditions used to effect a large number of Claisen rearrangements,[5a] that the ethers **3** and **4** rearrange with unusual ease. This suggested that the corresponding 5-allylamino compounds might also rearrange[6] and led us to examine the pyrolysis of 1,3-dimethyl-5-allylaminouracil (**8**). As expected, compound **8** is much more stable than the allyl ether **3**, and temperatures of at least 200° are required for rearrangement to take place at a reasonable rate. In refluxing tetralin (207°) compound **8** underwent partial rearrangement and, after a 12-hr period, the 6-allyl-5-aminouracil (**9**) was isolated in 24% yield.

The benzyloxyuracil **10** does not undergo the Claisen rearrangement, even though a 1,5-diene system is present. Instead, **10** partially rearranges when heated without solvent at 210° for 3 hr to give 6-benzyl-1,3-dimethyl-5-hydroxyuracil (**11**) in 20% yield. When **10** was refluxed in tetralin for 16 hr, the rearrangement product (**11**) was obtained in 30% yield. That compound **11** contains a 6-benzyl group, rather than a 6-*o*-tolyl group resulting from Claisen rearrangement, is clear from the nmr spectrum which shows a methylene rather than a *C*-methyl resonance. This rearrangement is analogous to the thermal conversion of phenylbenzyl ether[7] into *o*- and *p*-benzylphenol, a reaction that is thought to involve an intermolecular, free-radical mechanism.

Previous studies have shown that 5-hydroxyuracils are susceptible to direct electrophilic substitution at C-6. For example, 5-hydroxyuracil itself undergoes nitrosation,[8a] diazo coupling,[8b] and Mannich reactions[9]

(4) (a) Although Claisen rearrangements of 2-allyloxy-[4b] and 4-allyloxypyrimidines[4c] have been studied previously, no examples of the rearrangement of 5-allyloxypyrimidines had been reported prior to the present study. For a review of Claisen rearrangments in pyrimidines and other N-heterocyclic systems, see B. S. Thyagarajan, *Advan. Heterocycl. Chem.*, **8**, 143 (1967). (b) J. K. Elwood and J. W. Gates, *J. Org. Chem.*, **32**, 2956 (1967). (c) H. J. Minnemeyer, P. B. Clarke, and H. Tieckelmann, *ibid.*, **31**, 406 (1966).

(5) For reviews, see (a) D. S. Tarbell, *Org. React.*, **2**, 1 (1944); (b) A. Jefferson and F. Scheinmann, *Quart. Rev., Chem. Soc.*, **22**, 391 (1968).

(6) Relatively few amino-Claisen rearrangements are known. Some examples are given in ref 5b.

(7) F. M. Elkobaisi and W. J. Hickinbottom, *J. Chem. Soc.*, 1873 (1959); *ibid.*, 1286 (1960).

(8) (a) D. Davidson and M. T. Bogert, *Proc. Nat. Acad. Sci. U. S.*, **18**, 490 (1932); (b) M. T. Bogert and D. Davidson, *ibid.*, **18**, 215 (1932).

(9) D. E. O'Brien, R. H. Springer, and C. C. Cheng, *J. Heterocycl. Chem.*, **3**, 115 (1966).

to give 6-substituted products. More recently, we have shown[10] that isopropylidene-5-hydroxyuridine and 1,3-dimethyl-5- hydroxyuracil undergo base-catalyzed exchange of H-6 for deuterium. This reaction, and presumably the examples above, involves ionization of the 5-hydroxyl group to give a mesomeric anion in which C-6 has sufficient carbanion character to react with electrophiles.[10]

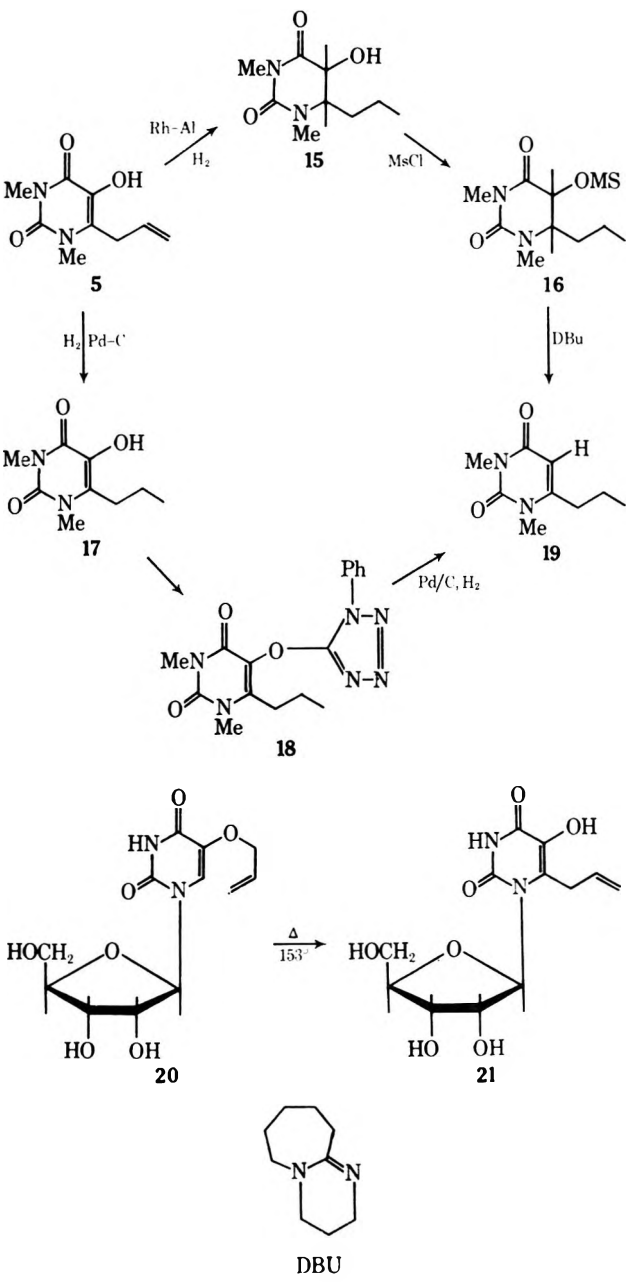
A further example of electrophilic substitution, namely hydroxymethylation, is shown in Scheme II. Thus treatment of the sodium salt of 1-methyl-5-hydroxyuracil (**13**) with an excess of aqueous formaldehyde affords the 6-hydroxymethyluracil **12** in 61% yield. Treatment of **13** with formaldehyde in the presence of an excess of sodium hydroxide results in the formation of the methylene-bridged compound **14**. The structure of **14** was apparent from the nmr spectrum, which shows ureide, hydroxyl, methylene, and methyl signals with intensities in the ratio 1:1:1:3. This type of diarylation reaction is frequently encountered during the hydroxymethylation of phenols.[11]

The final step (D → C) in Scheme I, involving removal of the 5-hydroxyl group from a 6-substituted 5-hydroxyuracil, was accomplished by using the two methods shown in Scheme III. These procedures are illustrated with 6-allyl-1,3-dimethyl-5-hydroxyuracil (**5**), but in principle they should be applicable to a variety of 6-substituted uracils. Hydrogenation of compound **5** over rhodium–alumina catalyst, followed by mesylation of the resulting dihydrouracil (**15**) afforded the 5-mesyl ester **16**. Treatment of **16** with 1,5-diazobicyclo[5.4.0]undecene-5 (DBU)[12] in refluxing tetrahydrofuran then gave 1,3-dimethyl-6-propyluracil (**19**, 48% yield) together with small amounts of two unidentified products. The structure of **19** was confirmed by comparison with authentic material prepared from 2-thio-6-propyluracil according to the method described by Burckhalter and Scarborough.[13]

The alternative synthesis of compound **19** shown in Scheme III is an extension of the procedure developed by Musliner and Gates[14] for removal of phenolic hydroxyl groups. As applied to the 5-hydroxy-6-propyluracil **17**, this method readily affords **19** in a high state of purity. Thus, condensation of **17** with 1-phenyl-5-chlorotetrazole in acetone in the presence of potassium carbonate afforded the 1-phenyltetrazolyl ether **18**. Hydrogenolysis of **18** with palladium/charcoal then gave 1,3-dimethyl-6-propyluracil (**19**) in more than 50% yield. These transformations appear to be the first examples of the replacement of a 5-hydroxyl group of a pyrimidine by hydrogen.

Preliminary studies on the extension of the above procedures to the nucleoside series have shown that 5-allyloxyuridine (**20**) can be prepared by selective allylation of 5-hydroxyuridine, and that **20** undergoes Claisen rearrangement in refluxing dimethylformamide to give the 6-allyl nucleoside **21** in excellent yield. The conversion of **21** into a series of 6-substituted pyrimidine nucleosides is currently being investigated.

SCHEME III



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 (unless otherwise stated) and tetramethylsilane as internal reference. First-order values are given for coupling constants (hertz) and chemical shifts. Ultraviolet spectra were measured on Cary Model 15 and Unicam SP 500 spectrometers. Evaporations were carried out under reduced pressure. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

5-Allyloxy-1,3-dimethyluracil (3).—Allyl bromide (8.6 ml, 0.1 mol) was added to a solution of 1 (7.8 g, 0.05 mol) in methanol (250 ml) containing 1.15 g (0.05 g-atom) of sodium. The solution was refluxed for 1 hr, cooled, and evaporated to dryness. The residue was partitioned between water and chloroform (three 50-ml portions), and the chloroform solution was dried (sodium sulfate) and concentrated to a syrup which crystallized from ethyl acetate to give 8 g (82%) of **3**: mp 103–104°; uv $\lambda_{max}^{pH\ 1-14}$ 281 mμ; nmr δ 7.50 s (1, H-6), 6.02 14-line m, width 37 Hz (1,

(10) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 2636 (1969).

(11) For a review, see H. Schnell and H. Krimm, *Angew. Chem., Int. Ed. Engl.*, **2**, 373 (1963).

(12) This reagent was introduced for the dehydrohalogenation of bromoalkanes by H. Oediger and Fr. Möller, *ibid.*, **6**, 76 (1967).

(13) J. H. Burckhalter and H. C. Scarborough, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 545 (1955).

(14) W. J. Musliner and J. W. Gates, *J. Amer. Chem. Soc.*, **88**, 4271 (1966).

-CH=), 5.47 m, 5.31 m, 5.17 m (2, $=CH_2$), 4.39 m (2, OCH_2), 3.27 s (3, NCH_3), and 3.17 ppm s (3, NCH_3).

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.93; H, 6.04; N, 14.23.

3-Benzyl-5-crotyloxy-1-methyluracil (4).—To 100 ml of methanol containing 460 mg (20 mg-atoms) of sodium was added 2.32 g (10 mmol) of compound **2**.[10] Technical grade crotyl bromide (2.6 g, ~20 mmol) was added and the solution was refluxed for 3 hr. The solution was concentrated to dryness and the residue was dissolved in benzene. The benzene solution was washed successively with dilute NaOH and water, dried, and concentrated to give a white solid (1.73 g, 60%) with mp 78–81°. Recrystallization from benzene–petroleum ether (bp 30–60°) gave pure **4**: mp 81–83°; uv $\lambda_{max}^{pH\ 1-14}$ 283 mμ; nmr δ 7.45 s (1, H-6), 7.21 s (5, phenyl), 5.67 m (2, CH=CH), 4.98 s (2, CH_2Ph), 4.28 m (2, OCH_2), 3.27 s (3, NCH_3), and 1.67 ppm m (3, CCH_3).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.14; H, 6.24; N, 9.61.

6-Allyl-1,3-dimethyl-5-hydroxyuracil (5).—Compound **3** (1 g) was melted and kept at 120° for 10 min. During this time, uv examination (pH ~10) of samples showed rapid loss of absorption at 281 mμ and appearance of a new peak at 316 mμ. Crystallization of the cooled melt from benzene–petroleum ether afforded 960 mg (96%) of **5**: mp 104–106°; uv $\lambda_{max}^{pH\ 1}$ 287 mμ; $\lambda_{max}^{pH\ 12}$ 316 mμ; nmr δ 8.40 s (1, 5 OH), 5.93 m (1, CH=), 5.22 m, 5.06 m, 4.95 m (2, $=CH_2$), 3.45 m (2, CH_2), 3.30 s (3, NCH_3), and 3.22 ppm s (3, NCH_3).

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.10; H, 6.12; N, 14.22.

3-Benzyl-5-hydroxy-1-methyl-6-methylallyluracil (6).—Pyrolysis of 180 mg (6.3 mmol) of **4** at 125° for 20 min, and crystallization of the melt from benzene–petroleum ether afforded 175 mg (97%) of **6**: mp 118–120°; uv $\lambda_{max}^{pH\ 1}$ 288 mμ; $\lambda_{max}^{pH\ 12}$ 319 mμ; nmr δ 8.39 s (1, 5 OH), 7.25 s (5, phenyl), 6.11 8-line m (1, CH=), four-proton group with 5.02 s (CH_2Ph) overlapping high-field part of multiplet pair at 5.20 and ~4.97 ($=CH_2$), 3.99 m (1, $CHCH_3$), 3.31 s (3, NCH_3), and 1.39 ppm d (3, CCH_3, J_{H,CH_3} = 7.0 Hz).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 66.85; H, 6.19; N, 9.55.

Mixed Pyrolysis of 3 and 4.—A mixture containing 196 mg (1 mmol) of **3** and 286 mg (1 mmol) of **4** was melted and kept at 125° for 20 min. Tlc of the melt on silica gel G_{254} (Merck) in benzene–ethyl acetate (4:1 v.v) revealed only two components. Fractionation of the mixture on a column containing 25 g of silica gel G, using the above solvent system, afforded 270 mg (95%) of **6** and 192 mg (98%) of **5**. Identification of **5** and **6** was made on the basis of mixture melting points and comparison of uv and nmr spectra with those of **5** and **6** prepared as above.

1,3-Dimethyl-5-allylaminouracil (8).—A solution of 8 g of 1,3-dimethyl-5-bromouracil (**7**) in 80 ml of freshly distilled allylamine (bp 56°) was refluxed for 5 hr. The solution was evaporated to dryness and the solid residue was partitioned between water and dichloromethane. The organic layer was dried over sodium sulfate and concentrated to a syrup which crystallized readily from hot ethyl acetate. The yield of **8**, mp 107–109°, was 5.3 g (70%). The analytical sample was obtained by sublimation *in vacuo* at 110°: uv $\lambda_{max}^{pH\ 1}$ 270 mμ; $\lambda_{max}^{pH\ 7-14}$ 302 mμ; nmr δ 6.65 s (1, H-6), 5.95 m (1, CH=), 5.38 m, 5.23 m, 5.08 m (2, $=CH_2$), 4.60 broad t (1, NH, $J_{NH,CH}$ = 6 Hz), 3.64 m (2, NCH_2), 3.35 s (3, NCH_3), and 3.30 ppm s (3, NCH_3).

Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.31; H, 6.57; N, 21.55.

6-Allyl-5-amino-1,3-dimethyluracil (9).—A solution of **8** (500 mg) in 5 ml of tetralin was refluxed for 12 hr. The solution was decanted from a small amount of tarry material, diluted with benzene (5 ml), and extracted with 0.01 *N* HCl (three 10-ml portions). The aqueous layer was neutralized with NaOH and extracted with chloroform. The chloroform solution was dried (sodium sulfate), concentrated to a small volume, and applied to two thick layer plates (20 × 20 cm with 30 g of Merck silica gel P_{254}). The plates were developed in ethyl acetate and the appropriate zones were removed and extracted with hot ethanol. Concentration of the combined extracts afforded a yellow syrup which crystallized spontaneously. The yield of **9** was 122 mg (24%): nmr δ 5.91 m, width 38 Hz (1, CH=), 5.22 m, 5.04 m, 4.95 m (2, $=CH_2$), 3.97 broad peak (2, NH_2), 3.40 m (2, CH_2), 3.29 s (3, NCH_3), and 3.21 ppm s (3, NCH_3). The picrate salt was prepared by addition of ethanolic picric acid to an ethanol solution of **9**. Recrystallization of the yellow solid from aqueous ethanol afforded the hemihydrate, mp 159–161°. The nmr spectrum of the picrate confirmed the presence of 0.5 H_2O of crystallization.

Anal. Calcd for $C_{15}H_{16}N_6O_9 \cdot 0.5H_2O$: C, 41.57; H, 3.95; N, 19.39. Found: C, 41.65; H, 3.81; N, 19.36.

5-Benzyloxy-1,3-dimethyluracil (10).—Benzyl chloride (2.3 ml, 20 mmol) was added to a solution of 1 (1.56, 10 mmol) in methanol (50 ml) containing 40 ml of 0.25 *N* NaOH (10 mmol). The mixture was refluxed for 5 hr and then concentrated to ~30 ml. The solid that precipitated was removed and crystallized from benzene–petroleum ether to give 2.16 g (88%) of **10**: mp 95–97°; uv $\lambda_{max}^{pH\ 1-14}$ 281 mμ; nmr δ 7.51 s (1, H-6), 7.34 s (5, phenyl), 4.87 s (2, CH_2Ph), 3.25 s (3, NCH_3), and 3.17 ppm s (3, NCH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.04; H, 5.67; N, 11.14.

6-Benzyl-1,3-dimethyl-5-hydroxyuracil (11). Method A.—Compound **10** (500 mg) was heated at 210° for 3 hr. A solution of the melt in ethanol was passed through a column containing ~10 ml of Dowex 1 (OH^-, equilibrated with ethanol). The column was washed with 50% ethanol until the effluent showed no uv absorption (fraction 1) and then with 1 *N* ammonium bicarbonate in 50% ethanol until the effluent failed to give a blue color with ferric chloride (fraction 2). Concentration of fraction 1 afforded 270 mg of slightly impure starting material. Fraction 2 was concentrated to half-volume, neutralized, and extracted with dichloromethane. Evaporation of the dried dichloromethane solution afforded a syrup which crystallized from aqueous methanol. The yield of **11**, mp 180–181°, was 102 mg (20%): uv $\lambda_{max}^{pH\ 1}$ 287 mμ; $\lambda_{max}^{pH\ 14}$ 316; nmr δ 8.47 s (1, 5 OH), 7.23 s (5, phenyl), 4.09 s (2, CH_2Ph), 3.24 s (3, NCH_3), and 3.15 ppm s (3, NCH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.41; H, 5.78; N, 11.64.

Method B.—A solution of 984 mg (4 mmol) of **10** in 10 ml of tetralin was refluxed for 16 hr. The dark brown solution was extracted with dilute NaOH and the aqueous alkaline solution was neutralized with HCl. Extraction with chloroform, followed by evaporation of the chloroform solution to dryness and crystallization of the residue from benzene–petroleum ether gave 300 mg (30.5%) of pure **11**, mp and mmp 180–181°.

6-Hydroxymethyl-5-hydroxy-1-methyluracil (12).—Sodium hydroxide (10 ml of 1 *N* solution) and aqueous formaldehyde (2 ml of ~37% solution, ~25 mmol) were added to a suspension of 1-methyl-5-hydroxyuracil (**13**) (1.42 g, 10 mmol) in 88 ml of water. The solution was kept at 50° for 1 hr, cooled, and passed through a column containing 30 ml of Dowex 50 (H^+). The column was washed with water until samples of the effluent failed to give a blue color with ferric chloride. Concentration of the effluent to ~10 ml, and cooling at 5°, afforded two crops of colorless crystals (1.05 g, 61%) with mp 195–196° eff: uv $\lambda_{max}^{pH\ 1}$ 289 mμ; $\lambda_{max}^{pH\ 10}$ 318 and 241 mμ; $\lambda_{max}^{pH\ 14}$ 313 and 245 mμ; nmr δ 11.45 broad s (1, NH), 8.43 s (1, 5 OH), 5.35 t (1, CH_2OH, $J_{H,OH}$ = 5.0 Hz), 4.46 d (2, CH_2), and 3.32 ppm s (3, NCH_3).

Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.27. Found: C, 41.86; H, 4.79; N, 16.02.

6,6′-Methylenebis(1-methyl-5-hydroxyuracil) (14).—1-Methyl-5-hydroxyuracil (**13**) (710 mg, 5 mmol) was dissolved in 50 ml of 1 *N* NaOH (50 mmol); aqueous formaldehyde (2 ml of ~37% solution, ~25 mmol) was added and the solution was heated at 50° for 3 hr. Acidification of the cooled solution with concentrated HCl resulted in the formation of a white, crystalline solid which was collected and washed successively with water, ethanol, and ether. The yield of **14** was 350 mg (47%): mp >305°; uv $\lambda_{max}^{pH\ 1}$ 292 mμ; $\lambda_{max}^{pH\ 10}$ 327 and 242 mμ; $\lambda_{max}^{pH\ 14}$ 322 and 245 mμ; nmr singlets at δ 11.35 (broad, NH), 8.58 (broad, OH), 3.98 (CH_2), and 3.15 ppm (NCH_3 + H_2O) with intensities in the ratio of 1:1:1:3.5. Removal of the water, NH, and OH peaks by addition of D_2O revealed methylene and *N*-methyl peaks with relative intensities of 1:3.

Anal. Calcd for $C_{11}H_{12}N_4O_6 \cdot 0.5H_2O$: C, 43.28; H, 4.29; N, 18.35. Found: C, 43.51; H, 4.22; N, 18.40.

1,3-Dimethyl-5-hydroxy-6-propyl-5,6-dihydrouracil (15).—A solution of **5** (1.96 g, 10 mmol) in ethanol (75 ml) was shaken with 5% rhodium-on-alumina catalyst (~50 mg) under hydrogen in a Parr apparatus for 17 hr. The catalyst was removed and the filtrate concentrated to a colorless syrup which was crystallized from benzene–petroleum ether. The yield of **15**, mp 95–98°, was 1.92 g (96%): nmr δ 5.80 broad peak (1, OH), 4.45 d (1, H-5, $J_{5,6}$ = 6.5 Hz), ~3.5 broad m (1, H-6), 3.0 s (6, *N*-methyls),

~1.4 broad band (4, CH_2CH_2), and ~0.9 ppm broad band (3, CCH_3).

Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 13.99. Found: C, 53.53; H, 7.78; N, 13.75.

1,3-Dimethyl-5-mesyloxy-6-propyl-5,6-dihydrouracil (16).—Mesyl chloride (0.8 ml, 10 mmol) was added dropwise to a solution of **15** (1 g, 5 mmol) in pyridine (15 ml) at 0° and the mixture was kept at room temperature for 17 hr. The dark solution was poured into ice-cold water and the gummy precipitate was extracted into ether. The ether layer was washed with 10% HCl and then with water, dried over potassium carbonate–sodium sulfate, and evaporated to dryness. Trituration of the syrupy residue with petroleum ether, with cooling in an acetone–Dry Ice bath, afforded solid material (1.23 g, 83%), mp 97–100°. Recrystallization from chloroform–petroleum ether did not change the melting point.

Anal. Calcd for $C_{10}H_{18}N_2O_5S$: C, 43.15; H, 6.52; N, 10.06. Found: C, 43.07; H, 6.39; N, 9.94.

1,3-Dimethyl-5-hydroxy-6-propyluracil (17).—Compound **5** (1.2 g, 6 mmol) was hydrogenated at atmospheric pressure in 30 ml of ethanol with 10% palladium/charcoal catalyst. Uptake of 6 mmol of hydrogen was complete within 5 min. The catalyst was removed and the filtrate evaporated to a solid which crystallized from ethyl acetate in quantitative yield: mp 95–97°; uv $\lambda_{max}^{pH\ 1}$ 285 mμ; $\lambda_{max}^{pH\ 14}$ 315 and 247 mμ; nmr ($CDCl_3$) δ 6.27 s (1, 5 OH), 3.43 s (6, *N*-methyls), 2.70 m (2, allylic CH_2), 1.65 m (2, CH_2), and 1.05 ppm t (3, CCH_3).

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.47; H, 6.99; N, 14.00.

1,3-Dimethyl-6-propyl-5-(1-phenyltetrazolyloxy)uracil (18).—Compound **17** (990 mg, 5 mmol) and 1-phenyl-5-chlorotetrazole (903 mg, 5 mmol)[15] were dissolved in 50 ml of dry acetone. Potassium carbonate (1.38 g, 10 mmol) was added and the mixture was stirred and refluxed overnight. The cooled mixture was filtered and the filtrate was evaporated to dryness. Crystallization of the residue from hot methanol afforded 1.45 g (85%) of **18**: mp 143–145°; uv $\lambda_{max}^{pH\ 1-14}$ 265 mμ; nmr ($CDCl_3$) δ ~7.6 m (5, phenyl), 3.46 s (3, NCH_3), 3.34 s (3, NCH_3), 2.66 m (2, allylic CH_2), 1.70 m (2, CH_2), and 1.00 ppm t (3, CCH_3).

Anal. Calcd for $C_{16}H_{18}N_6O_3$: C, 56.13; H, 5.30; N, 24.55. Found: C, 55.96; H, 5.25; N, 24.59.

1,3-Dimethyl-6-propyluracil (19). Method A.—A mixture of 1.03 g (3 mmol) of **18** and 210 mg of 10% palladium/charcoal in 250 ml of ethanol was shaken under hydrogen at atmospheric pressure for 7 hr. The catalyst was removed and the solution was concentrated to dryness. The crude syrup was added to a column of silica gel G (30 g, Merck) and eluted with chloroform–methanol (10:1 v/v). Concentration of the appropriate fractions afforded (in order of elution) 260 mg (48%) of **19**, 80 mg of a mixture of **19** and 1-phenyltetrazolone, and 449 mg (92.5%) of pure 1-phenyltetrazolone, mp 185–188° (lit.[16] 187°). Compound **19** (mp and mmp 60–61°) showed ir, uv ($\lambda_{max}^{pH\ 1-14}$ 268 mμ), and nmr spectra [($CDCl_3$) δ 5.53 s (1, H-5), 3.43 s (3, NCH_3), 3.35 s (3, NCH_3), 2.52 t (2, allylic CH_2), 1.67 sextet (2, CH_2), and 1.06 ppm t (3, CCH_3)] identical with those of authentic[13] **19**.

Method B.—A solution of 1,5-diazobicyclo[5.4.0]undecene-5 (1.7 ml, 11 mmol)[15] in 25 ml of tetrahydrofuran was added dropwise, under a nitrogen atmosphere, to a solution of **16** (2.78 g, 10 mmol) in 25 ml of tetrahydrofuran. The yellow solution was refluxed for 48 hr and then concentrated to dryness. The residue was extracted with benzene and the benzene solution was washed successively with cold, dilute sulfuric acid and water. Evaporation of the dried solution afforded a syrup which contained (tlc on Merck aluminum oxide HF_{254}, chloroform–methanol, 4:1) three uv-absorbing compounds. The syrup was fractionated on 100 g of basic alumina (Bio-Rad AG 10). Elution with chloroform afforded fractions from which 200 mg of unidentified material, mp 108–112°, was obtained. Elution with chloroform–methanol (4:1 v/v) then afforded 870 mg (48%) of **19** which was identified by comparison with **19** prepared as above, and with authentic material.[13] Continued elution with chloroform–methanol afforded **19** admixed with an unidentified compound. A sample (120 mg) of this unknown compound, obtained from the final fractions, had mp 126–129° after recrystallization of ethyl acetate–petroleum ether.

5-Allyloxyuridine (20).—Allylbromide (15 ml, 0.17 mol) was added to a solution of 5-hydroxyuridine (15.6 g, 0.06 mol) in 500 ml of 50% methanol containing 60 ml of 1 *N* NaOH (0.06 mol). The mixture was stirred at room temperature for 3 hr and the white solid (which began to precipitate after ~20 min) was removed and dried in air. Tlc (dichloromethane–methanol, 5:1 v/v) showed that the solid (11.8 g, 66%, mp 184–185°) contained only trace amounts of starting material. Recrystallization from boiling water afforded **20** with unchanged melting point: uv $\lambda_{max}^{pH\ 1}$ 279 mμ; λ_{min} 246 mμ; $\lambda_{max}^{pH\ 10}$ 276 mμ; λ_{min} 251 mμ; nmr δ 11.32 s (1, NH), 7.66 s (1, H-6), 6.3–5.7 m (2, H-1′ and $=CH_2$), 5.6–4.8 m (5, $=CH_2$ and 2′,3′,5′-hydroxyls), 4.35 m (1, OCH_2), 4.2–3.8 m (3, H-2′, H-3′, H-4′), and 3.63 ppm m (2, H-5′, H-5′). Removal of hydroxyl signals by addition of D_2O revealed $=CH_2$ as a multiplet with components at 5.50 m, 5.27 m, and 5.20 ppm m.

Anal. Calcd for $C_{12}H_{16}N_2O_7$: C, 48.00; H, 5.37; N, 9.33. Found: C, 47.81; H, 5.20, N, 9.24.

6-Allyl-5-hydroxyuridine (21).—A sample of compound **20** (1.85 g) was dissolved in 20 ml of near-boiling dimethylformamide and the solution was refluxed for 10 min. The pale-yellow solution was evaporated (50°, oil pump) to a syrup from which DMF was removed by codistillation with xylene. Tlc (dichloromethane–methanol, 5:1 v/v) of the dry syrup (1.8 g) showed the presence of **21** and very small amounts of 5-hydroxyuridine, formed presumably by cleavage of the allyloxy group of **20**. Crystallization of the syrup from ~5 ml of 85% ethanol took place slowly to give 1.5 g (79%) (in two crops) of **21** as the hemihydrate: mp 121–125°; uv $\lambda_{max}^{pH\ 1}$ 281 mμ; $\lambda_{max}^{pH\ 10}$ 312 mμ; $\lambda_{max}^{pH\ 14}$ 310, sh 255 mμ; nmr δ 11.47 s (1, NH), 8.47 s (1, OH), 5.55–6.2 (1, m, CH=), 4.8–5.4 m (5, H-1′, 2′-OH, 3′-OH, and $=CH_2$), 4.6 m (2, 5′-OH and H-2′), 4.10 q (1, H-3′), and 3.85 – 3.30 ppm m (6, CH_2, H-4′, H-5′, H-5′, and $^1/_2H_2O$). Removal of OH signals by addition of D_2O revealed signals at δ 5.33 d (H-1′, $J_{1'2'}$ = 4.5 Hz), 5.27 m, 5.08 m, 4.95 m ($=CH_2$), and 4.60 ppm m (H-2′).

Anal. Calcd for $C_{12}H_{16}N_2O_7 \cdot 0.5H_2O$: C, 46.60; H, 5.54; N, 9.06. Found: C, 46.48; H, 5.42; N, 8.82.

Registry No.—**3**, 28199-38-4; **4**, 28199-39-5; **5**, 28199-40-8; **6**, 28199-41-9; **8**, 28199-42-0; **9**, 28199-43-1; **9** picrate, 28199-44-2; **10**, 28199-45-3; **11**, 28199-46-4; **12**, 28199-47-5; **14**, 28199-48-6; **15**, 28199-49-7; **16**, 28199-50-0; **17**, 28199-51-1; **18**, 28199-52-2; **19**, 28267-45-0; **20**, 28192-74-7; **21**, 28192-75-8.

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The Reactions of Hydrogen Peroxide and Some of Its Derivatives with Uracil, Thymine, and Thymidine 5′-Phosphate

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Hydrogen peroxide undergoes both polar and free-radical reactions with uracil and thymine derivatives. Near neutrality, free-radical pathways are the most important for the reaction with thymidine 5′-phosphate. At more alkaline pH values, the predominant reaction is one in which the anion of the hydroperoxide attacks the neutral species of the substrate. The pH-rate profiles of these reactions show maxima midway between the pK_a values of the two reacting species. In addition to hydrogen peroxide, methyl hydroperoxide, *tert*-butyl hydroperoxide, peroxyacetic acid, and *m*-chloroperoxybenzoic acid show the same type of behavior. Thymine is less reactive than uracil in all cases.

Selective chemical modification of nucleic acids is an area of increasing interest for the study of the structure and function of these polymers. Rational application of these modifications to the polymers requires detailed knowledge of the mechanisms of the reactions with the monomeric units. We have reported a study of the reaction of *m*-chloroperoxybenzoic acid with nucleic acid components.[1,2] Uracil, thymine, and their nucleosides and nucleotides were each shown to undergo a reaction which exhibited a rate maximum in the alkaline range. There was no evidence for free-radical involvement. The results were accounted for by a mechanism in which the neutral substrate was attacked by the anion of the peroxy acid to form products which led to ring cleavage. On the other hand, the effects of hydrogen peroxide on nucleic acids and their components have generally been regarded as the results of radical-forming processes.[3,4] Since the results of Priess and Zillig[5] showed a strong pH dependence for the rate of reaction of hydrogen peroxide with both uracil and thymine, we thought it probable that a part of the reactivity of hydrogen peroxide with these nucleic acid components might be due to attack by the hydroperoxide anion rather than the hydroxyl radical. We have, therefore, reinvestigated the reaction of hydrogen peroxide and several of its derivatives with some nucleic acid components. We also report some comparative data on the reactivity of hydrazine and hydroxylamine.[4,6,7]

Materials and Methods.—Reactions of the peroxides in the alkaline region were followed by iodometric measurement of the concentration of peroxide as a function of time using initially equal concentrations of both reactants (*ca.* 3×10^{-3} *M*). Iodine was liberated quantitatively from the reaction of methyl hydroperoxide and of *tert*-butyl hydroperoxide with iodide in dilute acetic acid by allowing reaction times of 1 hr and 1.5 hr, respectively, and in the case of hydrogen peroxide, by the use of a molybdate catalyst.[8] The reactions of the peroxy acids with iodide were fast. Apparent second-order rate constants, calculated for total substrate and peroxide (*i.e.*, no correction for the per cent ionized), were obtained from slopes of $x/a(a-x)$ *vs.* time plots. The error in the rate constants is of the order of ±4%. The necessary blank corrections were made.[2] EDTA (1×10^{-4} *M*) was added in all experiments (except some of those with thymidine 5′-phosphate) to minimize metal-catalyzed chain decomposition.

The reactions of thymidine 5′-phosphate with hydrogen peroxide were followed by the method of Rhaese, *et al.*[9]

The reactions of hydroxylamine (salt-free) and hydrazine with uracil were followed by measurement of the decrease in the absorption of uracil at 258.5 mμ following dilution of aliquots 100-fold in pH 7 buffer. Reactions were run under pseudo-first-order conditions (*ca.* 1×10^{-2} *M* uracil and 0.5 to 1.2 *M* reagent). Pseudo-first-order rate constants were evaluated from log absorbancy *vs.* time plots, and the data restricted to 5–10% conversion in order to avoid interference from product absorption. The reagents were standardized according to Vogel.[10]

Phosphate and carbonate buffers were used throughout. Reagents were from commercial sources except for methyl hydroperoxide which was prepared by the procedure of Rieche and Hitz[11] as modified by Behrman, *et al.*[12]

Ultraviolet spectra were recorded on a Perkin-Elmer Model 202 instrument; extinction coefficients were measured using a Hitachi Perkin-Elmer Model 139. Urea, oxaluric acid, pyrazolone-3, and isoxazolone-5 were identified according to published procedures.[2,6,13] Urea was estimated quantitatively by the method of Coulombe and Favreau.[14]

Results

Products.—The products from the reactions of uracil and all of the peroxides in the alkaline region consisted of ring-cleavage fragments. All gave urea as one of the products. This was identified by paper chromatography on Whatman No. 1 paper using 1-butanol–

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TABLE I

Nucleophile[a]	pK_a'	k_{max}, M^{-1} min^{-1}	T, °C	Obsd pH_{max}	Calcd pH_{max} [b]	E_a, kcal mol^{-1}	Relative rate at 60°, pH 9	U/T rate[c] ratio
m-Chloroperoxybenzoic acid	7.4[d]	8.3	40	8.7–8.9	8.3	14.5	1576	4.4
Peroxyacetic acid	8.0[e]	3.3	40	8.6–9.0	8.6	14.5	688	4.1
Hydrogen peroxide	10.8[f]	0.74	60	9.8–9.9	9.8	15	24	4.1
Methyl hydroperoxide	10.6[g]	0.32	60	9.5–9.7	9.7	14.5	13	
tert-Butyl hydroperoxide	12.0[f]	0.04	60	9.8–10.3	10.4	20	1	2.2
Hydroxylamine	5.7[h]	0.067	40	7.3–7.6	7.4	10	4.3	
Hydrazine	7.1[h]	0.029	50	9.1–9.6	8.1	13	2.6	

[a] The ionic strength varied from 0.1 to 0.3 *M* for all cases except for *tert*-butyl hydroperoxide for which the range was 0.3–0.5 *M*. [b] The average of the pK_a' values for the indicated nucleophile and for uracil. [c] The ratio of the second-order rate constants for the reactions of uracil and thymine with the indicated peroxide at the pH of the observed rate maximum for uracil. [d] J. F. Goodman, P. Robson, and E. R. Wilson, *Trans. Faraday Soc.*, 58, 1846 (1962). [e] E. Koubek, M. L. Haggett, C. J. Battaglia, K. M. Ibne-Rasa, H. Y. Pyun, and J. O. Edwards, *J. Amer. Chem. Soc.*, 85, 2263 (1963). [f] W. F. Sager and J. C. Hoffsommer, J. *Phys. Chem.*, 73, 4155 (1969). [g] J. E. McIsaac, Jr., H. A. Mulhausen, and E. J. Behrman, Abstracts, 156th National Meeting of the American Chemical Society, Sept 1968, ORGN 70. [h] R. M. Izatt and J. J. Christensen in "Handbook of Biochemistry," H. A. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, pp J49 ff. This reference also gives pK_a' values for uracil, 9.1 (40°), 8.8 (60°).

ethanol–water (4:1:5, v/v) and 1-butanol–acetic acid–water (2:1:1, v/v) as solvents. Ehrlich's reagent was used to detect the spots.[2] Elution and rechromatography gave R_f values of 0.36 and 0.77, respectively. Prior treatment with urease eliminated these spots. The quantitative determination of urea is described later. Oxaluric acid was identified on similar chromatograms from the reactions of uracil with *m*-chloroperoxybenzoic acid, peroxyacetic acid, and hydrogen peroxide by coincidence of its R_f value with authentic material, by reaction with Ehrlich's reagent, and by hydrolysis in dilute HCl to oxalic acid and urea.[2] Oxaluric acid and the other expected intermediates in the hydrolytic decomposition of the initial addition product[2] could not be found for the more slowly reacting peroxides, presumably because their rates of decomposition exceed their rates of formation. The products of the reactions of thymine with *m*-chloroperoxybenzoic acid and with hydrogen peroxide are hydroxyacetone and urea.[2,15]

The hydrazine–uracil reaction mixture upon paper chromatography using 1-butanol–0.6 *N* ammonia (6:1) gave two spots corresponding to urea and pyrazolone-3.[6] Examination of the hydroxylamine–uracil reaction mixture after treatment with 1 *N* NaOH[13] showed the presence of urea and isoxazolone-5.

Kinetics.—Table I and Figure 1 present our kinetic results with uracil. The figure shows that in each case the pH-rate profile is a bell-shaped curve. The table reports the maximum observed second-order rate constant, the temperature and pH at which it was observed, as well as the activation energy for the reaction. Table I also presents data for the reaction of thymine with four peroxides at those pH values for which the corresponding reaction with uracil exhibits a rate maximum. Typical second-order plots are shown in Figure 2.

Effects of Radical Traps.—Table II shows that neither allyl alcohol nor acrylamide has any substantial effect on the extent of urea formation from uracil or from thymine at pH 9.8. Likewise, in experiments in which thymidine 5′-phosphate was monitored at 260 mμ, there was no difference in the rate of change in absorbancy with and without allyl alcohol under the following conditions: (1) 37°, pH 9.8, 1.5×10^{-2} *M* hydrogen peroxide, 1.0×10^{-2} *M* thymidine 5′-phosphate, $\pm 1 \times 10^{-2}$ *M* allyl alcohol; (2) 50°, pH 10.3, 2.5×10^{-2} *M* hydrogen peroxide, 1.5×10^{-2} *M* thymidine 5′-phosphate, $\pm 1.5 \times 10^{-2}$ *M* allyl alcohol. Figure 3 shows, in contrast, that at pH 7.4 the reaction of thymidine 5′-phosphate with hydrogen peroxide in the presence of ferric ions is markedly inhibited by the presence of allyl alcohol. In other experiments with thymidine 5′-phosphate at pH 7.4, we have shown that in the absence of allyl alcohol the omission of ferric ions or the addition of

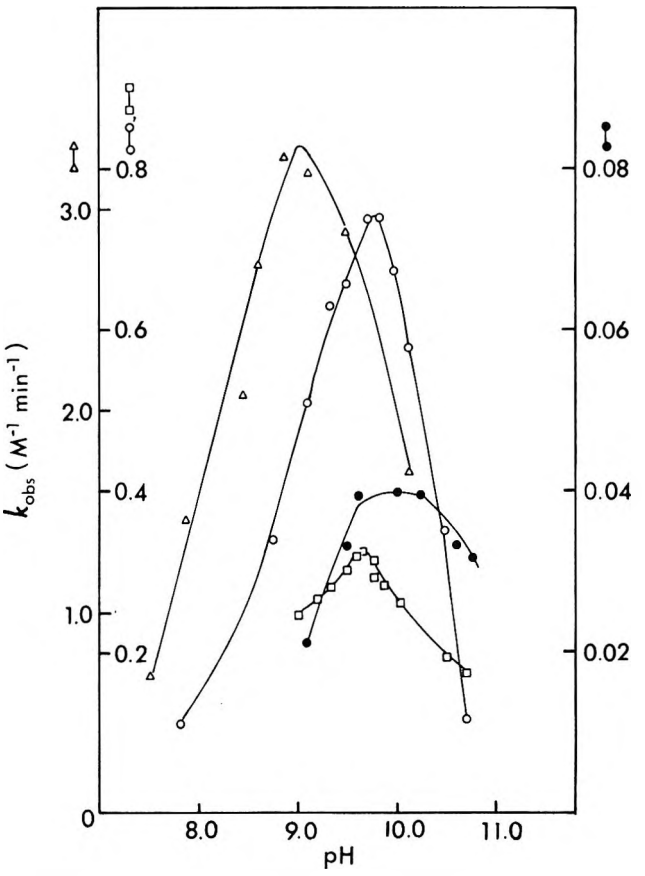


Figure 1.—pH-rate profiles for the reactions of uracil with hydrogen peroxide (○—○), methyl hydroperoxide (□—□), and *tert*-butyl hydroperoxide (●—●) at 60°, and for peroxyacetic acid (△—△) at 40°. Analogous data for the reaction with *m*-chloroperoxybenzoic acid are given in ref 2.

(15) O. Baudisch and L. W. Bass, *J. Amer. Chem. Soc.*, 46, 184 (1924).

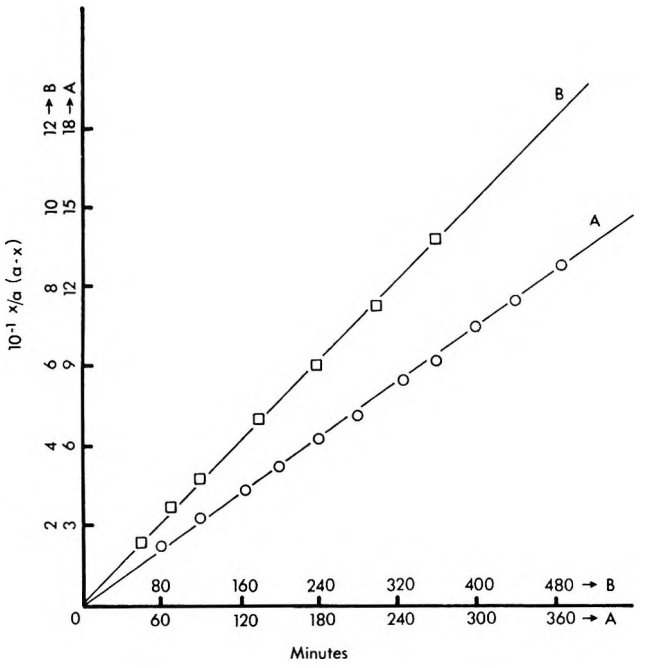


Figure 2.—Second-order plots for the reactions of uracil and thymine with H_2O_2 in the alkaline region. A, hydrogen peroxide and uracil concentrtions were 3.025×10^{-3} M initially, 50°, pH 9.95 in 0.05 M carbonate buffer. B, hydrogen peroxide and thymine concentrations were 5.665×10^{-3} M initially, 60°, pH 9.8 in 0.05 M carbonate buffer; a is the initial concentration of hydrogen peroxide and x is the concentration at time t.

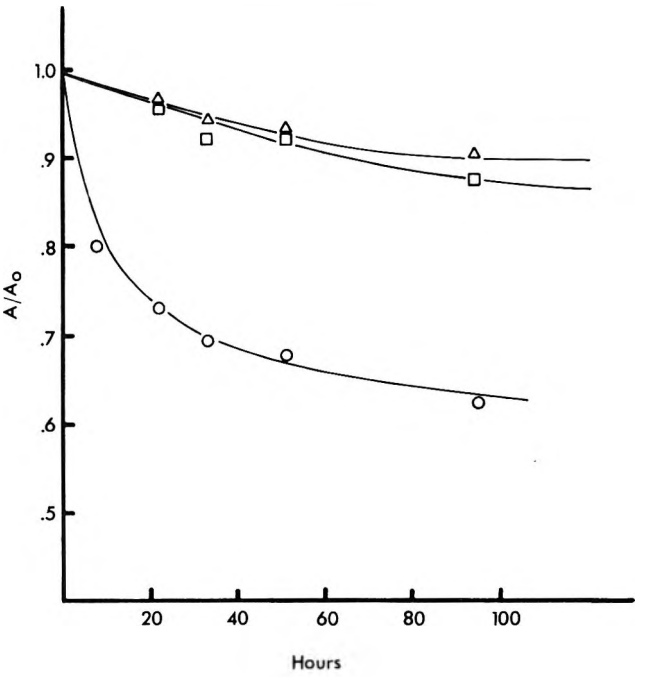


Figure 3.—The reaction of thymidine 5′-phosphate with H_2O_2 at pH 7.4. All reaction mixtures contained 5.6×10^{-2} M hydrogen peroxide, 8.6×10^{-3} M thymidine 5′-phosphate, and 1×10^{-1} M phosphate buffer, pH 7.4. O—O also contained 1×10^{-6} M ferric chloride; □—□, 1×10^{-5} M ferric chloride and 5×10^{-2} M allyl alcohol; △—△, 1×10^{-4} M EDTA and 5×10^{-2} M allyl alcohol. After 22 hr, hydrogen peroxide concentrations were 3.5×10^{-2} M, 3.8×10^{-2} M, and 3.3×10^{-2} M, respectively. After 94 hr, the corresponding values were 2.5×10^{-2} M, 1.8×10^{-2} M, and 1.6×10^{-2} M. Absorbancy measurements were made following dilution of aliquots 100-fold in the same buffer.

TABLE II

UREA FORMATION FROM THE REACTION OF HYDROGEN PEROXIDE WITH URACIL AND THYMINE

1. Uracil, 0.02 M; H_2O_2, 0.04 M, pH 9.8, 60°

Allyl alcohol, M	Mol of urea/mol of uracil, 5 hr	Mol of urea/mol of uracil, 22 hr
0	0.65	0.95
0.01	0.70	0.97
0.02	0.63	0.93

2. Uracil, 0.04 M; H_2O_2, 0.02 M, pH 9.8, 60°

Acrylamide, M	Mol of urea/mol of H_2O_2, 5 hr	Mol of urea/mol of H_2O_2, 22 hr
0	0.40	0.48
0.01	0.48	0.45
0.02	0.35	0.38

3. Thymine, 0.02 M; H_2O_2, 0.06 M, pH 9.8, 60°

Allyl alcohol, M	Mol of urea/mol of thymine, 5 hr	Mol of urea/mol of thymine, 22 hr
0	0.23	0.87
0.01	0.22	0.82
0.02	0.23	0.85

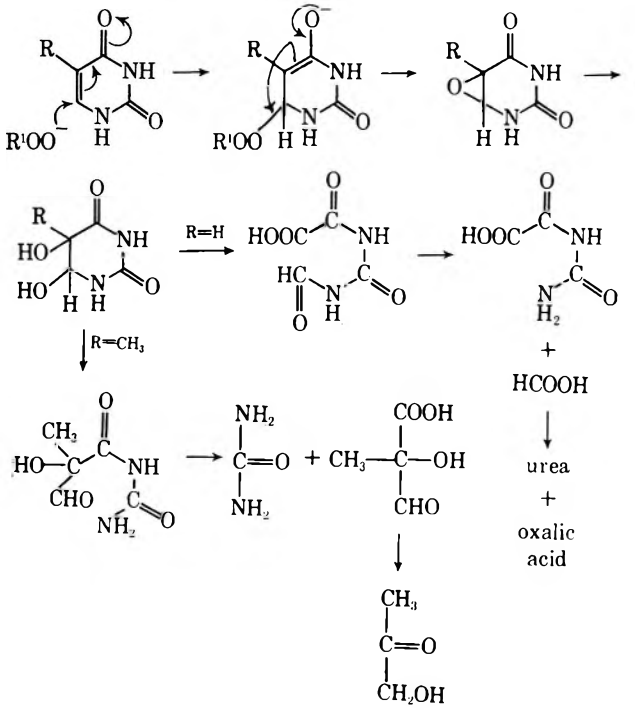
EDTA without ferric ions has little effect either on the rate of loss of absorbancy or on the rate of loss of hydrogen peroxide.

Discussion

Our evidence suggests that the rate maxima which we observe in the alkaline range are the result of bimolecular reactions between the peroxyanion and the neutral substrate. This mechanism requires first-order dependence on each of the reactants and an observed rate maximum midway between the pK_a values of the two reacting species. The rate falls off on the alkaline side because of formation of the anion of the substrate; the decrease on the acid side is due to protonation of the nucleophile. An alternative reaction between the un-ionized peroxide and the ionized base seems unlikely because in each case thymine reacts more slowly than uracil. Nucleophilic attack by the peroxyanion is also consistent with a large body of evidence in other systems.[16,17] We consider, because of the similarity of products, that the same reaction sequence postulated for the case of *m*-chloroperoxybenzoic acid[2] occurs for all of the hydroperoxides (Scheme I). For the case of hydrogen peroxide, it could be argued that the position of the rate maximum is also consistent with the idea that the reactive species is the anion of the hydroxyl radical (pK_a 11.9 ± 0.2[18]). There are several considerations which weigh against the participation of the hydroxyl radical, however. (1) Neither allyl alcohol nor acrylamide affects the rate or extent of formation of urea. Were the reaction sequence to involve a significant free-radical contribution, the addition of a radical trap known to react with hydroxyl radicals such as allyl alcohol or acrylamide[19,20] would result in a decrease in both the yield and rate of formation of a product of the sequence. (2) Homolysis of the alkyl substituted hydroperoxides would produce an alkoxide radical and a hydroxyl radical. The reactions of the alkoxide radical would not be pH-dependent. Were the reactivity of the substituted peroxides due to the reaction of the hydroxyl radical, the

(16) J. B. Lee and B. C. Uff, *Quart. Rev., Chem. Soc.*, **21**, 429 (1967).
(17) R. Curci and J. O. Edwards in "Organic Peroxides," Vol. 1, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1970.
(18) J. L. Weeks and J. Rabani, *J. Phys. Chem.*, **70**, 2100 (1966).
(19) D. H. Volman and J. C. Chen, *J. Amer. Chem. Soc.*, **81**, 4141 (1959).
(20) F. S. Dainton and M. Tordoff, *Trans. Faraday Soc.*, **53**, 499 (1957).

SCHEME I



rate maximum for a given substrate would be at the same pH for all of the hydroperoxides. (3) The observation of second-order kinetics, although conceivable for a radical pathway, is much commoner for nonradical pathways. For example, a nonchain radical mechanism involving rate-limiting homolysis of the peroxide and subsequent attack by the hydroxyl radical on the substrate would show no kinetic dependence on substrate concentration. In contrast to the evidence suggesting the predominance of polar reactions at alkaline pH values, the demonstration that allyl alcohol decreases the rate of loss of thymidine 5′-phosphate in the presence of hydrogen peroxide at pH 7.4 approximately sixfold is positive evidence that a radical pathway is involved under these conditions. There is some reaction of hydrogen peroxide with allyl alcohol, but the change in concentration of hydrogen peroxide due to this reaction is negligible (less than 10% at the highest concentration of allyl alcohol used) up to 30 hr and hence can only account for a small portion of the effect which we observe. The kinetics of the disappearance of thymidine 5′-phosphate under these conditions are complex since Rhaese, *et al.*,[9] have shown that several different reactions, all of which lead to decreases in the absorbancy, occur simultaneously.

Registry No.—Hydrogen peroxide, 7722-84-1; uracil, 66-22-8; thymine, 65-71-4; thymidine 5′-phosphate, 365-07-1; methyl hydroperoxide, 3031-73-0; *tert*-butyl hydroperoxide, 75-91-2; peroxyacetic acid, 79-21-0.

Acknowledgment.—We are grateful to the National Science Foundation (GB-7998) and the Frasch Foundation for support.

Chemistry of Cephalosporin Antibiotics. XXI. Conversion of Penicillins to Cephalexin[1]

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A laboratory synthesis from the biosynthetic penicillins is described for cephalexin (**7**), an orally active deacetoxycephalosporin antibiotic. Penicillins V and G were converted to sulfoxide trichloroethyl esters **3a** and **3b**, respectively, by an esterification to compounds **2a** and **2b** followed by sulfoxidation. The sulfoxide esters **3a** and **3b** were rearranged thermally to their corresponding deacetoxycephalosporin esters **4a** and **4b**. Proof of structure for **4a** and **4b** was supplied by their independent syntheses from 7-aminodeacetoxycephalosporanic acid (**9**). N-Deacylation of **4a** and **4b** afforded a common amino ester, 7-aminodeacetoxycephalosporanic acid trichloroethyl ester (**5d**). Compound **5d** was reacylated in mixed anhydride coupling reactions with *N*-trichloroethyloxycarbonyl-D-α-phenylglycine and with *N*-*tert*-butoxycarbonyl-D-α-phenylglycine. The doubly protected cephalexin derivatives **6** and **12** were deblocked yielding cephalexin in good yield.

Previous publications from these laboratories have disclosed the *in vitro* and *in vivo* biological,[2] toxicological,[3] and pharmacological[3,4] properties of the orally absorbed deacetoxycephalosporin antibiotic, cephalexin (**7**).

We have examined several synthetic routes to cephalexin. One already described by Ryan, *et al.*,[5] proceeds from cephalosporin C through 7-aminodeacetoxycephalosporanic acid (7-ADCA, **9**). Another, which forms the basis of this report, stems from the work of Morin, *et al.*,[6] on the conversion of penicillin sulfoxides to deacetoxycephalosporins. The latter demonstrated that phenoxymethylpenicillin sulfoxide methyl ester, when heated under reflux in toluene with *p*-toluenesulfonic acid, rearranged in about 20% yield to the corresponding deacetoxycephalosporin methyl ester. A plausible mechanism offered was a cleavage of the S–C bond in the thiazolidine ring of the penicillin sul-

(1) Cephalexin is the generic name for 7-(D-2-amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid; cephalexin monohydrate; KEFLEX, Lilly.

(2) (a) W. E. Wick, *Appl. Microbiol.*, **16**, (4), 765 (1967); (b) W. E. Wick and W. S. Boniece, "Proceedings of the 6th International Congress of Chemotherapy," Vienna, Austria, June 26–July 1, 1967, p 717–734.

(3) J. S. Wells, R. O. Froman, W. R. Gibson, N. V. Owen, and R. C. Anderson, *Antimicrob. Ag. Chemother.*, 489 (1968).

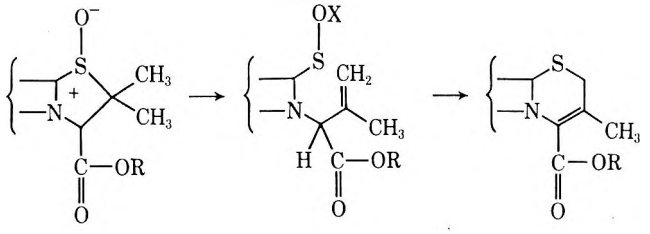
(4) R. S. Griffith and H. R. Black, *Clin. Med.*, **75** (11), 14 (1968).

(5) C. W. Ryan, R. L. Simon, and E. M. Van Heyningen, *J. Med. Chem.*, **12**, 310 (1969).

(6) (a) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **85**, 1896 (1963); (b) *ibid.*, **91**, 1401 (1969); (c) R. B. Morin and B. G. Jackson, U. S. Patent 3,275,626 (1966).

foxide to an unsaturated sulfenic acid (or anhydride) intermediate which recloses, with the sulfur adding to the terminal carbon of the double bond, to produce the more stable dihydrothiazine ring of the deacetoxycephalosporin (Scheme I).

SCHEME I



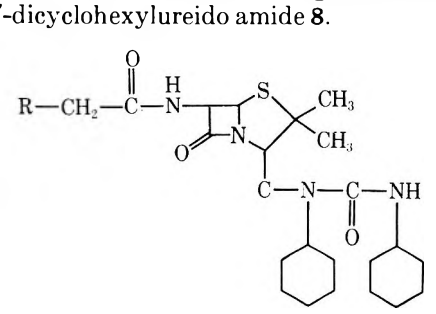
X = H, Ac, $(CH_2)_3SO_3H$

The potential utility of this transformation prompted an attempt to convert such a penicillin-derived deacetoxycephalosporin into cephalexin. Needed were (1) an improvement in yield in the penicillin sulfoxide rearrangement reaction, (2) a chemical or an enzymatic means of replacing the *N*-acyl function originally on the penicillins by the D-α-phenylglycyl moiety of cephalexin, and (3) an easily removable ester-protecting group for the carboxylic acid group in the starting penicillins. This paper describes solutions to these problems which led to a laboratory synthesis of cephalexin from the biosynthetic penicillins V and G (Scheme II).

Formation of Penicillin Sulfoxide Esters.—The earlier workers had found that the ring expansion of the free acid of phenoxymethylpenicillin sulfoxide was accompanied by extensive decarboxylation under the thermal and acidic requirements of the reaction.[6a] Further, the methyl ester employed in the original work could not be saponified satisfactorily without involvement of double-bond isomerization in the dihydrothiazine ring.[6b]

The trichloroethyl ester was a protecting group proven useful in the work of Woodward, *et al.*,[7] in a synthesis of cephalosporin C. Because it was anticipated that this ester might survive the working conditions of the rearrangement and subsequent side-chain cleavage reactions and could be removed without damage to the β-lactam dihydrothiazine ring system, it was deemed a suitable protecting group for our work.

Esterification of the penicillins **1a** and **1b** was achieved at first using trichloroethanol in the presence of *N*,*N*′-dicyclohexylcarbodiimide in methylene chloride solution containing dry pyridine. The yields of penicillin trichloroethyl esters **2a** and **2b** were reasonably good but were attended by a significant amount of the *N*,*N*′-dicyclohexylureido amide **8**.



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The occurrence of this by-product necessitated chromatographic separation or careful and repeated fractional crystallization of the desired esters. Because of this inconvenience and the relatively expensive condensing agent, we sought an alternative method of esterification. We had noted previously that cephalothin[8] reacts with chloroformates[9] to give stable carbonate esters which upon heating in anhydrous solutions undergo a quantitative decarboxylation to esters of the corresponding chloroformate. Accordingly, the penicillins **1a** and **1b** were allowed to react with trichloroethyl chloroformate in anhydrous acetone or tetrahydrofuran containing dry pyridine. The carbonate esters of the penicillins decarboxylated spontaneously at room temperature, affording satisfactory yields of the desired trichloroethyl esters **2a** and **2b**.

Because phenoxymethylpenicillin trichloroethyl ester (**2a**) is difficult to crystallize, it was used as an unpurified oil in the subsequent step.

Sulfoxidation[10] of these esters in chloroform solution using 85% *m*-chloroperbenzoic acid proceeded smoothly to penicillin sulfoxide esters **3a** and **3b**. No or only trace amounts of sulfones were observed in crude products by tlc.

Penicillin Sulfoxide Rearrangement.—As originally conceived, the penicillin sulfoxide rearrangement gave a low yield of the desired deacetoxycephalosporin along with non-β-lactam products[6b] that complicated the isolation procedure. The effects of a variety of acid catalysis and solvents,[11] and of time and temperature, on the course of the reaction were explored.

Ultimately, either acetic anhydride or propane sultone in combination with dimethylformamide or dimethylacetamide at temperatures below 135° was deemed most effective in promoting the desired transformation. Either phenoxymethyl (**3a**) or benzyl (**3b**) penicillin sulfoxide trichloroethyl ester was dissolved in dimethylformamide containing a fivefold excess of acetic anhydride and heated at 130° for 1 hr. The solvent and catalyst were removed under reduced pressure. The residual oil was redissolved in benzene and thoroughly washed with water. The benzene solution was dried and shown by thin layer chromatography and nmr spectroscopy to contain mainly deacetoxycephalosporin esters **4a** and **4b**, respectively.

These benzene solutions, when subjected to Florisil column chromatography, provided pure, crystalline samples of deacetoxycephalosporin esters that were identical (by elementary analyses, melting point, and ir spectra) with authentic phenoxy- (**4a**) and phenyl- (**4b**) acetamidodeacetoxycephalosporin trichloroethyl esters. The known esters were prepared by stepwise acylation of 7-ADCA (**9**) with phenoxy- and phenylacetyl chlorides to the respective acids **10a** and **10b** and esterification of these, using trichloroethyl chloroformate, with

(7) (a) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbüggen, *J. Amer. Chem. Soc.*, **88**, 852 (1966). (b) R. B. Woodward, South African Patent 65105 (Derwent No. 26,121) (1966). (c) The trichloroethyl ester was also successfully used as a protecting group for phosphates in peptide chemistry: F. Eckstein, *Angew. Chem., Int. Ed. Engl.*, **4**, 876 (1965).

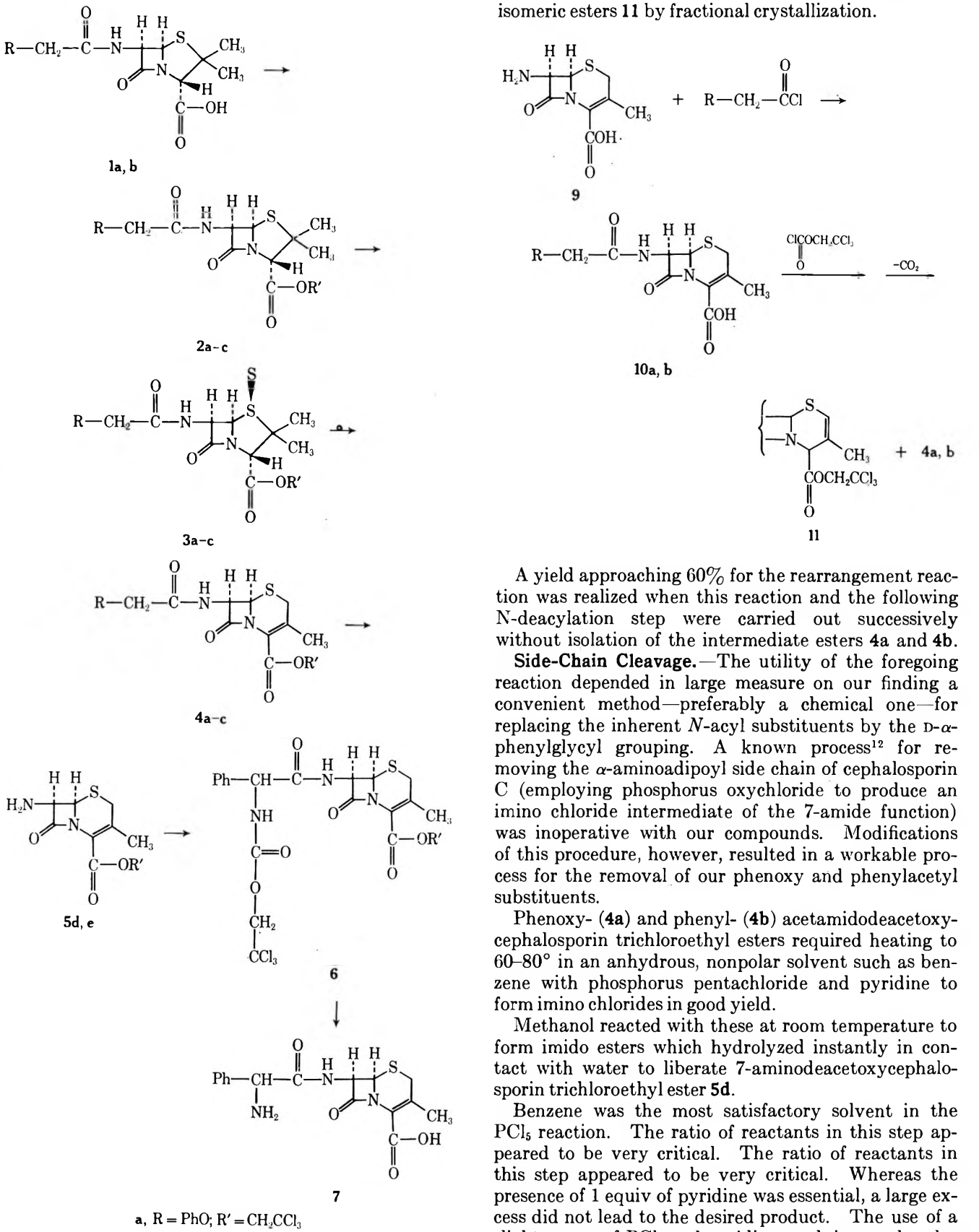
(8) Cephalothin is the generic name for 7-(thiophene-2-acetamido)-cephalosporanic acid; cephalothin sodium salt, KEFLIN, Lilly.

(9) R. R. Chauvette and E. H. Flynn, *J. Med. Chem.*, **9**, 741 (1966).

(10) C. J. Cavallito and J. H. Harley, *J. Org. Chem.*, **15**, 815 (1950).

(11) R. D. G. Cooper, Canadian Patent 817,883 (1969).

SCHEME II



a, R = PhO; R′ = CH_2CCl_3

b, R = Ph; R′ = CH_2CCl_3

c, R = PhO; R′ = CH_2–C$_6$H$_4$–OCH_3

d, R′ = CH_2CCl_3

e, R′ = CH_2–C$_6$H$_4$–OCH_2

subsequent separation of the desired products from Δ^2 isomeric esters **11** by fractional crystallization.

A yield approaching 60% for the rearrangement reaction was realized when this reaction and the following N-deacylation step were carried out successively without isolation of the intermediate esters **4a** and **4b**.

Side-Chain Cleavage.—The utility of the foregoing reaction depended in large measure on our finding a convenient method—preferably a chemical one—for replacing the inherent *N*-acyl substituents by the D-α-phenylglycyl grouping. A known process[12] for removing the α-aminoadipoyl side chain of cephalosporin C (employing phosphorus oxychloride to produce an imino chloride intermediate of the 7-amide function) was inoperative with our compounds. Modifications of this procedure, however, resulted in a workable process for the removal of our phenoxy and phenylacetyl substituents.

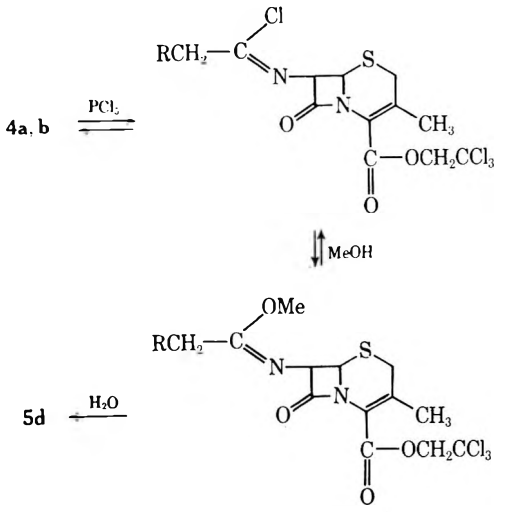
Phenoxy- (**4a**) and phenyl- (**4b**) acetamidodeacetoxycephalosporin trichloroethyl esters required heating to 60–80° in an anhydrous, nonpolar solvent such as benzene with phosphorus pentachloride and pyridine to form imino chlorides in good yield.

Methanol reacted with these at room temperature to form imido esters which hydrolyzed instantly in contact with water to liberate 7-aminodeacetoxycephalosporin trichloroethyl ester **5d**.

Benzene was the most satisfactory solvent in the PCl_5 reaction. The ratio of reactants in this step appeared to be very critical. The ratio of reactants in this step appeared to be very critical. Whereas the presence of 1 equiv of pyridine was essential, a large excess did not lead to the desired product. The use of a slight excess of PCl_5 and pyridine, each in equal molar ratio, over the amount of ester gave optimum yields of side-chain cleavage. The imido ester intermediate was

(12) (a) N. Rusting, J. C. Frielink, and C. F. van der Beek, Netherlands Patent 6,401,421 (Derwent No. 13,407) (1964). (b) The above process was also successfully applied to the side-chain cleavage of penicillin silyl esters: H. Wilhelm, O. Weissenberger, and M. G. van der Hoeven, Netherlands Patent 6,606,872 (Derwent No. 29,574) (1966).

hydrolyzed at room temperature, solubilized generally in a mixture of water–tetrahydrofuran at the existing pH (*ca.* 1.8). The resulting 7-ADCA trichloroethyl



ester (**5d**) so produced formed highly insoluble, crystalline salts with aromatic sulfonic acids, permitting its ready separation from the complex reaction mixtures. The yield of amido ester **5d**, isolated as a tosylate from either phenoxy- (**4a**) or phenyl- (**4b**) acetamidodeacetoxycephalosporanic acid trichloroethyl ester, was consistently 75–80%.

In the experiments in which the penicillin sulfoxide rearrangement was followed by side-chain cleavage without isolation of the first product, the overall yields ranged between 42 and 46%.

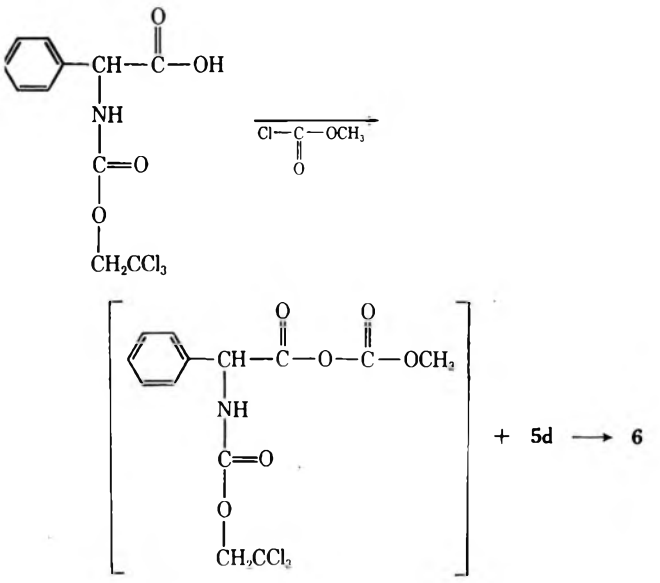
The preparation of 7-ADCA (**9**) from the trichloroethyl ester **5d** by removal of the ester grouping with zinc in acetic acid confirmed that the side-chain cleavage had occurred. The first reported preparation of 7-ADCA (**9**) was from a palladium-catalyzed hydrogenolysis of 7-ACA.[13]

Reacylation of this 7-ADCA trichloroethyl ester (**5d**) with phenoxy and phenyl acetyl chlorides in acetone (with urea in suspension to absorb HCl[14]) regenerated compounds **4a** and **4b**, respectively.

In the penicillin V series, we considered using the *p*-methoxybenzyl ester as a blocking group. Phenoxymethylpenicillin sulfoxide *p*-methoxybenzyl ester (**3c**) did not rearrange to a deacetoxycephalosporin (**4c**) as well as did the corresponding trichloroethyl ester. The relative lability of the *p*-methoxybenzyl group to acid was probably responsible for the lower yields experienced here and in the amide-cleavage reaction that followed. When compound **4c** was allowed to react with PCl_5 and cleaved in the manner described earlier, the expected 7-ADCA *p*-methoxybenzyl ester (**5e**) resulted in 47% yield. While we did not carry out the subsequent steps leading to cephalexin with this ester, we showed that the *p*-methoxybenzyl ester was indeed cleavable in anhydrous trifluoroacetic acid without adverse effect on the β-lactam. We generated the deacetoxycephalosporanic acid **10a** from **4c**.

Reacylation and "Deblocking."—In the reacylation of 7-aminodeacetoxycephalosporanic acid trichloroethyl ester (**5d**), the choice of the *N*-trichloroethyloxycarbonyl derivative of D-α-phenylglycine was one dictated by several considerations. It could be prepared from the same trichloroethyl chloroformate used for the protection of the carboxyl group in the penicillins, and could be removed simultaneously with the ester function in a final reductive "deblocking" step.

Consequently, D-α-phenylglycine was acylated, using trichloroethyl chloroformate in a Schotten–Baumann reaction. The N-protected amino acid was in turn used to acylate 7-ADCA trichloroethyl ester (**5d**) in a mixed anhydride coupling with methyl chloroformate. The resulting "doubly protected" cephalexin **6** was formed in near quantitative yield. This ease of acylation of amino ester **5d** is noteworthy compared with the difficulties commonly encountered in the acylation of 7-ACA[15] and 7-ADCA (**9**),[5] as their zwitterion forms in the same mixed anhydride reaction.



Compound **6** was recovered unchanged when treated with zinc dust in 90% aqueous acetic acid in the manner described for the formation of **9** from 7-ADCA trichloroethyl ester (**5d**). However, reductive cleavage of the protecting groups was effected using zinc dust in cold 90% aqueous formic acid, or using a zinc–copper couple in formic acid diluted ninefold with acetonitrile. In an experiment in which we followed the progress of the reaction at 15-min intervals by a biological assay for cephalexin (accurate to ±10%), the maximal yield of the antibiotic was reached within 45 min. The progress of the deblocking reactions could also be monitored by tlc and paper chromatograms.

Isolation of pure cephalexin was complicated by zinc ions that complexed with this compound. Components of the reaction mixture, such as zinc chloride or salts of formic acid, were shown to solubilize cephalexin in water–acetonitrile solutions from which it is usually precipitated at its isoelectric point.

The difficulties were alleviated either by removing the zinc ions as zinc sulfide or by passing these aqueous solutions at neutral pH through an imino diacetate resin (Bio-Rad, Chelex 100) to exchange sodium for zinc ions. Yields of cephalexin isolated from this "doubly protected" derivative (**6**) were approximately 60%.

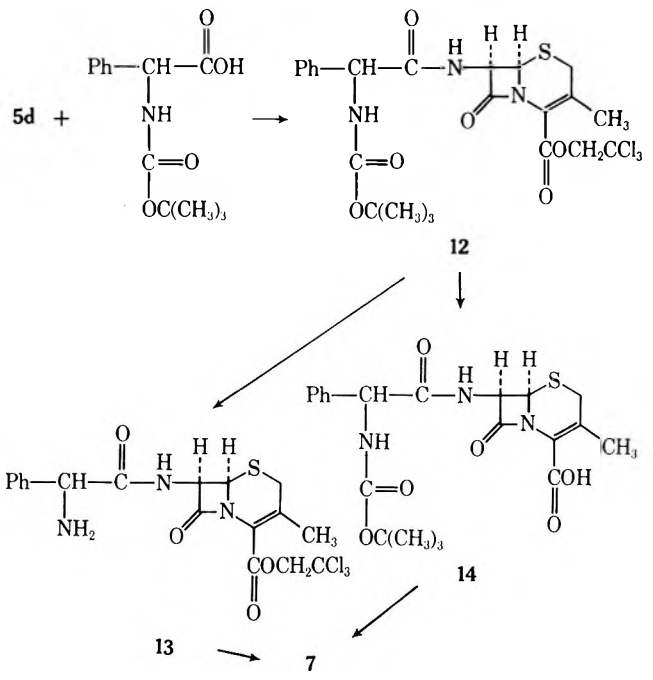
(13) R. J. Stedman, K. Swered, and J. R. E. Hoover, *J. Med. Chem.*, **7**, 117 (1964).

(14) H. M. Higgens, Jr., U. S. Patent 3,351,597 (1967).

(15) J. L. Spencer, E. H. F' nn, R. W. Roeske, F. Y. Siu, and R. R. Chauvette, *J. Med. Chem.*, **9**, 746 (1966).

The acylation of 7-ADCA trichloroethyl ester (**5d**) with *N*-*tert*-butoxycarbonyl-D-α- phenylglycine resulted in a "doubly protected" form of cephalexin (**12**) that necessitated stepwise deblocking (Scheme III). The

SCHEME III



acylation step proceeded in nearly quantitative yields in a wide variety of solvents (acetone, acetonitrile, dimethylformamide, ethyl acetate, methylene chloride). The *tert*-Boc group of **12** was removed by *p*-toluenesulfonic acid treatment in acetonitrile. Although thin layer chromatography indicated nearly complete reaction, cephalexin trichloroethyl ester (**13**) could not be crystallized as a tosylate salt and could only be crystallized with difficulty as the free amino ester. When the crude product was subjected to a zinc–HCl reduction in acetonitrile, the ensuing cephalexin was not pure. The alternate "stepwise-deblocking"scheme became clearly advantageous. We found that dimethylformamide was the best solvent for the deesterification step. Either glacial acetic acid or 98% formic acid, with or without water, in combination with dimethylformamide and zinc dust led to the isolation of *N*-*tert*-butoxycarbonylcephalexin (**14**) in greater than 90% yield. In this solvent a suspected competing reduction of trichloroethyl ester to dichloroethyl ester was apparently minimal.[16] One noteworthy advantage of this two-step process was that the resulting cephalexin derivative (**14**) was extractable into bicarbonate solution and back-titratable into organic solvent and could, therefore, be separated from troublesome inorganic and neutral organic[16] materials.

The action of *p*-toluenesulfonic acid on *N*-*tert*-butoxycarbonylcephalexin (**14**) was most facile in acetonitrile. Removal of the *tert*-Boc group was effected at room temperature within a few hours in this solvent. Under like conditions, compound **14** was either unchanged or little changed in solvents such as acetone, benzene, ethyl acetate, or ethanol, even after several days. The work-up and isolation of cephalexin from this reaction mixture was notably simple. As acetonitrile is an excellent antisolvent for cephalexin, the reaction mixture was diluted with water and adjusted to pH 4.5 with triethylamine or ammonium hydroxide. The cephalexin crystallized immediately in pure form in over 70% overall yield from 7-ADCA trichloroethyl ester (**5d**).

This synthesis, with suitable modifications, has been successfully implemented into a several-kilogram scale preparation of cephalexin.

Experimental Section[17]

2,2,2-Trichloroethyl 6-(Phenoxyacetamido)penicillanate (2a). Method A.—1a potassium salt (77.4 g, 200 mmol) was suspended in 1.5 l. of CH_2Cl_2, and pyridine hydrochloride (24 g, 200 mmol) was added. The suspension was cooled in an ice–H_2O bath for addition of trichloroethanol (30 g, 200 mmol) and then *N*,*N*′-dicyclohexylcarbodiimide (41.2 g, 200 mmol) in 250 ml of CH_2Cl_2, dropwise. The mixture was stirred at room temperature overnight and filtered. The filtrate was washed with 5% $NaHCO_3$ solution and then with H_2O, dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The residual oil, weighing 85 g, gave one spot in tlc.

Nmr and ir spectra of this crude product were consistent with that of the penicillin ester prepared by method B.

A 5-g sample of this oil crystallized (with difficulty) from 10 ml of ether and 35 ml of petroleum ether: recovery, 4.4 g; mp 70–80°.

Anal. Calcd for $C_{18}H_{19}Cl_3N_2O_5S$: C, 44.87; H, 3.97; N, 5.82. Found: C, 45.01; H, 4.17; N, 5.95.

Method B.—1a (8.0 g, 22.8 mmol) was dissolved in 70 ml of CaH_2-dried THF containing dry pyridine (1.8 g, 22.8 mmol). While the reaction mixture was stirred and cooled at ice-bath temperature, trichloroethyl chloroformate (4.8 g, 22.8 mmol) in 30 ml of the same solvent was added dropwise. Stirring was continued at room temperature overnight. After a brief reflux, the solvent was removed *in vacuo*. The residue was dissolved in cold EtOAc, and this was washed with 5% $NaHCO_3$ solution and H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. The residue (an oil weighing 9.8 g) did not crystallize, but gave satisfactory analysis and physical data, comparable to material prepared by method A.

Nmr (in $CDCl_3$) showed signals at τ 8.33 and 8.41 (2 s, 6 H, *gem*-di-CH_3), 5.40 (s, 2 H, α-CH_2), 5.35 (s, 1 H, C_3H), 5.19 (s, 2 H, ester CH_2), 4.28 (m, 2 H, C_5H and C_6H), and 3.17–2.4 (m, 6 H, aromatic and amide N–H). Ir (in $CHCl_3$) showed bands at 2.95 (amide NH), 5.6–5.7 (broad, β-lactam and ester carbonyls), 5.91 and 6.22 μ (amide carbonyl), and in the aromatic regions.

2,2,2-Trichloroethyl 6-(Phenoxyacetamido)penicillanate 1-Oxide (3a).—**2a** (25 g, 53 mmol) was dissolved in 250 ml of $CHCl_3$ and stirred in an ice–H_2O bath; 85% *m*-chloroperbenzoic acid (10 g, 50 mmol) in 150 ml of $CHCl_3$ was added dropwise over 30 min. Stirring and cooling were maintained for another 30 min. The reaction solution was washed with 5% $NaHCO_3$ solution and then with H_2O, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residual oil was redissolved in 100 ml of Et_2O (and a few drops of THF to clear the solution) and chilled for crystallization, yield 23.0 g (94%), mp 145–146°.

(16) When this neutral fraction was chromatographed over silica, eluting with benzene–ethyl acetate (3:1), a cephalexin derivative was isolated and shown by nmr and mass spectra to be the dichloroethyl ester. The nmr, in $CDCl_3$, showed a triplet centered at τ 4.1 ascribable to the dichloromethine proton and a doublet centered at τ 4.55 for the methylene protons, shifted from τ 5.1 in the normal trichloroethyl ester. This neutral fraction represented less than 7% weight of the starting material.

(17) All melting points were taken on a Mel-Temp apparatus and are uncorrected. All tlc was done using silica gel plates, C_6H_6–EtOAc (7:3) as eluent (unless otherwise stated), and an iodine chamber to develop the spots. Bioautographs (against *Bacillus subtilis* seeded agar plates) were made from paper chromatograms developed in *n*-BuOH–AcOH–H_2O. All evaporations were performed below 55° with a rotary vacuum evaporator. Nmr spectra were taken on a Varian Associates Model HR-60 spectrometer with TMS as internal standard. Uv spectra were recorded with a Cary spectrophotometer; ir spectra were recorded on Beckman IR-7 or Perkin-Elmer Models 21 or Infracord spectrophotometers.

Nmr (in $CDCl_3$) showed signals at τ 8.76 and 8.28 (2 s, 6 H, *gem*-di-CH_3), 5.51 (s, 2 H, α-CH_2), 5.23 (d, 2H, ester CH_2), 5.20 (s, 1 H, C_3H), 4.89 (d, 1 H, C_5H), 3.91 (q, 1 H, C_6H), 3.19–2.56 (m, 5 H, aromatic H), and 1.75 (d, 1 H, amide N–H). Ir (in $CHCl_3$) showed bands at 2.95 (amide NH), 5.50 and 5.61 (β-lactam and ester carbonyls, respectively), 5.90 and 6.65 μ (amide carbonyls), and in the aromatic regions.

Anal. Calcd for $C_{18}H_{19}Cl_3N_2O_6S$: C, 43.43; H, 3.85; N, N, 5.63; S, 6.44. Found: C, 43.66; H, 4.00; N, 5.78; S, 6.54.

2,2,2-Trichloroethyl 6-(Phenylacetamido)penicillanate (2b). Method A.—1b potassium salt (37.1 g, 100 mmol) was suspended in 1 l. of CH_2Cl_2. A slurry of pyridine hydrochloride (12 g, 100 mmol) in 50 ml of CH_2Cl_2 was added. A solution of 2,2,2-trichloroethanol (15 g, 100 mmol) in 50 ml of CH_2Cl_2 and then *N*,*N*′-dicyclohexylcarbodiimide (20.6 g, 100 mmol) in 100 ml of CH_2Cl_2 were added. The mixture was stirred at room temperature overnight and worked up as described for the preparation of **2a**. The product crystallized from Et_2O, yield 30.3 g (65%), mp 157–159°.

Nmr and ir spectra were consistent with that of material prepared by method B.

Method B.—1b potassium salt (8.5 g, 22.8 mmol) was suspended in 100 ml of molecular-sieve-dried Me_2CO containing dry pyridine (2.7 g, 34 mmol). The mixture was stirred at ice-H_2O temperature. 2,2,2-Trichloroethyl chloroformate (4.8 g, 22.8 mmol) in 30 ml of dry Me_2CO was added dropwise. Stirring and cooling were maintained overnight. Insoluble material was filtered. Addition of 50 ml of H_2O to the briefly warmed filtrate caused the product to crystallize, yield 7 g (66%), mp 160–161°.

Nmr (in $CDCl_3$) showed signals at τ 8.49 (s, 6 H, *gem*-di-CH_3), 6.41 (s, 2 H, α-CH_2), 5.55 (s, 1 H, C_3 H), 5.28 (s, 2 H, C_3 ester CH_2), 4.4 (m, 2 H, C_5 H and C_6 H), 3.75 (d, 1 H, amide NH), and 2.74 (s, 5 H, aromatic H). Ir (in $CHCl_3$) showed bands at 2.92 (amide NH), 5.6–5.7 (broad, β-lactam and ester carbonyls), 5.92 and 6.62 μ (amide carbonyl), and in the aromatic regions.

Anal. Calcd for $C_{18}H_{19}Cl_3N_2O_4S$: C, 46.41; H, 4.11; N, 6.02. Found: C, 46.75; H, 4.27; N, 5.99.

2,2,2-Trichloroethyl 6-(Phenylacetamido)pencillanate 1-Oxide (3b).—**2b** (4.7 g, 10 mmol) was dissolved in 50 ml of $CHCl_3$, The solution was stirred and cooled (to *ca.* 0°), and 85% *m*-chloroperbenzoic acid (2.2 g, 11 mmol) in 25 ml of $CHCl_3$ was added dropwise. The mixture was chilled for 2 hr. It was then washed with 5% $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue was triturated with Et_2O and dried to give 4.05 g (84%), mp 167–169°. Recrystallization from THF–Et_2O raised the melting point to 174–176°.

Nmr (in $CDCl_3$) showed signals at τ 8.74 and 8.25 (2s, 6 H, *gem*-di-CH_3), 6.4 (s, 2 H, α-CH_2), 5.23 (s, 1 H, C_3 H), 5.16 (q, 2 H, ester CH_2), 4.99 (d, 1 H, C_5 H), 3.97 (q, 1 H, C_6 H), 2.81 (d, 1 H, amide NH), 2.70 (s, 5 H, aromatic H). Ir (in $CHCl_3$) showed bands at 2.95 (amide NH) and 5.50, 5.62, and 5.90 μ (β-lactam, ester, and amide carbonyls, respectively).

Anal. Calcd for $C_{18}H_{19}Cl_3N_2O_5S$: C, 44.88; H, 3.97; N, 5.81; Cl, 22.07. Found: C, 45.04; H, 4.20; N, 5.73; Cl, 21.75.

***p*-Methoxybenzyl 6-(Phenoxyacetamido)penicillanate 1-Oxide (3c).**—1a potassium salt (3.9 g, 10 mmol) was suspended in 50 ml of DMF containing *p*-methoxybenzyl bromide (2.0 g, 10 mmol). The mixture was stirred at room temperature for 90 min. The mixture was diluted with C_6H_6 and washed three times with H_2O and then with 5% $NaHCO_3$ solution. The C_6H_6 solution was dried ($MgSO_4$) and evaporated to a clear gum *in vacuo*. This was redissolved in 50 ml of $CHCl_3$, chilled in an ice-H_2O bath, and treated with *m*-chloroperbenzoic acid (1.7 g, 10 mmol). The mixture was cooled, stirred for 15 min, and extracted with 50 ml of saturated $NaHCO_3$ solution and then with 30 ml of H_2O. The $CHCl_3$ solution was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residual glass was crystallized from THF–Et_2O to give 3.4 g (73% over-all yield from phenoxymethyl penicillin).

Nmr (in $CDCl_3$) showed signals at τ 8.96 and 8.39 (2s, 6 H, *gem*-di-CH_3), 6.2 (s, 3 H, OCH_3), 5.50 (s, 2 H, α-CH_2), 5.36 (s, 1 H, C_3 H), 5.0 (d, 1 H, C_5 H), 4.85 (d, 2 H, ester CH_2), 3.96 (q, 1 H, C_6 H), 3.2–2.62 (m, 9 H, aromatic H), and 1.75 (d, 1 H, amide NH). Ir (in $CHCl_3$) showed bands at 2.95 μ (amide NH), 5.55, 5.72, and 5.92 μ (β-lactam, ester, and amide carbonyls respectively), and in the aromatic region.

Anal. Calcd for $C_{24}H_{26}N_2O_7S$: C, 59.25; H, 5.39; N, 5.76; S, 6.59. Found: C, 59.49; H, 5.61; N, 5.97; S, 6.44.

2,2,2-Trichloroethyl 7-Phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (4a). 1. Rearrangement of Penicillin Sulfoxide Ester.—**3a** (4.6 g, 9.2 mmol) was dissolved in a mixture of 260 ml of DMF and Ac_2O (4.9 g, 48 mmol), preheated to 130°. The mixture was maintained at this temperature for 1 hr. The solvent and excess catalyst were removed by evaporation *in vacuo*. The residue was taken up in 500 ml of C_6H_6 for several H_2O washes. The C_6H_6 solution was dried ($MgSO_4$), concentrated to a smaller volume *in vacuo*, and passed through a Florisil column. The C_6H_6 solution was again concentrated to dryness *in vacuo*. The residual oil did not crystallize but appeared to be a single material (tlc). This material was identical (nmr, ir) with the deacetoxycephalosporanic acid trichloroethyl ester prepared by the following alternative methods.

2. Acylation and Esterification of 7-ADCA (9). 7-Phenoxyacetamido-3-methyl-3-cephem-4-carboxylic Acid (10a). Method A.—**9** (10.7 g, 50 mmol) was dissolved in 400 ml of H_2O and 300 ml of Me_2CO containing $NaHCO_3$ (14 g, 166 mmol). With stirring and cooling in ice, phenoxyacetyl chloride (8.5 g, 50 mmol) in 100 ml of dry Me_2CO was added dropwise. The mixture was stirred in the cold overnight. Me_2CO was evaporated *in vacuo*. The aqueous solution was washed with EtOAc and then acidified to pH 2.5 in the cold and in the presence of EtOAc. The organic layer was separated, washed with cold H_2O, dried ($MgSO_4$), and concentrated to a smaller volume from which the product crystallized to give 12.4 g (71%). For characterization a small sample was recrystallized from EtOAc–petroleum ether, mp 186–188° dec.

Nmr (in DMSO-d_6) showed signals at τ 7.99 (s, 3 H, C_3 CH_3), 6.73 and 6.40 (2d, 2 H, C_2 H_2), 5.40 (s, 2 H, α-CH_2), 4.95 (d, 1 H, C_6 H), 4.40 (q, 1 H, C_7 H), 3.21–2.58 (m, 5 H, aromatic H), and 1.48 (d, 1 H, NH). Ir (in a Nujol mull) showed bands at 2.97 (amide NH), 5.7–6.0 μ (broad, β-lactam, acid and amide carbonyl, respectively), and in aromatic region. Uv (in EtOH) showed maxima at 215 mμ (ϵ 12,600), 2.67 (7210), and 272 (6100).

The electrometric titration (in 66% aqueous DMF) showed a titratable group at 5.8 and an average molecular weight of 333 (calcd 349).

Anal. Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.13; H, 4.92; N, 8.01.

Method B.—**4c** (550 mg, 1.2 mmol) was dissolved in 20 ml of C_6H_6. Trifluoroacetic acid (3 ml) was added, and the mixture was stirred at room temperature for 30 min. The solvent and reagents were removed under reduced pressure. The residue was shaken with a C_6H_6–aqueous $NaHCO_3$ mixture. The aqueous portion was separated and acidified to pH 2. The crystalline precipitate, weighing 135 mg (33% yield), gave nmr and ir spectral data identical with those from the cephalosporanic acid **10a** prepared by the alternate procedure.

A mixture of this acid (**10a**) (85 g, 244 mmol), dry pyridine, (23.8 g, 300 mmol), and 2,2,2-trichloroethanol (36.6 g, 244 mmol) in 2.5 l. of CH_2Cl_2 was treated with *N*,*N*′-dicyclohexylcarbodiimide (55.6 g, 270 mmol) in 200 ml of the same solvent by dropwise addition. The mixture was stirred at room temperature overnight. The dicyclohexylurea was filtered. The solvent was replaced by cold EtOAc for successive cold washes with H_2O, 5% HCl, 5% $NaHCO_3$ solution, and H_2O. The EtOAc solution was dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was redissolved in 600 ml of anhydrous Et_2O. The ethereal solution was concentrated to about 300 ml and refrigerated for fractional crystallization of the Δ^3 ester from the more soluble isomeric Δ^2 product, yield 51.3 g (44%), mp 119°.

Nmr (in $CDCl_3$) showed signals at τ 7.86 (s, 3 H, C_3 CH_3), 6.89 and 6.51 (2 d, 2 H, C_2 H_2), 5.54 (s, 2 H, α-CH_2), 5.22 (d, 2 H, C_4 ester CH_2), 5.08 (d, 1 H, C_6 H), 4.29 (q, 1 H, C_7 H), and 3.30–2.45 (m, 6 H, aromatic H and amide NH). Ir (in $CHCl_3$) showed bands at 3.0 (amide NH) and 5.62, 5.79, and 5.94 μ (β-lactam, ester, and amide carbonyls, repectively), and in the aromatic region. Uv (in EtOH) showed maxima at 216 mμ (ϵ 13,100), 268 (6800), and 274 (6300).

Anal. Calcd for $C_{18}H_{17}Cl_3N_2O_5S$: C, 45.05; H, 3.57; N, 5.84. Found: C, 45.22; H, 3.77; N, 5.75.

3. Reacylation of 7-ADCA Ester (5d).—5d was acylated using phenoxyacetyl chloride in the manner described below for **4b**. The product, formed in 78% yield, was identical (nmr and ir) with material prepared by alternate methods.

2,2,2-Trichloroethyl 7-Phenylacetamido-3-methyl-3-cephem-4-carboxylate (4b). 1. Rearrangment of the Penicillin Sulfoxide Ester (3b).—**3b** (4.0 g, 8.5 mmol) dissolved in 200 ml of DMF containing Ac_2O (4 ml, 42 mmol) was placed in a preheated oil bath and heated for 1 hr at 130°. The solvent and catalyst were then removed by evaporation *in vacuo*. The residue was dis-

solved in 200 ml of C_6H_6, washed several times with H_2O, dried ($MgSO_4$), and concentrated to a smaller volume (about 50 ml). The concentrated C_6H_6 solution was passed through a Florisil column while eluting with additional C_6H_6 containing 5% EtOAc. The eluent was diluted with ether and refrigerated to induce crystallization. The pure product weighed 800 mg (20% yield), mp 162–164°.

Nmr (in $CDCl_3$) showed signals at τ 7.83 (s, 3 H, C_3 CH_3), 6.87 and 6.48 (2d, 2 H, C_2 H_2), 6.41 (s, 2 H, α-CH_2), 5.39–4.92 (three overlapping d, 3 H, ester CH_2 and C_6H), 4.25 (q, 1 H, C_7 H), 3.31 (d, 1 H, amide NH), and 2.70 (s, 5 H, aromatic H).

Anal. Calcd for $C_{18}H_{17}Cl_3N_2O_4S$: C, 46.62; H, 3.70; N, 6.04. Found: C, 46.87; H, 3.91; N, 6.01.

2. Acylation and Esterification of 7-ADCA (9). 7-Phenylacetamido-3-methyl-3-cephem-4-carboxylic Acid (10b).—9 (4.2 g, 20 mmol) was acylated with phenylacetyl chloride in the manner described for **10a**. The crude product was crystallized by trituration with petroleum ether and recrystallized from *i*-PrOH–petroleum ether, yield 3.5 g (53%), mp 198–200°.

The nmr and ir spectra were consistent with a deacetoxycephalosporanic acid.

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.43. Found: C, 57.92; H, 4.93; N, 8.33.

The acid product from above was esterified using *N,N'*-dicyclohexylcarbodiimide in the manner described with **10a**. The product was identical (melting point, nmr, and ir) with a sample prepared *via* the penicillin sulfoxide ester rearrangement.

3. Reacylation of 7-ADCA Ester (5d).—**5d**, regenerated from its tosylate (14 g, 27 mmol), was dissolved in 100 ml of molecular-sieve-dried Me_2CO. Urea (3.25 g, 54 mmol) was suspended to absorb the HCl from the acylation.[14] The reaction mixture was stirred during dropwise addition of phenylacetyl chloride (4.18 g, 27 mmol) in 50 ml of dry Me_2CO. The mixture was stirred for an additional hour and then filtered, and the Me_2CO was removed by evaporation. The residue was dissolved in cold EtOAc for successive cold washes with H_2O, 5% HCl, 5% $NaHCO_3$ solution, and H_2O. The EtOAc solution was dried ($MgSO_4$), concentrated to a smaller volume, and diluted with ether. The product crystallized at room temperature. The first crop weighed 5.35 g (43% yield). An additional crop raised the yield to 64%.

Nmr (in $CDCl_3$) showed signals at τ 7.82 (s, 3 H, C_3 CH_3), 6.90 and 6.50 (2d, 2 H, C_2 H_2), 6.42 (s, 2 H, α-CH_2), 5.17 (d, 2 H, C_4 ester CH_2), 5.01 (d, 1 H, C_6 H), 4.28 (q, 1 H, C_7 H), 3.30 (d, 1 H, amide NH), and 2.78 (s, 5 H, aromatic H). Ir (in CCl_3) showed bands at 2.95 (amide NH), 5.60, 5.75, and 5.95 μ (β-lactam, ester, and amide carbonyls, repectively), and in the aromatic region.

***p*-Methoxybenzyl 7-Phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (4c).**—**3c** (3.4 g, 7.0 mmol) and 3.5 ml of Ac_2O were added to 200 ml of DMF preheated to 134°. The solution was maintained at this temperature for 1 hr. The volatile portion of the mixture was removed *in vacuo*. The residual oil crystallized on standing. The product, after trituration with CCl_4, weighed 860 mg (26% yield).

Nmr (in $CDCl_3$) showed all the signals expected for a phenoxyacetamidodeacetoxycephalosporin and, in addition, signals at τ 6.23 (s, 3 H, *p*-OCH_3), 4.81 (s, 2 H, ester CH_2), and 3.2–2.5 (m, four additional aromatic H).

Anal. Calcd for $C_{24}H_{24}N_2O_6S$: C, 61.53; H, 5.16; N, 5.98. Found: C, 59.92; H, 5.32; N, 6.36.

2,2,2-Trichloroethyl 7-Amino-3-methyl-3-cephem-4-carboxylate (5d). *p*-Toluenesulfonic Acid Salt. 1. Cleavage of the Phenoxyacetyl Side Chain. Method A.—**4a** (2.2 g, 4.6 mmol) was dissolved in 120 ml of CaH_2-dried C_6H_6 containing dry pyridine (540 mg, 6.8 mmol). The solution was placed in a water bath at 65°. While stirring, PCl_5 (1.4 g, 6.8 mmol) was added, and the mixture was stirred at this temperature and under nitrogen for 2 hr. The C_6H_6 was removed *in vacuo* and replaced by 240 ml of MeOH. The solution was stored at room temperature under nitrogen overnight. The alcohol was removed *in vacuo*. The residue was redissolved in a mixture of H_2O–THF at room temperature for 15 min to effect hydrolysis. The organic solvent was evaporated. The aqueous portion, with its oily precipitate, was slurried with EtOAc and adjusted to pH near 7 with 1 *N* NaOH. The EtOAc solution was separated, washed with H_2O, dried ($MgSO_4$), and concentrated to about 80 ml. The concentrate was treated with *p*-toluenesulfonic acid monohydrate (875 mg, 4.6 mmol) in 70 ml of the same solvent to precipitate the product as a crystalline salt, 1.9 g (80% yield).

Nmr (in DMSO-d_6) showed signals at τ 7.76 (s, 3 H, C_3 CH_3), 7.70 (s, 3 H, TSH CH_3), 6.40 (s, 2 H, C_2 H_2), 4.91 τ (s, 2 H, ester CH_2), 4.80 (s, 2 H, C_6 H and C_7 H), and 2.90–2.34 (4s, 4 H, aromatic H). Ir (in a Nujol mull) showed bands at 5.65 (β-lactam carbonyl), 5.81 (ester carbonyl), 8.1 μ (SO_3), and in the aromatic region. Electrometric titration (in 66% aqueous DMF) showed a basic pK_a of 3.9 and an average molecular weight of 380 (calcd 346). A sample was recrystallized from EtOH–ether, mp 193–194° dec.

Anal. Calcd for $C_{17}H_{19}Cl_3N_2O_6S_2$: C, 39.42; H, 3.69; N, 5.41. Found: C, 39.50; H, 3.84; N, 5.23.

Method B.—**3a** (4.6 g, 9.2 mmol) was dissolved in 260 ml of DMF containing Ac_2O (4.9 g, 48 mmol). The mixture was heated in an oil bath at 130° for 1 hr. The solvent was evaporated *in vacuo*. The residue was dissolved in 500 ml of C_6H_6 and washed three times with 400-ml portions of H_2O (saturated NaCl solution was used to break an emulsion that formed). The C_6H_6 solution was dried ($MgSO_4$) and concentrated *in vacuo* to about 200 ml. To the concentrate were added dry pyridine (1.1 g, 13.9 mmol) and PCl_5 (2.9 g, 13.9 mmol); the mixture, under nitrogen, was stirred and heated in water bath at 65° for 2 hr. The C_6H_6 was replaced by 400 ml of cold MeOH. The MeOH was removed and the residue redissolved in 100 ml of H_2O and 200 ml of THF for 20 min at room temperature to hydrolyze the intermediate. The organic solvent was evaporated and the aqueous layer adjusted to pH 6.5 in the presence of EtOAc. The EtOAc layer was separated, washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to about 125 ml. *p*-Toluenesulfonic acid monohydrate (1.75 g, 9.2 mmol) in 25 ml of the same solvent was added. The product immediately crystallized, 2.2 g (46% over-all yield).

Method C.—In the manner identical with method B, propane sultone (5.6 g, 46 mmol) was used in the place of Ac_2O (42% over-all yield).

The 7-ADCA trichloroethyl ester (**5d**) from both reactions B and C gave nmr spectra consistent with the expected structure.

2. Cleavage of the Phenylacetyl Side Chain.—**4b** (800 mg, 1.7 mmol) was allowed to react in the manner described for **4a**, giving 660 mg (75% yield) of the same product.

2,2,2-Trichloroethyl 7-Amino-3-methyl-3-cephem-4-carboxylate (5d). 2-Naphthalenesulfonic Acid Salt.—Naphthalenesulfonic acid was as effective as *p*-toluenesulfonic acid in isolating the product from the side-chain cleavage. This amino ester salt also precipitated from EtOAc and recrystallized from EtOH–ether, mp 192–193° dec.

Nmr and ir spectra were consistent with the proposed product.

Anal. Calcd for $C_{20}H_{19}Cl_3N_2O_6S_2$: C, 43.36; H, 3.45; N, 5.05. Found: C, 43.56; H, 3.65; N, 4.92.

2,2,2-Trichloroethyl 7-Amino-3-methyl-3-cephem-4-carboxylate (5d). Free Amino Ester. Method A.—The free amino ester may be obtained from evaporation of the final EtOAc solution in the PCl_5 reaction. The oily residue crystallized on refrigeration for several hours or from EtOAc–methylcyclohexane or cyclohexene–petroleum ether solutions.

Nmr (in $CDCl_3$) showed signals at τ 8.03 (broad s, 2 H, amide NH_2), 7.82 (s, 3 H, C_3 CH_3), 6.79 and 6.36 (2d, 2 H, C_2 H_2), 5.28–4.96 (m, 4 H, ester CH_2, C_6 H and C_7 H).

Method B.—The free amino ester **5d** was also recovered from its tosylate by suspending the salt in H_2O–ether and adjusting the pH to near 7 with 1 *N* NaOH. The ethereal solution was separated, dried ($MgSO_4$), and evaporated to dryness *in vacuo*.

The residual oil slowly crystallized under refrigeration. This recrystallized, with difficulty, from wet cyclohexene, mp 82–84°.

Anal. Calcd for $C_{10}H_{11}Cl_3N_2O_3S \cdot H_2O \cdot C_6H_{10}$: C, 43.10; H, 5.19; N, 6.28. Found: C, 43.50; H, 5.15; N, 6.35.

***p*-Methoxybenzyl 7-Amino-3-methyl-3-cephem-4-carboxylate (5e) *p*-Toluenesulfonic Acid Salt.**—**4c** (984 mg, 2.1 mmol) was dissolved in 30 ml of dry C_6H_6 containing dry pyridine (245 mg, 3.1 mmol) and heated to 50° for 2 hr with PCl_5 (645 mg, 3.1 mmol). The C_6H_6 was replaced by 60 ml of cold MeOH. The solution was stirred at room temperature overnight, treated with H_2O for 20 min, and then evaporated to dryness *in vacuo*. The residue was redissolved in EtOAc–H_2O for adjustment to pH near 7. The EtOAc layer was separated, dried ($MgSO_4$), and treated with *p*-toluenesulfonic acid monohydrate (400 mg, 2.1 mmol). A crystalline precipitate was filtered, washed with Me_2CO, and vacuum dried. The product weighed 500 mg (47% yield), mp 162–165°.

Nmr (in DMSO-d_6) showed signals at τ 7.93 (s, 3 H, C_3 CH_3), 7.75 (s, 3 H, TSA CH_3), 6.49 (s, 2 H, C_2 H_2), 6.32 (s, 3 H, OCH_3),

4.89 (s, 4 H, β-lactam and ester CH_2), and 3.21–2.42 (m, 8 H, aromatic H).

Recrystallization from EtOH–ether provided an analytical sample.

Anal. Calcd for $C_{23}H_{26}N_2O_7S_2$: C, 54.52; H, 5.17; N, 5.53. Found: C, 54.30; H, 5.25; N, 5.67.

7-Amino-3-methyl-3-cephem-4-carboxylic Acid (9).—**5d** (freed from its tosylate, 2.1 g, 4 mmol) was dissolved in 50 ml of 90% aqueous AcOH, cooled in an ice–H_2O bath, and treated with 2 g of zinc dust. The mixture was stirred at below room temperature for 3 hr. AcOH was removed *in vacuo*. The residue was dissolved in 50 ml of cold H_2O, slurried with 100 ml of cold EtOAc, and acidified to pH below 1 with concentrated HCl. After filtration, the aqueous layer was separated and readjusted in the cold to pH 3.6 using NH_4OH. The crystalline product was filtered, washed with cold H_2O, vacuum dried, and weighed, 690 mg (81% yield).

Nmr (in D_2O–$NaHCO_3$) showed signals at τ 8.09 (s, 3 H, C_3 CH_3), 6.82 and 6.34 (2 d, 2 H, C_2 H_2), 5.28 (d, 1 H, C_6 H), and 4.96 (d, 1 H, C_7 H) and corresponded exactly with that of another sample of this material prepared by the catalytic hydrogenolysis of 7-aminocephalosporanic acid.[13]

Electrometric titration (in 66% aqueous DMF) showed pK_a values of 3.3 and 6.2 and an average molecular weight of 217 (calcd 214).

2,2,2-Trichloroethyl Chloroformate.—To a solution of $COCl_2$ (40 g, 405 mmol) in 200 ml of Na-dried C_6H_6 were added dropwise trichloroethanol (15.8 g, 106 mmol) and dry pyridine (12.0 g, 152 mmol) in 200 ml of dry C_6H_6 and 400 ml of anhydrous ether with occasional cooling to keep the temperature slightly below 20°. The addition required about 2 hr. The pyridine hydrochloride was removed by filtration. The filtrate was cooled and then poured into 1 l. of ice–H_2O, shaken in a separatory funnel. The organic layer was quickly separated, dried ($MgSO_4$), and evaporated *in vacuo*. Distillation over $CaCO_3$ gave 15 g (67% yield) of the chloroformate, bp 43° (0.5 mm), $n^{25}D$ 1.4698.

Nmr (in $CDCl_3$) showed a lone signal at τ 5.12. Ir (in $CHCl_3$) showed bands at 5.63 and 8.85 μ (broad).

Redistillation afforded an analytical sample.

Anal. Calcd for $C_3H_2Cl_4O_2$: Cl, 66.94. Found: Cl, 66.74.

***N*-(2,2,2-Trichloroethyloxycarbonyl)-D-α-phenylglycine.**—To a solution of D-α-phenylglycine (22.7 g, 150 mmol), 300 ml of H_2O, 160 ml of 1 *N* NaOH, and 150 ml of ether were added dropwise, over a period of 1 hr, 2,2,2-trichloroethyl chloroformate (42.5 g, 200 mmol) in 200 ml of Na-dried dioxane and simultaneously 200 ml of 1 *N* NaOH, while cooling at ice–alcohol temperature and while stirring. The mixture was maintained cold for an additional hour and then washed with large volumes of ether. The aqueous mixture, slurried with EtOAc, was acidified in the cold to pH 2.5 with syrupy phosphoric acid. The EtOAc solution was separated, washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. The residual oil crystallized when slurried with petroleum ether, yield 43 g (87%), mp 142–144°.

Nmr (in DMSO-d_6) showed signals at τ 5.17 (s, 2 H, *N*-carboxy CH_2), 4.74 (d, 1 H, α-CH), 2.56 (s, 5 H, aromatic H), and 1.82 (d, 1 H, amide NH).

Ir (in $CHCl_3$) showed bands at 2.92 (amide NH), 5.8 (broad, acid and carbamate carbonyls), and 6.67 μ (amide II and phenyl). Electrometric titration (in 66% aqueous DMF) showed a titratable group at 5.60 and an average molecular weight of 320 (calcd 327).

The sample was recrystallized from C_6H_6–petroleum ether.

Anal. Calcd for $C_{11}H_{10}Cl_3NO_4$: C, 40.45; H, 3.09; N, 4.29. Found: C, 40.60; H, 3.24; N, 4.55.

2,2,2-Trichloroethyl 7-[*N*-(2,2,2-Trichloroethyloxycarbonyl)-D-α-phenylglycylamido]-3-methyl-3-cephem-4-carboxylate (6).—To a solution of methyl chloroformate (2.1 g, 22 mmol) in 200 ml of CaH_2-dried THF, cooled in an ice–alcohol bath, was added dropwise a solution of *N*-(2,2,2-trichloroethyloxycarbonyl)-D-α-phenylgycine (7.2 g, 22 mmol), triethylamine (2.2 g, 22 mmol), and dimethylbenzylamine (6 drops) in 100 ml of dry THF. Cooling and stirring were maintained for 20 min following addition. Then **5d**, freed from its tosylate (10.4 g, 20 mmol), in 100 ml of the same solvent was added dropwise. The reaction mixture was stirred at ice–alcohol temperature for 3 hr. The solvent was removed *in vacuo*. The residue was redissolved in cold EtOAc for successive cold washes with H_2O, 5% HCl, 5% $NaHCO_3$ solution, and H_2O. The solution was dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was redissolved in 60 ml of CCl_4 for crystallization, yield 12.2 g (93%), mp 95°.

Nmr (in $CDCl_3$) showed signals at τ 7.82 (s, 3 H, C_3 CH_3), 6.94 and 6.54 (2 d, 2 H, C_2 H_2), 5.35 (s, 2 H, *N*-carboxy CH_2), 5.19 and 5.11 (2 d, 3 H, ester CH_2 and C_6 H), 4.58 (d, 1 H, α-CH), 4.24 (q, 1 H, C_7 H), 3.42 (d, 1 H, amide NH), and 2.69 (s, 5 H, aromatic H). Ir (in $CHCl_3$) showed bands at 2.95 (amide NH), 5.62 (β-lactam carbonyl), 5.78 (ester and carbamate carbonyls), 5.93 μ (amide carbonyl), and in the aromatic region.

The sample recrystallized from the same solvent.

Anal. Calcd for $C_{21}H_{19}Cl_6N_3O_6S$: C, 38.55; H, 2.92; N, 6.42. Found: C, 38.30; H, 2.98; N, 6.21.

2,2,2-Trichloroethyl 7-[*N*-(*tert*-Butoxycarbonyl)-D-α-phenylglycylamido]-3-methyl-3-cephem-4-carboxylate (12).—To a solution of methyl chloroformate (2.1 g, 22 mmol) in 200 ml of CaH_2-dried THF cooled in an ice–alcohol bath were added dropwise and with stirring *N*-(*tert*-butoxycarbonyl-D-α-phenylglycine (5.5 g, 22 mmol), triethylamine (2.2 g, 22 mmol), and dimethylbenzylamine (6 drops), in 100 ml of dry THF. Twenty minutes following addition, **5d** (10.4 g, 20 mmol) in 100 ml of dry THF was added dropwise. The mixture was stirred in the cold for 3 hr. The precipitated triethylamine hydrochloride was filtered and air-dried (3.0 g). The filtrate was evaporated *in vacuo*. The residual oil was redissolved in EtOAc for successive cold washes with H_2O, 5% HCl, 5% $NaHCO_3$ solution, and H_2O. The EtOAc solution was then dried ($MgSO_4$) and evaporated *in vacuo*. The residue weighed 11.5 g. This crude product was one-spot material in tlc and could be used directly in the next ester reductive cleavage step without further purification.

Nmr (in $CDCl_3$) showed signals at τ 8.60 (s, 9 H, *tert*-Bu), 7.82 (s, 3 H, C_3 CH_3), 6.90 and 6.50 (2 d, 2 H, C_2 H_2), 5.22 and 5.00 (2 d, 2 H, ester CH_2), 5.08 (d, 1 H, C_6H), 4.72 (d, 1 H, α-CH), 4.2 (q and d, 2 H, C_7H and amide NH) and 2.78–2.62 τ (d and s, 6 H, amide NH and aromatic). Ir (in $CHCl_3$) showed bands at 2.90 (amide NH), 5.57 (β-lactam carbonyl), and 5.75–5.90 μ (broad, ester and amide carbonyls).

In an identical preparation, the product was better characterized following a purification by recrystallization from either EtOH–H_2O or ether–petroleum ether, mp 130°.

Anal. Calcd for $C_{23}H_{26}Cl_3N_3O_6S$: C, 48.18; H, 4.53; N, 7.26. Found: C, 47.98; H, 4.58; N, 7.31.

2,2,2-Trichloroethyl 7-(D-α-Phenylglycylamido)-3-methyl-3-cephem-4-carboxylate (13).—Crude **12** (5.0 g, 8.6 mmol) was dissolved in 40 ml of MeCN containing *p*-toluenesulfonic acid monohydrate (4.1 g, 21.5 mmol) and stored at room temperature overnight. The solvent was removed *in vacuo*. The residue contained no starting material as observed in tlc. The residue was dissolved in 100 ml of EtOAc, cooled, and washed successively with 5% $NaHCO_3$ solution and H_2O. The EtOAc solution was dried and evaporated *in vacuo*. The residue weighed 3.8 g and was used directly in the following ester reductive cleavage step.

In an identical preparation, the product was purified for characteriztion by crystallization from EtOAc, mp 150°.

Nmr (in $CDCl_3$) showed signals at τ 8.07 (s, 2 H, NH_2), 7.80 (s, 3 H, C_3 CH_3), 6.82 and 6.40 (2 d, 2 H, C_2 H_2), 5.49–4.90 (m, 4 H, C_6 H, ester CH_2 and α-CH), 4.25 (q, 1 H, C_7 H), 2.69 (s, 5 H, aromatic H), and 1.98 (d, 1 H, amide NH).

Anal. Calcd for $C_{18}H_{18}Cl_3N_3O_6S$: C, 45.15; H, 3.79; N, 8.78. Found: C, 45.10; H, 4.07; N, 8.68.

7-[*N*-(*tert*-Butoxycarbonyl)-D-α-phenylglycylamido]-3-cephem-4-carboxylic Acid (14).—Crude **12** (from a 10-mmol run of its preparation) was dissolved in a mixture made from 25 ml of molecular-sieve-dried DMF and 7.5 ml of glacial AcOH (or 98% formic acid). The solution was cooled in an ice–H_2O bath and stirred for 3 hr with zinc dust (5.8 g, 89 mmol). The mixture was filtered, and the filtrate was taken up in H_2O and EtOAc. The EtOAc solution was washed with 5% HCl and then with H_2O, dried over $MgSO_4$, and evaporated to an amorphous white solid. This crude product, on examination in tlc (using MeCN–H_2O 4:1 system) contained a major component representing *tert*-Boc cephalexin and a faint spot corresponding possibly to the starting material. This crude product can be used directly in the following deblocking step.

In an identical preparation, the product was better characterized following purification. The crude product was dissolved in a EtOAc–H_2O mixture and adjusted to pH near 7 with 1 *N* NaOH. The aqueous phase was separated and back-titrated to pH 2.5 with 1 *N* HCl in the presence of EtOAc. The EtOAc solution was dried ($MgSO_4$) and evaporated *in vacuo*. The residue single-spot material in tlc (using a MeCN–H_2O 4:1 system) was crystallized from ether–hexane, mp 135° dec.

Nmr (in $CDCl_3$) showed signals at τ 8.60 (s, 9 H, *tert*-Bu), 7.90 (s, 3 H, C_3 CH_3), 7.0 and 6.58 (2d, 2 H, H_2), 5.14 (d, 1 H, C_6H), 4.67 (d, 1 H, α-CH), 4.34 (q, 1 H, C_7 H), 3.91 (d, 1 H, amide NH), and 2.69 (s, 5 H, aromatic H). Electrometric titration (in 66% aqueous DMF) gave a pK_a of 5.7 and an apparent molecular weight of 500 (calcd 448).

Anal. Calcd for $C_{21}H_{25}N_3O_6S$: C, 56.37; H, 5.63; N, 9.39. Found: C, 56.18; H, 5.80; N, 9.10.

7-(D-Amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic Acid (7). Method A.—6 (3.9 g, 6.0 mmol) was dissolved in 200 ml of 90% aqueous formic acid. The solution was cooled in an ice–H_2O bath. Zinc dust (3.9 g, 60 mg-atoms) was added, and the mixture was stirred for 55 min. The zinc was filtered and washed with 40 ml of aqueous formic acid. The filtrate and wash were combined and evaporated *in vacuo*, azeotroping with C_6H_6 to remove the last traces of formic acid. The residue was taken up in 80 ml of H_2O (pH 3.5) and treated with H_2S for 15 min. The precipitated zinc sulfide was filtered with the aid of Filter-Cel; the filtrate (pH 2) was concentrated to about 20 ml, cooled in ice, and adjusted to pH 7 with 50% NaOH. A slight amount of precipitate was removed by filtration. The solution was reacidified to pH 4.5 (isoelectric point of cephalexin) and diluted with 60 ml of MeCN. The crystallized product was pure cephalexin, 500 mg (24% yield).

Nmr (in D_2O–DCl) showed signals at τ 7.88 (s, 3 H, C_3 CH_3), 6.88 and 6.48 (2d, 2 H, C_2 H_2), 5.0 (d, 1 H, C_6 H), 4.53 (s, 1 H, α-CH), 4.29 (d, 1 H, C_7 H), and 2.32 (s, 5 H, aromatic H) and corresponded exactly with that of an authentic sample of cephalexin prepared according to Ryan, *et al.*[5]

In another run, the work-up was altered: The aqueous filtrate, following the zinc sulfide precipitation, was evaporated to dryness *in vacuo*. The residue was dissolved in 60 ml of MeCN by addition of triethylamine dropwise to pH 9. The mixture was filtered to remove insoluble impurities, and the filtrate was back-titrated to pH 6 with 1 *N* HCl. Cephalexin precipitated in 49% yield.

The bioautograph (*Bacillus subtilis* seeded agar plate of a paper chromatogram, developed in 1-butanol–AcOH–H_2O, 3:1:1) showed a single biologically active spot corresponding exactly in mobility and potency to authentic cephalexin at like concentration.

Method B.—Crude **13** was dissolved in 40 ml of MeCN and 6 ml of H_2O and stirred for 90 min in the cold with zinc dust (1.2 g, 18.4 mg-atoms) and 2 ml of concentrated HCl. The mixture was then filtered, and the filtrate was adjusted to pH 4.5 with NH_4OH. A white, crystalline precipitate developed. This was filtered, washed with MeCN, and vacuum dried, weight 2.5 g. Tlc (using MeCN–H_2O, 4:1 system) and an nmr spectrum of this material showed cephalexin as the major component.

Method C.—Crude **14** (from a 10-mmol run of its preparation) was dissolved in 50 ml of MeCN and treated with *p*-toluenesulfonic acid monohydrate (3.8 g, 20 mmol). The reaction solution was stored at room temperature overnight. The solution was cooled for the addition of 10 ml of H_2O and triethylamine to pH 4.8. After immediate precipitation, the product was filtered, washed with cold MeCN, and dried to constant weight in a vacuum dessicator. The over-all yield of cephalexin from **5d** has varied between 69 and 74%.

Anal. Calcd for $C_{16}H_{17}N_3O_4S$: C, 55.33; H, 4.93; N, 12.10. Found: C, 55.19; H, 5.19; N, 11.95.

Nmr, ir, and uv spectra were in agreement with those of authentic cephalexin.

Registry No.—**2a**, 19474-19-2; **2b**, 26774-86-7; **3a**, 19474-21-6; **3b**, 28180-78-1; **3c**, 28180-79-2; **4b**, 28180-80-5; **4c**, 28180-81-6; **5d**, 28180-82-7; **5d** *p*-toluenesulfonate salt, 28180-83-8; **5d** 2-naphthalenesulfonic acid salt, 28180-84-9; **5e** *p*-toluenesulfonate salt, 28180-85-0; **6**, 28292-01-5; **7**, 15686-71-2; **9**, 22252-43-3; **10a**, 10209-11-7; **10a** 2,2,2-trichloroethyl ester, 24647-47-0; **10b**, 27255-72-7; **12**, 28292-02-6; **13**, 28180-91-8; **14**, 28180-92-9; 2,2,2-trichloroethyl chloroformate, 17341-93-4; *N*-(2,2,2-trichloroethyloxycarbonyl)-D-α-phenylglycine, 26553-34-4.

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Specific, Reversible Acylation of Free Peptides Containing Lysine[1]

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Differences in reactivity between α- and ε-amino groups makes possible specific N^{ϵ}-acylation of free peptides containing lysine, in good yield and under simple experimental conditions. Alanyllysylalanine and N^{α}-, N^{ϵ}-, and N^{α},N^{ϵ}-diacyl derivatives thereof were synthesized and used as standards. Reaction of the free tripeptide with *tert*-butylazidoformate at pH 7 was primarily at the N^{α} position. Reaction in pyridine–water–triethylamine was at the N^{ϵ} position. Reaction with trifluoroacetic anhydride in trifluoroacetic acid yielded only the N^{α}-acyl product. The two ε-amino groups of porcine β-melanotropin can be specifically acylated with *tert*-butylazidoformate in good yield either in water at pH 10.5 or in pyridine–water–triethylamine. Formation of triacyl-β-melanotropin, in which the terminal amino group is also acylated, required extended reaction times and larger excesses of reagent.

In a semisynthetic preparation of the lysine-10 analog of human β-melanotropin (β-MSH), a suitably blocked tetrapeptide azide was reacted with naturally occurring porcine β-MSH.[2] The latter compound contains two ε-amino as well as a terminal α-amino group. Although a solution pH of 6.5 was employed to maintain ε-amino sites in a protonated, unreactive form, considerable coupling at N^{ϵ} positions did occur. The present report describes methods to utilize this apparently very high N^{ϵ}-amino reactivity to effect specific N^{ϵ}-acylation of free peptides containing lysine.

Free lysine has been the subject of a number of specific derivatization studies. Bezas and Zervas prepared N^{ϵ}-benzylidine lysine by virtue of product insolubility and rapid precipitation from solution.[3] Weygand and Geiger synthesized N^{α}-trifluoroacetyllysine with trifluoroacetic anhydride in trifluoroacetic acid;[4] in this case, strong acid so repressed N^{ϵ}-ammonium–amino

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TABLE I
IDENTIFICATION OF TRIPEPTIDE DERIVATIVES

Amino acid	Ala-Lys-Ala	Dnp / Dnp-Ala-Lys-Ala	Dnp / Boc-Ala-Lys-Ala	Dnp / Tfa-Ala-Lys-Ala	Boc / Dnp-Ala-Lys-Ala
Lysine	1.03 (1)[a]	0.08 (0)	0.02 (0)	0.02 (0)	1.04 (1)
Alanine	1.96 (2)	1.00 (1)	2.00 (2)	2.00 (2)	0.97 (1)

[a] Ratios found (theoretical).

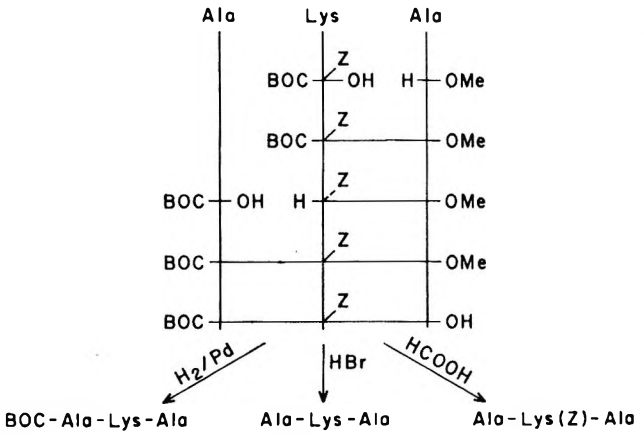

Figure 1.—Synthesis of derivatives of alanyllysylalanine.

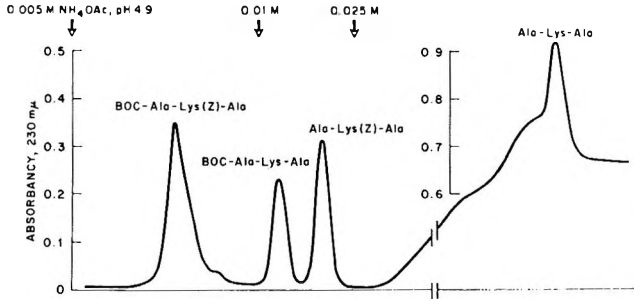

Figure 2.—Resolution of derivatives of alanyllysylalanine on carboxymethyl cellulose.

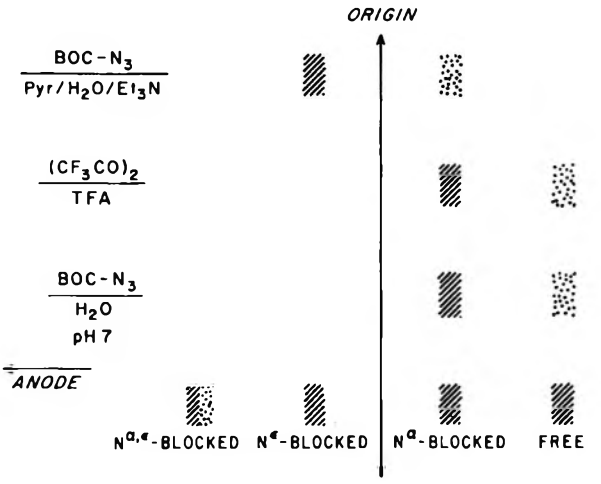

Figure 3.—Electropherogram of derivatives of alanyllysylalanine in borate buffer, pH 8.9.

equilibria that no N^{ϵ}-acylation occurred. LeClerq and Benoiton[5] in a systematic study of conditions for specific acylation of lysine found that nitrophenyl acetate effects N^{ϵ}-acetylation at pH 11. No α-acetylation was observed even with excess reagent and prolonged reaction times. Since both α- and ϵ-acetylation occur at lower pH, it appears that at pH 11 there is very rapid N^{ϵ}-aminolysis, while hydrolysis is so much faster than α-aminolysis that none of the latter takes place. None of the abovementioned studies was extended to peptides.

Ala-Lys-Ala,[6] used as a model peptide for initial acylation studies, was prepared as shown in Figure 1. This route yielded authentic N^{α}-, N^{ϵ}-, and $N^{\alpha,\epsilon}$-diacyl products as well as free tripeptide. Blocked and partially deblocked dipeptide intermediates were obtained in oily form. Blocked tripeptide ester and acid were obtained in solid, chromatographically and analytically pure form. Partially and fully deblocked tripeptide acids were characterized by electrophoresis, thin layer chromatography, amino acid analysis,[7] and dinitrophenylation.[8] A mixture of all four tripeptide derivatives was resolvable on carboxymethyl cellulose (Figure 2). The order of elution of products indicated that adsorption as well as ion exchange chromatography was occurring, since the α-free compound was retained more strongly than the ϵ-free product. Electrophoresis in a borate buffer, pH 8.9 (Figure 3), afforded rapid and complete resolution of all four derivatives. In experiments to determine ideal conditions for specific acylation, products were detected by ninhydrin after acid spray to deblock any diacyl derivative formed during the acylation step.

At pH 7 in water, *tert*-butylazidoformate[9] (2 μl/mg peptide) reacted with Ala-Lys-Ala to give N^{α}-Boc-tripeptide (Figure 3) with no observable N^{ϵ}-acyl product. These results were in contrast to those previously reported[2] in which a blocked tetrapeptide azide coupled to β-MSH both at α- and ϵ-amino sites, even at lower pH. Exposure of Ala-Lys-Ala in trifluoroacetic acid to trifluoroacetic anhydride also afforded N^{α}-blocked material (Figure 3) as described with free lysine.[4] Boc- and Tfa-tripeptides were characterized further by dinitrophenylation and amino acid analysis, which confirmed that α-acylation occurred (Table I). These analyses were performed on crude reaction products, indicating the high yields and degree of specificity of the acylation reactions described.

Similar acylation experiments with naturally occurring porcine β-MSH[10] did not produce similar results. At pH 7 even after 1.5 hr, very little acylation occurred (Figure 4). After 1 hr at pH 10.5 in water, *tert*-butylazidoformate (2 μl/mg peptide) and β-MSH react to form a new ninhydrin positive product in high yield

(5) J. LeClerq and L. Benoiton, *Can. J. Chem.*, **46**, 1047 (1968).
(6) E. Brand, B. F. Erlanger, J. Polatnik, H. Sachs, and D. Kirschenbaum, *J. Amer. Chem. Soc.*, **73**, 4027 (1951).
(7) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).
(8) F. Sanger, *Biochem. J.*, **39**, 507 (1945).
(9) L. A. Carpino, A. Gizu, and B. A. Carpino, *J. Amer. Chem. Soc.*, **81**, 955 (1959).
(10) G. V. Upton, A. B. Lerner, and S. Lande, *J. Biol. Chem.*, **241**, 5585 (1966).

TABLE II

IDENTIFICATION OF β-MSH DERIVATIVES

Amino acid	β-MSH[c]	β-MSH, dinitrophenylated[b]	$N^{\alpha},N^{\epsilon},N'^{\epsilon}$-Tri-Boc-β-MSH, dinitrophenylated[b]	$N^{\epsilon},N'^{\epsilon}$-Di-Boc-β-MSH, dinitrophenylated[b]
Lysine	2.09 (2)[a]	0.01 (0)	1.95 (2)	1.98 (2)
Aspartic acid	1.95 (2)	1.05 (1)	1.90 (2)	1.15 (1)
Glutamic acid	2.05 (2)	1.80 (2)	2.03 (2)	1.85 (2)
Glycine	2.00 (2)	2.12 (2)	1.95 (2)	1.95 (2)

[a] Ratios found (theoretical). [b] Products were exposed to fluorodinitrobenzene and then acid hydrolyzed and analyzed quantitatively. [c] The sequence of porcine β-MSH is Asp-Glu-Gly-Pro-Tyr-Lys-Met-Glu-His-Phe-Arg-Trp-Gly-Ser-Pro-Pro-Lys-Asp: J. I. Harris and P. Roos, *Nature*, **178**, 90 (1956).

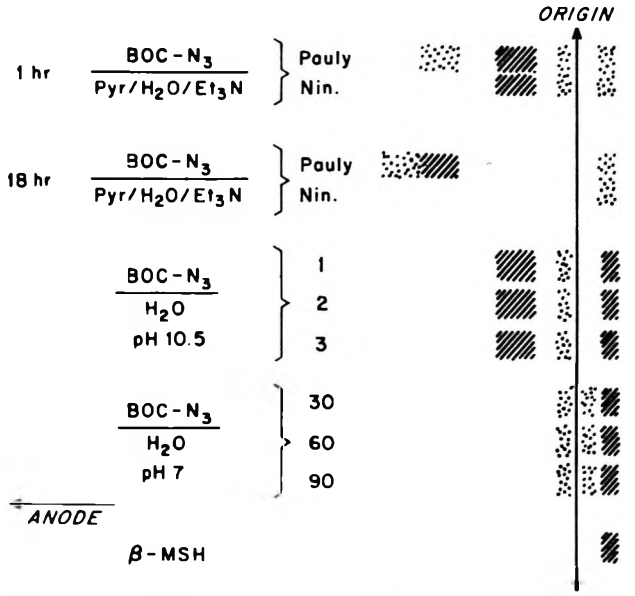

Figure 4.—Electropherogram of derivatives of β-melanotropin in pyridine acetate buffer, pH 6.5.

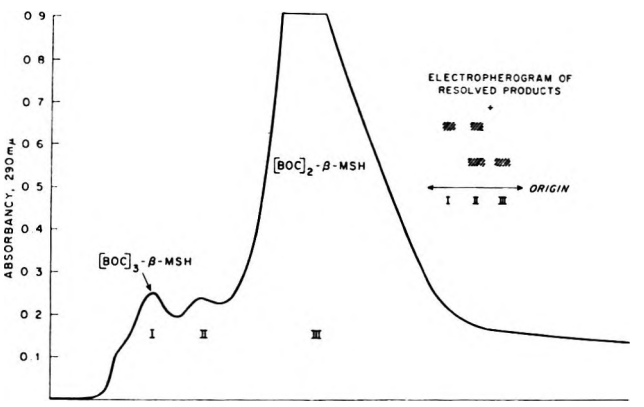

Figure 5.—Resolution of derivatives of β-melanotropin on carboxymethyl cellulose.

(Figure 4). Characterization by dinitrophenylation and amino acid analysis (Table II) following purification by chromatography on carboxymethyl cellulose (Figure 5) showed the product to be $N^{\epsilon},N'^{\epsilon}$-di-Boc-β-MSH; both lysines but only one aspartyl residue were recovered. The same product was produced after 1 hr in pyridine–water–triethylamine 10:10:1. On standing overnight with double amounts of *tert*-butylazidoformate, 4 μl/mg peptide, in pyridine–water–triethylamine, β-MSH is transformed into ninhydrin negative $N^{\alpha},N^{\epsilon},N'^{\epsilon}$-tri-Boc-β-MSH (Figure 4). This product was also characterized by dinitrophenylation and amino acid analysis (Table II). Both lysyl residues and the amino-terminal aspartyl residue are recovered in this case, indicating that all amino moieties are blocked. Exposure of Ala-Lys-Ala to *tert*-butylazidoformate, 2 μl/mg peptide, for 1 hr in the same pyridine buffer also afforded specific N^{ϵ}-acylation in good yield (Figure 3, Table I).

Thus the relatively low reactivity of *tert*-butylazidoformate, coupled with high nucleophilicity of N^{ϵ}-amino groups, appears to afford direct preparation of N^{ϵ}-acyl derivatives of lysine-containing peptides in reasonable yield and under simple reaction conditions. This technique, designed to allow semisynthetic studies with naturally occurring peptides obtained from tryptic hydrolysates, may also find some utility in totally synthetic methodology as well. The procedure makes possible stepwise Edman degradation of naturally occurring lysine-containing peptides for purposes of structure–activity studies, since formation of the stable N^{ϵ}-phenylthiocarbamyl derivatives of lysine can be blocked reversibly. Finally, specific N^{ϵ}-acylation with stable blocking groups may be useful for sequence determination by subtractive Edman degradation techniques.[11] In the usual procedure, recoveries of lysine are low, often making difficult an unequivocal determination of sequence of lysine-containing peptides. Stable N^{ϵ}-acyl derivatives may also be ideal substrates in solid phase Edman degradation techniques.[12]

Experimental Section

Materials and Methods.—All solvents were reagent grade and redistilled; triethylamine (Eastman) was distilled over potassium hydroxide pellets; *tert*-butyleazidoformate (Pierce) was shaken with powdered calcium carbonate prior to use; dicyclohexylcarbodiimide (Eastman), trifluoroactic acid and anhydride (Eastman), 97% formic acid (Aldrich), and fluorodinitrobenzene (Eastman) were all used directly.

Amino acids were purchased from Mann Laboratories; Ala-OMe·HCl was prepared by the method of Brenner and Huber,[13] Boc-Lys(Z) by that of Anderson and McGregor,[14] and Boc-Ala by that of Schwyzer, *et al.*[15]

Thin layer chromatography (tlc) was performed in a sandwich-type apparatus in two systems: system 1, chromar 500 (Mallinckrodt) with chloroform–methanol 95:5; system 2, chromogram, cellulose (Eastman) with butanol–acetic acid–water 4:1:5. Electrophoresis on Whatman 3-mm paper was performed in two buffers: buffer 1, 0.02 *M* sodium borate, pH 8.9; buffer 2, pyridine–acetic acid–water 100:900:4, pH 6.5, in a Savant LT-2A tank. Melting points, uncorrected, were measured on a Thomas-Hoover apparatus. Optical rotations were taken with an O. C. Rudolph and Sons polarimeter, Model 70. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory. Amino acid analyses of peptide hydrolysates prepared as described[7] were made with a Beckman Analyzer, Model 120B.

(11) C. H. W. Hirs, S. Moore, and W. H. Stein, *J. Biol. Chem.*, **236**, 633 (1960).

(12) L. M. Dowling and G. R. Stark, *Biochemistry*, **8**, 4726 (1969).

(13) M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953).

(14) G. W. Anderson and A. C. McGregor, *J. Amer. Chem. Soc.*, **79**, 6180 (1957).

(15) R. Schwyzer, P. Sieber, and H. Kappeler, *Helv. Chim. Acta*, **42**, 2622 (1959).

For dinitrophenylation,[8] 3 mg of peptide and 10 μl of fluorodinitrobenzene were dissolved in 1 ml 5% aqueous triethylamine, stirred in the dark for 4 hr, and evaporated to dryness; aliquots of product were then hydrolyzed for analysis.

N^{α}-*tert*-Butyloxycarbonyl-N^{ϵ}-benzyloxycarbonyllysylalanine Methyl Ester (a).—To an ice-cold solution of 1.6 g of Ala-OMe·HCl (11.3 mmol) and 1.5 ml of triethylamine in chloroform (10 ml) was added 4.0 g of Boc-Lys(Z)[14] (10.3 mmol) in chloroform (10 ml), followed by a cold solution of 2.12 g of DCC[16] (10.3 mmol) in chloroform (10 ml). After 0.5 hr in the cold and 3 hr at room temperature, the mixture was filtered and the filtrate chilled and extracted three times each with cold 0.05 *N* HCl, water, saturated sodium bicarbonate, and water, dried over magnesium sulfate, and evaporated *in vacuo:* yield 4.4 g (91%); homogeneous on tlc, R_f 0.94, system 1; ultraviolet (uv) positive and ninhydrin negative. Amino acid analysis: Ala, 0.93; Lys, 1.07.

N^{ϵ}-Benzyloxycarbonyllysylalanine Methyl Ester Hydrochloride (b).—Dipeptide a, 1.5 g (3.2 mmol), was dissolved in 4 *N* methanolic HCl (45 ml), left at room temperature for 1 hr, and evaporated four times *in vacuo* with methanol: yield 1.24 g of oil (97%); homogeneous on tlc, R_f 0.0, system 1; uv and ninhydrin positive.

N^{α}-*tert*-Butyloxycarbonylalanyl-N^{ϵ}-benzyloxycarbonyllysylalanine Methyl Ester (c).—To an ice-cold solution of 1.2 g of dipeptide ester b (3 mmol) and triethylamine (0.5 ml) was added 0.57 g of Boc-Ala[15] (3 mmol), followed by 0.62 g of DCC (3 mmol). After standing 0.5 hr in the cold and overnight at room temperature, the mixture was filtered and the filtrate treated as described for peptide a, yield 1.08 g. Traces of side product were removed by extraction with ether: yield 0.9 g (56%); mp 132–136°; $[\alpha]^{19}D$ −38.5° (*c* 1, ethanol); homogeneous on tlc, R_f 0.42, system 1; uv positive and ninhydrin negative. Amino acid analysis: Ala, 1.96; Lys, 1.03.

Anal. Calcd for $C_{26}H_{40}N_4O_8$: C, 58.2; H, 7.51; N, 10.4. Found: C, 58.6; H, 7.50; N, 10.4.

N^{α}-*tert*-Butyloxycarbonylalanyl-N^{ϵ}-benzyloxycarbonyllysylalanine (d).—To a solution of 1 g of tripeptide ester c (1.8 mmol) in 10 ml of methanol, 2.8 ml of 1 *N* sodium hydroxide (aqueous) was added in a dropwise manner. The resultant oily suspension was stirred at room temperature for 1.5 hr, diluted with 50 ml of water, and extracted with ethyl acetate. The aqueous phase was cooled to 0°, acidified to pH 3 with cold 1 *N* hydrochloric acid, extracted into fresh ethyl acetate, and washed with cold water until washings were neutral. The organic phase was then dried over magnesium sulfate and evaporated *in vacuo*. The residue was extracted with ether, yield (insoluble residue) 0.76 g. On standing an additional 85 mg precipitated from the ethereal mother liquor: total yield 0.84 g (89%); mp 94–97°; $[\alpha]^{19}D$ −29.6° (*c* 1, ethanol); homogeneous on tlc, R_f 0.28, system 1; uv positive and ninhydrin negative. Amino acid analysis: Ala, 2.03; Lys, 0.97.

Anal. Calcd for $C_{25}H_{38}N_4O_8$: C, 57.5; H, 7.32; N, 10.7. Found: C, 57.3; H, 7.60; N, 10.5.

Alanyllysylalanine Dihydrobromide (e).—Blocked tripeptide d (0.52 g, 1 mmol) was dissolved in acetic acid saturated with hydrobromic acid (4 ml), left at room temperature for 1 hr, and precipitated with ether, and the precipitate was washed exhaustively with ether. The product was stored *in vacuo* over sodium hydroxide pellets: yield 0.41 g (91%); mp 162–165°; $[\alpha]^{19}D$ −26.2° (*c* 2, 0.5 *N* hydrochloric acid) (as *crystalline* monohydrochloride,[6] $[\alpha]^{23}D$ −42.5°); trace of second component on tlc, major component R_f 0.30, system 2; uv negative and ninhydrin positive; homogeneous on electrophoresis, buffer 1, ninhydrin positive. Amino acid analysis: Ala, 1.90; Lys, 1.07. Amino acid analysis after dinitrophenylation showed only alanine.

Alanyl-N^{ϵ}-benzyloxycarbonyllysylalanine Monoformate.—Blocked tripeptide d, 25 mg (0.51 mmol), was dissolved in 1 ml of 97% formic acid and left for 1 hr at room temperature.[17] The mixture was evaporated *in vacuo*, taken up in water, and lyophilized: yield 21 mg (91%); mp 209–213°; $[\alpha]^{19}D$ −23.5° (*c* 0.85, 0.005 *M* ammonium acetate, pH 4.9); traces of starting material and free tripeptide on tlc, major component R_f 0.84, system 2; uv and ninhydrin positive; single component on electrophoresis, buffer 1, ninhydrin positive. Amino acid analysis: Ala, 2.00; Lys 1.00. Amino acid analysis after dinitrophenylation: Ala, 0.98; Lys, 1.02.

N^{α}-*tert*-Butyloxycarbonylalanyllysylalanine.—Blocked tripeptide d, 26 mg (0.5 mmol), was dissolved in methanol (10 ml) neutralized with triethylamine to an apparent pH of 7 using pH indicator paper, hydrogenated over a palladium catalyst in a stream of hydrogen for 2.5 hr, and filtered, and the filtrate was evaporated *in vacuo* and the residue taken up in water and lyophilized: yield 16 mg (84%); mp 110–114°; $[\alpha]^{19}D$ −34.9° (c 0.3, 0.005 *M* ammonium acetate, pH 4.9); homogeneous on tlc, R_f 0.75, system 2; ninhydrin positive; homogeneous on electrophoresis, buffer 1, ninhydrin positive. Amino acid analysis: Ala, 1.93; Lys, 1.20. Amino acid analysis after dinitrophenylation showed less than 1% lysine relative to alanine.

Reaction of Alanyllysylalanine with *tert*-Butylazidoformate. 1. In Water, pH 7.—Peptide e, 2 mg, in 2 ml of water was titrated to pH 7 with a Radiometer pH-Stat and reacted with *tert*-butylazidoformate (4 μl) under nitrogen at constant pH and with vigorous stirring. After 0.5 hr the mixture was extracted with ether and the aqueous phase lyophilized. On electrophoresis in buffer 1, the major product exhibited the same mobility as authentic Boc-Ala-Lys-Ala (Figure 3). Results of amino acid analysis after dinitrophenylation confirm that N^{α}-acylation occurred (Table I).

2. In Pyridine–Water–Triethylamine.—A solution of peptide e (2 mg) and *tert*-butylazidoformate (4 μl) in pyridine–water–triethylamine 10:10:1 was kept at room temperature 1 hr and extracted with 1 ml of ether and the aqueous phase was evaporated *in vacuo* and lyophilized. On electrophoresis in buffer 1, the major component exhibited the same mobility as authentic Ala-Lys(Z)-Ala (Figure 3). Results of amino acid analysis after dinitrophenylation confirm that N^{ϵ}-acylation occurred (Table I).

Reaction of Porcine β-Melanotropin with *tert*-Butylazidoformate. 1. In Water, pH 10.5.—β-Melanotropin (2 mg) in 2 ml of water was titrated to pH 10.5 with a Radiometer pH-Stat and reacted with 4 μl of *tert*-butylazidoformate at constant pH, with vigorous stirring and under nitrogen for 0.5, 1, or 1.5 hr with similar results. The mixture was extracted with 2 ml of ether and the aqueous phase lyophilized. Results of electrophoresis in buffer 2 are shown in Figure 4. The product was ninhydrin positive.

2. In Pyridine–Water–Triethylamine.—A solution of β-MSH (40 mg) and *tert*-butylazidoformate (80 μl) in pyridine–water–triethylamine 10:10:1 (1 ml) was stored at room temperature for 1 hr and extracted with 1 ml of ether and the aqueous phase evaporated *in vacuo*. The residue was chromatographed on a 1.2 × 90 cm column of carboxymethyl cellulose, Whatman CM-52 with a 0.005 *M* ammonium acetate buffer, pH 4.9, using a flow rate of 0.1 ml/min (Figure 5). The major component after lyophilization, 24 mg (60%), was electrophoretically homogeneous in buffer 2 (Figure 5, insert). Amino acid analysis after dinitrophenylation (Table II) identified the product to be $N^{\epsilon},N'^{\epsilon}$-di-Boc-β-MSH.

Preparation of Fully Acylated β-Melanotropin.—A solution of 5 mg of β-MSH and 25 μl of *tert*-butylazidoformate in 1 ml of pyridine–water–triethylamine 10:10:1 was left at room temperature overnight. The mixture was evaporated *in vacuo*, taken up in water, and lyophilized. Results of electrophoresis in buffer 2 are shown in Figure 4; the product was ninhydrin negative. Amino acid analysis after dinitrophenylation identified the product to be $N^{\alpha},N^{\epsilon},N'^{\epsilon}$-tri-Boc-β-MSH.

Registry No.—a, 22839-06-1; b, 27909-28-0; c, 27909-29-1; d, 27909-30-4; e, 27909-31-5; alanyl-N^{ϵ}-benzyloxycarbonyllysylalanine monoformate, 27909-32-6; N^{α}-*tert*-butyloxycarbonylalanyllysylalanine, 27909-33-7.

(16) J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, **77**, 1067 (1955).
(17) B. Halpern and D. E. Nitecki, *Tetrahedron Lett.*, 3031 (1967).

Intramolecular Catalysis. III. Catalysis by Oxygen-Containing Groups in the Acetylation of Hydroxy Steroids[1,2]

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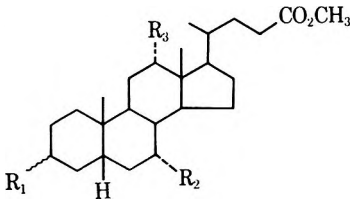
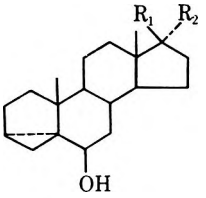
Methyl 7α-hydroxycholanate gives the same low yield on acetylation in the presence of methyl deoxycholate 3-acetate as in its absence; consequently the 3α-acetoxy and 12α-hydroxyl groups of methyl cholate 3-acetate act *intramolecularly*, enhancing acetylation of the 7-hydroxyl. The 6β-hydroxyl group is influenced somewhat it its reaction with acetic anhydride and pyridine by substituents at carbon 17. The 12α-hydroxyl group is also influenced by the side chain; in general, the larger the side chain the lower its reactivity toward acetylation. The 7α-hydroxyl acetylates similarly regardless of configuration of an enhancing 3-acetoxy group, in support of an inductive mechanism. Rates of acetylation of hydroxy steroids with acetic anhydride and pyridine were measured by glpc. Methyl lithiocholate, methyl 12α-hydroxycholanate, and methyl 7α-hydroxycholanate decreased in rate in that order. Methyl 7α,12α-dihydroxycholanate illustrates intramolecular catalysis by the 12-hydroxyl, its 7-hydroxyl undergoing acetylation 25 times as fast as in the absence of the 12-hydroxyl. Methyl cholate 3-*p*-nitrobenzoate (**1g**), prototype of uv-absorbing bile acid esters, was acetylated with acetic anhydride in pyridine. Aliquots were separated by tlc, recovered from absorbent, and analyzed spectrophotometrically. The 7-hydroxyl in **1g** is found to be much more reactive than in methyl 7α-hydroxycholanate.

One inhibiting and two enhancing effects were shown to be responsible for the selective acetylation of methyl 3α-acetoxy-7α,12α-dihydroxycholanate (methyl cholate 3-acetate, **1a**): (1) the 12α-hydroxyl group is deactivated by the side chain; (2) the 7 α-hydroxyl group is activated by the 3α-acetoxy group and (3) also by the 12α-hydroxyl group.[1] As part of an approach toward



1a, R_1 = AcO---; R_2 = R_3 = OH
b, R_1 = H; R_2 = OH; R_3 = H
c, R_1 = $C_7H_7SO_3$---; R_2 = R_3 = OH
d, R_1 = AcO—; R_2 = R_3 = OH
e, R_1 = HO---; R_2 = R_3 = H
f, R_1 = H; R_2 = R_3 = OH
g, R_1 = *p*-$NO_2C_6H_4CO_2$---; R_2 = R_3 = OH
h, R_1 = *p*-$NO_2C_6H_4CO_2$---; R_2 = OAc; R_3 = OH
i, R_1 = *p*-$NO_2C_6H_4CO_2$---; R_2 = R_3 = OAc

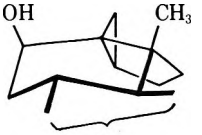


2a, R_1 = R_2 = H
b, R_1R_2 = =O
c, R_1R_2 = -OCH_2CH_2O-
d, R_1 = $C_6H_5CO_2$-; R_2 = H
e, R_1 = HO; R_2 = C≡CH

elucidating the mechanisms of intramolecular catalysis by the acetoxy and hydroxy (and possibly other) groups, we have compared a series of hydroxy steroids with respect to their ease of acetylation by acetic anhydride and pyridine.

The relatively low reactivity of the hydroxyl group in methyl 7α-hydroxycholanate (**1b**, 3–7% yield, Table I) is altered in the presence of the 3α-acetoxy group and the 12α-hydroxyl group (66–70% yield for **1a**). The 3 and 12 substituents conceivably could act on the 7α-hydroxyl *intermolecularly*. The acetylation of methyl 7α-hydroxycholanate (for which a new synthesis from methyl chenodeoxycholate is described in the Experimental Section) in only 4% yield in the presence of an equimolar amount of methyl deoxycholate 3-acetate, however, proves that the effect of the 3 and 12 substituents is *intramolecular* in methyl cholate 3-acetate.

In order to determine the effects of substituents at C-17 on the reactivity of the 6β-hydroxyl group, the series **2a–e** (prepared by rearrangement of the corresponding Δ⁵-3β-tosylates) was treated with acetic anhydride and pyridine at room temperature for 24 hr. The yields of acetate isolated by chromatography are shown in Table I. The ethylenedioxy group in **2c** has no effect, but enhancement of 6β-hydroxyl reactivity is observed with the keto group of **2b**, the benzoyloxy group of **2d**, and the hydroxyl and ethynyl groups of **2e**. The 44–49% yield of acetate obtained with **2a** is at first surprising, as the 6β-hydroxyl might be assumed to encounter 1,3-diaxial nonbonded interaction with the C-18 methyl, as the 7α-hydroxyl apparently does with the C-4 methylene in **1b**, which acetylates in only 3–7% yield. Inspection of molecular models, however, shows that the bicyclo[3.1.0]hexane A ring distorts the B ring in such a way as to separate methyl and hydroxyl more than in the normal chair conformation (**2f**).



2f

(1) For convenience in reference, we are now assigning to our earlier papers in the series Intramolecular Catalysis the following numbers: (a) I, R. T. Blickenstaff and B. Orwig, *J. Org. Chem.*, **32**, 815 (1967); (b) II, R. T. Blickenstaff and B. Orwig, *ibid.*, **34**, 1377 (1969).

(2) Taken in part from the M.S. thesis of Y. C. Kim, Indiana University, 1970. Supported in part by Public Health Service Grant No. GM 360-09.

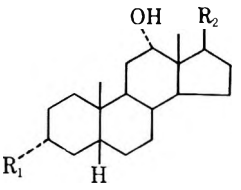
TABLE I
ACETYLATION OF HYDROXY STEROIDS WITH ACETIC ANHYDRIDE AND PYRIDINE

No.	Compd	Yield of acetate, %: Standard conditions[a]	Yield of acetate, %: Pyridine replacing benzene
1a	Methyl cholate 3-acetate	66–70	55–62[b]
1b	Methyl 7α-hydroxycholanate	3–7	
1b	Methyl 7α-hydroxycholanate with an equimolar amount of methyl deoxycholate 3-acetate	4	
1d	Methyl 3β-acetoxy-7α,12α-dihydroxycholanate		55–57
2a	3α,5-Cycloandrostan-6β-ol	44–49	
2b	3α,5-Cycloandrostan-6β-ol-17-one	59–61	
2c	17,17-Ethylenedioxy-3α,5-cycloandrostan-6β-ol	47	
2d	17β-Benzoyloxy-3α,5-cyclo-androstan-6β-ol	57	
2e	17α-Ethynyl-3α,5-cyclo-androstane-6β,17β-diol	58–63	
3a	Methyl 12α-hydroxycholanate	5–8	
3b	Methyl deoxycholate 3-acetate	11–13	
3c	5β-Pregnan-12α-ol-20-one	18–21	
3d	3α-Acetoxy-5β-pregnan-12α-ol-20-one	32–36	
3e	3α-Tosyloxy-5β-pregnan-12α-ol-20-one	31–39	
3f	24-Methyl-24-homocholane-12α,24-diol	10–12	
3g	Cholan-12α-ol	5–10	
3h	5β-Pregnan-12α-ol	45–50	
4a	20-Methyl-5β-pregna-3-ene-12α,20-diol		<1
4b	Methyl 12α-hydroxy-3-cholenate	4	8

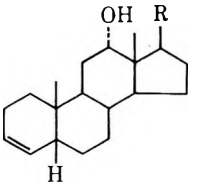
[a] Steroid (0.37 mmol), Ac_2O (0.1 ml), pyridine (0.1 ml), and benzene (0.84 ml), room temperature, 24 hr. [b] Average of three runs, 57%.

The slight enhancing effect of the 3α-acetoxy group on 12α-hydroxyl reactivity is shown (Table I) by comparing the 5–8% yield previously obtained with methyl 12α-hydroxycholanate (**3a**) with the 11–13% yield obtained with the 3-acetate (**3b**) of methyl deoxycholate. This is verified in the pregnane series by comparing the 18–21% yield obtained previously with 5β-pregnan-12α-ol-20-one (**3c**) with the yield obtained with the 3-acetate (**3d**); in addition, the tosylate group of 5β-pregnane-3α,12α-diol-20-one 3-tosylate (**3e**) is similarly enhancing.

A series of 12α-hydroxyl compounds was compared to assess the influence of the side chain on 12-hydroxyl group reactivity. In addition to those compounds already described,[1b] two derivatives (**3f** and **4a**) containing *tert*-hydroxyl groups in the side chain were prepared by Grignard reactions on methyl 12α-hydroxycholanate and on 5β-pregna-3-en-12α-ol-20-one, respectively. The series **3h**, **3c**, **3a**, **3g**, and **3f** illustrates that 12α-hydroxyl group reactivity decreases as the side chain increases in size. 20-Methyl-5β-pregna-3-ene-12α,20-diol (**4a**) does not fit neatly in the series as it gives less than a 1% yield of acetate. Such low reactivity is not the result of its being tested in pyridine (it is insoluble in the standard benzene mixture), because methyl 12α-hydroxy-3-cholanate (**4b**) gives the same or higher yield in pyridine compared to the benzene medium. Neither is it due to the ring-A unsaturation, as methyl 12α-hydroxycholanate (**3a**) and the Δ^3 analog (**4b**) do not differ significantly. It may be noted that the two hydroxyls of **4a** are close enough for strong H bonding, and that Wall, *et al.*,[3] found this to inhibit acetylation of a 12β-hydroxyl.



3a, $R_1 = H$; $R_2 = CH(CH_3)CH_2CH_2CO_2CH_3$
b, $R_1 = AcO$; $R_2 = CH(CH_3)CH_2CH_2CO_2CH_3$
c, $R_1 = H$; $R_2 = COCH_3$
d, $R_1 = AcO$; $R_2 = COCH_3$
e, $R_1 = C_7H_7SO_3$; $R_2 = COCH_3$
f, $R_1 = H$; $R_2 = CH(CH_3)CH_2CH_2C(CH_3)_2OH$
g, $R_1 = H$; $R_2 = CH(CH_3)CH_2CH_2CH_3$
h, $R_1 = H$; $R_2 = C_2H_5$



4a, $R = C(CH_3)_2OH$
b, $R = CH(CH_3)CH_2CH_2CO_2CH_3$

We have suggested[1b] intramolecular general acid–general base catalysis for the mechanism of action of the 3α-acetoxy and 12α-hydroxyl groups of methyl cholate 3-acetate (**1a**) in its reaction with the acetylpyridinium ion, the existence of which has now been verified experimentally.[4] On the other hand, it is necessary also to consider inductive effects, even though they are generally thought to drop off very fast as the length of saturated carbon chain between substituent group and reaction center increases. Recently several groups have reported long-distance inductive effects. The rate of addition of bromine to a Δ^5 double bond is shown to be influenced by substituents not only at C-3, but also those at C-17.[5] Acetolysis rates of 11α-tosylates are influenced by the type of substitution in ring A in the sapogenin series.[6] Solvolysis rates of 3-tosylates are decreased by electronegative substituents at C-17, *across the entire steroid nucleus*.[7] We have examined this question in a preliminary fashion by comparing the behavior of methyl cholate 3-acetate (**1a**) with methyl 3β-acetoxy-7α,12α-dihydroxycholanate

(3) M. E. Wall, F. I. Carroll, and G. S. Abernethy, *J. Org. Chem.*, **29**, 604 (1964).

(4) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 2125 (1969); G. A. Olah and P. J. Szilagyi, *ibid.*, **91**, 2949 (1969).

(5) V. Schwarz and S. Hermanek, *Collect. Czech. Chem. Commun.*, **29**, 2360 (1964).

(6) K. Takeda, K. Tanida, and K. Horiki, *J. Org. Chem.*, **31**, 734 (1966).

(7) P. E. Peterson, unpublished results. We are grateful to Dr. Peterson for providing a prepublication copy of his manuscript and for calling our attention to this phenomenon. An alternative explanation is offered by Kogan, *et al.*, for some long-range effects in 17-substituted 4-androsten-3-ones (G. A. Kogan, V. N. Leonov, S. N. Ananchenko, and I. V. Torgov, 7th International Symposium on the Chemistry of Natural Products, Riga, June 1970, p 406). They interpret alterations of ORD curves of the ring-A chromophore in terms of ring-D distortions caused by type and configuration of substituents and transmitted to ring A by the Barton effect.

(**1d**). The latter was synthesized by the action of tetrabutylammonium acetate on methyl cholate 3-tosylate (**1c**). It was too insoluble to be tested in the benzene mixture, but in pyridine both epimers, **1a** and **1d**, evidenced the same amount of 7-acetylation. This result, to be expected if the 3-acetoxy groups exert an inductive effect on the 7-hydroxyl, requires reexamination of the proposed mechanism.[1b]

The first approximations of relative reactivity based on yield comparisons in this work are confirmed for several of these compounds (**1b**, **1e**, **1f**, and **3a**) whose rates of acetylation have been measured by a glpc method. The acetylation with acetic anhydride and pyridine was carried out in benzene solution under conditions shown to be responsive to intramolecular influences.[1] Aliquots were quenched in methanol, then examined by glpc directly, rather than undergoing conversion to trimethylsilyl ethers.[8] Inasmuch as ratios of the two peaks of each aliquot are determined, these transfers need not be quantitative. Peak areas (except for methyl 7α,12α-dihydroxycholanate (**1f**), for which peak heights are used) were converted to mole ratios by means of standard curves prepared from known mixtures of hydroxy steroid and acetate.

The method was developed with methyl lithocholate, methyl 7α-hydroxycholanate, and methyl 12α-hydroxycholanate representing the three hydroxyl groups of methyl cholate, and with methyl 7α,12α-dihydroxycholanate. As Eliel and Lukach had found alicyclic alcohols to follow second-order kinetics,[9] rate constants for the steroid acetylations were calculated from the standard expression

$$k = \frac{2.303}{t(b-a)} \log \frac{a(b-x)}{b(a-x)}$$

where a = starting concentration of steroid, b = starting concentration of acetic anhydride, and x = concentration of each having reacted at time t. It was assumed that no side reactions took place, and x values were calculated from the glpc measurements.[10] Typical values for methyl lithocholate are given in Table II. By varying the concentrations of reactants, the reaction was clearly shown to be first order in methyl lithocholate and in acetic anhydride, and (at these concentrations) zero order in pyridine (Table III).[11]

TABLE II

TYPICAL KINETIC RUN IN THE REACTION OF METHYL LITHOCHOLATE WITH ACETIC ANHYDRIDE AND PYRIDINE

Time, hr	$x/(a-x)$	x	$a-x$	$b-x$	k	Reaction, %
1.0	0.225	0.067	0.302	0.998	0.192	18.1
1.5	0.343	0.094	0.275	0.971	0.191	25.4
2.0	0.462	0.116	0.253	0.949	0.187	31.4
3.17	0.766	0.160	0.209	0.905	0.183	43.3
3.5	0.985	0.182	0.187	0.883	0.201	49.1
4.0	1.133	0.195	0.174	0.871	0.197	52.7
5.0	2.095	0.249	0.129	0.816	0.225	67.3
7.83	3.617	0.289	0.080	0.776	0.222	78.1
					Av 0.200 ± 0.015	

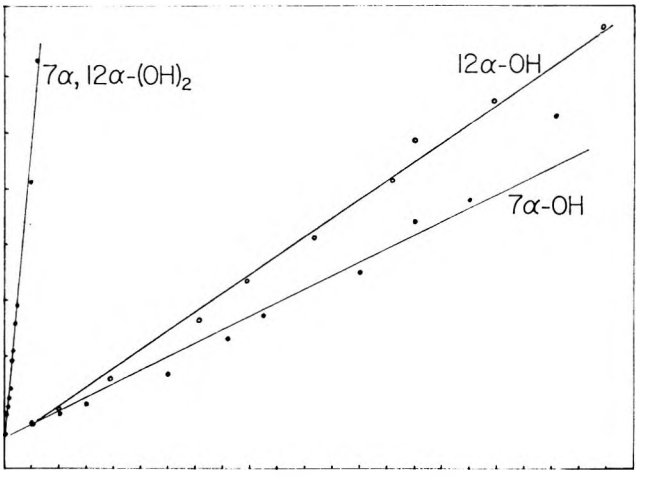


Figure 1.—Second-order rate plots for the acetylation of methyl 7α,12α-dihydroxycholanate, methyl 12α-hydroxycholanate, and methyl 7α-hydroxycholanate.

TABLE III

ACETYLATION OF METHYL LITHOCHOLATE WITH ACETIC ANHYDRIDE AND PYRIDINE IN BENZENE

Initial concentration (M) Steroid	Ac_2O	C_5H_5N	Time (min)	Product ROAc	
0.369	1.065	1.24	30	0.0335	
0.369	1.065	1.24	40	0.0445	
0.369	1.065	1.24	60	0.067	
0.035	1.065	1.24	30	0.0038	$m^a = 0.924$
0.360	0.533	1.24	40	0.023	$n^a = 0.957$
0.369	1.065	0.62	30	0.0317	$j^a = 0.078$

[a] From $(\Delta X/\Delta T_1)/(\Delta X/\Delta T_2) = k(\text{steroid})_1^m(Ac_2O)_1^n(C_5H_5N)_1^j / k(\text{steroid})_2^m(Ac_2O)_2^n(C_5H_5N)_2^j$; see ref 11.

Second-order plots for the other two monohydroxy steroids are shown in Figure 1. The rate constants given in Table IV clearly indicate the large difference in the reactivity of the 3α-hydroxyl compared with the 7α- and 12α-hydroxyls. The rate constants for the latter two verify our observation[1b] that in the absence of other nuclear substituents the 12α-hydroxyl is the more reactive. When both the 7α- and 12α-hydroxyls are present in the same molecule, however, the 7-hydroxyl is the more reactive; methyl 7α,12α-dihydroxycholanate (**1f**) had been converted in 56% yield to methyl 7α-acetoxy-12α-hydroxycholanate.[1b] In the present work methyl 7α,12α-dihydroxycholanate was found to acetylate (presumably at the 7-OH) at a rate 25 times that of methyl 7α-hydroxycholanate, verifying the

TABLE IV

RATES OF ACETYLATION WITH ACETIC ANHYDRIDE AND PYRIDINE IN BENZENE AT ROOM TEMPERATURE

Compound	k, M^{-1} sec^{-1}	Ratio of rates
Methyl lithocholate	$55.6 \pm 4.2 \times 10^{-6}$	68.5
Methyl 7α-hydroxycholanate	$0.81 \pm 0.15 \times 10^{-6}$	1
Methyl 12α-hydroxycholanate	$1.12 \pm 0.19 \times 10^{-6}$	1.4
Methyl 7α,12α-dihydroxycholanate	$20.5 \pm 4.5 \times 10^{-6}$	25.3

(8) The 7α- and 12α-hydroxyl groups are known to undergo silylation very slowly [T. Briggs and S. R. Lipsky, *Biochim Biophys. Acta*, **97**, 579 (1965)], a factor which would greatly complicate analysis of aliquots from methyl 7α- and 12α-hydroxycholanates.

(9) E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).

(10) Mole fractions calculated from peak areas of glc curves were used to calculate rate constants for the reaction of trimethylaluminum and benzophenone: E. C. Ashby and J. T. Laemmle, *J. Org. Chem.*, **33**, 3398 (1968).

(11) F. Daniels and R. A. Alberty, "Physical Chemistry," Wiley, New York, N. Y., 1955, p 330.

TABLE V

KINETIC RUN OF THE ACETYLATION OF METHYL CHOLATE 3-*p*-NITROBENZOATE WITH ACETIC ANHYDRIDE AND PYRIDINE

Time, hr	Acetate		Alcohol		$x/(a-x)$	x	$\log \frac{a(b-x)}{b(a-x)}$	k	% completion
	Dilution	Absorbance	Dilution	Absorbance					
1	10	0.530	50	0.610	0.174	0.0547	0.0453	0.145	14.8
2	10	0.958	50	0.589	0.321	0.0896	0.0828	0.137	24.3
3	20	0.637	50	0.532	0.479	0.120	0.117	0.129	32.5
5	25	0.872	50	0.538	0.810	0.165	0.185	0.122	44.7
7	25	0.718	50	0.280	1.28	0.207	0.263	0.124	56.1
9	25	0.759	20	0.516	1.84	0.239	0.342	0.126	64.8
11	50	0.695	20	0.595	2.92	0.275	0.464	0.140	74.5
13	50	0.440	25	0.400	2.20	0.254	0.387	0.099	68.8
16	50	0.450	25	0.304	2.92	0.276	0.467	0.097	74.8
24	50	0.395	10	0.345	5.72	0.314	0.676	0.093	85.1
39	100	0.168	10	0.200	8.40	0.330	0.813	0.093	89.4
34	100	0.317	10	0.206	15.4	0.347	1.05	0.102	94.0
39	50	0.338	5	0.171	19.8	0.351	1.14	0.097	95.1

Av $0.116 \pm 0.019\ M^{-1}\ hr^{-1}$

catalytic effect of the 12α-hydroxyl group on the 7α-hydroxyl.

Bile acids and their derivatives, like other steroids, absorb uv radiation when dissolved in concentrated sulfuric acid,[12] but in the usual spectral solvents they are transparent. Methyl cholate was made uv absorbing for the present work by converting it to the 3-*p*-nitrobenzoate ester (**1g**).[13] Its rate of acetylation by acetic anhydride and pyridine was determined by chromatographing aliquots of the reaction mixture on tlc plates, recovering starting material and product separately, and measuring them spectrophotometrically. The *p*-nitrobenzoate ester **1g** was not soluble in the benzene medium used previously; so the reaction was carried out in pyridine. The product formed initially is assumed to be the 7-monoacetate (**1h**) by analogy with the known conversion of methyl cholate 3-acetate to the 3,7-diacetate.[1b] Beginning with 4 hr, a third spot appeared on the tlc plate, which was always much weaker than the 7-acetate spot. It was shown to be the 7,12-diacetate (**1i**) of methyl cholate 3-*p*-nitrobenzoate by comparison with an authentic sample by tlc. Consequently, the two acetate spots were combined and measured together as representing total 7-acetate. Data for a typical run are given in Table V.[14]

The second-order rate constant of $31.3 \times 10^{-6}\ M^{-1}\ sec^{-1}$ is 39 times that for the acetylation of methyl 7α-hydroxycholanate by the glpc method. This implies that the 3α-*p*-nitrobenzoyloxy and/or 12α-hydroxyl groups catalyze acetylation of the 7α-hydroxyl, a result analogous to our earlier finding that the 7-hydroxyl of methyl cholate 3-acetate acetylates in much higher yield than that of methyl 7α-hydroxycholanate.

Experimental Section[15]

Methyl 7α-Hydroxycholanate (**1b**).—A solution of 4.44 g (11.3 mmol) of chenodeoxycholic acid in 50 ml of methanol containing 5 drops of concentrated HCl was refluxed 3.5 hr, cooled to room temperature, made turbid with aqueous $NaHCO_3$, and evaporated in an open dish. The oily residue was dissolved in ether and chromatographed on 133 g of Al_2O_3. The fraction eluted by ether–methanol (24:1 to 22:3), 4.75 g, an oil (containing a little solvent), was dried by azeotropic distillation of benzene, dissolved in 30 ml of pyridine (previously dried over KOH), and treated with 4.75 g (25 mmol) of *p*-toluenesulfonyl chloride. After standing overnight at room tempersture, the mixture was poured over crushed ice; the oil that separated gradually solidified. Filtering, washing with dilute HCl and H_2O, and then vacuum drying gave 6.36 g (quantitative yield) of crude methyl 7α-hydroxy-3α-tosyloxycholanate, crystallized twice from methanol: mp 128.5–129.0°; ir 2.76, 5.79, 6.22, 8.53 μ (SO_3).

Anal. Calcd for $C_{32}H_{48}O_6S$: C, 68.54; H, 8.63; S, 5.72. Found: C, 68.73; H, 8.61; S, 5.62.

A solution of 4.40 g (7.85 mmol) of the tosylate in 35 ml of freshly distilled collidine was refluxed 2.5 hr, cooled to room temperature, and poured into ice-cold, dilute H_2SO_4, causing an oil to separate. It was extracted into ether, washed with dilute acid and H_2O, dried over Na_2SO_4, and evaporated to give an oil, 2.495 g (82%), which slowly solidified. Crystallization from CH_3OH–H_2O, followed by three crystallizations from acetone–H_2O gave the analytical sample of methyl 7α-hydroxy-3-cholenate: slight melting at 112°, mp 117–120°; ir 2.73, 5.72, 6.03 (w, C=C), 8.58 μ (this is a strong band, but appreciably weaker than the 8.53-μ band of the tosylate).

Anal. Calcd for $C_{25}H_{40}O_3$: C, 77.28; H, 10.38. Found: C, 77.52; H, 10.31.

Hydrogenation of the olefin, 2.00 g, mp 101–112°, in absolute EtOH with 5% Pd/C at 50 psi for 22 hr gave 2.015 g of an oil, which was dissolved in benzene and chromatographed on 60 g of Al_2O_3. The fraction eluted by benzene–ether (4:1 to 2:3) and by ether (1.270 g) crystallized from acetone–H_2O to give 953 mg of methyl 7α-hydroxycholanate: mp 78.5–79.5° (lit.[1b] 78.5–80.0°); ir 2.73, 5.76, 9.08, 9.73, 9.87, 10.1 μ.

Methyl Cholate 3-Tosylate (**1c**).—Methyl cholate (4.33 g, 15 mmol) and *p*-toluenesulfonyl chloride (3.24 g, 17 mmol) were mixed in 50 ml of pyridine and the homogeneous solution was allowed to stand at 5–10°. After 3 hr it was poured onto crushed ice and acidified with concentrated HCl. Chloroform extraction and solvent removal *in vacuo* gave a viscous, yellow oil, thin layer chromatography of which indicated six to eight components. After numerous attempts at purification *via* various supports and solvent systems, it was found that benzene–methanol (99:1) on 225 g of Florisil (30–60 mesh) did a creditable (though not entirely satisfactory) job of separation. After initial elution of several unidentified components, the tosylate was found relatively pure in several succeeding cuts. Later fractions were contaminated with starting material. The nearly pure intermediate fractions were combined, the solvent was removed, and the resi-

(12) L. L. Smith and S. Bernstein in "Physical Properties of the Steroid Hormones," L. L. Engle, Ed., Macmillan, New York, N. Y., 1963, p 321.

(13) Our first approch was the successful synthesis of phenacyl cholate, but we were unable to obtain pure 3-monoacetate and 3,7-diacetate derivatives of it.

(14) Preliminary experiments indicate that this procedure is applicable to some other uv-absorbing steroids. Testosterone, 11α-hydroxyprogesterone, and 11α-hydroxy-17α-methyltestosterone were run as described herein except that methanol–benzene mixtures (rather than $CHCl_3$–AcOH) were used in developing the tlc plates. The method failed, however, with cortisol and estrone; cortisol acetate crystallized out during the reaction and aliquots of the estrone acetylation did not separate adequately by tlc.

(15) The acetylation procedure and compounds not described in this section are described in ref 1b. Melting points were taken on a Unimelt apparatus and are uncorrected. Infrared spectra were determined as mineral oil mulls with an Infracrod. Ultraviolet spectra were determined with a Cary 15 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

due was recrystallized from methanol–water. There was obtained 1.693 g of the tosylate as small, white needles: mp 133–134°; ir 2.85 (OH), 5.80 (C=O), 7.42, 8.56 μ (SO_2–O).

Anal. Calcd for $C_{32}H_{48}O_7S$: C, 66.63; H, 8.36; S, 5.56. Found: C, 66.74; H, 8.36; S, 5.54.

Methyl 3β-Acetoxy-7α,12α-dihydroxycholanate (1d).—The 3α-tosylate (1c, 1.876 g, 3.25 mmol) and tetrabutylammonium acetate (2.355 g, 8.56 mmol)[16] were combined in 90 ml of acetone, and the resulting solution was refluxed under nitrogen for 29 hr and then allowed to stand at room temperature for 3 days. Ths solvent was allowed to evaporate and the residue chromatographed on 193 g of Florisil. Benzene–methanol (66:1) initially eluted the starting tosylate as well as some very minor components, then the 3β-acetate. Appropriate fractions were combined, the solvent was removed, and the residue was crystallized from methanol–water. The product (528 mg, 35%) was isolated as long needles: mp 191–193°; ir 2.87 (OH), 5.80 μ (C=O).

Anal. Calcd for $C_{27}H_{44}O_6$: C, 69.79; H, 9.55. Found: C, 69.68; H, 9.60.

The 7-acetate, **methyl 3β,7α-diacetoxy-12α-hydroxycholanate**, crystallized out of acetone–H_2O: mp 146–147°; ir 2.79, 5.79, 5.87, 7.91, 9.80 μ.

Anal. Calcd for $C_{29}H_{46}O_7$: C, 68.74; H, 9.15. Found: C, 68.50; H, 8.87.

Methyl Cholate 3-*p*-Nitrobenzoate (Methyl 7α,12α-Dihydroxy-3-*p*-nitrobenzoyloxycholanate (1g)).—Following the conditions used in the preparation of methyl cholate 3-benzoate,[17] a solution of methyl cholate (4.22 g, 10 mmol) in 30 ml of sodium-dried benzene was distilled to half volume, then cooled to room temperature. The solution was stirred while pyridine (1.25 ml) and then a solution of 1.85 g (10 mmol) of *p*-nitrobenzoyl chloride in 10 ml of benzene were added over a 20-min period. More benzene (30 ml) was added as the mixture thickened; stirring was continued at room temperature for 2 hr, after which the benzene layer was washed with three 20-ml portions of 0.5 *N* HCl, then 0.2 *N* HCl, and finally H_2O. The benzene solution was dried over Na_2SO_4 and evaporated under vacuum; a solution of the residue in 20 ml of benzene was diluted with 100 ml of ether and refrigerated overnight. A small amount of solid was filtered, mp 189–190°, and lacked an ir band in the OH region, but was not further characterized. The filtrate was concentrated to 10 ml, diluted with 100 ml of MeOH, and refrigerated overnight. The crystals were filtered, washed with cold MeOH, and dried: mp 216–218° (some preparations, mp 223–234°); ir 2.80, 5.83, 6.25, 6.54, 7.89, 8.29, 8.50, 9.05, 9.12, 10.38, 10.99, 11.39, 11.68, 13.92 μ.

Anal. Calcd for $C_{32}H_{45}O_8N$ (571.72): C, 67.23; H, 7.93; N, 2.45. Found: C, 67.15; H, 8.02; N, 2.36.

Methyl Chlolate 3-*p*-Nitrobenzoate 7-Acetate (Methyl 7α-Acetoxy-12α-hydroxy-3α-*p*-nitrobenzoyloxycholanate (1h)).—Acetic anhydride (0.5 ml) was added to a solution of 1g (1.058 g, 1.70 mmol) in 4 ml of dry pyridine, and the solution was made up to a volume of 5.0 ml with pyridine. The solution stood 2 days in the drybox at room temperature and then was transferred in 15 ml of ether to a separatory funnel containing 10 ml of H_2O. The ethereal layer was washed with three 5-ml portions of H_2O and then evaporated to dryness under vacuum. A solution of the residue in 5 ml of acetone was diluted with 50 ml of petroleum ether (bp 30–60°) and refrigerated overnight. The crystalline product was filtered, washed with petroleum ether, and vacuum dried: mp 189–190°; ir 2.79, 5.84, 5.90, 6.27, 6.60, 7.89, 8.20, 9.00, 9.11, 9.91, 10.80, 12.00, 12.80, 13.99 μ.

Anal. Calcd for $C_{34}H_{47}O_9N$ (613.76): C, 66.54; H, 7.72; N, 2.28. Found: C, 66.36; H, 7.71; N, 2.07.

Methyl Cholate 3-*p*-Nitrobenzoate 7,12-Diacetate (Methyl 7α,12α-Diacetoxy-3α-*p*-nitrobenzoyloxycholanate (1i).—A solution of 423 mg (0.74 mmol) of 1g and 0.2 ml of acetic anhydride in 1.8 ml of pyridine was refluxed 2 days, cooled to room temperature, and transferred in 10 ml of ether to a separatory funnel containing 2.5 ml of H_2O. The ethereal layer was washed with three 2.5-ml portions of H_2O and then evaporated to dryness under vacuum. All attempts to crystallize this product failed. Its solution in $HCCl_3$ was diluted with petroleum ether, causing an oil to separated. The supernatent was decanted and the residue was vacuum dried, leaving an amorphous solid: mp 87–88°, ir 5.92, 6.25, 6.59, 7.68, 7.78, 8.55, 10.7, 11.42, 13.99 μ.

Anal. Calcd for $C_{36}H_{49}O_{10}N$ (655.80): C, 65.93; H, 7.53; N, 2.14. Found: C, 65.99; H, 7.42; N, 2.07.

3α,5-Cycloandrostan-6β-ol (2a).—Androstenolone was reduced to 5-androsten-3β-ol according to Shoppee and Krueger.[18] Tosylation with *p*-toluenesulfonyl chloride and dry pyridine (KOH) at room temperture gave a 95% yield of crude tosylate, which crystallized from acetone to give fine needles: mp 129–130° (lit.[19] mp 136°); ir 6.21, 8.40, 8.50 μ (SO_3). The rearrangement was carried out similarly to that of Julia, *et al.*,[20] except for a shorter reaction time. The tosylate (3.218 g, 7.52 mmol) and potassium acetate (3.218 g, 32.8 mmol) were heated to reflux in a mixture of 520 ml of acetone and 120 ml of H_2O for 2.5 hr. Evaporation in an open dish left a residue, the organic portion of which was dissolved in $HCCl_3$ and dried over $CaCl_2$; evaporation of the $HCCl_3$ left 2.467 g of an oil, which was taken up in petroleum ether–benzene (4:1) and chromatographed on 74 g of Al_2O_3. Petroleum ether and mixtures of it with benzene (up to 40% benzene) eluted variable amounts of nonpolar compounds from which in one case was crystallized (out of ether–methanol) a solid, mp 188–190°, lacking hydroxyl and carbonyl absorption in the ir, with the formula $C_{19}H_{29}OC_{19}H_{29}$ indicated by analysis.

Anal. Calcd for $C_{38}H_{58}O$: C, 85.97; H, 11.01. Found: C, 85.79; H, 11.11.

After a small intermediate fraction, benzene eluted 107 mg of an oil with ir identical with the product obtained on acetylation of **2a**, but which was exceedingly difficult to crystallize. One sample out of methanol melted at 60–68°, and on a second crystallization out of methanol–H_2O melted at 72–81° (lit.[21] mp 59–60°; erroneously described as the 6α epimer). After an intermediate cut of 90 mg (mixture), benzene–ether (9:1 to 3:2) eluted 1.217 g (54% yield) of **3α,5-cycloandrostan-6β-ol**: after two crystallizations from methanol–H_2O, mp 69–71.8° (lit.[21] mp 52–53°, erroneously described as the 6α epimer[22]); ir 2.82, 9.50, 9.75 (OH), 9.82 μ (Δ). This material is a solvate (methanol) that is stable to vacuum drying at room temperature. For analysis it was vacuum dried above its melting point.

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.34; H, 11.48.

Elution of the column with benzene–ether (2:3) gave an additional 174 mg of product (2a), slightly contaminated with the final fraction, most of which was eluted with ether, 396 mg of a solid material exhibiting OH and C=O absorption in the ir, but otherwise unidentified.

3α,5-Cycloandrostan-6β-ol-17-one (2b) was prepared similarly and crystallized from acetone–petroleum ether: mp 132–135° (lit.[19] mp 136–138°); ir 2.84, 5.85 (C=O), 9.51, 9.70, 9.75, 9.81 (Δ), 9.90 μ.

The **acetate** crystallized out of acetone–H_2O: mp 109–112° (lit.[19] mp 113–114°); ir 5.78 (C=O), 8.10, 9.80 μ (Δ).

17,17-Ethylenedioxy-3α,5-cycloandrostan-6β-ol (2c) was prepared similarly and crystallized from acetone: mp 141–143° (lit.[20] mp 142–144°); ir 2.79, 9.6 (OH), 9.81 μ (Δ).

The **acetate** crystallized out of acetone–H_2O: mp 109–110°, ir 5.82 (C=O), 9.81 μ (Δ).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.92; H, 8.82.

17β-Benzoyloxy-3α,5-cycloandrostan-6β-ol (2d).—17β-Benzoyloxy-5-androsten-3β-yl tosylate, mp 147–149° (lit.[23] mp 150.2–153.6°), was similarly subjected to *i*-steroid rearrangement; the product crystallized out of acetone: mp 105–106°; ir 2.79, 3.05, 5.90 (C=O), 9.35 (OH), 9.75 μ (Δ). Attempts to obtain this compound analytically pure were unsuccesful. Its identity is indicated by its method of preparation, its ir absorption curve, and its conversion to the acetate derivative.

The **acetate** crystallized out of acetone–H_2O: mp 98.2–99°; ir 5.81 (acetate C=O), 5.90 (benzoate C=O), 9.79 μ (Δ).

Anal. Calcd for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 76.83; H, 8.20.

17α-Ethynyl-3α,5-cycloandrostane-6β,17β-diol (2e).—17α-Ethynyl-5-androstene-3β,17β-diol was tosylated similarly to 5-

(16) R. Baker, J. Hudec, and K. L. Rabone, *J. Chem. Soc. C*, 1605 (1969).
(17) W. H. Hoehn and H. L. Mason, *J. Amer. Chem. Soc.*, **62**, 569 (1940).
(18) C. W. Shoppee and G. Krueger, *J. Chem. Soc.*, 3641 (1961).
(19) A. Butenant and L. Suranyi, *Ber.*, **75**, 591 (1942).
(20) S. Julia, C. Neuville, and M. Davis, *Bull. Soc. Chim. Fr.*, 297 (1960).
(21) A. F. Wagner, N. E. Wolff, and E. S. Wallis, *J. Org. Chem.*, **17**, 529 (1952).
(22) "Selected Constants; Optical Rotatory Power. Ia. Steroids," Pergamon Press, Elmsford, N. Y., 1965, p 45i.
(23) R. T. Blickenstaff and E. L. Foster, *J. Org. Chem.*, **26**, 5029 (1961).

androsten-3β-ol to give an 84% yield of the 3-tosylate, crystallized from methanol–H_2O: mp 139–140°; ir 2.98, 3.1, 6.26 (aromatic ring), 8.40, 8.51 (SO_3), 9.65 μ (OH).

Anal. Calcd for $C_{28}H_{36}SO_4$: C, 71.75; H, 7.74; S, 6.84. Found: C, 71.79; H, 7.52; S, 6.69.

i-Steroid rearrangement of the tosylate gave a crude product, which was chromatographed on silica gel. The fraction eluted by benzene–ether (4:1) and obtained in 62% yield was crystallized from methanol–H_2O, 17α-ethynyl-3α,5-cycloandrostane-6β,17β-diol: mp 110–115°; ir 2.9, 3.0, 4.75 (C≡C, very weak), 9.56 (OH), 9.70 (OH), 9.82 μ (Δ).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.20; H, 9.61. Found: C, 80.06; H, 9.44.

The 6-acetate crystallized out of acetone–H_2O: mp 70–73°; ir 2.9 sh, 3.05, 5.85 (C=O), 9.56 (OH), 9.81 μ (Δ).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.98; H, 8.95.

Methyl deoxycholate 3-acetate (3b) was prepared by acetylation of methyl deoxycholate under conditions which convert methyl cholate to its 3-acetate.[24] The crude product was chromatographed twice on alumina and crystallized twice from methanol–H_2O to give the 3-acetate, mp 112–113° (lit.[25] mp 128–129.5°). Although the melting point could not be raised, the sample gave a single spot by tlc with R_f intermediate between methyl deoxycholate and its diacetate, so it was assumed to be pure.

3α-Acetoxy-5β-pregnan-12α-ol-20-one (3d) was prepared similarly, except that in this case the crude product was a mixture of diacetate (25%) and 3-monoacetate (75%) which was separated by chromatography on alumina. Benzene and ether eluted the diacetate and then ether–methanol (9:1) eluted **3d**, crystallized from acetone–H_2O, mp 143–145°. Another crystallization gave the analytical sample: mp 144–145.4°; ir 2.80, 5.85, 7.92, 9.70 μ.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.07; H, 9.31.

24-Methyl-24-homocholane-12α,24-diol (3f) was prepared by a Grignard reaction with methyl 12α-hydroxycholanate under conditions similar to the preparation of **4a** (below); the crude product, an oil, was chromatographed on Al_2O_3. The column was developed with benzene and with ether; then the product (no C=O in the ir) was eluted with 4% MeOH in ether, 85% yield, and crystallized from MeOH–H_2O, mp 65–70°. Crystallization from MeOH–H_2O gave the analytical sample: mp 68–70°; ir 2.9, 8.7, 9.7 μ.

Anal. Calcd for $C_{25}H_{46}O_2$: C, 79.94; H, 11.87. Found: C, 79.56; H, 11.57.

20-Methyl-5β-pregna-3-ene-12α,20-diol (4a).—A solution of 3.16 g (10 mmol) of 5β-pregna-3-en-12α-ol-20-one[1b] in 50 ml of benzene was added slowly to a stirred solution of Grignard reagent (prepared from 28.4 g, 0.20 mol, of methy iodide and 4.88 g of Mg) in 50 ml of ether. The condenser was turned and the ether distilled out; the remaining solution was heated under reflux (benzene) for 12 hr. The cooled reaction mixture was diluted with benzene, washed with cold aqueous 25% NH_4Cl (containing a few drops of 50% H_2SO_4) and then with water, and dried over Na_2SO_4. Evaporation left a solid product, which was crystallized from methanol, 2.041 g (61.5% yield), mp 156–157°. A second crystallization from methanol gave the analytical sample: mp 173–174°; ir 2.82, 8.52, 9.29, 9.56, 9.62 μ.

Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.50; H, 10.91. Found: C, 79.56; H, 10.94.

Methyl 12α-hydroxy-3-cholanate (4b) was prepared by dehydrotosylation of methyl deoxycholate 3-tosylate as described by Chang, *et al.*[26]

Kinetic Measurements by Glpc.—The steroid (0.37 mmol) was weighed diretly into a 1-ml volumetric flask. Pyridine (0.100 ml) and benzene (about 0.5 ml) were added to effect solution,[27] acetic anhydride (0.100 ml) was added to start the reaction, and the volume was quickly made up to 1 ml with benzene. The stoppered flask was kept in a drybox at room temperature (25 ± 1°) and unmeasured aliquots were withdrawn periodically with Pasteur pipets and transferred directly into methanol. Samples that had evaporated to dryness were redissolved in acetone for chromatography in a MicroTek 220 fitted with a flame ionization detector and a Disc integrator. Two or three separate injections of each aliquot were averaged. The samples were chromatographed on either a 6-ft 1% OV-17 on Chrom G column (methyl lithocholate, methyl 7α-hydroxycholanate, and methyl 7α,12α-dihydroxycholanate) or a 4-ft 3% polysulfone on Chrom Q column (methyl 12α-hydroxycholanate). Separations were satisfactory using a column temperature of 290° and a carrier gas (N_2) flow rate of 55 ml/min. Surprisingly, with methyl lithocholate the alcohol had a shorter retention time than the acetate, though with the other three the reverse was true.

For rate calculations, the value of a was taken as 0.370 mol/l. based on the sample of steroid weighed, and b was assumed to be 1.065 mol/l. based on the volume of Ac_2O pipetted. Reactions were followed to 78–87% of completion. This level was reached in 30 hr in the case of methyl 7α,12α-dihydroxycholanate; at 174 hr there was no starting material left and the product was a mixture of 71% 7-monoacetate and 29% diacetate.

Kinetic Runs by Uv.—Methyl cholate 3-*p*-nitrobenzoate (1g, 212 mg, 0.37 mmol) was weighed into a 1-ml volumetric flask and dissolved in about 0.6 ml of pyridine which had been dried over molecular sieve type 4A. When solution was complete, 0.10 ml (1.065 mmol) of acetic anhydride was added to start the reaction and immediately pyridine was added to the mark. The flask was stoppered tightly, swirled gently to mix the contents, and kept in a drybox at room temperature (25 ± 1°). In taking aliquots of the reaction mixture, Pasteur pipets were used to transfer about 10 μl of the solution to a test tube containing 0.2 ml of H_2O. The tube was capped, shaken briefly, and refrigerated until the next step was carried out.

Contents of the tubes were evaporated by warming in a wire rack on the hot plate, care being taken to avoid excessive heating of the residue. Drops of condensate which appeared on the walls of the tubes were removed with facial tissues, after which the tubes were dried in a vacuum desiccator. Chloroform (0.1 ml) was added to each tube and the solutions were spotted on thin layer plates coated with silica gel containing lead manganese-activated calcium silicate phosphor. The plates were developed in 4% acetic acid in $HCCl_3$ and observed in a uv view box. The two spots from each aliquot were scraped from the plate separately and transferred to volumetric flasks (chosen so as to give absorbances between 0.2 and 0.7). The flasks were filled to the mark with MeOH, and the contents were mixed and allowed to settle. A portion of each supernatant was centrifuged to ensure removal of the silical gel; a blank was prepared similarly by scraping an unused portion of the plate. Spectra exhibited a maximum at 259 mμ, whose absorbance was measured employing the absorbance at 400 mμ as a base line.

A standard curve was prepared with ten mixtures of 1g and 1h ranging in composition from a mole ration of 1h to 1g of 0.10 to 9.00. A plot of the ratio of acetate absorbance to alcohol absorbance *vs.* mole ratio gave a straight line with a slope of 1.00 (least mean squares). Consequently, the $x/(a - x)$ values in Table V are equivalent to the ratio of acetate absorbance to alcohol absorbance (corrected for dilution to 50 ml).

During the acetylation, beginning with 5 hr three spots appeared on the thin layer plates. The fastest moving spot was found to have the same R_f as an authentic sample of the 7,12-diacetate (1i). It was assumed to arise from the 7-monoacetate (1h); consequently both spots were measured together representing total 7-acetate.

A duplicate run to that in Table V gave an average k of 0.115 ± 0.016 M^{-1} hr^{-1}.

Registry No.—**1b**, 28050-19-3; **1c**, 28192-77-0; **1d**, 28192-78-1; **1g**, 28192-79-2; **1h**, 28192-80-5; **1i**, 28192-81-6; **2a**, 2574-55-2; **2b**, 663-39-8; **2c**, 28192-84-9; **2c** acetate, 1624-79-9; **2d**, 28192-86-1; **2d** acetate, 28192-87-2; **2e**, 7253-33-0; **2e** 6-acetate, 28192-89-4; **3d**, 28192-90-7; **3f**, 28192-91-8; **4a**, 28192-92-9; methyl 7α-hydroxy-3α-tosyloxycholanate, 28192-93-0; methyl 7α-hydroxy-3-cholenate, 28192-94-1; methyl 3β,7α-diacetoxy-12α-hydroxycholanate, 28192-95-2; 17α-ethynyl-5-androstene-3β,17β-diol 3-tosylate, 28192-96-3.

(24) R. Grand and T. Reichstein, *Helv. Chim. Acta*, **28**, 347 (1945).

(25) T. F. Gallagher and W. P. Long, *J. Biol. Chem.*, 162, 521 (1946).

(26) F. C. Chang, A. Feldstein, J. R. Gray, G. S. McCaleb, and C. H. Sprunt, *J. Amer. Chem. Soc.*, **79**, 2167 (1957).

(27) In the case of methyl 7α,12α-dihydroxycholanate it was necessary to raise the proportion of pyridine to 0.3 ml (replacing benzene) to keep it in solution, but this change is believed to have no significant influence on the rate.

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Studies of the Synthesis of the B, C, and D Rings of Gibberellic Acid[1]

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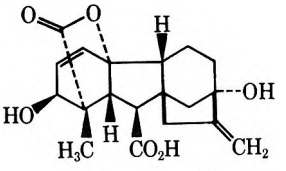
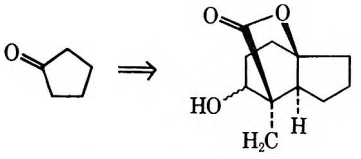
Cyclopentenones **3** and **7** have been condensed with butadiene to give the tetrahydroindene **4** and tetrahydro-1-indanone **8** derivatives, respectively. The tetrahydroindene **4** results from condensation on the enolic double bond of the enol form of **3** and is of no use for the synthesis of gibberellic acid. The tetrahydro-1-indanone **8** was saponified and subjected to iodolactonization to give iodolactone **10**. Removal of the iodine gave keto lactone **16** which was condensed with the anion of dimethyl sulfone to give the β-keto sulfone **17**. Oxidation of **17** afforded the triketone **18** which cyclized smoothly with base to give the tricyclic sulfone **19** possessing the skeleton of the B, C, and D rings of gibberellic acid. Attempts to remove the extraneous D ring keto group from sulfone met with failure. An alternative elaboration of **17** was carried out. The extraneous keto group of the β-keto sulfone moiety was removed by a six-step sequence to give the diketo sulfone **29**. However, cyclization of **29** failed to give tricyclic material and the corresponding methyl ester, **32**, cyclized to an undesired β-keto sulfone **33**.

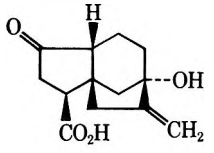
The total synthesis of the gibberellins has attracted a great deal of attention in the past several years. In considering the problem, it is attractive to construct the A ring in the final stages of the synthesis because of its great chemical sensitivity. Our earlier model studies provided an attractive approach for assembling the A ring as illustrated by the elaboration of cyclopentanone into the AB ring system of gibberellic acid.[5]



gibberellic acid



Therefore, our synthetic target is the tricyclic compound **1**.[6] Our general approach to this problem is to



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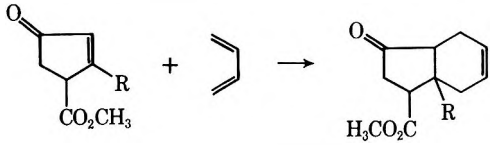
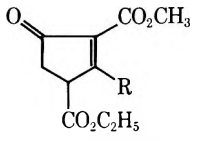
begin with a substituted cyclopentenone and generate the BC rings by means of a Diels–Alder reaction. Our

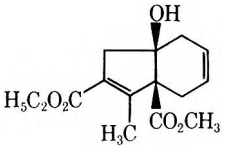


first effort involved the condensation of cyclopentenone **2** with 2-methoxybutadiene, a reaction which gives a monocyclic product.[7] In a further attempt, the con-



2, R = CH_2CH_2CN
3, R = CH_3

densation of butadiene with the more easily obtained cyclopentenone **3** was examined. A simple adduct was obtained in good yields, but the material proved to have structure **4** rather than the expected structure **5**. This result appears to be another manifestation of the enolic character of **2** and **3**.



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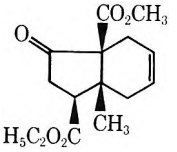

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The structure follows from both spectroscopic examination and chemical transformations. The ultraviolet spectrum shows λ_{max}^{EtOH} 231 nm (ε 6550) as found for similar compounds.[7] The infrared spectrum shows hydroxyl absorption, and the material did not form a 2,4-dinitrophenylhydrazone. The pmr spectrum shows the methyl group as a triplet (J = 2 Hz) owing to homoallylic coupling as previously observed in related compounds.[7] Saponification affords the corresponding dibasic acid and catalytic hydrogenation readily reduces the disubstituted double bond. Reduction of the dihydro derivative with potassium in liquid ammonia affords the saturated dibasic acid. Treatment of **4** with a

(1) The authors gratefully acknowledge financial support from the National Science Foundation (Grant GP 9427) and a Public Health Service Career Program Award (1-K3-NB-28,105) from the National Institute of Neurological Disease and Blindness.

(2) Alfred P. Sloan Research Fellow, 1965–1967.

(3) National Institutes of Health Postdoctoral Fellow, Fellowship 1-F2-GM-39,115-01.

(4) NDEA Predoctoral Fellow, 1966–1969.

(5) L. J. Dolby and R. J. Milligan, *J. Amer. Chem. Soc.*, **88**, 4536 (1966).

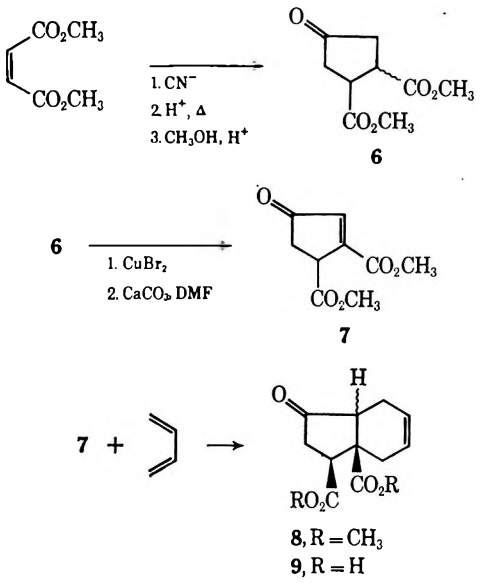
(6) All asymmetric synthetic products described are racemic mixtures. Only one enantiomorph for each is drawn for convenience of representation and discussion. Nomenclature is for the enantiomorph indicated.

(7) L. J. Dolby, C. A. Elliger, S. Esfandiari, and K. S. Marshall, *J. Org. Chem.*, **33**, 4508 (1968).

solution of sodium iodide and acetic acid in refluxing diglyme yielded a mixture of *cis*- and *trans*-1-methyl-2-carboxyindan. This mixture and the corresponding mixture of methyl esters were identified by comparison with authentic material.

Since our efforts to elaborate **2** met with failure, we turned to a new cyclopentenone derivative, 3,4-dicarbomethoxycyclopent-2-enone. This material may be obtained in large quantity and serves well as a dienophile (Scheme I).

SCHEME I

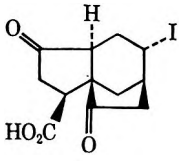


The structure and purity of the material from the dimerization of dimethyl maleate with sodium cyanide are uncertain.[8] The spectra are complicated by the presence of enolic material and a number of stereoisomers is possible. However, all of the possible structures would lead to a mixture of *cis*- and *trans*-cyclopentanone-3,4-dicarboxylic acid on vigorous acid hydrolysis. The trans isomer can be obtained from the mixture by crystallization.[8] In practice it is most convenient to esterify the mixture of acids and use the ester mixture in the next steps. Bromination of the ester mixture with cupric bromide gives a mixture of bromo ketones which is dehydrohalogenated by the action of calcium carbonate in *N*,*N*-dimethylformamide to give the desired 3,4-dicarbomethoxycyclopent-2-enone. The yield of the unsaturated ketone is about 25% based on dimethyl maleate.

The Diels–Alder condensation of the unsaturated ketone with butadiene proceeds smoothly to give a mixture of the tetrahydro-1-indanone diesters **8**. Although the kinetic products would be anticipated to possess cis-ring junctures, the isolated products also contain trans-fused material (14%), owing to epimerization under the reaction conditions. Under similar conditions, cyclopentenone and butadiene produce both diastereomers of the expected tetrahydro-1-indanone.[9]

Saponification of the crude reaction mixture gives a mixture (75% cis to 25% trans) of the corresponding diacids **9** in 77% yield based on cyclopentenone **7**. A pure sample, mp 176–177.5° dec, is easily isolated by crystallization and contains the same cis to trans ratio of diacids.

The next stages of the synthesis required selective oxygenation of the double bond to introduce the bridgehead oxygen of the CD ring of gibberellic acid and subsequent elaboration of the ring juncture carbonyl function. Selective oxygenation of the double bond was accomplished by iodolactonization to give **10**. The structure and stereochemistry of this material were established by X-ray crystallography.[10]



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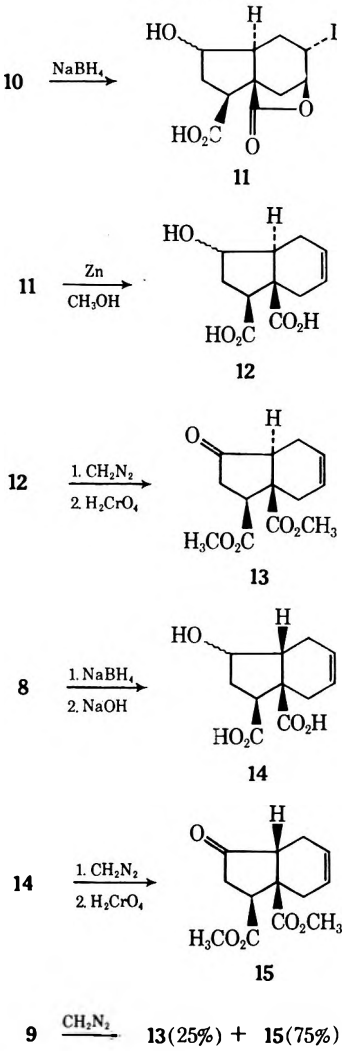
With the relative stereochemistry of the iodolactone **10** established, it is possible to determine the stereochemistry of the Diels–Alder adducts **8** and their corresponding diacids **9** (Scheme II).

SCHEME II



The tetrahydro-1-indanone **13** with a known trans-ring juncture is prepared from the *trans*-hydroxy diacid

(8) A. Michael and J. Ross, *J. Amer. Chem. Soc.*, **53**, 2394 (1931).
(9) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **28**, 31 (1963).
(10) The authors are indebted to Professor Ian Paul and his collaborators of the University of Illinois for the X-ray crystallographic study of the iodolactone **10**: C. A. Maier, J. A. Kapecki, and I. C. Paul, *ibid.*, **36**, 1299 (1971).

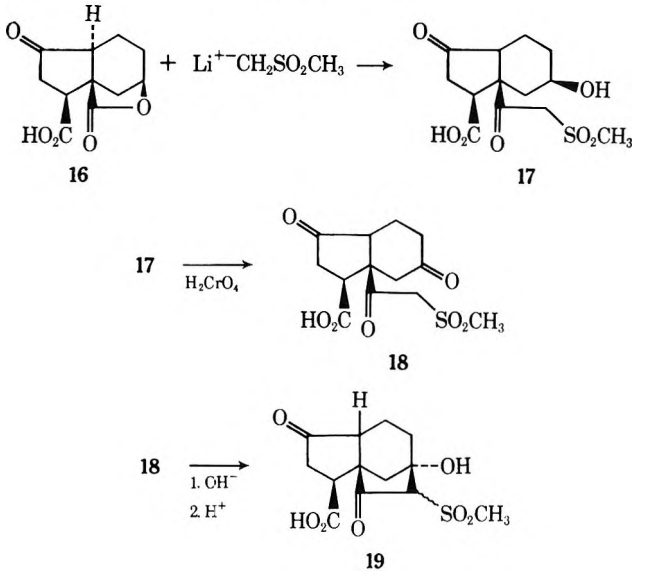
12, mp 170–171°, an intermediate in the degradation of the iodolactone **10** (see Scheme II). The pmr spectrum of **13** shows two 3 H singlets at δ 3.68 and 3.70 for the carbomethoxy protons. Sodium borohydride reduction of a pure sample of the Diels–Alder adducts **8** followed by saponification leads to the *cis*-hydroxy diacid **14**, mp 154–156°. Chromic acid oxidation of the esterified diacid **14** gives the tetrahydro-1-indanone **15** with a cis-ring juncture. The pmr spectrum shows two 3 H singlets at δ 3.70 and 3.72 for the carbomethoxy protons. The cis isomer **15** can also be isolated from the diazomethane esterified keto diacid **9** by crystallization.

The pmr spectrum of the purified Diels–Alder adduct **8** indicates the presence of 86% of the cis isomer and 14% of the trans isomer. Examination (pmr) of the diazomethane esterified diacids **9** indicates an isomeric mixture of 75% cis and 25% trans. The yields (19–25%) of **10** are the same starting with either crude or purified diacid. It is apparent that only the trans isomer undergoes iodolactonization.

The synthesis was continued from compound **10** in spite of the fact that it possesses a trans-ring juncture, whereas the corresponding fusion in gibberellic acid is cis. Since the keto group of the five-membered ring makes all of the intermediates subject to epimerization at the ring juncture, this synthetic approach is foredoomed to failure unless the cis-fused isomer of the critical intermediate **1** is at least comparable in stability to the trans-fused isomer. We take the optimistic view of this situation.

Accordingly, the iodine was efficiently replaced by hydrogen through the action of tri-*n*-butyltin hydride.[11] The keto lactone **16** was then elaborated following the method developed by House and his collaborators[12] (Scheme III). The condensation of **16** with dimethyl

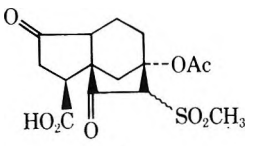
SCHEME III



sulfone proceeds smoothly to give the β-keto sulfone **17** in 55% yield. Both compounds **17** and **18** obtained by chromic acid oxidation of **17** exist at least in part as lactols as indicated by an absorption at 1780 cm^{-1} in their infrared spectra.

(11) H. G. Kuivila, *Advan. Organometal. Chem.*, **1**, 47 (1964).
(12) H. O. House and J. K. Larsen, *J. Org. Chem.*, **33**, 61 (1968).

Due to the possibility of base-induced epimerization of the ring juncture during the formation of **17**, the stereochemistry at the ring juncture is not definitely known beyond the keto lactone **16**. The triketone **18** is smoothly cyclized to **19**, obtained in 68% yield, by action of methanolic potassium hydroxide. This is in contrast to the cyclization of a very closely related compound with a cis-ring juncture which gave an equilibrium mixture containing only 10% of tricyclic material.[12] The structure of **19** follows from its spectral properties and subsequent transformations. The pmr spectrum of **18** shows a broad multiplet at δ 4.60 (two protons) which is ascribed to the methylene protons adjacent to the sulfone. This absorption is absent from the spectrum of **19**, but a sharp singlet appears at δ 4.44 (one proton) attributed to the methine proton adjacent to the sulfone. Moreover, the bridgehead hydroxy group was acetylated with acetyl chloride to give the tricyclic acetate **20** which was esterified with diazomethane to yield the ester **21**. The spectral properties of these materials were in agreement with structure **19**.



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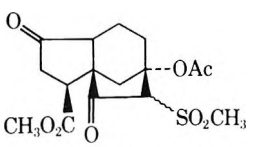

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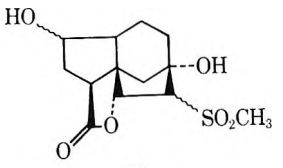
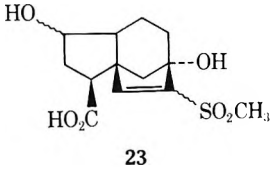
The next problem in elaborating compound **19** was the removal of the extraneous oxygen of the D ring. We hoped that reduction of **19** would lead to lactone **22**. The action of strong base in **22** would then likely give the vinyl sulfone **23**. However, reduction of **19** with sodium borohydride afforded an intractable mixture of



22



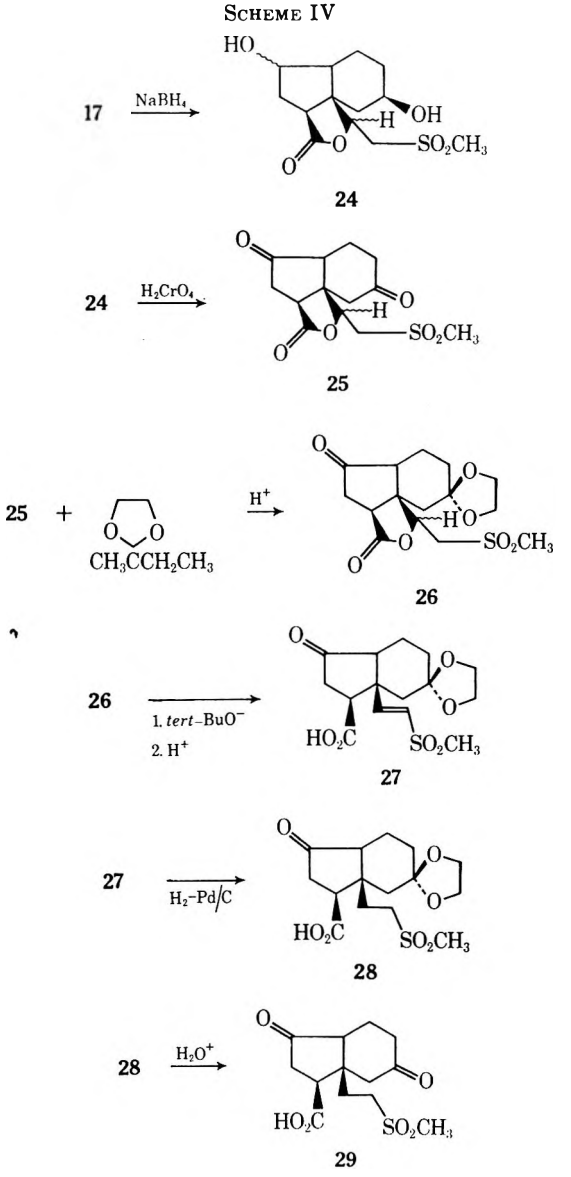
23

no less than seven compounds, and we were unable to characterize any of the products. This approach was abandoned in favor of a sequence involving removal of the offending oxygen prior to closure of the D ring (Scheme IV).

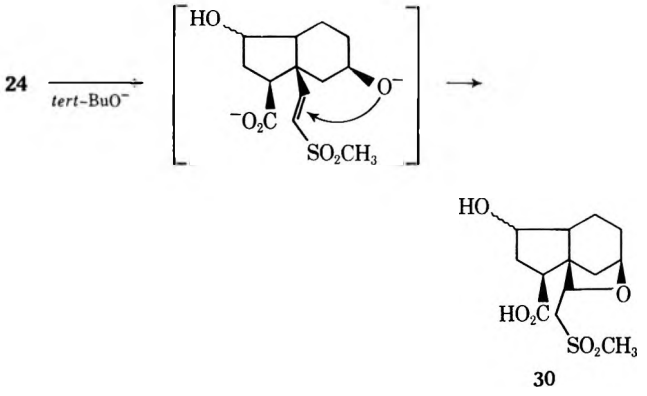
The transformations of Scheme IV are unexceptional for the most part. Ketal formation from the diketo lactone **25** gave very good yields (87%) of the monoketal **26**. The spectroscopic evidence clearly showed that only the six-membered ring carbonyl was involved in ketal formation. The pmr spectrum in perdeuteriodimethyl sulfoxide of the vinyl sulfone **27** showed a singlet at δ 6.85 which changed to an AB quartet (J = 15 Hz) in perdeuterioacetone. Accordingly, the double bond is assigned the trans configuration. Hydrogenation and hydrolysis of **27** proceeded smoothly although surprisingly vigorous conditions were required to remove the protecting group.

The overall transformation accomplished in Scheme IV could have been accomplished in fewer steps if base-induced elimination could have been successfully car-

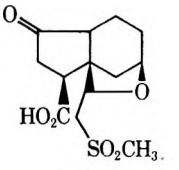
SCHEME IV



ried out on the dihydroxy lactone **24** or the diketone **25**. Treatment of **24** with potassium *tert*-butoxide afforded a cyclic ether to which we assign structure **30**. It appears that the desired vinyl sulfone is formed but then suffers nucleophilic addition to the double bond.



The spectral properties of **30** are in accord with the assigned structure; in particular, the pmr spectrum shows no vinyl protons although **30** is clearly a carboxylic acid. Oxidation of **30** with chromic acid affords only a monoketone **31**, and the infrared spectrum of this material shows a new maximum at 1740 cm^{-1} as expected on the basis of structure **30**.



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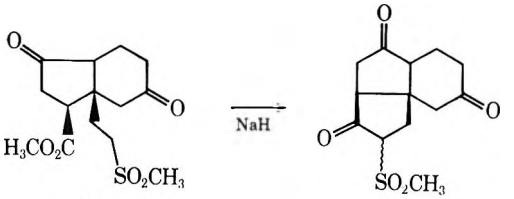
Attempted elimination of the diketone **25** resulted in a deep seated rearrangement. The product, $C_{12}H_{16}O_4S$, has lost the carboxyl group with the appearance of an α,β-unsaturated ketone grouping. Moreover, the pmr spectrum showed absorption which could be ascribed to a methyl group attached to a methine carbon. Although the structure of this product has not been established, it is clearly not the desired vinyl sulfone.

The successful completion of the transformations of Scheme IV provided the desired diketo sulfone **29** for cyclization. Unfortunately, all of our attempts to cyclize **29** met with failure, and only starting material could be isolated. Since the strongly alkaline conditions converted the carboxyl group of **29** to carboxylate, it was considered that this negative charge might be inhibiting the desired cyclization. Accordingly, **29** was esterified and treatment of the ester with sodium hydride produced a new compound. However, the new compound is clearly not the desired tricyclic system and its properties are consistent with structure **33**.



32 **33**

Experimental Section[13]

cis-**2-Carbethoxy-3aβ-carbomethoxy-7aβ-hydroxy-3-methyl-3a,4,7,7a-tetrahydroindene** (**4**).—A solution of 56.4 g (0.25 mol) of cyclopentenone **3**, benzene (120 ml), 80 ml of liquid 1,3-butadiene, and 2.5 g of 2,6-di-*tert*-butylphenol (added as an inhibitor) was heated at 180° in a sealed bomb for 42 hr. The resulting yellow mixture was concentrated under reduced pressure to leave a viscous yellow oil (99 g). This oil was mixed with 1500 ml of 40% potassium carbonate solution and extracted with three 500-ml portions of ether. The basic aqueous layer was acidified with concentrated hydrochloric acid to pH 2 and extracted with three 200-ml portions of ether. These extracts were dried and concentrated to give 15.0 g of **3**. The ethereal solution of neutral material was washed with water, dried, and concentrated under vacuum. Distillation of the residual oil in a modified Hickman molecular still [bath temperature 110–120°

(13) All melting and boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. Reactions involving strong bases or organometallic reagents were carried out under nitrogen. Infrared spectra were determined with a Beckman IR-5A infrared spectrophotometer. Unless otherwise stated, the ultraviolet spectra were determined in 95% ethanol with a Cary Model 15 recording spectrophotometer. The nuclear magnetic resonance spectra were determined at 60 MHz with a Varian Model A-60 nmr spectrometer. The chemical shift values are expressed in δ values (ppm) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a CEC, Model 21-110 mass spectrometer equipped with a direct inlet system at an ionizing potential of 70 eV. The microanalyses were performed either by Berkeley Analytical Laboratory, Berkeley, Calif., Chemalytics, Inc., Tempe, Ariz., or Micro-Tech Laboratories Inc., Skokie, Ill.

(0.15 mm)] separated 24.0 g (34%) of crude **4** as a colorless viscous oil. A pure sample of the **4** was obtained by glc on a 1.5-m column packed with 10% silicone on Chromosorb W at 200°: ir $\tilde{\nu}_{max}^{CCl_4}$ 3590, 3520, 1735, 1715, and 1645 cm^{-1} (weak); pmr (CCl_4) δ 1.28 (t, J = 7 Hz, 3 H), 2.1 (t, J = 2 Hz, 3 H), 2.02–3.20 (complex multiplets, 5 H), 2.7 (q, J = 2 Hz, 2 H), 3.72 (s, 3 H), 4.20 (q, J = 7 Hz, 2 H), and 5.83 (broad singlet, 2 H); uv λ_{max}^{EtOH} 231 nm (ϵ 6550).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.28; H, 7.14. Found: C, 64.48; H, 7.08.

***cis*-2-Carbethoxy-3aβ-carbomethoxy-7aβ-hydroxy-3-methyl-3a,4,5,6,7,7a-hexahydroindene.**—A sample of **4** (1.4 g, 5.0 mmol) was hydrogenated (1 atm) in ethanol over 0.1 g of 10% Pd/C. Filtration of the resulting mixture, followed by removal of the solvent, gave 1.41 g (100%) of the title compound as a colorless oil: ir $\tilde{\nu}_{max}^{CCl_4}$ 3600–3400 (broad), 1730, 1710, and 1640 cm^{-1}; pmr ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H), 0.85–2.9 (complex multiplets, 9 H), 2.16 (t, J = 2 Hz, 3 H), 2.68 (q, J = 2 Hz, 2 H), 3.74 (s, 3 H), and 4.20 (q, J = 7 Hz, 2 H); uv λ_{max}^{EtOH} 231 nm (ϵ 5200).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.42; H, 7.85.

***cis*-2,3aβ-Dicarboxy-7aβ-hydroxy-3-methyl-3a,4,7,7a-tetrahydroindene.**—A mixture of 2.80 g (10.0 mmol) of **4**, 2 N aqueous sodium hydroxide (100 ml), and 95% ethanol (50 ml) was refluxed for 1 hr. The reaction mixture was concentrated under reduced pressure, diluted with 50 ml of water, and extracted with ether. The aqueous phase was then acidified with hydrochloric acid to pH 2 and extracted with two 100-ml portions of ether. The ether was washed with 200 ml of brine and dried. Evaporation of the solvent and trituration with chloroform gave 0.75 g (31.4%) of diacid: mp 183–184°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600–2800 (broad), 1740, 1710, and 1640 cm^{-1}; pmr [$(CD_3)_2CO$–$(CD_3)_2SO$, 9:1] δ 1.83–2.65 (complex multiplets, 5 H) 2.10 (t, J = 2 Hz, 3 H), 2.73 (q, J = 2 Hz, 2 H), and 5.79 (broad, 2 H); uv λ_{max}^{EtOH} 233 nm (ϵ 7710).

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.51; H, 5.88. Found: C, 60.14; H, 5.83.

***cis*-2,3aβ-Dicarboxy-7aβ-hydroxy-3-methyl-3a,4,5,6,7,7a-hexahydroindene.**—In 75 ml of ethanol and 0.2 g of 10% Pd/C was dissolved 0.476 g (2.0 mmol) of *cis*-2,3aβ-dicarboxy-7aβ-hydroxy-3-methyl-3a,4,7,7a-tetrahydroindene. The hydrogenation was carried out at room temperature and at atmospheric pressure until the hydrogen uptake ceased. Filtration of the catalyst, followed by removal of the solvent and trituration with chloroform, gave 0.39 g (81%) of the diacid. A sample was purified by sublimination (150°, 0.01 mm) and crystallization from acetonitrile: mp 213–214°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600–2700 (broad), 1730, and 1710 cm^{-1}; pmr [$(CD_3)_2SO$] δ 0.85–2.8 (complex multiplets, 9 H), 2.02 (t, J = 2 Hz, 3 H), and 2.58 (q, J = 2 Hz, 2 H); uv λ_{max}^{EtOH} 233 nm (ϵ 7380).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.96; H, 6.71. Found: C, 59.71; H, 7.06.

Birch Reduction of *cis*-2,3aβ-Dicarboxy-7aβ-hydroxy-3-methyl-3a,4,5,6,7,7a-hexahydroindene.—In a 50-ml flask was placed 0.24 g (0.001 mol) of the diacid in liquid ammonia (25 ml) at −80° and 0.4 g (0.01 g-atom) of potassium metal was added with rapid stirring. The stirring was continued for 10 min after the final addition and then 7 ml of dry 2-propanol was added during 15 min. The cooling bath was removed and the stirring was continued until the ammonia had evaporated. The reaction mixture was diluted with water (30 ml), cooled in ice, and acidified with concentrated hydrochloric acid to pH 2. The resulting mixture was extracted with two 100-ml portions of ethyl acetate. The ethyl acetate was dried and evaporated. Trituration with chloroform gave 0.183 g (75.6%) of *cis*-2,9β-dicarboxy-8β-hydroxy-3-methylhydrindan. Recrystallization from benzene–ethyl acetate afforded the pure diacid as white crystals: mp 186–188°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3700–2700 (broad), 1730, and 1710 cm^{-1}; pmr [CD_3CN–$(CD_3)_2SO$, 9:1] δ 0.8–3.2 (complex multiplets, 13 H), 1.07 (d, J = 6 Hz, 3 H), and 8.75 (broad singlet, 2 H).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.11; H, 7.57.

1-Methyl-2-carboxyindan.—To 3.92 g (14 mmol) of **4** was added 10.5 g (70 mmol) of sodium iodide, 10 ml of glacial acetic acid, and 60 ml of freshly distilled diglyme. The reaction mixture was refluxed for 2 hr during which carbon dioxide evolved. The reaction mixture was then poured onto ice (200 g) and extracted with two 200-ml portions of ether. The ether was dried and concentrated under reduced pressure. The residue was saponified in a refluxing solution of 40% aqueous sodium hydroxide (5 ml) and of methanol (50 ml) for 30 min. The solvent was removed under reduced pressure and the residue was diluted with water (200 ml) and extracted with three 60-ml portions of ether. The aqueous phase was acidified with concentrated hydrochloric acid and extracted with three 100-ml portions of ether. The ether was dried and concentrated under reduced pressure. Distillation of the residue in a modified Hickman molecular still gave 0.75 g (30.4%) of *cis*- and *trans*-1-methyl-2-carboxyindan as a colorless oil which solidified on standing. The solid was sublimed [170° (0.5 mm)] and recrystallized from ethanol–water to give a mixture of cis and trans acids as white crystals: mp 68–73°; mp 77–80° after recrystallization from hot water (lit.[14] mp 82°); ir $\tilde{\nu}_{max}^{CCl_4}$ 1700 cm^{-1}; pmr (CCl_4) δ 1.20 and 1.42 (two sets of doublets, J = 6.5 Hz, 3 H), 2.50–3.80 (complex multiplets, 4 H), 7.10 (s, 4 H), and 11.95 (s, 1 H); uv λ_{max}^{EtOH} 272 nm (ϵ 2357), 266 (1947), and 260 (1400).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 75.00; H, 6.82. Found: C, 74.83; H, 6.96.

Treatment of the acid mixture in ether solution with excess ethereal diazomethane gave the corresponding methyl esters as a colorless oil. Gas chromatography (1.5-m column packed with 10% silicone on Fluoropak at 200°) purified a sample of this ester which was found to be identical with an authentic sample prepared by the method of Roser[14] by comparison of their glc retention times (33 min), ir, and pmr spectra: ir $\tilde{\nu}_{min}^{CCl_4}$ 1730 cm^{-1}; pmr (CCl_4) δ 1.1 and 1.4 (two sets of doublets, J = 7 Hz, 3 H), 2.5–3.65 (complex multiplet, 4 H), 3.69 and 3.72 (two singlets, 3 H), and 7.13 (s, 4 H).

Condensation of Dimethyl Maleate with Sodium Cyanide.—Dimethyl maleate (14.4 g, 50 mmol) was refluxed for 6 hr with stirring with sodium cyanide (2.45 g, 50 mmol) in dry methanol (100 ml). The solvent was removed under reduced pressure and the residue was taken up in water (200 ml). The aqueous solution was washed with two 100-ml portions of ether to remove starting material after which it was acidified with concentrated hydrochloric acid to pH 2 and extracted with three 100-ml portions of ethyl acetate. The ethyl acetate solution was washed twice with 100-ml portions of saturated salt solution, dried, and evaporated under pressure to give 10.5 g (73%) of crude cyanotricarbomethoxycyclopentanone. Distillation of the residue through a short-path still gave a colorless viscous oil: bp 173–176° (1.5 mm) [lit.[8] bp 190–200° (4 mm)]; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3500–2700 (very broad) and 1735 cm^{-1}; pmr ($CDCl_3$) δ 2.8 (complex multiplets, 2 H), 3.43 and 3.48 (two singlets, 1 H), 3.75 (two sets of four singlets, 9 H), 4.2 (complex multiplet, $^2/_3$ H), and 10.0 (s, $^1/_3$ H).

Large-Scale Preparation of the Diester Mixture 6.—In a 2000-ml flask equipped with a reflux condenser were placed sodium cyanide (73.5 g, 1.5 mol) and anhydrous methanol (750 ml). The cyanide was partially dissolved with swirling and diethyl maleate (516 g, 3.0 mol) was added. The resulting mixture heated at reflux overnight and then 650–700 ml of methanol was removed by simple distillation, and water (500 ml) was added to the dark brown residue. To the resulting solution was slowly added concentrated hydrochloric acid (500 ml) (CAUTION: HCN) and the mixture was refluxed for 3 hr after which 900 ml of water and hydrogen chloride was removed by simple distillation. The residue was diluted with 500 ml of water and saturated with 150 g of ammonium sulfate followed by a 12–20-hr continuous extraction with ethyl acetate. The ethyl acetate solution was dried and evaporated under reduced pressure to give the crude mixture of cyclopentanone-3,4-dicarboxylic acids. Without further purification, the crude diacid was dissolved in 1000 ml of dry methanol and placed in a 2000-ml flask equipped with a mechanical stirrer and Soxhlet extractor containing 3-Å molecular sieves. To this stirring solution was added 90 g of Dowex 50 W-X8 acidic ion exchange resin and the mixture was refluxed for 24 hr. (The esterification has also been done by allowing the methanol solution of the diacid to stand overnight with 5% by weight anhydrous hydrogen chloride.) The acidic ion exchange resin was filtered off and the excess methanol removed under reduced pressure to give a crude yellow oil. Fractionation of the crude diester through a 70-cm Podbielniak tantalum spiral column gave 150 g (50%) of a cis and trans mixture of the diester **6**; bp 125–155° (1.5 mm). The overall yield for the three steps varied from 45 to 55%.

(14) W. Roser, *Justus Liebigs Ann. Chem.*, **247**, 157 (1888).

3,4-Dicarbomethoxycyclopent-2-enone (7).—In a 1000-ml flask equipped with a mechanical stirrer and a reflux condenser were placed 40 g (0.20 mol) of the keto diester **6**, cupric bromide (98.12 g, 0.44 mol), and tetrahydrofuran (600 ml). The heterogeneous mixture was refluxed with vigorous stirring for 2 hr. The cuprous bromide was filtered off and the solvent was removed under pressure to give the crude bromo ketone as a green oil.

The crude bromo ketone was dissolved in dimethylformamide (50 ml) and placed in a 250-ml flask equipped with a magnetic stirrer. To this stirring solution was added 22 g (0.22 mol) of calcium carbonate and the resulting mixture was kept at 90–100° for 1 hr. The very dark brown reaction mixture was poured over 250 g of crushed ice and the precipitate was filtered off. The aqueous mixture was then extracted with four 200-ml portions of ethyl acetate. The ethyl acetate solution was dried and evaporated under reduced pressure to give 40 g of a very dark brown oil. Distillation gave 21 g (53%) of the α,β-unsaturated ketone **7** as a pale yellow oil: bp 120–125° (1.5 mm); ir $\tilde{\nu}_{max}^{CCl_4}$ 1735 and 1620 cm^{-1}; pmr (CCl_4) δ 2.6 (complex multiplets, 2 H), 3.7 (s, 3 H), 3.82 (s, 3 H), 4.0 (complex multiplet, 1 H), and 6.8 (d, J = 2 Hz, 1 H); uv λ_{max}^{EtOH} 227 nm (ϵ 5530), and $\lambda_{max}^{EtOH-NaOH}$ 245 nm (ϵ 2880) and 297 (6930).

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.62; H, 5.51.

3β,3aβ-Dicarbomethoxy-3a,4,7,7a-tetrahydro-1-indanone (8).—Into a stainless steel bomb cooled to 0° were placed the diester **7** (80.0 g, 0.404 mol), dry benzene (100 ml), 2,6-di-*tert*-butylphenol (6.0 g), and 1,3-butadiene (218 g, 330 ml, 4.04 mol). The bomb was sealed and heated at 130–135° for 3 days. After cooling, the contents were concentrated under reduced pressure to give 211.4 g of gummy residue. The crude diester was separated from the butadiene polymer by vigorously extracting the residue with five 200-ml portions of boiling methanol. The boiling methanol mixture was filtered through a 1/2-in. Celite bed and concentrated under reduced pressure to give 76.1 g of crude orange oil. Fractionation of the oil gave 50.0 g (48.9%) of a mixture of the indanone diesters **8** as a colorless oil: bp 131–133° (1.0 mm); ir $\tilde{\nu}_{max}^{CHCl_3}$ 1745 and 1730 cm^{-1}; nmr ($CDCl_3$) 1.80–3.42 (complex multiplets, 8 H), 3.72 (s, 0.42 H), 3.80 (s, 2.54 H), 3.82 (s, 2.54 H), 3.91 (s, 0.50 H), and 5.78 (m, 2 H).

3β,3aβ-Dicarboxy-3a,4,7,7a-tetrahydro-1-indanone (9).—The crude product from a condensation similar to the one described above was refluxed for 8 hr with 15% aqueous potassium hydroxide (1200 ml) and ethanol (250 ml). The basic solution was separated from the rubbery polymer and extracted with two 300-ml portions of chloroform after which it was acidified with concentrated hydrochloric acid to pH 2 and extracted with four 300-ml portions of ethyl acetate. The ethyl acetate solution was dried and concentrated to give 69.5 g (77.5%) of crude diacid **9**, as a brown viscous oil which crystallized on standing. A small sample was recrystallized once from ethyl acetate and twice from acetone: mp 180–182° dec; ir $\tilde{\nu}_{max}^{KBr}$ 3300–2500 (broad), 1730, and 1690 cm^{-1}; pmr [$(CD_3)_2CO$] δ 1.83–3.5 (complex multiplets, 8 H), 5.65 (broad doublet, 2 H), and 6.38 (broad singlet, 2 H).

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.77; H, 5.29.

A sample recrystallized only once from ethyl acetate, mp 176–177.5°, was esterified with an ethereal solution of diazomethane. The composition of the mixture of the tetrahydro-1-indanones was 75% of the cis isomer **15** and 25% of the trans isomer **13**.

***trans*-3β,9β-Dicarboxy-5β-hydroxy-6α-iodo-8α-1-hydrindanone-9β→5β-lactone (10).**—To a solution of iodine (50.8 g, 0.2 mol) and of potassium iodide (99.6 g, 0.6 mol) in 300 ml of water was added diacid **9** (44.8 g, 0.2 mol) dissolved in 1000 ml of 0.5 *M* sodium bicarbonate solution. The mixture was stored in the dark at room temperature for 20 hr. This mixture was mixed with ethyl acetate (400 ml), cooled to 0°, and acidified with 2 *N* sulfuric acid to pH 2. The ethyl acetate layer was separated and the aqueous solution was extracted with three 400-ml portions of ethyl acetate. The combined ethyl acetate fractions were washed with four 200-ml portions of 10% aqueous sodium thiosulfate, dried, and evaporated to give a dark orange solid–liquid mixture. Ethyl acetate (50 ml) was added and the mixture was cooled to 0° and filtered to give 17.5 g (25%) of the iodolactone **10** as a light brown solid, mp (iodine evolution) 165°, melting to dark oil at 180°. Recrystallization from acetone afforded pure iodolactone as white crystals: mp (iodine evolution) 170°, melting to dark oil at 184°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600–2700 (broad), 1775, 1740, and 1705 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.7–3.9 (complex multiplets, 8 H), 4.67 (broad triplet, J = 3.5 Hz, 1 H), 5.0 (broad triplet, J = 4.0 Hz, 1 H), and 12.7 (broad singlet, 1 H).

Anal. Calcd for $C_{11}H_{11}IO_5$: C, 37.74; H, 3.17; I, 36.25. Found: C, 37.63; H, 3.21; I, 36.06.

***trans*-3β,9β-Dicarboxy-1,5β-dihydroxy-6α-iodo-8α-hydrindan-9β→5β-lactone (11).**—The keto iodolactone **10** (4.47 g, 12.7 mmol) was partially dissolved in a solution of methanol (200 ml) and water (30 ml) and cooled to 0° with an ice bath. To this stirring, cooled suspension was added a solution of sodium borohydride (1.46 g, 38.4 mmol) dissolved in methanol (200 ml) and ice (50 g). After vigorous gas evolution had ceased, the clear solution was stirred at 0° for 4 hr and then at room temperature overnight. The slightly cloudy reaction mixture was carefully acidified to pH 1 with concentrated hydrochloric acid and the excess methanol removed under reduced pressure. Water (200 ml) was added to the residue and the mixture saturated with ammonium sulfate. The saturated solution was extracted with five 100-ml portions of ethyl acetate. The combined ethyl acetate layers were washed once with brine, dried, and concentrated to give 1.98 g (44.2%) of crude **11** as a white solid. Material recrystallized from acetone gave very small white crystals: mp (iodine evolution) 170–173°, 175–176° dec; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600, 3200, 1783, and 1740 cm^{-1}; pmr [$(CD_3)_2CO$–$(CD_3)_2SO$, 4:1] δ 1.80–3.20 (complex multiplets, 9 H), 4.18 (broad t, J = 5 Hz, 1 H), and 4.76 (m, 2 H).

Anal. Calcd for $C_{11}H_{13}IO_5$: C, 37.52; H, 3.72; I, 36.04. Found: C, 37.76; H, 3.51; I, 35.62.

***trans*-3β,3aβ-Dicarboxy-1-hydroxy-3a,4,7,7aα-tetrahydroindan (12).**—In a 50-ml flask equipped with a magnetic stirrer and a reflux condenser were placed the hydroxyiodo lactone **11** (570 mg, 1.62 mmol), zinc dust (210 mg, 3.24 mg-atoms), and anhydrous methanol (30 ml). The resulting mixture was refluxed for 20 hr. After the reaction mixture was allowed to cool to room temperature, it was carefully acidified with 2 *N* sulfuric acid (6.0 ml) and the excess zinc filtered off. The excess methanol was removed and the ammonium sulfate saturated aqueous layer was extracted with four 30-ml portions of ethyl acetate. The combined ethyl acetate layers washed once with brine, dried, and concentrated gave 344 mg (94.0%) of crude **12**. Recrystallization from ethyl acetate gave pure diacid **12** as very small crystals: mp 170–171°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3500, 3250–2850, and 1745 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.53–3.1 (complex multiplets, 8 H), 4.10 (broad t, J = 5 Hz, 1 H), and 5.68 (m, 3 H).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.32; H, 6.12.

***trans*-3β,3aβ-Dicarbomethoxy-3a,4,7,7aα-tetrahydro-1-indanone (13).**—In a 50-ml flask were placed the hydroxy diacid **12** (57.9 mg, 0.256 mmol) and freshly distilled tetrahydrofuran (5.0 ml). The magnetically stirred solution was cooled to 0° with an ice bath. Excess ethereal diazomethane was added and the slightly yellow solution was stirred 15 min at 0° and overnight at room temperature. The colorless solution was concentrated to give 64.8 mg (100%) of *trans*-3β,3aβ-dicarbomethoxy-1-hydroxy-3a,4,7,7aα-tetrahydroindan as a colorless oil: ir $\tilde{\nu}_{max}^{CHCl_3}$ 3450, 3040, 2980, 2850, and 1735 cm^{-1}; pmr ($CDCl_3$) δ 1.8–3.4 (complex multiplets, 8 H), 3.68 (s, 3 H), 3.70 (s, 3 H), 4.28 (m, 2 H), and 5.72 (m, 2 H).

The hydroxy diester was taken up in acetone (5.0 ml, distilled from potassium permanganate) and cooled to 0° with an ice bath. To this solution was added 0.2 ml of 8 *N* Jones reagent and the resulting mixture was stirred at 0° for 75 min. The excess reagent was destroyed with 2-propanol (10 ml), and the chromium salts were filtered off. The green solution was concentrated and the residue was taken up in hot ethyl acetate (5.0 ml), dried, and concentrated to yield 43.0 mg (66.7%) of crystalline *trans*-keto diester **13**. Material recrystallized from benzene–hexane gave small needles: mp 108–110°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3040, 2960, 2850, 1745, and 1735 cm^{-1}; pmr ($CDCl_3$) δ 1.8–4.25 (complex multiplets, 8 H), 3.62 (s, 3 H), 3.73 (s, 3 H), and 5.72 (m, 2 H).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.15; H, 6.50.

***cis*-3β,3aβ-Dicarboxy-1-hydroxy-3a,4,7,7aβ-tetrahydroindan (14).**—A pure sample of the Diels–Alder adducts **8** (5.52 g, 12.8 mmol) was taken up in methanol (50 ml), placed in a 250-ml erlenmeyer flask, and cooled to 0° with an ice bath. A solution of sodium borohydride (1.24 g, 32.8 mmol) in methanol (30 ml) and ice (20 g) was slowly added at 0°. The resulting solution was stirred 2 hr at 0° and then overnight at room temperature. Water (100 ml) was added and the methanol removed under reduced pressure. The aqueous mixture was extracted with

four 30-ml portions of ether. The combined ethereal layers were dried and concentrated to give 4.25 g (76.5%) of crude 3β,3aβ-dicarbomethoxy-1-hydroxy-3a,4,7,7a-tetrahydroindan as a light yellow oil: ir $\tilde{\nu}_{max}^{CHCl_3}$ 3500, 3040, 2960, 2850, and 1735 cm^{-1}; pmr ($CDCl_3$) δ 1.60–3.30 (complex multiplets, 8 H), 3.56 (broad s, 6 H), 4.10–4.50 (m, 1 H), and 5.71 (m, 2 H).

Without further purification, the crude hydroxy diester (2.31 g, 9.1 mmol) was taken up in 95% ethanol (10 ml) and placed in a 100-ml flask equipped with a magnetic stirrer and reflux condenser. To this light yellow solution was added 15% sodium hydroxide (50 ml) and the resulting mixture refluxed 12 hr. The reaction mixture was allowed to cool to room temperature and extracted with three 50-ml portions of chloroform. The aqueous layer was carefully acidified to pH 1 with concentrated hydrochloric acid. The acidic, ammonium sulfate saturated mixture was extracted with three 50-ml portions of ethyl acetate. The combined ethyl acetate layers were dried and concentrated to yield 1.99 g (97%) of hydroxy diacid **14** as a white foam. The foam was taken up in 5.0 ml of hot ethyl acetate and allowed to crystallize: mp 154–156°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3500, 3250–2850, and 1742 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.32–3.80 (complex multiplets 8 H), 4.12 (m, 1 H), and 5.62 (m, 3 H).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.79; H, 6.21.

***cis*-3β,3aβ-Dicarbomethoxy-3a,4,7,7aβ-tetrahydro-1-indanone (15).**—In a 50-ml flask equipped with a magnetic stirrer were placed the hydroxy diacid **14** (178 mg, 0.79 mmol) and freshly distilled tetrahydrofuran (8.0 ml). The resulting solution was cooled to 0° and excess ethereal diazomethane was added. The yellow solution was stirred at 0° for 15 min and then overnight at room temperature. The colorless solution was concentrated to give 200 mg (99.1%) of *cis*-3β,3aβ-dicarbomethoxy-1-hydroxy-3a,4,7,7aβ-tetrahydroindan as a colorless oil: ir $\tilde{\nu}_{max}^{CHCl_3}$ 3600, 3500, 3040, 3029, 2980, 2940, 2850, and 1735 cm^{-1}; pmr ($CDCl_3$) δ 1.7–3.4 (complex multiplets, 8 H), 3.68 (broad s, 6 H), 3.7–4.4 (m, 2 H), and 5.70 (m, 2 H).

The hydroxy diester was taken up in acetone (5.0 ml, distilled from potassium permanganate) and cooled to 0° with an ice bath. To the stirring solution was added 8 *N* Jones reagent (0.6 ml) at 0° and the mixture stirred at 0° for 75 min. The excess reagent was destroyed with 2-propanol (15 ml) and the chromium salts were filtered off. The concentrated residue was taken up in hot ethyl acetate (15 ml), dried, and concentrated to give 149 mg (75.0%) of *cis*-keto diester **15** as a slightly yellow oil, which was crystallized from benzene–hexane: mp 62.5–63°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3040, 2960, 2920, 2850, 1745 (sh), and 1735 cm^{-1}; pmr ($CDCl_3$) δ 1.80–3.43 (complex multiplets, 8 H), 3.70 (s, 3 H), 3.72 (s, 3 H), and 5.71 (m, 2 H).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.92; H, 6.26.

The *cis*-keto diester **15** was also prepared from the diazomethane treatment of the keto diacids **9**, mp 176–177.5°, followed by selective crystallization of the cis isomer away from the minor trans isomer.

***trans*-3β,9β-Dicarboxy-5β-hydroxy-8α-1-hydrindanone-9β→5β-lactone (16).**—In a 500-ml flask equipped with a magnetic stirrer were placed iodolactone **10** (17.5 g, 50 mmol) and freshly distilled tetrahydrofuran (200 ml). The suspension was cooled to 5° and 44 g (0.15 mol) of tri-*n*-butyltin hydride was added with stirring over 15 min. The cooling bath was removed and the mixture was allowed to warm to room temperature during which time a clear solution was obtained. After stirring, at room temperature, for an additional 12 hr, the solvent was removed under reduced pressure and the residue was taken up in ethyl acetate (200 ml). The ethyl acetate solution was extracted with three 100-ml portions of saturated sodium carbonate solution. The carbonate solutions were cooled to 0°, acidified with 2 *N* sulfuric acid, and extracted with three 250-ml portions of ethyl acetate. The ethyl acetate solutions were combined and washed twice with 150-ml portions of 10% sodium thiosulfate solution and once with 200-ml of brine. After drying and removal of solvent, the residue was taken up in ethyl acetate (25 ml), cooled, and filtered to give 8.52 g (76%) of keto lactone **16** as a light tan solid, mp 193–195°. The crude keto lactone was recrystallized twice from acetone to give pure keto lactone: mp 195–197°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600–2500 (broad), 1775, and 1740 cm^{-1}; pmr (CD_3CN) δ 1.0–3.7 (complex multiplets, 10 H), 4.9 (complex multiplet, 1 H), and 8.2 (broad singlet, 1 H).

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.68; H, 5.51.

3β-Carboxy-5β-hydroxy-9β-(1′-oxo-2′-(methylsulfonyl)ethyl)-1-hydrindanone (17).—In a 1000-ml flask equipped with a reflux condenser, a magnetic stirrer, a dropping funnel, and a septum were placed 15.04 g (0.16 mol) of dimethyl sulfone and freshly distilled tetrahydrofuran (600 ml). Air was excluded from the flask and a 1.6 *M* hexane solution of *n*-butyllithium (100 ml, 0.16 mol) was injected through the septum. The milky suspension was refluxed with stirring for 2 hr and then keto lactone **16** (8.96 g, 40 mmol) and dry tetrahydrofuran (100 ml) was added over 30 min. The stirring mixture was refluxed for 16 hr, cooled to room temperature, and acidified with concentrated hydrochloric acid (20 ml). This solution was concentrated on 30 g of silica gel under reduced pressure. The solid material was placed on a column of silica gel (50 g) packed in a water jacketted continuous chromatography column. The excess dimethyl sulfone was eluted with chloroform. The crude sulfone was eluted with 50% ethyl acetate–chloroform. Removal of the solvent left 12.0 g of a light tan foam. Trituration of this foam with ethyl acetate (20 ml) gave 7.0 g (55%) of the sulfone **17** as a white solid. Recrystallization from acetone afforded pure **17**: mp 184–186°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600–2700 (broad), 1780, 1740, and 1315 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.0–3.4 (complex multiplets, 12 H), 2.95 (s, 3 H), 3.85 (broad singlet, 1 H), and 4.75 (broad doublet, 2 H).

Anal. Calcd for $C_{13}H_{18}O_7S$: C, 49.06; H, 5.70; S, 10.05. Found: C, 48.79; H, 5.72; S, 10.02.

3β-Carboxy-9β-(1′-oxo-2′-(methylsulfonyl)ethyl)-1,5-hydrindanone (18).—To a cold (0°) solution of 5.57 g (17.5 mmol) of **17** in acetone (250 ml) was added dropwise with stirring 5 ml of aqueous 8 *N* chromic acid solution. The reaction mixture was stirred at 0° for 90 min and then the excess oxidant was destroyed with excess 2-propanol. The chromium salts were filtered off and washed with hot acetone, and then the green solution was concentrated under reduced pressure. The residue was taken up in hot ethyl acetate, dried, and concentrated to give 5.5 g of a white foam. The white foam was crystallized from ethyl acetate to afford 4.5 g (88.5%) of **18** as white crystals: mp 176–178°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3700–2700 (broad), 1780, 1740, 1720, and 1315 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.8–3.6 (complex multiplets, 11 H), 3.08 (s, 3 H), and 4.6 (broad doublet, 2 H); mass spectrum molecular ion peak at *m/e* 316 (calcd mol wt, 316.3).

Anal. Calcd for $C_{13}H_{16}O_7S$: C, 49.37; H, 5.10; S, 10.12. Found: C, 49.23; H, 5.12; S, 9.94.

2β-Carboxy-8α-hydroxy-9-(methylsulfonyl)tricyclo[6.2.1.0^{1,5}]-undecane-4,10-dione (19).—A solution of the triketo sulfone **18** (4.4 g, 13.9 mmol) in anhydrous methanol (100 ml) and potassium hydroxide (5.0 g) was refluxed for 1 hr, during which a precipitate formed. The resulting mixture was cooled, acidified with concentrated hydrochloric acid, and concentrated under reduced pressure. The residue was taken up in hot ethyl acetate, dried, and concentrated to give 4.4 g of a foam. Crystallization from ethyl acetate (3 days at room temperature) afforded 3.0 g (68.2%) of **19** as white crystals: mp 234–236°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3700–2700 (broad), 1740, 1310, and 1140 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.5–3.8 (complex multiplets, 11 H), 3.08 (s, 3 H), 4.44 (s, 1 H); mass spectrum molecular ion peak at *m/e* 316 (calcd mol wt, 316.3).

Anal. Calcd for $C_{13}H_{16}O_7S$: C, 49.37; H, 5.10; S, 10.12. Found: C, 49.39; H, 5.21; S, 9.95.

8α-Acetoxy-2β-carboxy-9-(methylsulfonyl)tricyclo[6.2.1.0^{1,5}]-undecane-4,10-dione (20).—A solution of **19** (0.95 g, 3.0 mmol) in acetyl chloride (75 ml) was refluxed for 19 hr. The excess acetyl chloride was removed under reduced pressure followed by the addition and evaporation of two 100-ml portions of ethyl acetate to give the crude acetate as a solid. Crystallization from ethyl acetate afforded 0.46 g (43%) of the tricyclic sulfone acetate as white crystals: mp 261° dec; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600–2900 (broad), 1740, and 1320 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.6–3.8 (complex multiplets, 10 H), 2.05 (s, 3 H), 3.08 (s, 3 H), and 4.65 (s, 1 H)

Anal. Calcd for $C_{15}H_{18}O_8S$: C, 50.28; H, 5.06; S, 8.93. Found: C, 50.52; H, 5.01; S, 8.87.

8α-Acetoxy-2β-carbomethoxy-9-(methylsulfonyl)tricyclo[6.2.-1.0^{1,5}]undecane-4,10-dione (21).—To a solution of 0.1074 g (0.3 mmol) of the tricyclic acetate **20** in dry tetrahydrofuran (20 ml) was added 0.08 *M* ethereal diazomethane (10.0 ml) at 0°. The solvents were removed and the residue crystallized from ethyl acetate to give 0.085 g (76%) of the methyl ester **21**: mp 216–220°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600, 3500, 1745, 1315, 1240, and 1150 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.65–3.80 (complex multiplets, 10 H), 2.08 (s, 3 H), 3.15 (s, 3 H), 3.65 (s, 3 H), and 4.88 (s, 1 H).

Anal. Calcd for $C_{16}H_{20}O_8S$: C, 51.61; H, 5.41; S, 8.59. Found: C, 51.45; H, 5.38; S, 8.68.

3β-Carboxy-1,5β-dihydroxy-9β-(1′-hydroxy-2′-(methylsulfonyl)ethyl)-hydrindan-3β→1′-lactone (24).—To a cold (0°) solution of the sulfone **17** (4.14 g, 13 mmol) absolute ethanol (200 ml) was added with stirring sodium borohydride (4.94 g, 0.13 mol) in 200 ml of absolute ethanol over a period of 30 min. The reaction mixture was stirred at room temperature for 9 hr, acidified with anhydrous hydrogen chloride to pH 2, and stirred for an additional 1 hr. The reaction mixture was concentrated on 15 g of silica gel under reduced pressure. The solid material was placed on top of a silica gel (35 g) chromatography column packed in chloroform. The column was washed with ethyl acetate (2 l.) and the ethyl acetate solution was concentrated to give 3.20 g of a white foam. Crystallization of this foam from ethyl acetate afforded 1.2 g (30.4%) of the dihydroxy lactone **24** as white crystals: mp 187–189°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3540, 1780, 1305, and 1135 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.0–5.0 (complex multiplets, 17 H), and 2.98 (s, 3 H); mass spectrum molecular ion peak at *m/e* 304 (calcd mol wt, 304.3).

Anal. Calcd for $C_{13}H_{20}O_6S$: C, 51.30; H, 6.62; S, 10.53. Found: C, 51.39; H, 6.60; S, 10.34.

3β-Carboxy-9β-(1′-hydroxy-2′-(methylsulfonyl)ethyl)-1,5-hydrindandione-3β→1′-lactone (25).—To a cold solution of 3.22 g (10.6 mmol) of crude **24** in acetone (200 ml) was added dropwise with stirring 2 ml of aqueous 8 *N* chromic acid solution. The reaction mixture was stirred at 0° for 60 min and then the excess oxidant was destroyed with 2-propanol. After the chromium salts were filtered off and washed with hot acetone, the green organic solution was concentrated under reduced pressure. The residue was taken up in hot ethyl acetate (250 ml), dried, and concentrated to give 3.01 g of a white foam. The white foam was crystallized from ethyl acetate to give **25** (1.4 g, 44% from **17**) as white crystals: mp 197–198°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 1780, 1740, 1720, 1305, and 1138 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.90–4.30 (complex multiplets, 12 H), 3.05 (s, 3 H), 5.0 (two sets of doublets, *J* = 3 Hz, 1 H).

Anal. Calcd for $C_{13}H_{16}O_6S$: C, 52.00; H, 5.37. Found: C, 51.92; H, 5.25.

3′β-Carboxy-9′β-(1′′-hydroxy-2′′-(methylsulfonyl)ethyl)spiro-(1,3-dioxolane-2,5′-1′-hydrindanone)-3′β→1′′-lactone (26).—A mixture of **25** (1.5 g, 5.0 mmol), *p*-toluenesulfonic acid monohydrate (40 mg), and 50 ml of 2-ethyl-2-methyl-1,3-dioxolane[15] was heated and the liberated 2-butanone admixed with the dioxolane reagent distilled through a short-path column at such a rate that 20 ml of distillate was collected over a period of 4 hr; 20 ml of dioxolane reagent was added; and the mixture was refluxed for 20 hr. The excess dioxolane reagent was removed under reduced pressure and the solid residue was crystallized from acetonitrile to give the monoketal **26** (1.5 g, 87%) as white crystals: mp 252–254°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 1780, 1740, 1310, and 1135 cm^{-1}; pmr [$(CD_3)_2SO$] δ 0.9–4.4 (complex multiplets, 12 H), 3.05 (s, 3 H), 3.91 (s, 4 H), and 4.9 (m, 1 H); mass spectrum molecular ion peak at *m/e* 344 (calcd mol wt, 344.4).

Anal. Calcd for $C_{15}H_{20}O_7S$: C, 52.33; H, 5.85; S, 9.29. Found: C, 52.31; H, 5.89; S, 9.00.

3′β-Carboxy-9′β-(*trans*-2′′-(methylsulfonyl)ethynyl)spiro(1,3-dioxolane-2,5′-1′-hydrindanone) (27).—A sample of the monoketal **26** (1.20 g, 3.5 mmol) was refluxed for 5 hr in 0.17 *N* potassium *tert*-butoxide in *tert*-butyl alcohol (200 ml). The cooled reaction mixture was acidified with concentrated hydrochloric acid (3.5 ml) and concentrated under reduced pressure. The residue was taken up in ethyl acetate, dried, and evaporated to afford the crude sulfone **27** (1.12 g) which was crystallized from ethyl acetate to give pure material (0.71 g, 59%): mp 203–205°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600–2800 (broad), 1740 (broad), 1630 (weak), 1305, and 1138 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.0–3.5 (complex multiplets, 10 H), 3.0 (s, 3 H), 3.92 (s, 4 H), 6.85 (s, by the addition of deuterated acetone, this singlet was converted to an AB quartet, *J* = 15 Hz, 2 H); uv λ_{max}^{EtOH} shoulder at 205 nm (ε 2900); mass spectrum molecular ion peak at *m/e* 344 (calcd mol wt, 344.4).

Anal. Calcd for $C_{15}H_{20}O_7S$: C, 52.33; H, 5.85; S, 9.29. Found: C, 52.27; H, 5.55; S, 9.32.

3′β-Carboxy-9′β-(2′′-(methylsulfonyl)ethyl)spiro(1,3-dioxolane-2,5′-1′-hydrindanone) (28).—A solution of (0.516 g, 1.5 mmol) in absolute methanol (150 ml) with 10% Pd/C (200 mg) was hydrogenated at atmospheric pressure and room temperature until the hydrogen uptake ceased. The reaction time for pure material was usually 5 min; however, for crude material several hours were needed. Filtration of the catalyst followed by removal of the solvent gave a white solid (0.501 g). Crystallization from benzene–ethyl acetate afforded 0.42 g (81%) of the keto sulfone **28**: mp 174–175°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600–2800 (broad), 1740, 1305, and 1138 cm^{-1}; pmr [$(CD_3)_2CO$–$(CD_3)_2SO$, 9:1] δ 0.9–3.6 (complex multiplets, 14 H), 2.92 (s, 3 H), 3.92 (unsymmetrical doublet, *J* = 1.5 Hz, 4 H), and 6.6 (broad singlet, 1 H); mass spectrum molecular ion peak at *m/e* 346 (calcd mol wt, 346.4).

Anal. Calcd for $C_{15}H_{22}O_7S$: C, 52.02; H, 6.40; S, 9.24. Found: C, 51.81; H, 6.28; S, 9.48.

3β-Carboxy-9β-(2′-(methylsulfonyl)ethyl)-1,5-hydrindandione (29).—Keto sulfone **28** (0.97 g, 2.8 mmol) was refluxed with 3 *N* hydrochloric acid (20 ml) for 9 hr. The product was isolated with ethyl acetate and crystallized from benzene–ethyl acetate to give pure **28** (0.57 g, 68%): mp 138–139°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600–2800 (broad), 1740, 1720, 1305, and 1140 cm^{-1}; pmr [$(CD_3)_2CO$] δ 1.0–3.6 (complex multiplets, 14 H), 2.97 (s, 3 H), and 8.13 (s, 1 H); mass spectrum molecular ion peak at *m/e* 302 (calcd mol wt, 302.3).

Anal. Calcd for $C_{13}H_{18}O_6S$: C, 51.66; H, 6.00; S, 10.60. Found: C, 51.33; H, 5.83; S, 10.54.

3β-Carbomethoxy-9β-(2′-(methylsulfonyl)ethyl)-1,5-hydrindandione (32).—Diketo sulfone **29** (0.302 g, 1 mmol) was heated under reflux for 24 hr with anhydrous methanol (150 ml) and anhydrous hydrogen chloride (15 g). The solvent was removed under reduced pressure and the residue was crystallized from ethyl acetate to give pure ester (0.196 g, 62%): mp 151–152°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 1725 (broad), 1305, and 1140 cm^{-1}; pmr (CD_3CN) δ 1.6–3.5 (complex multiplets, 14 H), 2.89 (s, 3 H), and 3.73 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}O_6S$: C, 53.16; H, 6.37; S, 10.11. Found: C, 53.29; H, 6.24; S, 10.24.

2β-Carboxy-4-hydroxy-10-((methylsulfonyl)methyl)-8α-9-oxatricyclo[6.2.1.0^{1,5}]undecane (30).—A sample of **24** (1.0 g, 3.3 mmol) was refluxed with 0.132 *N* potassium *tert*-butoxide in *tert*-butyl alcohol (100 ml) for 6 hr. The cooled reaction mixture was acidified with concentrated hydrochloric acid and concentrated under reduced pressure. The residue was taken up in ethyl acetate, dried, and crystallized from ethyl acetate to give **30** (0.81 g, 81%) as white crystals: mp 189–191°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3550, 3480–3000 (broad), 1730, 1300, 1160, and 1135 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.2–4.0 (complex multiplets, 14 H), 2.95 (s, 3 H), and 4.0–4.35 (complex multiplets, 2 H).

Anal. Calcd for $C_{13}H_{20}O_6S$: C, 51.31; H, 6.62. Found: C, 50.98; H, 6.76.

2β-Carboxy-10-((methylsulfonyl)methyl)-8α-9-oxatricyclo[6.2.-1.0^{1,5}]undecan-4-one (31).—A sample of **30** (0.456 g, 1.5 mmol) in acetone (50 ml) was treated with 8 *N* chromic acid solution (1 ml). After stirring at 0° for 2 hr the excess chromic acid was destroyed with 2-propanol and the chromium salts were filtered and washed with hot acetone. The acetone solution was evaporated under reduced pressure and the residue was crystallized from benzene–ethyl acetate to give **31** (0.36 g, 79%) as white crystals: mp 184–186°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 3600–2700 (broad), 1740 (broad), 1300, 1185, and 1135 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.0–3.9 (complex multiplets, 12 H), 3.02 (s, 3 H), 4.15–4.7 (complex multiplet, 2 H); mass spectrum molecular ion peak at *m/e* 302 (calcd mol wt, 302.3).

Anal. Calcd for $C_{13}H_{18}O_6S$: C, 51.66; H, 6.00. Found: C, 51.63; H, 6.02.

Reaction of the Diketo Lactone 25 with Potassium *tert*-Butoxide.—A sample of diketo lactone **25** (1.2 g, 4.0 mmol) was refluxed with 0.16 *N* potassium *tert*-butoxide in *tert*-butyl alcohol for 3 hr. The resulting solution was acidified with hydrochloric acid and concentrated on silicic acid (15 g) under reduced pressure. The residue was placed on top of a column of silicic acid (50 g) and eluted with 25% ethyl acetate–chloroform (2:1). Evaporation of the effluent afforded 0.6 g of a dark red oil which was crystallized from ethyl acetate to give 0.31 g (30%) of red crystalline material which was further crystallized twice from acetone to give white crystals: mp 145–146°; ir $\tilde{\nu}_{max}^{CH_3CN}$ 1700, 1295, and 1135 cm^{-1}; pmr [$(CD_3)_2SO$] δ 1.25 (d, *J* = 7 Hz, 3 H), 1.7–3.8 (complex multiplets, 9 H), 3.0 (s, 3 H), and 4.55 (broad triplet, *J* = 5 Hz, 1 H); uv λ_{max}^{EtOH} 234 nm (ε 11,600); mass spectrum very weak molecular ion peak at *m/e* 256 and abundant fragment peak at *m/e* 177 (M − $CH_3SO_2\cdot$) (calcd mol wt, 256.3).

Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.25; H, 6.29; S, 12.48. Found: C, 56.10; H, 6.13; S, 12.60.

(15) H. J. Dauben, Jr., B. Löken, and H. J. Ringold, *J. Amer. Chem. Soc.*, **76**, 1359 (1954).

11-(Methylsulfonyl)-9α-tricyclo[7.3.0.0^{1,6}]dodecane-3,7,10-trione (33).—A sample of **32** (95 mg, 0.3 mmol) in dry glyme (20 ml) was added to a suspension of oil-free sodium hydride (0.144 g, 0.60 mmol) in glyme (40 ml), and the mixture was refluxed for 8 hr. The cooled reaction mixture was acidified with concentrated hydrochloric acid and evaporated under reduced pressure. The residue was leached with hot ethyl acetate and concentrated to give 0.091 g of light brown foam which was separated on a 20 × 20 silica gel (PF_{254}) thin layer plate eluted with ethyl acetate. Collection of two components (R_f 0.48 and 0.54) gave an isomeric mixture of **33** (47 mg, 45%) which crystallized from ethyl acetate: mp 166–169°; ir $\bar{\nu}_{max}^{CH_3CN}$ 3700–3400 (broad, partly as enol form), 1745, 1720, 1310, and 1145 cm^{-1}; pmr (CD_3CN) δ 1.7–2.9 (complex multiplets, 12 H), 3.08, 3.16 (two singlets because of the two isomeric forms, 3 H), and 4.3 (complex multiplet, 1 H); mass spectrum molecular ion peak at *m/e* 284. The exact molecular weight determined by high resolution mass spectrometry was 284.078 (calcd for $C_{13}H_{16}O_5S$, 284.075) and for M − CH_3SO_2· was 205.092 (calcd for $C_{12}H_{13}O_3$, 205.089).

Registry No.—**4,** 28269-01-4; *cis*-**6,** 28269-02-5; *trans*-**6,** 28269-03-6; **7,** 26269-04-7; *cis*-**8,** 28269-05-8; *trans*-**8,** 28269-06-9; *cis*-**9,** 28269-07-0; *trans*-**9,** 28269-08-1; **10,** 28269-09-2; **11,** 28269-10-5; **12,** 28269-11-6; **14,** 28269-12-7; **16,** 28269-13-8; **17,** 28269-14-9; **18,** 28269-15-0; **19,** 28269-16-1; **20,** 28392-70-3; **21,** 28269-17-2; **24,** 28269-18-3; **25,** 28269-19-4; **26,** 28269-20-7; **27,** 28269-21-8; **28,** 28392-71-4; **29,** 28278-27-5; **30,** 28278-28-6; **31,** 28278-29-7; **32,** 28278-30-0; 11α-**33,** 28278-31-1; 11β-**33,** 28278-32-2; *cis*-2-carbethoxy-3aβ-carbomethoxy-7aβ-hydroxy-3-methyl-3a,4,5,6,7,7a-hexahydroindene, 28278-33-3; *cis*-2,3aβ-dicarboxy-7aβ-hydroxy-3-methyl-3a,4,7,7a-tetrahydroindene, 28278-34-4; *cis*-2,3aβ-dicarboxy-7aβ-hydroxy-3-methyl-3a,4,5,6,7,7a-hexahydroindene, 28278-35-5; *cis*-2,9β-dicarboxy-8β-hydroxy-3-methylhydrindan, 28278-36-6; *cis*-1-methyl-2-carboxyindene, 28278-37-7; *trans*-1-methyl-2-carboxyindan, 28278-38-8; *trans*-3β,3aβ-dicarbomethoxy-1-hydroxy-3a,4,7,7aα-tetrahydroindan, 28278-39-9; 3β,3aβ-dicarbomethoxy-1-hydroxy-3a,4,7,7a-tetrahydroindan, 28278-40-2; *cis*-3β,3aβ-dicarbomethoxy-1-hydroxy-3a,4,7,7aβ-tetrahydroindan, 28278-41-3.

Synthesis and Properties of Some 1-Halophospholenes[1]

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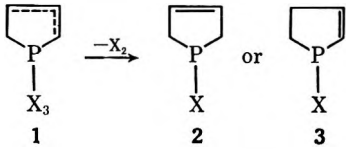
Two methods have been devised for preparing the previously unknown 1-halophospholenes. These compounds, which are formally cyclic phosphinous halides, resulted from reduction (dehalogenation) of diene–phosphorus trihalide cycloadducts with triphenylphosphine, as well as from reduction with hexachlorodisilane of 1-halophospholene oxides. Examples of both 2- and 3-phospholene derivatives were prepared. Structures were assigned from nmr spectral data. Of particular value was the exceptionally large (over 40 Hz) value for coupling of ^{31}P with the vinyl proton at the 2 position of the 2-phospholene derivatives. The halophospholenes were hydrolyzed to give cyclic secondary phosphine oxides (characterized as their chloral adducts). Successful displacement of halogen with a secondary amine as well as with a Grignard reagent demonstrates further the synthetic utility of these substances in phospholene chemistry.

The discovery of the cycloaddition of dienes with phosphonous dihalides[2] has made possible the synthesis of a number of derivatives of the phospholene ring system and stimulated a considerable amount of work on this family of compounds.[3] To date no 1-halophospholenes, where phosphorus is trivalent, have been prepared; yet these compounds, which may be classed as cyclic phosphinous halides, should be particularly valuable as synthetic intermediates in this family. We report in this paper two methods which have made these compounds available, and describe several reactions leading to new phospholene derivatives.

Reduction of Diene–Phosphorus Trihalide Cycloadducts.—We have previously shown that the diene–phosphonous dihalide cycloadducts may be reduced (dehalogenated) with magnesium in tetrahydrofuran to form 1-alkyl- or arylphospholenes.[4] Application of this reaction to cycloadducts from phosphorus trihalides[5] (**1**; the position of the double bond is uncertain) should provide the desired 1-halophospholenes (**2** or **3**).



1 **2** **3**

(1) Supported by Public Health Service Research Grant CA-05507 from the National Cancer Institute.

(2) W. B. McCormack, U. S. Patents, 2,663,736 and 2,663,737 (Dec 22, 1953).

However, the magnesium–THF system, when applied to isoprene–PCl_3 or PBr_3 cycloadducts, provided none of the desired product; the only material isolated was the 1,4-dihalobutane from cleavage of the solvent.[6] It was then found that the dehalogenation could be successfully accomplished with triphenylphosphine in methylene chloride as solvent. The other product of the reaction, presumably the dihalotriphenylphosphorane, is partially soluble in the reaction medium, but is precipitated with pentane. Its removal from the reaction medium was considered desirable as the halogen exchange process is probably reversible. Unreacted cycloadduct is also precipitated in this step. The halophospholenes are then recovered by distillation. Products and yields are included in Table I. The halides are highly reactive substances, sensitive to air and to water; even protected from these, some products proved to be unstable, precipitating orange solids on standing. The most unstable was compound **3a** which began to decompose in the receiver even before distillation was complete, and was obtained in only 5% yield. On the other hand, compound **2a** remained unchanged on standing for several weeks; it was obtained in 79%

(3) For a review, see L. D. Quin in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, Chapter 3.

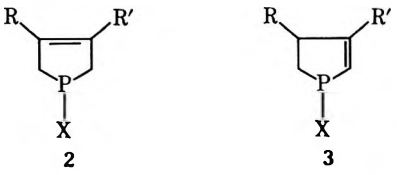
(4) L. D. Quin and D. A. Mathewes, *J. Org. Chem.*, **29,** 836 (1964).

(5) U. Hasserodt, K. Hunger, and F. Korte, *Tetrahedron*, **19,** 1563 (1963).

(6) A. G. Anderson and F. J. Freenor, *J. Amer. Chem. Soc.*, **86,** 5037 (1964), have reported a similar cleavage of THF by dibromotriphenylphosphorane.

TABLE I

1-HALOPHOSPHOLENES SYNTHESIZED



2 3

Compound						
	R	R′	X	Method[a]	Yield	Bp, °C (mm)
2a	CH_3	CH_3	Br	A	79[b]	99–102 (27)
2b	H	H	Br	A	23	77–80 (32)
2c	H	CH_3	Cl	B	26	61–63 (17)
3a	H	H	Cl	A	5[c]	67–68 (32)
3b	H	CH_3	Cl	B	58[d]	67–70 (18)
3c	H	CH_3	Br	A	42[e]	94–98 (30)

[a] A, cycloadduct with triphenylphosphine; B, oxide of the 1-halophospholene with hexachlorodisilane. [b] Product from one reduction contained as much as 10% 2 isomer while other reductions gave pure 3 isomer. [c] Method B gave 1% yield. [d] Method A gave 21% yield containing 30% 2c. [e] Product contained 30% of 3-phospholene isomer.

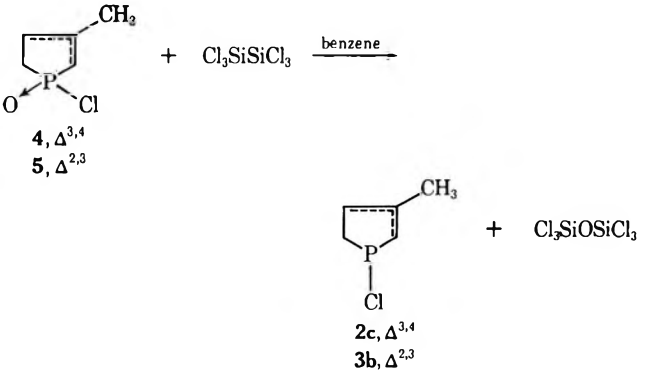
yield. The low yields are therefore more a reflection of product instability than of process inefficiency.

A possible yield-reducing complication in this process is the further reaction of the 1-halophospholenes with triphenylphosphine. Tributylphosphine has been reported to react with halophosphines to form products containing the P–P bond,[7] and indeed, when a methylene chloride solution of **2a** and **2b** was treated with triphenylphosphine, an immediate exothermic reaction occurred, precipitating yellow solid. The products have not been examined. To minimize the occurrence of this side reaction in the reduction process, the triphenylphosphine was slowly added to the cycloadduct, which was used in excess (20%).

The location of the double bond in phospholene derivatives obtained from cycloadducts has been a troublesome matter.[3] Originally, all cycloadducts formed from phosphonous dihalides were assumed to contain the 3-phospholene ring; if on subsequent reaction a product was obtained with the 2-phospholene ring, this was thought to be the result of rearrangement during the particular reaction. It is now known, however, that for cycloadducts formed from phosphonous dihalides the position of the double bond is already established in the cycloadduct itself.[8] Thus, cycloadducts from methylphosphonous dichloride and phenylphosphonous dibromide are 3-phospholene derivatives, while those from phenylphosphonous dichloride are 2-phospholenes (except where the diene is 2,3-dimethylbutadiene). Such a study on the cycloadducts from phosphorus trihalides has not yet been carried out, although it is known that adducts from the tribromide lead on alcoholysis or hydrolysis to 3-phospholenes while those from the trichloride generally lead to 2-phospholenes.[5,9] As will be discussed later in this paper, spectral properties of the 1-halophospholenes establish clearly the location of the double bond and reveal that to some extent the same trend is followed, the bromides being 3-phospholenes, while the chlorides are 2-phospholenes. However, some products proved to be mixtures of isomers (see Table I), and one bromide (**3c**) proved to be largely (70%) the 2 isomer rather than the expected 3 isomer. To account for these cases, it has to be assumed either that the cycloadducts are rearranged in the reaction medium during the reduction process (*e.g.*, by the base triphenylphosphine) or that the halophospholene products rearrange after their formation, perhaps during distillation. Certainly the former explanation is a possibility, for we have found that the isoprene–phosphorus tribromide adduct can under certain conditions of hydrolysis give 1-hydroxy-3-methyl-2-phospholene oxide as the main product, just as the trichloride adduct does, whereas earlier reports describe reactions of this adduct in which only 3 isomers are obtained.[9] On the other hand, evidence has also been obtained for thermal rearrangement of the halophospholenes; a sample of pure **2a** after heating at 100° for 2 hr was found to contain about 10–15% of the 2-phospholene isomer. Distillation of the products should therefore be conducted rapidly, with the lowest practical temperatures, to minimize the formation of unwanted isomer.

This synthesis has been most useful in obtaining 1-bromo-3-phospholene (**2b**) and its 3,4-dimethyl derivative (**2a**). The latter is formed in particularly high yield, and both are obtained relatively free of isomer. Some reactions of the halides are described later in this paper.

Reduction of 1-Halophospholene Oxides.—The effectiveness of silicon hydrides for reduction of phosphoryl compounds was first announced in 1965,[10] and more recently hexachlorodisilane has been employed for this purpose.[11] We have found that the latter reagent may be used to reduce 1-halophospholene oxides, which are cyclic phosphinic halides, to the corresponding halophospholenes. Two reactions of this type were successfully conducted on oxides **4** and **5**; data are given in Table I. The products, however, showed some contamination from silicon-containing material, as evi-



denced by a Si–O–Si stretching band in their infrared spectra. In one case the halophospholene (**3b**) was obtained in more than twice the yield as from cycloadduct reduction. The synthesis of 1-chloro-3-methyl-3-phospholene (**2c**) is of note; this compound could not have been obtained from the cycloadduct, which leads mainly to the 2-phospholene isomer (**3b**). This is, therefore, a particular advantage of the phosphinic chloride ap-

(7) S. E. Frazier, R. P. Nielsen, and H. H. Sisler, *Inorg. Chem.*, **3**, 292 (1964).

(8) L. D. Quin, J. P. Gratz, and T. P. Barket, *J. Org. Chem.*, **33**, 1034 (1968).

(9) K. Hunger, U. Hasserodt, and F. Korte, *Tetrahedron*, **20**, 1593 (1964).

(10) H. Fritzsche, U. Hasserodt, and F. Korte, *Chem. Ber.*, **98**, 171 (1965).

(11) K. Naumann, G. Zon, and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 2788 (1969).

proach to the halophospholenes, although more steps are involved in the over-all process.

Since cycloadduct reduction had given only a 5% yield of 1-chloro-2-phospholene (**3a**), an attempt to improve the yield by the phosphinic chloride reduction method was made. However, this was even less successful (1% yield). As noted, the poor yield in this case is attributable to the instability of the product.

The phosphinic chlorides (**4** and **5**) used in this study have been previously prepared[5,9] from the reaction of thionyl chloride with the acids, or phosgene with the methyl esters. The location of the double bond in these compounds has been established.[12] The reported synthetic procedures were used, except that oxalyl chloride was substituted for phosgene in the synthesis of **4**. While this reagent was easier to handle and the over-all yield was better, the product contained a significant amount (30%) of the 2 isomer (**5**). It is not known if the rearrangement occurred in the chlorination medium or on distillation of the product. The undesired 2 isomer, which is not noted to form in the phosgene reaction, was removed readily by fractional distillation.

Spectral Properties of 1-Halophospholenes.—The proton nmr spectra of the six 1-halophospholenes prepared in this study are summarized in Table II. The

TABLE II

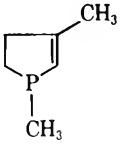
SPECTRAL PROPERTIES OF 1-HALOPHOSPHOLENES

Compd[h]	$\nu_{C=C}^{neat}$, cm^{-1}	^{1}H nmr, δ, ppm (J, Hz)[a] =CH	-CH$_2$-	C-CH$_3$	^{31}P nmr, ppm[d]
2a	1676[b]	...	3.52 (20.0)[c]	2.28	−104.8
2b	1627	6.60 (6.5)[c]	3.66 (2.05)[c]	...	−111.4
2c	1655	5.92[e]	2.97, 3.30[f]	2.27	−127.5
3a	...[f]	6.30–7.80[e]	2.20–3.50[e]	...	...[g]
3b	1601	6.52 (46.5)[c]	2.50–3.46[e]	2.46 (3.5)[c]	−132.5
3c	1601	6.75 (46.5)[c]	2.80–3.90[e]	2.62 (3.5)[c]	−130.6

[a] Neat with external TMS. [b] Weak. [c] Doublet. [d] Neat; relative to 85% H_3PO_4. [e] Multiplet. [f] Unsymmetrical doublet, peak separation 20 Hz. [g] Not determined. [h] Structures can be found in Table I.

spectra permitted conclusive assignment of the position of the double bond in these compounds. Structure **2a** was obvious from the absence of a vinyl proton signal, as well as from the simplicity of the spectrum, which consisted only of two signals. The methyl groups gave a singlet, while the ring methylenes appeared as a doublet (J = 20 Hz) with additional small splitting, apparently from the methyl protons. The doublet was due to coupling with ^{31}P, as revealed by double irradiation experiments. Structure **2b** is also symmetrical; it gave a sharp doublet (J = 20.5 Hz) for the ring methylenes, as well as a doublet for the vinyl protons. The coupling constant (6.5 Hz) of the latter is in accord with that of 1-alkyl-3-phospholenes.[8]

Structures with the double bond in the 2,3 position were evident particularly from the totally different characteristic of the vinyl proton signals. When a substituent was present at the 3 position (**3b**, **3c**), the 2 proton was again a doublet but with an enormous coupling constant (46.5 Hz) with ^{31}P. This same feature is found in several other related structures with trivalent phosphorus and is an obvious characteristic of the system. Thus, structures **6** and **7**, prepared in this study, had J_{PCH} = 42 and 40 Hz, respectively, while in earlier work[8] structure **8** was found to have J_{PCH} = 42.[13] Few data are available for phosphines with sp^2 carbon;



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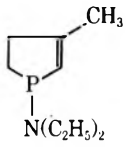

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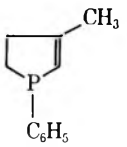

8

a value of 11.74 for J_{PCH} has been reported for trivinylphosphine.[14] It thus appears that the fixed geometry of the 2-phospholenes may be associated with the large J_{PCH}. A similar situation prevails for J_{PCH} in saturated cyclic phosphines, where an apparent relation between J_{PCH} and the dihedral angle formed by the orbital of the lone electron pair on phosphorus and the α-CH has been noted.[15] Maximum values are observed where the dihedral angle is small. It may be that the orientation of the lone pair on phosphorus is also important in establishing J_{PCH} for the proton on sp^2 carbon; implication of the electron pair in the effect is evident from the observation that the corresponding oxides have normal values (*e.g.*, J_{PCH} = 25.7 Hz for the oxide of **6**[8]). A more direct explanation of the influence of the electron pair on J_{PCH} might involve modification of the structure about the P—C=C unit through p_π–p_π conjugation, a point to be brought up later in this paper. This would give the P–C bond partial double-bond character. Suitable phosphine models with definite P–C double-bond character are not presently available to explore this correlation further; phosphorins (phosphabenzenes) are potentially useful in this sense, but up to the present none have been reported in the literature where a proton is present at the 2 position.

Compound **2c** is isomeric with **3b**, and its spectrum differed considerably in the methylene region. The signal of **2c** was a distorted doublet, having a peak separation of the same size (20 Hz) as observed for the symmetrical 3-phospholenes **2a** and **2b**. The signal of **3b**, wherein structural differences between the two methylene groups are more pronounced, was a complex multiplet. Differences also occurred in the vinyl proton signals (Table II).

Finally, the structure **3a** is characterized in particular by the extreme complexity of the vinyl signals, where, in keeping with other 2-phospholene derivatives bearing no substituents on positions 2 and 3,[12] cross-ring coupling occurs. Had this compound possessed the 3-phospholene ring, a simple spectrum such as that of **2b** would have been observed.

The methylene signals of the symmetrical compounds **2a** and **2b** warrant further comment. In the first place, the signals would seem to be at unusually low field (δ 3.5–3.6 ppm). Few data are available for proton nmr spectra of phosphinous halides, and we are aware of none for cyclic forms. Dimethylphosphinous chloride is reported to have δ 1.54 ppm;[16] replacement of chlo-

(12) H. Weitkamp and F. Korte, *Z. Anal. Chem.*, **204**, 245 (1964).

(13) Unusually large coupling has also been observed for the α protons of 1-methylphosphole [J_{PCH} = 38.5 Hz: L. D. Quin, J. G. Bryson, and C. G. Moreland, *J. Amer. Chem. Soc.*, **91**, 3308 (1969)] and 1,3,4-trimethylphosphole (J_{PCH} = 41 Hz: L. D. Quin and S. G. Borleske, unpublished results).

(14) W. A. Anderson, R. Freeman, and C. A. Reilly, *J. Chem. Phys.*, **39**, 1518 (1963).

(15) J. P. Albrand, D. Gagnaire, J. Martin, and J. B. Robert, *Bull. Soc. Chim. Fr.*, 40 (1969).

(16) J. F. Nixon and R. Schmutzler, *Spectrochim. Acta*, **22**, 565 (1966).

rine by bromine should, if anything, cause a slight upfield shift because of its lower electronegativity. While the methylene group is allylic in **2a** and **2b**, it is not reasonable to expect a downfield shift relative to the saturated model of the magnitude seen. In the second place, the methylene signal is a doublet. In 1-alkyl-3-phospholenes, the methylene protons are nonequivalent; they couple with each other and ^{31}P to give an ABX pattern.[8] The nonequivalency is due to the stable, pyramidal geometry about trivalent phosphorus, fixing one proton cis to the P substituent, the other trans. The absence of this nonequivalency in the 1-halo-3-phospholenes is therefore suggestive of a loss of configurational integrity about phosphorus. Both of these characteristics can be explained if the halogen is undergoing rapid intermolecular exchange.[17] This process accomplishes inversion at phosphorus and has already been invoked to account for the identity of the methyl groups in 2-chloro-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane when measured neat at room temperature.[18] At lower temperatures, or in inert solvents, the exchange is retarded and two distinct signals appear for the methyls cis and trans to the chlorine on phosphorus. Furthermore, the methyls absorbed at lower field in a neat sample when exchange was occurring than in dilute solution. Exchange was also postulated for ethylene chlorophosphite,[19,20] and more recently an example of exchange in an acyclic compound [$(Me)_2CHPClNMe_2$] was reported.[21]

To test for the possible occurrence of the exchange in the halophospholenes, compound **2a** was subjected to a dilution study with hexane. The results are given in Table III, where it can be seen that upfield shifts expected for retardation of exchange did occur. Although the peaks were slightly broadened, the doublet character of the CH_2 signal remained intact, and, if exchange is indeed involved in this halide, it apparently is still proceeding even in the dilute solutions used at a rate sufficient to cause equivalency of the methylene protons. Attempts to study the halide at low temperatures were thwarted by freezing of the neat sample at about $-10°$ or precipitation of solid from the hexane solutions. However, a hexane solution of **2b** proved more satisfactory to employ in a low-temperature study. A solution 0.0835 mole fraction in **2b** had the expected doublet (J = 20 Hz) at probe temperature. At $-20°$, both peaks were broadened and showed fine structure; at $-40°$, the doublet had disappeared and a multiplet of several peaks was present. The multiplet has not been analyzed, but its appearance is typical of the AB signal of an ABX system. This experiment therefore strongly indicates the occurrence of the exchange process in the 1-bromo-3-phospholenes. The process may also occur in the 2-phospholenes, but these compounds have not been examined. Table III also contains ^{31}P nmr data for the hexane solutions of **2a**, where a pronounced upfield shift on dilution may be noted. This is the shift expected if one considers that an exchanging P–Br bond has more ionic character with increased positivity at phosphorus than does a static bond. The effect correlates with the upfield shift in the proton signals on dilution, for it is to be expected that diminished positivity at phosphorus will be associated with greater shielding at C–H bonds.

TABLE III

EFFECT OF DILUTION ON NMR CHARACTERISTICS OF 1-BROMO-3,4-DIMETHYL-3-PHOSPHOLENE (2a)

Mole fraction of 2a[a]	$\delta(CH_2)$, ppm	$\delta(CH_3)$, ppm	$\delta(^{31}P)$, ppm[b]
1.00	3.50	2.25	−104
0.495	3.28	2.03	...
0.311	3.17	1.95	−97.4
0.192	3.12	1.89	...
0.137	3.10	1.86	−94.9

[a] Solvent, *n*-hexane. [b] H_3PO_4 standard.

A difference in the proton spectra for chlorine *vs.* bromine in 1-halo-2-phospholene may be seen from considering the data for **3b** and **3c**. While the spectra are very similar, the bromo compound has its corresponding protons at lower field. This effect cannot be explained by electronegativity differences of the halogens, which should act to produce the opposite effect. The effect can be explained on the exchange basis, however, since it is known that bromides participate more readily in this process than do chlorides,[17] and a possible connection between exchange and deshielding has already been noted.

The ^{31}P chemical shift values for the 1-halophospholenes are in keeping with their phosphinous halide structure; the range covered (−104.8 to −132.5 ppm) surrounds the values for the acyclic models $(C_2H_5)_2PCl$ (−119.0 ppm) and $(C_2H_5)_2PBr$ (−116.2 ppm).[22] As for these models, the bromides absorb at slightly higher field than do the chlorides (*e.g.*, bromide **3c** −130.6, chloride **3b** −132.5 ppm), and the 3-phospholene is at higher field than the 2 isomer (*cf.* **2c**, −127.5 ppm, with **3b**).

Another difference for isomer pair **2c** and **3b** is found in their infrared spectra, where the C=C stretching vibration of the 2 isomer occurs at lower frequency and with greater intensity than the 3 isomer. These effects are well known for oxy derivatives of phospholenes[8,12] and for vinyl *vs.* allyl groups in other phosphoryl compounds,[23] but they do not appear to have been observed for trivalent phosphorus compounds. It is obvious that a conjugative effect is present, and as is discussed elsewhere[24] it is believed that the conjugation is of type p_π–p_π.

Reactions of 1-Halophospholenes.—Consistent with their phosphinous halide character, the 1-halophospholenes are highly susceptible to nucleophilic displacement reactions. Some reactions of this type were performed in this study.

Hydrolysis occurs rapidly on addition to water (or to ether saturated with water), but the process is preferably conducted in concentrated hydrochloric acid to suppress disproportionation to the phosphine and

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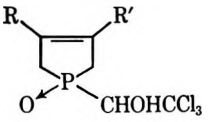
TABLE IV
CHLORAL ADDUCTS OF PHOSPHOLENE OXIDES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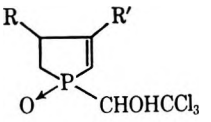
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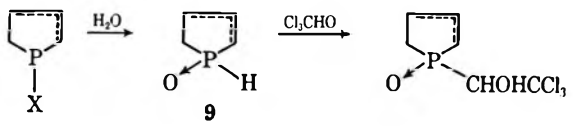
Compound No.	R	R′	Source	Mp, °C	$\nu_{C=C}$, Nujol, cm^{-1}	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Phosphorus, % Calcd	Phosphorus, % Found	Chlorine, % Calcd	Chlorine, % Found
10a	CH_3	CH_3	**2a**	166.5–168.5	...[a]	$C_8H_{10}Cl_3O_2P$	34.37	34.49	5.06	4.86	11.08	11.06	38.04	38.21
10b	H	H	**2b**	172.5–173	1616	$C_6H_8Cl_3O_2P$	28.89	29.02	3.24	3.45	12.41	12.62	42.63	42.33
10c	H	CH_3	**2c**	162.5–163.5	1650	$C_7H_{10}Cl_3O_2P$	31.90	31.77	3.83	3.84	11.75	11.80	40.37	40.40
11a	H	H	**3a**	160.5–161	1588	$C_6H_8Cl_3O_2P$	28.89	28.71	3.24	3.17	12.41	12.48	42.63	42.62
11b	H	CH_3	**3b** or **3c**	159.0–160.5	1614	$C_7H_{10}Cl_3O_2P$	31.90	31.67	3.83	3.89	11.75	11.75	40.37	40.31

[a] Not observed.

phosphinic acid.[25] From this reaction, the secondary phosphine oxides (**9**) can be obtained. This is the first


9

report on the synthesis of such oxides in the phospholene family and demonstrates one aspect of the synthetic value of the halophospholenes. These oxides proved to be oils or low-melting, hygroscopic solids, difficult to purify, and were more conveniently handled as their adducts with chloral. These derivatives were in fact used for analytical purposes in this series of compounds (Table IV). The infrared properties of the adducts were useful in showing that the double bond had not migrated during the reactions. Thus, those adducts expected to be 3-phospholene derivatives (**10b** and **10c**) from the assignment of the starting halophospholene had $\nu_{C=C}$ at higher frequency[8,12] than did those expected to be 2 isomers (**11a** and **11b**).

An example of nucleophilic displacement with an amine consisted of the reaction of halide **3c** (containing about 10% of 3 isomer) with diethylamine. The product (**7**), a distillable liquid, was easily characterized from its nmr spectrum; the vinyl proton doublet at δ 5.87 had the expected large coupling (J = 40.0 Hz).

A particularly valuable property of the halophospholenes is their reaction with Grignard reagents. This provides an alternative route to the tertiary phosphines of this family, which have previously been prepared only from reduction of the diene–phosphonous dihalide cycloadducts[4] or of the phospholene oxides derived from the adducts by hydrolysis.[4,26] The phosphonous dihalides required as starting materials are of limited availability or prepared only by tedious processes.[27] Furthermore, the use of alkylphosphonous dichlorides as exemplified by the methyl derivative[8] leads only to the 3-phospholene series, and no 1-alkyl-2-phospholenes are reported in the literature. We have demonstrated the utility of the halophospholenes as precursors to the tertiary phosphines by preparing 1,3-dimethyl-2-phospholene (**12**) from either **3b** or **3c** in good yield. Compound **12** possessed the expected nmr spectral feature of large (42.0 Hz) coupling of the vinyl proton with phosphorus. Other spectral differences with regard to the previously prepared 3 isomer[8] are discussed elsewhere.[24]


12

Experimental Section

Melting and boiling points are uncorrected. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Proton nmr spectra were run on a Varian A-60 spectrometer; ^{31}P nmr spectra were obtained on a Varian V-4300B spectrometer at 19.3 MHz. Infrared spectra were recorded on Perkin-Elmer Models 137 and 237 spectrometers. Dienes were purchased from commercial sources and were used as received. Hexachlorodisilane was obtained from Peninsular ChemResearch, Inc. Oxalyl chloride[28] and 1-methoxy-3-methyl-3-phospholene oxide[8] were prepared according to published procedures. All operations involving trivalent phosphorus were conducted in a nitrogen atmosphere.

Formation of Diene–Phosphorus Trihalide Adducts.—An equimolar amount of phosphorus trihalide was added to the diene containing 2–4% of cupric stearate. A fourfold excess by volume of hexane was used as a solvent, and a brown bottle with a Teflon cap was used as a reaction vessel. The bottle was sealed with tape and allowed to stand for a 4-week period before using.[29] The adduct, usually crystalline, was then filtered in a drybox, washed with pentane, and thoroughly dried under vacuum to remove all solvents and unreacted starting material. Yields were not calculated.

Synthesis of 1-Halophospholenes. A. Triphenylphosphine Reduction.—The adduct (20% excess) was suspended in methylene chloride in a ratio of 50 g to 100 ml, and triphenylphosphine in an equal volume of methylene chloride was slowly added in 25- to 50-ml increments. The flask was shaken after each addition and allowed to stand for several minutes before more triphenylphosphine was added. After the final addition, sufficient pentane was added to precipitate any solids in solution. The solids were removed by filtration and washed with pentane. The filtrate and washings were combined and the solvents removed at atmospheric pressure; the resulting product was then distilled.

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(27) In connection with another program, we have prepared 1-benzyl-3-phospholene from benzylmagnesium chloride and halide **2b** and have found this to be the preferred route to this phosphine: P. Coggon, J. F. Engel, A. T. McPhail, and L. D. Quin, *J. Amer. Chem. Soc.*, **92**, 5779 (1970).

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(29) Butadiene can be collected at Dry Ice–acetone temperature and added directly to the hexane solution of phosphorus trihalide. In all cases precaution should be taken against possible excessive pressure buildup during early stages of adduct formation.

Yields and boiling point values are reported in Table I and spectral data in Table II.

B. Hexachlorodisilane Reduction.—Hexachlorodisilane in benzene (1:2 v/v) was added to the appropriate 1-chlorophospholene oxide dissolved in an equal volume of benzene. A mild exothermic reaction occurred; the mixture was stirred overnight at room temperature, filtered if necessary to remove any solid, and stripped of solvent at atmospheric pressure. The product was then distilled under vacuum. Yields are recorded in Table I and spectral data in Table II.

Synthesis of 1-Chloro-3-methyl-3-phospholene Oxide (4).—To 10.0 g (0.068 mol) of 1-methoxy-3-methyl-3-phospholene oxide in 25 ml of benzene was added 10.1 g (0.080 mol) of oxalyl chloride in 25 ml of benzene. The reaction flask was cooled in an ice bath during addition; a vigorous evolution of gas occurred. When addition was complete the mixture was allowed to warm to room temperature and then stirred at room temperature overnight. The benzene was removed and the product distilled, bp 94–120° (1.8 mm). Comparison of the proton nmr spectrum of the product with spectra of authentic samples[8] indicated a mixture of $\Delta^{2,3}$ and $\Delta^{3,4}$ isomers (about 3:7). Fractional distillation gave 4.3 g (41.7%) of **4** containing only a trace of 2 isomer, bp 97–100° (1.8 mm); bp 77° (0.5 mm) has been reported.[8]

Synthesis of 1-Hydroxy-3-methyl-2-phospholene Oxide.—The cycloadduct (114 g, 0.55 mol) obtained from isoprene and PCl_3 was added to 200 g of ice. The resulting red solution was extracted continuously with methylene chloride. Removal of the solvent yielded 25.6 g (39.8%) of crude product. Recrystallization from ether–methylene chloride gave a white solid: mp 120.5–121.5° (lit.[30] mp 116–117°); nmr ($CDCl_3$ external TMS) δ 2.48 (singlet, CH_3), 2.22–3.40 (complex multiplet, $-CH_2-$), 6.40 (doublet, J = 23.0 Hz, C=CH), 13.1 ppm (singlet, OH).

Hydrolysis of the cycloadduct from isoprene and phosphorus tribromide followed by extraction with methylene chloride yielded 42.8% of crude product which on recrystallization gave a white solid, mp 120.5–121.5°. A mixture melting point of the products from the two reactions showed no depression and the nmr spectra were identical.

Synthesis of 1-Chloro-3-methyl-2-phospholene Oxide (5).—Thionyl chloride (59.5 g, 0.05 mol) in 50 ml of benzene was added dropwise to 28.9 g (0.25 mol) of 1-hydroxy-3-methyl-2-phospholene oxide slurried in 100 ml of benzene. After addition the mixture was refluxed for 2 hr; the benzene and excess thionyl chloride were removed at atmospheric pressure and the product was distilled. The yield was 30.5 g (80.4%), bp 116–117° (2 mm), lit.[8] bp 91° (0.07 mm).

Synthesis of 1-Chloro-2-phospholene Oxide.—Crude 1-hydroxy-2-phospholene oxide (18.5 g, 0.15 mol) obtained by the hydrolysis of the cycloadduct from phosphorus trichloride and butadiene was slurried in 100 ml of benzene, and 35.8 (0.30 mol) of thionyl chloride in 50 ml of benzene was added dropwise over a 30-min period. The mixture was refluxed for 1 hr and then distilled. The yield was 18.5 g (89.4%), bp 107–109.5° (2.2 mm), lit.[5] bp 105–110° (0.20 mm).

Conversion of Phosphinous Halides to Secondary Phosphine Oxides.—The following general procedure was used. The phosphinous halide (5–10 g) was slowly added to chilled concentrated HCl (10–50 ml). The mixture was allowed to warm to room temperature and then stirred overnight at that temperature. The solution was extracted continuously for at least 24 hr with methylene chloride. The organic layer was separated and dried. Removal of the solvent left an oil or low-melting solid. The phosphine oxides were characterized by conversion to chloral adducts as described in the next section.

An alternate procedure for hydrolysis when only a small amount of phosphinous halide was available was to add wet ether to the halide. The oil which formed could be used directly in the conversion to chloral adducts.

Chloral Adducts of 1-Halophospholenes.—The following general procedure was used. The crude phosphine oxide (1–2 g) was dissolved in 10 ml of isopropyl alcohol, and 2 g of chloral hydrate in 10 ml of isopropyl alcohol was added. A few drops of sodium methoxide in methanol were added and the mixture allowed to stand overnight. Alternatively, the mixture can be heated for several hours on a steam bath without the addition of sodium methoxide. In either case removal of the solvent gave a crude product that could be recrystallized from ethanol–water. Analytical and spectral data are given in Table IV.

Synthesis of 1,3-Dimethyl-2-phospholene (12).—1-Chloro-3-methyl-2-phospholene (10.4 g, 0.085 mol) in an equal volume of ether was added dropwise to an ice-cooled flask containing methylmagnesium iodide (prepared from 2.92 g-atoms of magnesium and 17.0 g of methyl iodide). The mixture was allowed to warm to room temperature and refluxed for 3 hr. After cooling, the mixture was hydrolyzed with 75 ml of 10% NH_4Cl and stirred for 1 hr. The organic layer was separated and the water layer extracted with 250 ml of ether. After removal of ether, the product was distilled and yielded 5.40 g (55.6%) of 1,3-dimethyl-2-phospholene: bp 139.5–141.5°; nmr (neat, external TMS) δ 1.23 (doublet, J = 2.8 Hz, P-CH_3), 2.13 (doublet, J = 1.0 Hz, C-CH_3), 1.54–3.16 (complex, $-CH_2CH_2-$), 5.90 ppm (doublet, J = 42.0 Hz, C=CH); ir $\nu_{C=C}^{neat}$ 1613 cm^{-1}. A sample (in benzene) was converted into the benzyl bromide salt which was recrystallized from chloroform–ethyl acetate: mp 133.5–134.5°; nmr ($CDCl_3$, internal TMS) δ 1.92 (singlet, C-CH_3), 2.45 (doublet, J = 14.5 Hz, P-CH_3), 2.60–3.25 (complex, $-CH_2CH_2-$), 4.55 (doublet, J = 16.5 Hz, benzyl $-CH_2-$), 6.33 ppm (J = 29.0 Hz, C=CH).

Anal. Calcd for $C_{13}H_{18}BrP\cdot H_2O$: C, 51.45; H, 6.65; P, 10.21. Found: C, 51.13; H, 6.59; P, 10.36.

Synthesis of 1-(*N*,*N*-Diethylamino)-3-methyl-2-phospholene (7).—A solution of 4.4 g (0.060 mol) of diethylamine in 10 ml of dry ether was cooled to 0°. 1-Bromo-3-methyl-2-phospholene (5.3 g, 0.030 mol), containing about 10% of the 3 isomer, was added to the cold solution with vigorous stirring over 45 min. After the addition was complete, the mixture was allowed to warm to room temperature and stirred 1 hr. The white solid was removed by filtration and the liquid distilled, bp 98–102° (19 mm), yield 39.5%. Gas chromatography showed the product to contain about 90% 7 and 10% 3 isomer. Spectra follow: nmr (neat, external TMS) δ 1.25 (triplet, J = 7 Hz, CH_3CH_2-) 3.08 (quartet, J = 7 Hz, N-CH_2), 1.75–3.42 (complex, $-CH_2-CH_2-$), 2.14 (singlet with fine splitting, ring CH_3), 5.87 ppm (doublet, J = 40 Hz, C=CH); ir $\nu_{C=C}^{neat}$ 1604 cm^{-1}.

Anal. Calcd for $C_9H_{18}NP$: N, 8.18; P, 18.09. Found: N, 8.20; P, 17.90.

Registry No.—**2a**, 28273-33-8; **2b**, 28273-34-9; **2c**, 28273-35-0; **3a**, 28273-36-1; **3b**, 28273-37-2; **3c**, 28273-38-3; **7**, 28273-39-4; **10a**, 28273-40-7; **10b**, 28273-41-8; **10c**, 28273-42-9; **11a**, 28273-43-0; **11b**, 28273-44-1; **12**, 28273-45-2; 1-hydroxy-3-methyl-2-phospholene oxide, 3858-24-0.

Acknowledgment.—We thank Mr. Ronald C. Stocks for preparing compound **7**, and Mr. Joseph J. Breen for obtaining ^{31}P nmr spectra.

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Studies on the Syntheses of Heterocyclic Compounds. CCCXCIV.[1] Total Syntheses of (±)-Dasycarpidone and (±)-3-Epidasycarpidone. Formal Total Syntheses of (±)-Uleine and (±)-3-Epiuleine

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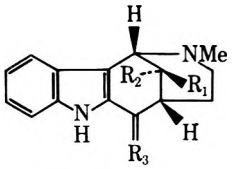
Syntheses of the racemic forms of the indole alkaloids, dasycarpidone (**1**), 3-epidasycarpidone (**3**), uleine (**2**), and 3-epiuleine (**4**), together with that of so-called isodasycarpidone (**15**) and isoepidasycarpidone (**16**), are described. The key step in the approach to the compounds **7** and **8** involved a condensation of indolylmagnesium bromide with methyl 3-ethylisonicotinate 1-oxide (**6**).

In our previous paper,[2] we reported a synthesis of deethyldasycarpidone (**5**) by the Grignard reaction. We now wish to report syntheses of (±)-dasycarpidone (**1**) and (±)-3-epidasycarpidone (**3**) by the above reaction. An alternative and different approach to the total synthesis of **1** and **3** has been reported.[3,4] Our synthesis is based on the production of intermediate **7** by a Grignard reaction.



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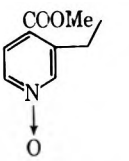
2, R_1 = H; R_2 = Et; R_3 = CH_2
3, R_1 = Et; R_2 = H; R_3 = O
4, R_1 = Et; R_2 = H; R_3 = CH_2
5, R_1 = R_2 = H; R_3 = O

Grignard condensation of indolylmagnesium bromide with methyl 3-ethylisonicotinate 1-oxide (**6**) in tetrahydrofuran and methylene dichloride in the presence of benzoyl chloride was carried out to give a mixture of the desired condensation product **7** and its structural isomer **8**, both of which were separated as described in the Experimental Section. The ir spectrum ($CHCl_3$) of both **7** and **8** showed an absorption band due to indole NH at 3430 cm^{-1} and an ester carbonyl band at 1725 cm^{-1}. An absorption band due to the C=C double bond was very weak in **7** but was observed at 1600 cm^{-1} in **8** as a very strong absorption. The nmr spectra (δ) of both compounds lacked a signal due to an indole β proton, but the N hydrogen of the indole ring was observed. The signal of the methyl group was observed at 3.92 in **7** and at 3.96 ppm in **8**. The other methyl signal due to the ethyl group of **7** resonated at 1.0 ppm, whereas that of **8** resonated at 1.27 ppm. An ortho coupling in the pyridine ring was observed in **7** but was absent in **8**. The mass spectra of both compounds showed the same molecular ions at *m/e* 280. Treatment of **7** with methyl iodide in methanol gave a pyridinium methiodide (**9**), which on catalytic reduction yielded a stereoisomeric mixture of the amino esters **11**. After normal saponification, the resulting amino acids **13** were heated with polyphosphoric acid at 90–95° by Dolby's method[4] to yield a mixture of 2-acylindoles, which on preparative thick layer chromatography afforded (±)-dasycarpidone (**1**) and (±)-3-epidasycarpidone (**3**), the ratio of the two compounds being about 2:1. Our synthetic syrupy dasycarpidone (**1**) had uv, ir, nmr, and mass spectra identical with published physical data.[5] The identity of synthetic **1** was also confirmed by the formation of crystalline picrate, mp 239–240° dec (lit.[4] 240°). The mass spectrum of (±)-3-epidasycarpidone (**3**), mp 166–168° (lit. 168–169°,[4] 164–166°[6]) was identical with that of dasycarpidone, and the nmr and uv absorptions coincided with those reported for (±)-3-epidasycarpidone[5] (**3**). Furthermore, ir spectra and tlc behavior of **1** and **3** were identical with those of authentic samples donated by Professor Joule. Since **1** and **3** had been converted into uleine (**2**) and 3-epiuleine (**4**) by Joule and his coworkers,[3] an alternative formal total synthesis of **2** and **4** has been accomplished.

The so-called (±)-isodasycarpidone (**15**) and (±)-iso-3-epidasycarpidone (**16**) were synthesized as follows. Treatment of **8** with methyl iodide afforded a pyridinium methiodide **10**, whose catalytic reduction yielded a mixture of the amino esters **12**. Normal sa-



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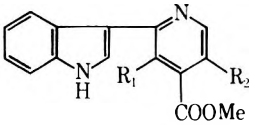

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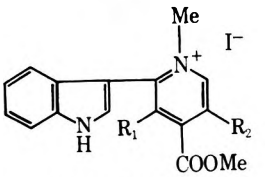
8, R_1 = H; R_2 = Et



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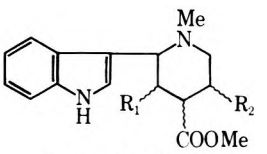
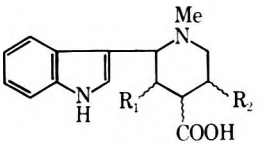
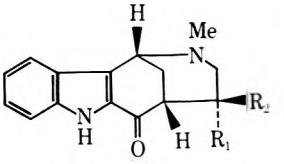
10, R_1 = H; R_2 = Et



11, R_1 = Et; R_2 = H
12, R_1 = H; R_2 = Et



13, R_1 = Et; R_2 = H
14, R_1 = H; R_2 = Et



15, R_1 = Et; R_2 = H
16, R_1 = H; R_2 = Et

(1) Part CCCXCIII: T. Kametani, K. Takahashi, S. Shibuya, and K. Fukumoto, *J. Chem. Soc. C*, in press.
(2) T. Kametani and T. Suzuki, *ibid.*, in press.
(3) A. Jackson, N. D. V. Willson, A. J. Gaskell, and J. A. Joule, *ibid.*, 2738 (1969).
(4) L. J. Dolby and H. Biere, *J. Amer. Chem. Soc.*, **90**, 2699 (1968).
(5) J. A. Joule, M. Ohashi, B. Gilbert, and C. Djerassi, *Tetrahedron*, **21**, 1717 (1965).
(6) A. J. Gaskell and J. A. Joule, *Chem. Ind. (London)*, 1089 (1967).

ponification afforded the amino acids **14**, which were heated with polyphosphoric acid to yield a mixture of 2-acylindoles. Careful thick layer chromatography afforded (±)-isodasycarpidone (**15**) and (±)-isoepidasycarpidone (**16**); the ratio of both compounds was also about 2:1. The ir spectra ($CHCl_3$) of both compounds showed absorption bands at 3430 (indole NH), 2780 (NMe), and 1645 cm^{-1} (conjugated C=O), but differences in the finger print region were observed. In the nmr spectra of the two epimers of isodasycarpidone, the methyl protons due to the ethyl group of (±)-isodasycarpidone (**15**) resonated at 1.0 ppm, whereas the corresponding signal of (±)-iso-5-epidasycarpidone (**16**) was observed at 1.1 ppm. Since the ethyl group of **15** lies over the aromatic π-electron system, this epimer would be expected to show a methyl signal at a higher field as in the case of (±)-dasycarpidone and (±)-3-epidasycarpidone.[6] It is interesting that catalytic reduction of the pyridinium methiodides **9** and **10** afforded a higher ratio of dasycarpidone to epidasycarpidone type compounds than Dolby's method.[4]

Experimental Section[7]

Methyl 3-Ethylisonicotinate 1-Oxide (6).—To a mixture of 120 ml of acetic acid and 21 ml of 30% hydrogen peroxide was added 10 g of methyl 3-ethylisonicotinate; the mixture was heated at 70–80° for 24 hr. After the reaction mixture had been condensed to one-third volume under reduced pressure, the resulting residue was basified with potassium carbonate and extracted with chloroform. The extract was dried over K_2CO_3 and evaporated to give a syrup, whose recrystallization from benzene–hexane gave 8 g of the *N*-oxide **6** as colorless needles: mp 69–70°; ir ($CHCl_3$) 1720, 1665, 1140, and 1100 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.96; H, 5.98; N, 8.01.

3-Ethyl-2-(3-indolyl)-4-methoxycarbonylpyridine (7) and 5-Ethyl-2-(3-indolyl)-4-methoxycarbonylpyridine (8).—A solution of 16 g of indole in 150 ml of tetrahydrofuran was added to a solution of ethylmagnesium bromide (prepared by the reaction of 18 g of ethylbromide with 4 g of magnesium turnings at −10° for 10 min). The reaction mixture was stirred at room temperature for 30 min, and then 500 ml of methylene dichloride was added in order to bring the complex into solution. To a cooled solution at −30° was added a mixture of 20 g of methyl 3-ethylisonicotinate 1-oxide (**6**) and 18.2 g of benzoyl chloride at this temperature within 30 min. The mixture was stirred at 50° for 24 hr and then decomposed with a solution of 7 g of ammonium chloride in 100 ml of water. After the solvent had been distilled off *in vacuo*, the resultant residue was extracted with ether. The extract was then washed with water and again extracted with 10% hydrochloric acid solution. The acidic solution was basified with ammonia and then extracted with chloroform. The extract was washed with sodium chloride solution, dried over K_2CO_3, and evaporated to give 8.6 g of a brown syrup, which was chromatographed on 200 g of silica gel using chloroform as an eluent. Evaporation of the above eluate afforded a mixture of 3 g of compounds **7** and **8**, which were triturated with methanol to separate **7** as crystals. Recrystallization from methanol–ether afforded 900 mg of colorless prisms: mp 185–186°; ir ($CHCl_3$) 3430, 1725 cm^{-1}; nmr δ ($CDCl_3$) 1.0 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.7 (2 H, q, J = 7.0 Hz, CH_2CH_3), 3.92 (3 H, s, CO_2CH_3), 6.95–7.2 (4 H, m, Ar H), 7.4–7.65 (1 H, m, Ar H), 7.43 (1 H, d, J = 6 Hz, 5-H), 8.56 (1 H, d, J = 6 Hz, 6-H), 9.0–9.2 (1 H, NH of indole ring, exchanged with D_2O); m/e 280 (M^+), 255, 249, and 221.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.75; H, 5.35; N, 9.95.

An excess of ether saturated with hydrogen chloride gas was added to the above filtrate, and the hydrochloride of **8** was obtained. Recrystallization from methanol–ether afforded 450 mg of yellow needles: mp 178–180°; ir (KBr) 3400, 1730, 1640, and 1600 cm^{-1}; m/e 280 (M^+), 255, 249, and 221.

Anal. Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.45; H, 5.40; N, 8.84. Found: C, 64.90; H, 5.58; N, 9.04.

The above hydrochloride was freed to give compound **8** (360 mg) as a pale yellow syrup, whose recrystallization from chloroform–hexane afforded colorless needles: mp 99–100°; ir ($CHCl_3$) 3430, 1725, and 1600 cm^{-1}; nmr δ ($CDCl_3$) 1.27 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.94 (2 H, q, J = 7.0 Hz, CH_2CH_3), 3.96 (3 H, s, CO_2CH_3), 7.2–7.4 (3 H, m, Ar H), 7.72 (1 H, d, J = 3.0 Hz, Ar H), 8.06 (1 H, s, 3-H), 8.35 (1 H, m, Ar H), 8.63 (1 H, s, 6-H), 8.75–8.9 (1 H, NH of indole ring, exchanged with D_2O); m/e 280 (M^+).

3-Ethyl-2-(3-indolyl)-4-methoxycarbonyl-1-methylpyridinium Iodide (9).—To a solution of 300 mg of **7** in 50 ml of methanol was added 10 ml of methyl iodide, and the mixture was refluxed for 4 hr. The solvent and reagent were evaporated to give 480 mg of a yellow syrup (**9**) [ir ($CHCl_3$) 3430, 2920, and 1740 cm^{-1}; nmr δ ($CDCl_3$) 0.9 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.92 (2 H, q, J = 7.0 Hz, CH_2CH_3), 4.0 (3 H, s, NMe), 4.55 (3 H, s, CO_2CH_3)], whose crystallization was so difficult that it was used in the following reaction.

3-Ethyl-2-(3-indolyl)-4-methoxycarbonyl-1-methylpiperidine (11).—The methiodide **9** (480 mg) was reduced with hydrogen in methanol over Adams catalyst at atmospheric pressure and room temperature. The solution was filtered and then evaporated to give a residue which was basified with 10% ammonia and extracted with ether. The extract was washed with sodium chloride solution, dried over K_2CO_3, and distilled off to give 320 mg of a stereoisomeric mixture of amino ester **11**: ir ($CHCl_3$) 3430, 2900, 2750, and 1720 cm^{-1}; m/e 300 (M^+).

3-Ethyl-4-hydroxycarbonyl-2-(3-indolyl)-1-methylpiperidine (13), (±)-Dasycarpidone (1), and (±)-3-Epidasycarpidone(3).—A mixture of 269 mg of the amino ester **11**, 1 g of potassium hydroxide, 10 ml of water, and 20 ml of ethanol was refluxed for 3 hr. The above mixture was then neutralized with concentrated hydrochloric acid, and the solvent was evaporated completely to give a residue, which was extracted with dry ethanol to give 200 mg of the carboxylic acid **13** as a powder. Without purification, the acid **13** was treated with polyphosphoric acid (prepared from 2 ml of phosphoric acid and 4 g of phosphorus pentoxide) at 90–95° for 1.5 hr. After the addition of 5 ml of water, the reaction mixture was basified with ammonia and then extracted with ether. The extract was washed with sodium chloride solution, dried over K_2CO_3, and distilled off to give 70 mg of a pale yellow syrup. Preparative thick layer chromatography (ethyl acetate–benzene–methanol, 2:2:1) on silica gel afforded 34 mg of (±)-dasycarpidone (**1**) [ir ($CHCl_3$) 3400, 2900, 2875, and 1640 cm^{-1}; uv (EtOH) 316 and 237 nm (log ϵ 4.30 and 4.15); nmr δ ($CDCl_3$) 0.88 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.34 (3 H, s, NMe), 4.25 (1 H, d, J = 2.5 Hz, β-indolic CHN), 7.0–7.8 (4 H, m, Ar H), 10.20–10.50 (1 H, NH of indole ring, exchanged with D_2O); m/e 268 (M^+), 253, 239, 225, 211, 198, and 183], whose picrate was recrystallized from ethanol to afford a yellow powder [mp 239–240° dec (lit.[4] 240°)] and 15 mg of (±)-3-epidasycarpidone (**3**) [ir 3400, 2800, 2775, and 1650 cm^{-1}; uv (EtOH) 314 and 238 nm (log ϵ 4.01 and 3.88); nmr δ ($CDCl_3$) 1.08 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.3 (3 H, s, NMe), 4.2 (1 H, d, J = 2.5 Hz, β-indolic CHN), 7.0–7.8 (4 H, m, Ar H), 9.6–9.9 (1 H, NH of indole ring, exchanged with D_2O); m/e 268 (M^+), 253, 239, 225, 211, 198, and 183], which was triturated with methanol to give crystals. Recrystallization of **3** from ethanol–ether gave colorless cubes, mp 166–168° (lit. 168–169°,[4] 164–166°[6])].

5-Ethyl-2-(3-indolyl)-4-methoxycarbonyl-1-methylpyridinium Iodide (10).—To a solution of 360 mg of **8** in 40 ml of methanol was added 10 ml of methyl iodide, and the mixture was refluxed for 6 hr. The solvent and reagent were evaporated to give 559 mg of a yellow syrup, whose recrystallization from methanol–ether gave the methiodide **10** as yellow needles: mp 140–142°; ir ($CHCl_3$) 3430, 2920, and 1730 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}IN_2O_2$: N, 6.63. Found: N, 6.77.

5-Ethyl-2-(3-indolyl)-4-methoxycarbonyl-1-methylpiperidine (12).—The methiodide **10** (519 mg) was reduced with hydrogen in methanol over Adams catalyst at atmospheric pressure and room temperature. After the solution had been filtered and evaporated, the residue was basified with 10% ammonia and

(7) The ir spectra were taken in chloroform unless otherwise noted with a Hitachi EPI-S2 spectrometer. Uv spectra were taken in ethanol solution on a Hitachi EPS-3 recording spectrometer. Mass spectra were measured on a Hitachi RMU-7 mass spectrometer. Nmr spectra were measured in deuteriochloroform solution, using tetramethylsilane as an internal standard, on a Hitachi R-20 instrument. The melting points are uncorrected.

extracted with ether. The extract was washed with sodium chloride solution, dried over K_2CO_3, and distilled off to give 330 mg of a stereoisomeric mixture of amino ester **12** [ir ($CHCl_3$) 3450, 2900, 2750, 1720, and 1600 cm^{-1}; *m/e* 300 (M^+)], which was used in the following reaction without purification because of difficult crystallization.

(±)-Isodasycarpidone (15) and (±)-Iso-5-epidasycarpidone (16).—A mixture of 300 mg of the amino esters **12**, 1 g of potassium hydroxide, 10 ml of water, and 20 ml of ethanol was refluxed for 5 hr. The resulting mixture was neutralized with concentrated hydrochloric acid and the solvent was evaporated completely to give a residue, which was extracted with dry ethanol. Removal of the extract gave 270 mg of 5-ethyl-4-hydroxycarbonyl-2-(3-indolyl)-1-methylpiperidine (**14**) as a powder, which was treated with polyphosphoric acid (prepared from 2 ml of phosphoric acid and 4 g of phosphorus pentoxide) at 90–95° for 1 hr. To the reaction mixture was added 5 ml of water, and the resulting mixture was basified with ammonia and extracted with ether. The extract was washed with sodium chloride solution, dried over K_2CO_3, and distilled off to give 98 mg of a pale yellow syrup, whose preparative thick layer chromatography (ethyl acetate–benzene–methanol, 2:2:1) on silica gel afforded 16 mg of (±)-isodasycarpdione (**15**) and 9 mg of (±)-iso-3-epidasycarpidone (**16**). Recrystallization of **15** from methanol–ether gave colorless needles: mp 220–221°; ir ($CHCl_3$) 3430, 2900, 2780, and 1645 cm^{-1}; nmr δ ($CDCl_3$) 1.0 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.25 (3 H, s, NMe), 4.3 (1 H, t, J = 2.5 Hz, β-indolic CHN), 7.0–7.8 (4 H, m, Ar H), 9.7–10.0 (1 H, NH of indole ring, exchanged with D_2O); *m/e* 268 (M^+), 253, 240, 225, 211, 196, and 183.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75 56; H, 7.87; N, 10.70.

Recrystallization of **16** from methanol–ether gave colorless needles: mp 201–202°; ir 3430, 2900, 2780, and 1645 cm^{-1}; nmr δ ($CDCl_3$). 1.1 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.3 (3 H, s, NMe), 4.35 (1 H, t, J = 2.5 Hz, β-indolic CHN), 7.0–7.8 (4 H, m, Ar H), 10.4–10.8 (1 H, NH of indole ring, exchanged with D_2O); *m/e* 268 (M^+), 253, 240, 225, 211, 196, and 183.

Registry No.—**1**, 18700-27-1; **2**, 19775-50-9; **3**, 18688-38-5; **4**, 19775-51-0; **6**, 28199-31-7; **7**, 28199-32-8; **8**, 28199-33-9; **8** HCl, 28199-34-0; **9**, 28199-35-1; **10**, 28199-36-2; **15**, 28192-70-3; **16**, 28192-71-4.

Acknowledgment.—We thank Professor J. A. Joule, Chemistry Department of Manchester, Manchester M 139 PL, for a gift of natural dasycarpidone and (±)-3-epidasycarpidone and for the data of its ir and nmr spectra. We also thank Dr. L. J. Dolby, department of Chemistry, University of Oregon, Eugene, for a gift of epidasycarpidone. We are grateful to Miss Y. Tadano for nmr spectral determination, Mr. T. Ohuchi for mass spectral measurements, and Miss A. Kawakami and Miss C. Yoshida, Pharmaceutical Institute, Tohoku University, for microanalyses.

Notes

Studies on the Syntheses of Heterocyclic Compounds. CCCXCV. The Synthesis of Homopetaline-Type Compounds

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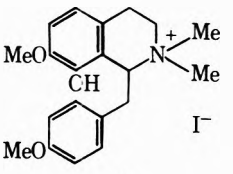
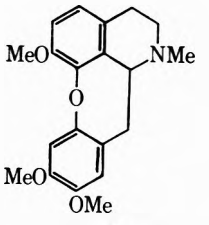
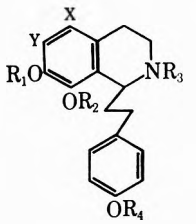
Petaline (**1**)[1,2] and cularine (**2**)[3] are benzylisoquinoline alkaloids having the oxygenated function at the C-7 and C-8 positions on the isoquinoline ring. The former was synthesized by Brossi[4] and the latter by Kametani.[5–7]



1



2



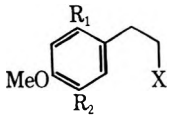
3, $R_1 = R_3 = R_4 = Me$; $R_2 = X = Y = H$
9, $R_1 = R_3 = R_4 = Me$; $R_2 = Y = H$; $X = Br$
13, $R_1 = R_2 = R_3 = R_4 = Me$; $X = H$; $Y = NHCOOEt$
14, $R_1 = R_2 = R_3 = R_4 = Me$; $X = H$; $Y = NH_2$
15, $R_1 = R_2 = R_3 = R_4 = Me$; $X = Y = H$
16, $R_1 = R_3 = Me$; $R_2 = R_4 = X = Y$ H

Several unsuccessful attempts have been made[8,9] to prepare 7,8-dioxygenated isoquinolines by the Bischler–Napieralski or Pictet–Spengler reaction. Therefore, we reinvestigated the synthesis of 7,8-dioxygenated isoquinolines by the above two methods.

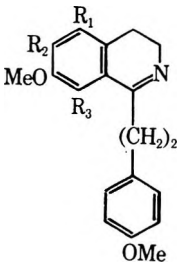
(1) N. J. McCorkindale, D. S. Magrill, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron Lett.*, 3841 (1964).
(2) N. J. McCorkindale, A. W. McCulloch, D. S. Magrill, B. Caddy, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron*, **25**, 5457 (1969).
(3) R. H. F. Manske, *J. Amer. Chem. Soc.*, **72**, 55 (1950).
(4) G. Grethe, M. Uskokovič, and A. Brossi, *Tetrahedron Lett.*, 1599 (1966); *J. Org. Chem.*, **33**, 2500 (1968); *Helv. Chim. Acta*, **53**, 874 (1970).
(5) T. Kametani and K. Fukumoto, *Chem. Ind. (London)*, 291 (1963); *J. Chem. Soc.*, 4289 (1963).
(6) T. Kametani, S. Shibuya, S. Seino, and K. Fukumoto, *Tetrahedron Lett.*, 25 (1964); *J. Chem. Soc.*, 4146 (1964).
(7) T. Kametani and S. Shibuya, *Tetrahedron Lett.*, 1897 (1965); *J. Chem. Soc.*, 5565 (1965).
(8) R. D. Haworth and W. H. Perkin, *ibid.*, **127**, 1448 (1925).
(9) A. R. Battersby, S. Southgate, and J. Staunton, *ibid.*, *C*, 502 (1966).

Homologs of petaline (**1**) have now been synthesized by using bromine or a substituted amino group to block those positions usually involved in the cyclization to isoquinolines.

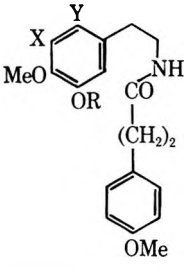
Schotten–Baumann reaction of 5-benzyloxy-2-bromo-4-methoxyphenethylamine (**4**)[10] and 4-methoxyphenylpropionyl chloride (**5**) gave the corresponding amide **6**, which was debenzylated by hydrochloric acid to give the starting phenolic bromo amide **7**. Bischler–Napieralski reaction of amide **7** with phosphoryl chloride in boiling chloroform gave the 3,4-dihydroisoquinoline **8**, whose methiodide was reduced with sodium borohydride to give the 1,2,3,4-tetrahydro-2-methylisoquinoline **9**, which was characterized as its oxalate. Debromination of this bromoisoquinoline (**9**) was achieved by catalytic hydrogenation on Raney nickel to give compound **3**, whose structure was assigned by its nmr spectrum, the C-5 and C-6 protons being shown as a typical AB type of doublets. Thus, we developed a new method for preparing 7,8-dioxygenated isoquinoline derivatives.



4, R_1 = Br; R_2 = OCH_2Ph; X = NH_2
5, R_1 = R_2 = H; X = COCl



8, R_1 = Br; R_2 = H; R_3 = OH
11, R_1 = H; R_2 = NHCOOEt; R_3 = OMe
12, R_1 = H; R_2 = OMe; R_3 = NHCOOEt



6, R = CH_2Ph; X = H; Y = Br
7, R = X = H; Y = Br
10, R = Me; X = NHCOOEt; Y = H

The over-all yield of the above sequence was not impressive, and so the following route was examined. Cyclization of the amide **10** gives two types of isoquinolines (**11** and **12**) arising by cyclization ortho and para to a removable group ($NHCO_2Et$ group in **10**).[11] The methiodide of 3,4-dihydroisoquinoline (**11**), prepared in a previous paper,[11] was reduced as usual to the 1,2,3,4-tetrahydro-2-methylisoquinoline **13**. Hydrolysis of the ethoxycarbonylamino group of this compound (**13**) with potassium hydroxide gave the 6-aminoisoquinoline **14**, whose diazonium salt was treated with hypophosphorous acid to give the 7,8-dimethoxyisoquinoline **15**. Demethylation of **15** with 20% hydrochloric acid[12] gave the 8-hydroxy-7-methoxyisoquinoline **3** in addition to 1,2,3,4-tetrahydro-8-hydroxy-1-(4-hydroxyphenethyl)-7-methoxy-2-methylisoquinoline (**16**). The former compound was fully identical with an authentic sample of **3** spectroscopically; the structure **16** was assigned as described in the Experimental Section.

These two routes have been found suitable for the synthesis of 7,8-dioxygenated isoquinolines which are difficult to prepare by the usual methods.

(10) T. Kametani, S. Shibuya, and M. Satoh, *Chem. Pharm. Bull.*, **16**, 953 (1968).

(11) T. Kametani, K. Fukumoto, M. Kawazu, and M. Fujihara, *J. Chem. Soc. C*, 2209 (1970).

Experimental Section[13]

N-(5-Benzyloxy-2-bromo-4-methoxyphenethyl)-4-methoxyphenylpropionamide (6).—To a mixture of 5-benzyloxy-2-bromo-4-methoxyphenethylamine (**4**) (prepared from 3.72 g of its hydrochloride by the usual method), 15 ml of 5% sodium hydroxide, and 60 ml of chloroform was added dropwise a solution of 2.4 g of 4-methoxyphenylpropionyl chloride (**5**) in 20 ml of chloroform with stirring at 2–5° during 30 min; stirring was continued at 2–5° for 30 min and then at room temperature for 2 hr. The organic layer was separated, washed with 5% hydrochloric acid and water, dried over Na_2SO_4, and evaporated *in vacuo* to give 3.93 g (81.3%) of the amide **6** as colorless needles (from benzene), mp 164–165°, ir ($CHCl_3$) 3380 and 1650 cm^{-1}.

Anal. Calcd for $C_{26}H_{28}BrNO_4$: C, 62.65; H, 5.67; Br, 16.03; N, 2.95. Found: C, 62.75; H, 5.73; Br, 15.85; N, 2.95.

N-(2-Bromo-5-hydroxy-4-methoxyphenethyl)-4-methoxyphenylpropionamide (7).—A mixture of 8.2 g of the above amide (**6**), 300 ml of concentrated hydrochloric acid, 150 ml of ethanol, and 150 ml of acetone was refluxed on a water bath for 1.5 hr, and the excess of reagent and solvents was distilled off to give a residue which was extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to afford 5.65 g (84.8%) of the phenolic amide **7** as pale brown prisms (from benzene): mp 137–138°; ir ($CHCl_3$) 3480, 3400, and 1657 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}BrNO_4$: C, 55.89; H, 5.19; Br, 19.58; N, 3.43. Found: C, 56.08; H, 5.15; Br, 19.32; N, 3.35.

5-Bromo-1,2,3,4-tetrahydro-8-hydroxy-7-methoxy-1-(4-methoxyphenethyl)-2-methylisoquinoline (9).—A mixture of 2.7 g of the phenolic amide **7**, 27 ml of phosphoryl chloride, and 50 ml of chloroform was refluxed for 30 min, and an additional 1.4 ml of phosphoryl chloride was then added. The mixture was refluxed for a further 40 min. The excess reagent and chloroform were distilled off *in vacuo*, and the residue was washed with ether, basified with 10% ammonia, and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to leave a pale brown viscous syrup, which was converted into its oxalate by the usual method. The oxalate was washed with ether and basified with 10% ammonia, and the separated oil was extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to give 1.52 g of the 3,4-dihydroisoquinoline **8** as a pale brown syrup, whose methiodide was prepared by the standard method. To a solution of the methiodide in 100 ml of methanol was added 1 g of sodium borohydride in portions with stirring at 0°; stirring was continued at 0° for 2 hr. The mixture was then set aside at room temperature overnight. After evaporation of the solvent at atmospheric pressure, the residue was treated with aqueous ammonium chloride solution and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to leave a pale brown viscous syrup, which was extracted with ether. After removal of an insoluble material, the extract was evaporated *in vacuo* to give 657 mg of a brown syrup, which was purified on thin layer chromatography (silica gel GF 254 nach Stahl, 1 × 200 × 200 mm) using ether to afford 193 mg (7.2%) of the tetrahydroisoquinoline **9** as a pale brown viscous syrup: mass spectrum *m/e* 405 (M^+), 407 ($M^+ + 2$) (isotope ion), 270 (base peak), 272 (isotope ion of *m/e* 270); ir ($CHCl_3$) 3560 cm^{-1}; nmr τ ($CDCl_3$) 7.58 (3 H, s, NMe), 6.23 (3 H, s, OMe), 6.15 (3 H, s, OMe), 5.40 (1 H, broad signal, OH), 3.22

(12) A. Brossi, Symposium Papers of 13th Symposium on the Chemistry of Natural Products, Sapporo, Japan, 1969, p 177.

(13) The ir and uv spectra were taken with Type EPI-3 and EPS-3 Hitachi recording spectrometers, respectively. Mass spectra were measured with a Hitachi RMS-4 mass spectrometer. Nmr spectra were measured with JNM C-60 spectrometer with tetramethylsilane as an internal standard.

(2 H, d, J = 9 Hz, 3'-H and 5'-H), 3.05 (1 H, s, 6-H), and 2.84 (2 H, d, J = 9 Hz, 2'-H and 6'-H). The oxalate formed colorless needles (from ethanol–ether), mp 177–178°.

Anal. Calcd for $C_{20}H_{24}BrNO_3 \cdot C_2H_2O_4$: C, 53.23; H, 5.28; Br, 16.10; N, 2.82. Found: C, 53.05; H, 5.32; Br, 15.86; N, 3.01.

1,2,3,4-Tetrahydro-8-hydroxy-7-methoxy-1-(4-methoxyphenethyl)-2-methylisoquinoline (3).—A solution of 30 mg of the bromoisoquinoline 9 in 40 ml of ethanol was shaken in a current of hydrogen on 10 mg of Raney nickel at room temperature and atmospheric pressure. After absorption of the calculated amount of hydrogen, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to give 20 mg (83.3%) of *N*-norhomopetaline (**3**) as a viscous syrup: mass spectrum m/e 327 (M^+); ir ($CHCl_3$) 3520 cm^{-1}; uv (EtOH) 279.5 and 284 nm (log ϵ 3.41 and 3.40); nmr τ ($CDCl_3$) 7.57 (3 H, s, NMe), 6.25 (3 H, s, OMe), 6.16 (3 H, s, OMe), 4.47 (1 H, broad signal, OH), 3.44 (1 H, d, J = 8.5 Hz, 6-H), 3.27 (1 H, d, J = 8.5 Hz, 5-H), 3.23 (2 H, d, J = 9 Hz, 3'H and 5'-H), and 2.86 (2 H, d, J = 9 Hz, 2'-H and 6'-H). The oxalate formed pale brown needles (from methanol–ether), mp 171–172°.

Anal. Calcd for $C_{20}H_{25}NO_3 \cdot C_2H_2O_4 \cdot 0.25H_2O$: C, 62.62; H, 6.45; N, 3.32. Found: C, 62.51; H, 6.36; N, 3.33.

6-Ethoxycarbonylamino-1,2,3,4-tetrahydro-7,8-dimethoxy-1-(4-methoxyphenethyl)-2-methylisoquinoline (13).—A mixture of 2 g of 6-ethoxycarbonylamino-3,4-dihydro-7,8-dimethoxy-1-(4-methoxyphenethyl)isoquinoline[11] (**11**), 1.5 ml of methyl iodide, and 25 ml of methanol was refluxed for 2.5 hr and allowed to stand at room temperature overnight. After evaporation of the solvent *in vacuo*, the residue was washed with ether and taken up in 50 ml of methanol. To this solution was added 1 g of sodium borohydride in small portions at 0° with stirring during 30 min; stirring was continued at 0° for 30 min. After the mixture had been set aside at room temperature overnight, the excess of reagent was decomposed with acetic acid and the solvent was distilled off *in vacuo*. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over K_2CO_3, and evaporated *in vacuo* to leave 2 g (96.5%) of the tetrahydroisoquinoline **13** as a brown viscous syrup: mass spectrum m/e 428 (M^+); ir ($CHCl_3$ 3410 and 1732 cm^{-1}; uv (EtOH) 279.5 and 286 nm (log ϵ 3.80 and 3.75); nmr τ ($CDCl_3$) 8.67 (3 H, t, J = 7.0 Hz, CH_3CH_2), 7.58 (3 H, s, NMe), 6.27 (3 H, s, OMe), 6.23 (3 H, s, OMe), 6.17 (3 H, s, OMe), 5.76 (2 H, q, J = 7.0 Hz, CH_3CH_2), 3.18 (2 H, d, J = 9.0 Hz, 3'-H and 5'-H), 2.89 (1 H, NH), 2.80 (2 H, d, J = 9.0 Hz, 2'-H and 6'-H), and 2.40 (1 H, s, 5-H). The oxalate was recrystallized from methanol–ether to give colorless needles, mp 159–160°.

Anal. Calcd for $C_{24}H_{32}N_2O_5 \cdot C_2H_2O_4$: C, 60.22; H, 6.61; N, 5.40. Found: C, 60.05; H, 6.91; N, 5.26.

6-Amino-1,2,3,4-tetrahydro-7,8-dimethoxy-1-(4-methoxyphenethyl)-2-methylisoquinoline (14).—A mixture of 480 mg of the 6-ethoxycarbonylaminoisoquinoline **13**, 1.5 g of potassium hydroxide, and 30 ml of methanol was refluxed for 5.5 hr and the solvent was then removed by distillation *in vacuo*. The residue was extracted with chloroform, and the extract was washed with water, dried over K_2CO_3, and evaporated *in vacuo* to give 350 mg (87.5%) of the 6-aminoisoquinoline **14** as a pale brown viscous syrup: mass spectrum m/e 356 (M^+); ir ($CHCl_3$) 3450, 3360, and 1620 cm^{-1}; uv (EtOH) 280.5 and 286.5 nm (log ϵ 3.79 and 3.80); nmr τ ($CDCl_3$) 7.58 (3 H, s, NMe), 6.24 (9 H, s, 3 OMe), 3.75 (1 H, s, 5-H), 3.18 (2 H, d, J = 8.5 Hz, 3'-H and 5'-H), and 2.81 (2 H, d, J = 8.5 Hz, 2'-H and 6'-H). The oxalate gave pale brown needles (from methanol–ether), mp 151–152°.

Anal. Calcd for $C_{21}H_{28}N_2O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 60.64; H, 6.86; N, 6.15. Found: C, 61.05; H, 6.90; N, 6.10.

1,2,3,4-Tetrahydro-7,8-dimethoxy-1-(4-methoxyphenethyl)-2-methylisoquinoline (15).—To a solution of 310 mg of the aminoisoquinoline **14** in 8 ml of 1 *N* sulfuric acid was added dropwise 1.2 ml of 10% sodium nitrite with stirring at 0–5° during 15 min; the mixture was stirred at 0° for 1 hr. To this solution was added 0.6 ml of 30% hypophosphorous acid at 0°; the mixture was stirred at 0° for 2 hr, then set aside at room temperature for 2 days, basified with concentrated ammonia, and extracted with chloroform. The extract was washed with water, dried over K_2CO_3, and evaporated *in vacuo* to leave 287 mg of a pale brown viscous syrup, which was subjected to chromatography on 3.0 g of silica gel, eluting with ether to give 166 mg (56.0%) of the 7,8-dimethoxyisoquinoline **15** as a pale brown viscous syrup: mass spectrum m/e 341 (M^+); nmr τ ($CDCl_3$) 7.54 (3 H, s, NMe), 6.28 (3 H, s, OMe), 6.22 (3 H, s, OMe), 6.16 (3 H, s, OMe), 3.20 (2 H, s, 5-H and 6-H), 3.16 (2 H, d, J = 9.0 Hz, 3'-H and 5'-H), and 2.78 (2 H, d, J = 9.0 Hz, 2'-H and 6'-H). The oxalate was recrystallized from methanol–ether to give colorless needles: mp 164–165°; uv (EtOH) (oxalate) 279.5 and 285.5 nm (log ϵ 3.82 and 3.80).

Anal. Calcd for $C_{21}H_{27}NO_3 \cdot C_2H_2O_4$: C, 64.02; H, 6.77; N, 3.25. Found: C, 63.91; H, 6.77; N, 3.26.

Demethylation of 15 (Formation of *N*-Norhomopetaline).—A mixture of 500 mg of the above isoquinoline **15** and 20 ml of 20% hydrochloric acid was heated at 120° for 2 hr and then evaporated *in vacuo* to leave a gum, which was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to leave 440 mg of a brown viscous syrup, which was chromatographed on 20 g of silica gel. Evaporation of the first chloroform–methanol (97:3, v/v) eluate *in vacuo* gave 95 mg (19.8%) of *N*-norhomopetaline (**3**) as a pale brown viscous syrup, whose spectroscopic data were superimposable on those of the authentic sample. The oxalate gave pale brown needles (from methanol–ether), mp and mmp 170–171.5°. The second eluate gave 50 mg (10.8%) of the 4',8-dihydroxyisoquinoline **16** as a red viscous oil: mass spectrum m/e 313 (M^+); ir ($CHCl_3$) 3570 and 3510 cm^{-1}; nmr τ ($CDCl_3$) 7.57 (3 H, s, NMe), 6.18 (3 H, s, OMe), 4.91 (2 H, broad signal, 2 OH), 3.45 (1 H, d, J = 8.0 Hz, 6-H), 3.35 (2 H, d, J = 8.5 Hz, 3'-H and 5'-H), 3.26 (1 H, d, J = 8.0 Hz, 5-H), and 3.01 (2 H, d, J = 8.5 Hz, 2'-H and 6'-H); m/e 192 (base peak) [$M^+ - (CH_2)_2C_6H_4OH$].

Registry No.—**3**, 28116-36-1; **3** oxalate, 28116-37-2; **6**, 28116-38-3; **7**, 28116-39-4; **9**, 28116-40-7; **9** oxalate, 28116-41-8; **13**, 28116-42-9; **13** oxalate, 28201-46-9; **14**, 28116-43-0; **14** oxalate, 28116-44-1; **15**, 28116-45-2; **15** oxalate, 28116-46-3; **16**, 28116-47-4.

Acknowledgment.—We thank Mr. M. Yamazaki and Dr. M. Kawazu, Tanabe Seiyaku Co. Ltd., for their encouragements and Mr. S. Hirata, Miss A. Kawakami, Miss C. Yoshida, Miss R. Kato, Miss T. Yoshida, and Miss Y. Tadano, Pharmaceutical Institute, Tohoku University, for microanalyses and for spectral measurements. We also thank the Analytical Centre of Organic Chemistry Research Laboratory, Tanabe Seiyaku Co. Ltd., for microanalyses and spectral determinations.

Studies on the Syntheses of Heterocyclic Compounds. CCCXCVI.[1] An Alternative Total Synthesis of (±)-Galanthamine

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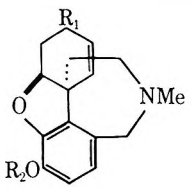
Galanthamine,[2] an *Amaryllidaceae* alkaloid isolated from *Lycoris radiata*, was assigned structure **1** by Barton.[3] A synthesis based on biogenetic lines was also carried out. Recently, some of the present authors reported total syntheses of (±)-galanthamine (**1**) and

(1) Part CCCXCV: T. Kametoni, K. Fukumoto, and M. Fujihara, *J. Org. Chem.*, **36**, 1293 (1971).

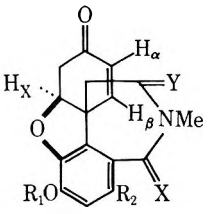
(2) W. C. Wildman, *Alkaloids*, **11**, 348 (1968), and references cited therein; T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," Hirokawa Publishing Co., Tokyo, and Elsevier, Amsterdam, 1968, pp 196, 296.

(3) D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 806 (1962).

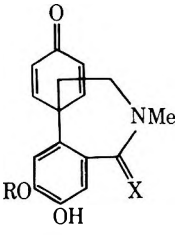
(±)-epigalanthamine (**2**) by the reduction of the narwedine-type enones (**3**) and (**4**) prepared from the amides **5** and **6**, respectively.[4-6] Since natural and synthetic galanthamines appear to possess analgesic activity[5,7] comparable to that of morphine, we report an alternative total synthesis of (±)-galanthamine.



1, R_1 = ◄OH; R_2 = Me
2, R_1 = ---OH; R_2 = Me

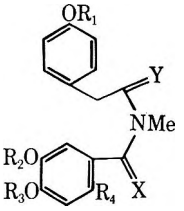


3, R_1 = Me; R_2 = Br; X = O; Y = H_2
4, R_1 = Me; R_2 = Br; X = H_2; Y = O
8, R_1 = Me; R_2 = H; X = O; Y = H_2

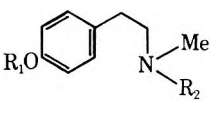


9, R = Me; X = O

The oxidation of 3-hydroxy-*N*-(4-hydroxyphenethyl)-4-methoxy-*N*-methylbenzamide (**7**) was studied, since this compound was more readily available than the amides **5** and **6**. It was expected that coupling might occur at two positions, ortho and para to the hydroxy group, with the formation of narwedine-type enone **8** and dienone **9**. Schotten–Baumann reaction of 4-benzyloxy-*N*-methylamine (**10**) with 3-benzyloxy-4-methoxybenzoyl chloride afforded the corresponding amide **11**, whose debenzylation gave the diphenolic amide **7**.



5, $R_1 = R_2 = H$; R_3 = Me; R_4 = Br; X = O; Y = H_2
6, $R_1 = R_2 = H$; R_3 = Me; R_4 = Br; X = H_2; Y = O
7, $R_1 = R_2 = R_4 = H$; R_3 = Me; X = O; Y = H_2
11, $R_1 = R_2 = CH_2Ph$; R_3 = Me; R_4 = H; X = O; Y = H_2



10, $R_1 = CH_2Ph$; R_2 = H

Phenolic oxidation of **7** with potassium ferricyanide gave a 5% yield of **8**. The nmr spectrum showed the α- (τ 4.13) and β-olefinic protons (τ 3.63) in accordance with the expected coupling mode and signals of aromatic protons similar to those of **3** at 3.11 and 2.51 as a doublet. A second compound, **9**, was obtained in 10% yield, whose nmr spectrum showed the α- and β-olefinic protons as an AB quartet and two aromatic protons as singlets. Although this dienone, **9**, had previously been obtained on oxidation of the amide **5** as a colorless syrup,[4] we could here obtain the dienone **9** as pure crystals. Reduction of **8** with lithium aluminum hydride gave (±)-galanthamine (**1**) and (±)-epigalanthamine (**2**). Thus, an alternative synthesis of (±)-galanthamine has been accomplished from compound **7**, more simple and more easily available than the starting materials **5** and **6** used in the previous papers.[4-6] Phenolic oxidation of the amide **7** with vanadium oxytrichloride[8] gave **8** and **9** in 2 and 2.5% yields, respectively, but in the case of short reaction time only the ortho-coupled compound **9** was obtained.

Experimental Section[9]

3-Benzoyloxy-*N*-(4-benzyloxyphenethyl)-4-methoxy-*N*-methylbenzamide (11).—To a stirred suspension of 2 g of 4-benzyloxy-*N*-methylphenethylamine (**10**) in a mixture of 4.5 ml of 10% sodium hydroxide solution and 50 ml of chloroform was added dropwise a solution of 3-benzyloxy-4-methoxybenzoic acid chloride (prepared from 2 g of the acid by the usual way) in 50 ml of chloroform at room temperature. After the stirring had been continued for 0.5 hr, the organic layer was washed with water, dried over Na_2SO_4, and evaporated to give 3 g of the amide **11** as colorless needles (from *n*-hexane), mp 78–78.5°.

Anal. Calcd for $C_{31}H_{31}NO_4$: C, 77.31; H, 6.49; N, 2.91. Found: C, 77.77; H, 6.30; N, 3.24.

3-Hydroxy-*N*-(4-hydroxyphenethyl)-4-methoxy-*N*-methylbenzamide (7).—(a) A mixture of 6 g of the preceding amide **11**, 120 ml of 48% hydrobromic acid, and 200 ml of ethanol was warmed at 55–60° on a water bath for 1 hr. The solvent was evaporated *in vacuo* and the remaining residue was extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution and water and dried over Na_2SO_4. Evaporation of the solvent afforded 1.5 g of the amide **7** as colorless prisms (from *n*-hexane), mp 185–186°.

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36. Found: C, 67.32; H, 6.54.

(b) A solution of 6 g of the amide **11** in 100 ml of methanol was shaken in a current of hydrogen with 2.5 g of 10% palladium/charcoal until the uptake of hydrogen ceased. After the catalyst had been filtered off, the solvent was evaporated to give 3 g of the phenolic amide, mp 185–186° (from *n*-hexane), which was identical with the authentic specimen, prepared by procedure a, by comparison of spectroscopic data and mixture melting point.

Phenol Oxidation of 7.—(a) To a solution of 2.3 g of **7** in 500 ml of chloroform was added rapidly a mixture of 9.8 g of potassium ferricyanide and 100 ml of 5% sodium hydrogen carbonate solution with vigorous stirring at 55–60°; the stirring was continued for 1.5 hr. The chloroform layer was separated, washed with water, dried over Na_2SO_4, and evaporated to give 1 g of a brown syrup, which was chromatographed on 20 g of silica gel with chloroform as eluent. Evaporation of the first chloroform eluate gave 120 mg of the narwedine-type enone **8** as colorless prisms (from ethanol): mp 269–271°, ir ($CHCl_3$) 1683, 1639, and 1620 cm^{-1}; nmr τ ($CDCl_3$) 6.79 (3 H, s, NMe), 6.10 (3 H, s, OMe), 5.15 (1 H, m, H_x), 4.13 (1 H, d, J = 10.0 Hz, H_α), 3.63 (1 H, s, J = 10.0 and 2 Hz), 3.11, 2.51 (2 H, each d, J = 8.0 Hz, Ar H); mass spectrum (70 eV) *m/e* 299 (M^+).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.53; H, 5.77; N, 5.02.

(4) T. Kametani, K. Yamaki, H. Yagi, and K. Fukumoto, *J. Chem. Soc., C*, 2602 (1969).

(5) T. Kametani, K. Yamaki, C. Seino, S. Shibuya, K. Fukumoto, K. Kigasawa, M. Hiiragi, F. Satoh, and T. Hayasaka, *ibid.*, in press.

(6) T. Kametani, K. Yamaki, S. Shibuya, K. Fukumoto, K. Kigasawa, F. Satoh, M. Hiiragi, and T. Hayasaka, *ibid.*, in press.

(7) W. C. Wildman, *Alkaloid*, **6**, 376 (1960).

(8) M. A. Schwartz and R. A. Holton, *J. Amer. Chem. Soc.*, **92**, 1090 (1970), and references cited therein.

(9) Ir spectra were measured with a Type EPI-3 Hitachi recording spectrometer and nmr spectra with a Hitachi R-20 spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal reference unless otherwise noted. Mass spectra were taken with a Hitachi RMU-7 mass spectrometer.

Elution with 1% methanol–chloroform gave 300 mg of the dienone 9 as colorless needles (from ethanol): mp 265–267°; ir ($CHCl_3$) 3510, 1660, 1630 cm^{-1}; nmr τ ($CDCl_3$) 6.80 (3 H, s, NMe), 6.13 (3 H, s, OMe), 3.73 (1 H, d, J = 10 Hz, H_α), 2.92 (1 H, d, J = 10 Hz, H_β), 3.39, 2.55 (2 H, each s, Ar H); mass spectrum (70 eV) m/e 299 (M^+) and 256 ($M^+ - 43$).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.49; H, 5.59; N, 4.95.

(b) To a stirred solution of 1 g of 7 in 50 ml of chloroform was added dropwise 1.5 g of vanadium oxytrichloride at room temperature. After the mixture had been stirred for 4 hr, the excess of vanadium oxytrichloride was decomposed with water, and the separated chloroform layer was washed with water, dried over Na_2SO_4, and evaporated to give 0.5 g of a brownish syrup, which was chromatographed on 10 g of silica gel. Elution with chloroform gave 20 mg of the enone 8 as colorless prisms, mp 269–271°, whose spectroscopic data were identical with those of the authentic sample 8. Removal of the eluent with 1% methanol–chloroform (20 ml) afforded 25 mg of the dienone 9 as colorless needles, mp 265–267°, and, finally, successive elution with the same eluent gave 100 mg of the starting material 7 as colorless needles, mp 167–169°.

In this case when the above reaction was carried out for a short time (2 hr), the para-coupled compound 9 was not observed.

(±)-Galanthamine (1) and (±)-Epigalanthamine (2).—To a stirred suspension of 50 mg of lithium aluminum hydride in 20 ml of tetrahydrofuran was added dropwise a solution of 22 mg of 8 in 50 ml of tetrahydrofuran at room temperature. The mixture was refluxed on a water bath for 10 hr. The mixture was then decomposed with 20% sodium hydroxide solution. The inorganic substance was removed by filtration and the solvent was evaporated to give 18 mg of a colorless syrup which was chromatographed on 0.6 g of alumina. Elution with ethyl acetate–benzene (1:1) gave 13 mg of (±)-galanthamine (1) as colorless needles (from ether), mp 121–123°, whose spectroscopic data and chromatographic behavior were identical with those of the authentic (±)-galanthamine and natural (−)-galanthamine. Subsequent elution with ethanol–chloroform (1:9) gave a small amount of material whose chromatographic data were identical with those of authentic (±)-epigalanthamine, but the substance could not be isolated in the pure state.

Registry No.—1, 23173-12-8; 7, 28129-09-1; 8, 28129-07-9; 9, 27994-91-8; 11, 28129-10-4.

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Spectral Effects Attributable to Conjugation with Trivalent Phosphorus among Some 2-Phospholenes[1]

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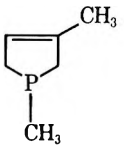
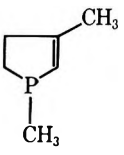
Synthetic work in this laboratory with phospholenes has made available pairs of isomers which differ in the position of the double bond. In compiling spectral data for these compounds, we have observed consistent differences which can be associated with conjugation of phosphorus with the double bond of the 2-phospholene system. The differences to be described have apparently not been reported upon previously; in part, this may be due to nonavailability of a series of vinylic–allylic models, although the differences appear particularly strong in our cyclic compounds. The existence of a conjugative effect for trivalent phosphorus and the relative importance of utilization of its d or p orbitals have remained points of uncertainty; the opinion has been expressed that there may be a weak involvement of the lone pair on phosphorus in delocalization,[2] but the view has also been taken that acceptance of electrons in the d orbitals of phosphorus may be more significant.[3]

The spectral differences we have encountered so far (infrared and ^{31}P and ^1H nmr) are particularly well displayed by the isomeric 1,3-dimethylphospholenes (Ia[4] and Ib[5]). The conjugative effect is clearly revealed by



Ia



Ib

characteristics of the C=C stretching band in the ir spectra. For the allylic isomer Ia, this band appears at 1658 cm^{-1}, while the vinylic isomer Ib has a band of considerably greater intensity at lower frequency (1613 cm^{-1}). The frequency and intensity differences are those expected for diminished double-bond character and polarization in the vinylic isomer through delocalization involving phosphorus. The low electronegativity of phosphorus suggests that the effect is not due to induction. Enamines exhibit similar intensification of the C=C absorption,[6] but apparently this has not been previously observed for vinylphosphine derivatives. In the Raman spectrum, the C=C absorption of di-*n*-butylvinylphosphine is at considerably lower frequency than that of 1-hexene, but the relative intensities are similar.[7] This observation was interpreted to indicate that little, if any, p_π–p_π conjugation prevails among vinylphosphines.[3]

That the conjugative effect is in the direction to endow phosphorus with some positive character is suggested by the nmr spectra of compounds Ia and Ib. The ^{31}P signal for the vinylic compound is at considerably lower field than that of the allylic isomer (Ia, +32.6; Ib, +15.2). Acyclic vinylphosphines do not exhibit appreciable chemical shift differences from their saturated counterparts; for example, trivinylphosphine has a value of +20.7 ppm,[8] while that of triethylphosphine is +20.4 ppm.[9] It is apparent that the phospholene system is unique; in view of the conjugative effect

(1) Supported by Public Health Service Research Grant CA-05507 from the National Cancer Institute.

(2) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam, 1967, p 3.

(3) E. N. Tsvetkov, D. I. Lobanov, M. M. Makhamatkhanov, and M. I. Kabachnik, *Tetrahedron*, **25**, 5623 (1969).

(4) L. D. Quin, J. P. Gratz, and T. P. Barket, *J. Org. Chem.*, **33**, 1034 (1968).

(5) D. K. Myers and L. D. Quin, *ibid.*, **36**, 1285 (1971).

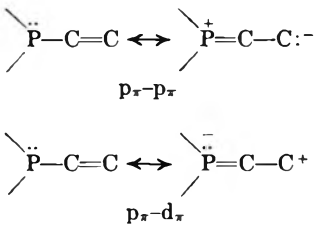
(6) N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.*, **76**, 2781 (1954).

(7) E. M. Popov, E. N. Tsvetkov, C. Chung-yu, and T. Y. Medved, *Zh. Obshch. Khim.*, **32**, 3255 (1962).

(8) L. D. Quin, J. G. Bryson, and C. G. Moreland, *J. Amer. Chem. Soc.*, **91**, 3308 (1969).

(9) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, *Top. Phosphorus Chem.*, **5**, 249 (1967).

clearly seen in its ir spectrum, it is reasonable to attribute the strong deshielding in the vinylic isomer to reduced electron density on phosphorus as a result of p_π–p_π conjugation. Had the conjugative effect been of the type p_π–d_π, electron density on phosphorus would have been increased.



It is possible that bond angle differences prevail about phosphorus in the phospholene isomers and may contribute to the shift differences. The present state of knowledge of ^{31}P chemical shifts of phosphines unfortunately does not permit an evaluation of the importance of this factor at this time.

The ^{1}H nmr spectra also show differences possibly attributable to conjugation. The P–CH_3 signal of Ib (δ 1.23 ppm) is downfield relative to that of Ia (δ 1.14 ppm), an effect again explicable on the basis of increased positive character at phosphorus. Differences in the chemical shift of the vinylic proton may also be associated with conjugation; the signal for Ib is 0.2 ppm downfield from that of Ia (Ia, δ 5.70; Ib δ 5.90 ppm). However, the vinyl proton is α to phosphorus in Ib, and β in Ia, and some of the difference in the chemical shift may be associated with the proximity of the proton to phosphorus. As has been discussed elsewhere, there is an enormous difference in P–H coupling constants for the vinylic proton in 2- and 3-phospholenes (*e.g.*, 7 Hz for Ia,[4] 42 Hz for Ib[5]). Any relevance of this difference to the conjugative effect, and modification of bonding at phosphorus, cannot be established at this time.

The concept of p_π–p_π conjugation therefore seems capable of explaining the spectral differences noted for these phospholene derivatives. For *acyclic* trivalent phosphorus systems, however, it has recently been argued that weak d_π–p_π interaction is operative and that p_π–p_π conjugation is negligible.[3] The geometry of the cyclic compounds may be responsible for the more well-defined p_π–p_π conjugation observed; the opportunity for overlap is possibly greater when the orbitals to participate are not associated with the freely rotating atoms of an acyclic system.

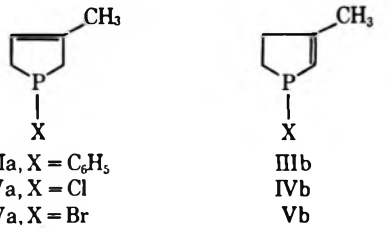
Some of the spectral differences discussed above have also been observed for other isomeric phospholenes (Table I). Thus, the ^{31}P signal for 1-benzyl-2-phospholene (IIb) is at lower field by 23.5 ppm than that of the 3 isomer, and in their ^{1}H nmr spectra, the benzylic CH_2 of IIb is downfield (δ 2.85 ppm) from that of IIa (δ 2.72 ppm). Conjugation is also indicated for the vinylic isomer of the 1-phenyl-3-methylphospholenes (III) by both the infrared effect and the downfield shift in the ^{31}P signal of 22.6 ppm. The cyclic phosphinous halides (IV and V) likewise exhibit both effects, although the magnitude of the ^{31}P shift is much less than that seen for the tertiary phosphines. This may be due to π bonding of halogen with phosphorus, a feedback mechanism acting in addition to p_π–p_π conjugation and partly compensating for the positivity developing on phosphorus through the latter mechanism. Finally, in the rather special case of the 1-alkylphospholes, some properties have also been interpreted to be consistent with electron delocalization from phosphorus.[8,10]

TABLE I

SPECTRAL DATA FOR PHOSPHOLENES

Compound	$\nu_{C=C}$, cm^{-1} [a]	τ (^{31}P), ppm[b]
Ia	1658	+32.6
Ib	1613	+15.2
IIa[c,d]	...[e]	+23.4
IIb[c,d]	...[e]	0.0
IIIa	1660	+18.6
IIIb	1618	−4.0
IVa	1655	−127.5
IVb	1601	−132.5
Va[c]	1655	−120.5
Vb[c]	1601	−130.6

[a] Obtained with a Perkin-Elmer Model 237 spectrophotometer. [b] Obtained with Varian V-4300B spectrometer at 19.3 MHz, 85% H_3PO_4 as standard. [c] Values obtained on a mixture of isomers. [d] ^{1}H nmr spectrum (neat) contained benzyl CH_2 signals (slightly broadened singlets) at 2.72 (IIa) and 2.85 ppm (IIb). [e] Not well separated from phenyl bands.



IIIa, X = C_6H_5
IVa, X = Cl
Va, X = Br

IIIb
IVb
Vb

Experimental Section

The synthesis of the following compounds has been reported elsewhere: Ia,[4] Ib,[5] IIa,[4] IIb,[4] IVa,[5] IVb.[5] A mixture of compounds Va and Vb (3:7) was also available from earlier work[5] and was used directly in this study.

1-Benzyl-3- (and -2-) phospholene.—A solution of benzylphosphonous dichloride (26.0 g, 0.135 mol) and butadiene (7.67 g, 0.142 mol) in 40 ml of cyclohexane (containing 0.2 g of copper stearate as polymerization inhibitor), after standing several months, had precipitated 15.1 g of cycloadduct. This was hydrolyzed by addition to ice, and the resulting phospholene oxide was extracted with chloroform and distilled: 5.2 g (20%), bp 151–159° (0.3 mm). Gas chromatography showed a ratio of 1-benzyl-3-phospholene oxide to 1-benzyl-2-phospholene oxide of 1:2. The oxide mixture was placed in 100 ml of dry benzene; the solution was cooled to 0° and reduced by treatment with 14 g of trichlorosilane in 20 ml of benzene, added over a 20-min period. After the solution was stirred for 30 min at room temperature and refluxed for 2 hr, it was cooled and treated with 100 ml of 30% NaOH. Layers were separated, and the aqueous layer was extracted with benzene. Distillation gave 2.7 g, bp 68–72° (0.25 mm), of 1-benzyl-3-phospholene (IIa) and 1-benzyl-2-phospholene (IIb). Spectral properties for the mixture, which was not separated, are recorded in Table I. The major product (about 75%) was IIb, which has been prepared by a different route.[10]

Registry No.—Ia, 15450-84-7; Ib, 28273-45-2; IIa, 28278-52-6; IIb, 28278-53-7; IIIa, 28278-54-8; IIIb, 28278-55-9; IVa, 28278-56-0; IVb, 28273-36-1; Va, 28273-34-9; Vb, 28278-59-3.

Acknowledgment.—Compounds IIa and IIb were prepared by Mr. John F. Engel in connection with another study.[10]

(10) P. Coggon, J. F. Engel, A. T. McPhail, and L. D. Quin, *J. Amer. Chem. Soc.*, **92**, 5779 (1970).

Stereochemistry of an Intermediate in a Synthetic Route to Gibberellic Acid. A Structure with a Short Carbon–Oxygen Intermolecular Contact[1]

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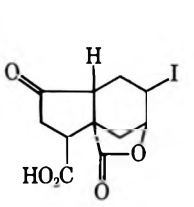
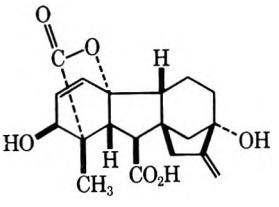
Received September 15, 1970

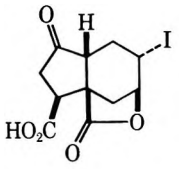
Dolby and associates[3] have prepared **1** as a possible intermediate in the synthesis of gibberellic acid (**2**).[4] While most of the stereochemical details of **1** have been established,[3] the question as to whether the hydrindanone system is *cis*-**3** or *trans*-**4** was unanswered. A crystal structure analysis of **1** was undertaken to resolve this stereochemical uncertainty in a short period of time.



1



2



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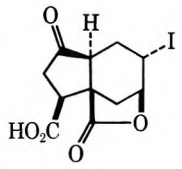

4

Experimental Section

A crystalline sample of **1** was kindly supplied by Professor Lloyd Dolby of the University of Oregon. The crystals are colorless platelets with mp 166° dec. Crystal data for $C_{11}H_{11}O_5I$ are M = 350.10, monoclinic; a = 6.07 (2), b = 21.94 (5), c = 8.89 (2) Å, β = 102° 35′ (20′), $V = 1155 \times 10^{-24}$ cm^3, ρ_{measd} = 1.98 g cm^{-3}, Z = 4, ρ_{calcd} = 2.01 g cm^{-3}; systematic absences: $h0l$ when $h = 2n + 1$, $0k0$ when $k = 2n + 1$; space group $P2_1/a$. The cell dimensions were determined from precession photographs using Mo Kα radiation (λ 0.7107 Å). The density was determined by flotation in a mixture of bromoform and *n*-hexane. A total of 879 nonzero structure amplitudes was obtained from visual measurements on equiinclination Weissenberg photographs (Cu Kα radiation) taken on a crystal mounted about the a axis.

The structure was solved by the heavy atom method and has been refined to an R factor[5] of 0.14 on all observed data[6] by least-squares methods. Anisotropic temperature factors were introduced for the iodine atom; positional and isotropic thermal parameters were refined for all other nonhydrogen atoms. Hydrogen atoms were not included in any calculations. The scattering factor curves used were those for neutral iodine, carbon, and oxygen from the compilation in "International Tables for X-Ray Crystallography,"[7] the curve for iodine being corrected for the real component of anomalous dispersion.[8] The final atomic coordinates and thermal parameters are listed in Table I.

TABLE I
FINAL ATOMIC COORDINATES AND FINAL TEMPERATURE PARAMETERS[a,b]

	x	y	z	B_θ (Å^2)
C(1)	0.748 (7)	0.175 (1)	0.457 (3)	0.8 (6)
C(2)	0.627 (7)	0.189 (1)	0.596 (3)	0.6 (6)
C(3)	0.695 (7)	0.139 (1)	0.711 (3)	1.2 (6)
C(4)	0.693 (7)	0.077 (1)	0.646 (3)	0.9 (6)
C(5)	0.835 (8)	0.071 (2)	0.519 (4)	1.6 (7)
C(6)	0.703 (7)	0.112 (1)	0.402 (3)	0.1 (5)
C(7)	0.753 (7)	0.117 (1)	0.236 (3)	1.2 (6)
C(8)	0.617 (7)	0.178 (2)	0.168 (3)	1.2 (6)
C(9)	0.671 (8)	0.214 (2)	0.320 (4)	2.0 (8)
C(10)	0.460 (9)	0.093 (2)	0.396 (4)	2.3 (8)
C(11)	0.636 (8)	0.066 (2)	0.127 (4)	1.7 (7)
O(1)	0.678 (6)	0.011 (1)	0.191 (3)	2.9 (6)
O(2)	0.534 (4)	0.073 (1)	−0.004 (2)	0.6 (4)
O(3)	0.625 (6)	0.272 (1)	0.317 (3)	2.3 (5)
O(4)	0.288 (5)	0.091 (1)	0.301 (3)	2.2 (5)
O(5)	0.466 (5)	0.072 (1)	0.549 (3)	1.7 (5)
I	1.0326 (7)	0.1506 (1)	0.8584 (3)	c

[a] Coordinates are given as fractions of the unit cell edge with estimated standard deviations in parentheses. The origin is in "International Tables for X-Ray Crystallography." [b] Isotropic thermal parameters (B_θ) are expressed as $\exp[-(B_\theta \sin^2\theta/\lambda^2)]$. Anisotropic thermal parameters are expressed as $\exp[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)]$. [c] b_{11}, 0.033 (2); b_{22}, 0.00260 (8); b_{33}, 0.0053 (3); b_{12}, −0.0014 (6); b_{13}, 0.0182 (10); b_{23}, −0.0010 (3).

Results and Discussion

A view of the structure is shown in Figure 1, from which it is apparent that the stereochemistry is trans as in **4**. Bond lengths and angles[6] agree within the accuracy of the analysis (C–C length ± 0.04 Å) with accepted values.[9]

The six-membered ring [C(1)–C(6)] is in the chair conformation with the iodine atom in an axial orientation. The five-membered lactone ring [C(4), C(5), C(6), C(10) and O(5)] is in an "envelope" conformation with C(5) lying 0.71 Å out of the best plane through the five atoms of the lactone group. The cyclopentanone ring [C(1), C(6), C(7), C(8), and C(9)] is in the "half-chair" conformation with C(6) and C(7) lying −0.37 and 0.39 Å (*i.e.*, on opposite sides) from the best plane through C(1), C(9), C(8), and O(3).

(1) This structure determination was carried out as part of formal lecture and laboratory courses in X-ray crystallography taught at the University of Illinois in the fall of 1968. The preliminary crystal examination, collection of the X-ray data, and solution of the structure were carried out during normal class hours. The principal aim of the investiation was to demonstrate the relative ease and rapidity of an X-ray structural solution, based on film methods, to a chemical problem. While no special effort was made to obtain highly accurate intensity measurements, or the maximum amount of data, or to refine fully the structure, the chemical problem was unquestionably resolved. We acknowledge the assistance, interest, and enthusiasm of Ramsey Gitany, Gary Heugen, Rich Klobuchar, Nicholas J. Loy, and Celeste Stepien.

(2) Alfred P. Sloan Research Fellow.

(3) L. J. Dolby, S. Esfandiari, C. A. Elliger, and K. S. Marshall, *J. Org. Chem.*, **36**, 1277 (1971).

(4) The stereochemistry of gibberellic acid was established as a result of two X-ray studies: F. McCapra, A. I. Scott, G. A. Sim, and D. W. Young, *Proc. Chem. Soc.*, 185 (1962); *J. Chem. Soc. C*, 1577 (1966); and J. A. Hartsuck and W. N. Lipscomb, *J. Amer. Chem. Soc.*, **85**, 3414 (1963).

(5) $R = \Sigma||F_{obsd}| - |F_{calcd}||/\Sigma|F_{obsd}|$.

(6) The final list of h, k, l, $|F_{obsd}|$, and F_{calcd} and the detailed values of bond lengths, angles, and intermolecular contacts will appear following these pages in the microfilm edition of this volume of the Journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit $3.00 for photocopy or $2.00 for microfiche.

(7) "International Tables for X-Ray Crystallography," Vol. III, C. H. MacGillavry and G. D. Rieck, Ed., Kynoch Press, Brimingham, England, 1962, pp 201–209.

(8) Reference 7, pp 213–216.

(9) O. Kennard in ref 7, pp 275–276.

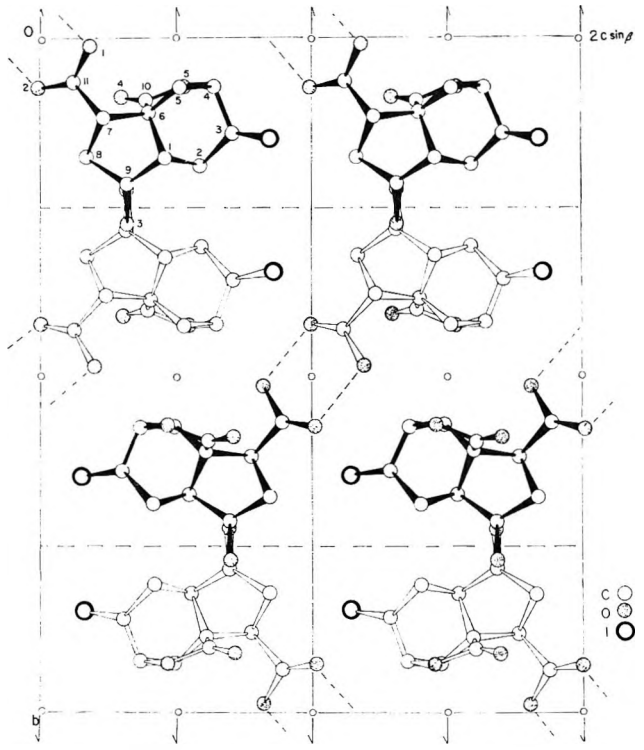

Figure 1.—View of the molecular packing down the *a* axis.

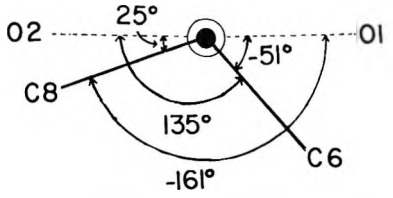

Figure 2.—The torsion angles around the C(7)–C(11) bond. The angle ABCD is considered positive, if, when looking from B to C, atom A has to be rotated clockwise to eclipse atom D.

The torsion angles involving the carboxyl group are shown in Figure 2. Both the C–O bond lengths [C(11)–O(2), 1.20 (4); C(11)–O(1), 1.34 (4) Å] and the torsion angles around the C–C (carboxyl) bond, according to Dunitz and Strickler,[10] suggest that C(11)–O(2) is the double bond in the carboxyl group. The O(1)···O(2) distance involved in an intermolecular hydrogen bond is 2.63 (3) Å. Of particular note is the C(9)···O(3) ($^1/_2 + x$, $^1/_2 - y$, z) contact of 2.79 (5) Å (Figure 3). This rather short distance between a carbon atom of a carbonyl group and the oxygen atoms of a symmetry-related carbonyl group is similar in length to those observed in chloranil[11] and in alloxan,[12,13] although the geometric disposition of groups resembles rather that found in perdeuterated violuric acid monohydrate.[14] There may also be a C–H···O hydrogen bond (length 3.23 Å) between C(7) and O(4) (at $1 + x$, y, z) al-

(10) J. D. Dunitz and P. Strickler, "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Ed., W. H. Freeman, San Francisco, Calif., 1968, pp 595–602.

(11) S. S. C. Chu, G. A. Jeffrey, and T. Sakurai, *Acta Crystallogr.*, **15**, 661 (1962).

(12) W. Bolton, *ibid.*, **17**, 147 (1964).

(13) C. K. Prout and S. C. Wallwork, *ibid.*, **21**, 449 (1966).

(14) B. M. Craven and Y. Mascarenhas, *ibid.*, **17**, 407 (1964).

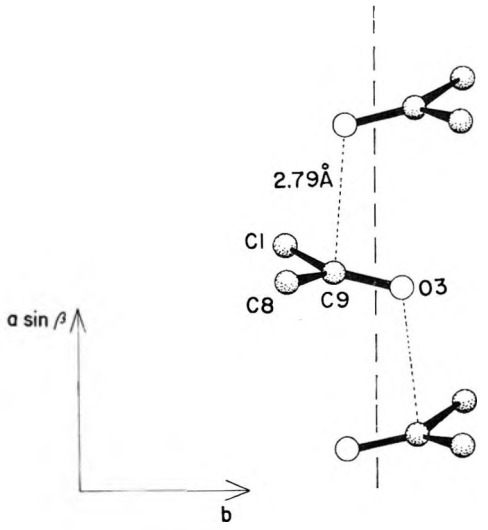

Figure 3.—The arrangement of carbonyl groups looking along the *z* direction.

though the existence of such interactions is still a matter of lively debate.[15,16]

Registry No.—4, 28128-99-6.

(15) J. Donohue in ref 10, pp 443–465.

(16) W. C. Hamilton and J. A. Ibers, "Hydrogen Bonding in Solids," W. A. Benjamin, New York, N. Y., 1968, pp 182–183.

The Effect of Alkyl Substitution on the Boron-11 Chemical Shifts in Aminoboranes and Borates[1a]

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There is considerable evidence[2] that ^{11}B chemical shifts are controlled by the degree of electron occupancy of the vacant p_z orbital on boron. Thus, compounds containing trivalent boron absorb at much lower field than do quadrivalent boron complexes, and the shift to low field is greatest for compounds in which trivalent boron is attached to groups lacking p or π electrons. Trimethylborane, for example, has the lowest known chemical shift (−86.4 ppm[3]) relative to boron trifluoride etherate (EBT),[4] while compounds with groups capable of donating electrons to boron appear at much higher field (*e.g.*, −18.1 ppm for trimethyl borate).[3]

(1) (a) Reported in part at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970; (b) National Science Foundation Undergraduate Research Participant, 1969.

(2) (a) G. R. Eaton, *J. Chem. Educ.*, **46**, 547 (1969); (b) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. II, Pergamon Press, New York, N. Y., 1968, p 970; (c) P. C. Lautherbur in "Determination of Organic Structure by Physical Methods," Vol. II, F. C. Nachod and W. D. Phillips, Ed., Academic Press, New York, N. Y., 1962, p 476.

(3) W. D. Phillips, H. C. Miller, and E. L. Muetterties, *J. Amer. Chem. Soc.*, **81**, 4496 (1959).

(4) All chemical shifts reported in this paper are relative to EBT.

If this was the only factor involved, one would expect the chemical shift of boron to depend on the π-donating ability of the attached group. In fact, one would expect a dimethylamino group to be more effective than a methoxy group. However, for aliphatic boron compounds the reverse appears to be true; thus, tris(dimethylamino)borane absorbs at much lower field (−27.2 ppm[5]) than does trimethyl borate. Until this and other anomalies are resolved, the quantitative prediction of ^{11}B chemical shifts will be impossible.

The more effective shielding of boron by an alkoxy group than by an alkylamino group may be explained in at least two ways. The presence of additional pairs of unshared electrons on atoms adjacent to boron, over and above those needed for π bonding, may increase the shielding on boron.[6] Alternatively, steric repulsion between the alkyl groups may decrease the shielding of boron.

In order to obtain information about the effect on nonbonding interactions on the ^{11}B chemical shift, we have prepared a series of alkylaminoboranes (I–III) and alkyl borates (IV) and measured their boron chemical shifts. These results are summarized in Table I.

$(RNH)_3B$
Ia, R = methyl
b, R = ethyl
c, R = *n*-propyl
d, R = isopropyl
e, R = *sec*-butyl
f, R = *tert*-butyl

$(R_2N)_3B$
IIa, R = methyl
b, R = ethyl
c, R = *n*-propyl
d, R = isopropyl

$(R_2N)_2BCl$
IIIa, R = methyl
b, R = ethyl
c, R = isopropyl

$(RO)_3B$
IVa, R = *n*-butyl
b, R = isobutyl
c, R = *sec*-butyl
d, R = *tert*-butyl
e, R = *n*-pentyl
f, R = isopentyl
g, R = neopentyl

The chemical shifts of the compounds listed in Table I were independent of solvent and the line widths narrowed on dilution. This is apparently due to lowering of the viscosity of the sample.[7]

The most favorable conformation for an adjacent group containing p electrons to shield boron will be when the unshared pair of electrons and the p_z orbital on boron are coplanar. If nonbonded interactions reduce this coplanarity, shielding of boron will be decreased. Oxygen may therefore be able to shield boron better than nitrogen because the borates have fewer nonbonded interactions than the aminoboranes. An unshared pair of electrons has fewer nonbonded repulsive interactions than an alkyl group.[8]

This hypothesis is supported by the results in Table I. The alkyl borates (series IV) are shielded compared to the monoalkylaminoboranes (series I) which are shielded compared to the dialkylaminoboranes (series II). The molecular structure of trisdimethylaminoborane (IIa)[9] further supports this interpretation. The structure indicates that the dimethylamino groups are twisted out of the BN_3 plane by 32.8°. Despite this twist the B–N bond length suggests considerable boron–nitrogen π bonding. Dewar and Rona have suggested that nitrogen need not be planar for effective π bonding with boron.[10]

TABLE I
^{11}B CHEMICAL SHIFTS FOR COMPOUNDS I–IV

Compd	Ref	Solvent	Chemical shift[a]	Line width,[b] Hz
Ia	*c*		−24.6[d]	
Ib	*c*	Neat	−23.6	91
		Benzene	−23.3	68
Ic	*e*	Neat	−23.7	174
		Benzene	−23.3	91
Id	*c*	Neat	−22.5	134
		Benzene	−22.4	96
Ie	*c*	Neat	−22.9	215
		Benzene	−22.6	116
If	*c*	Neat	−22.8	185
		Benzene	−22.7	91
IIa			−27.2[f]	
IIb			−28.7[d]	
IIc	*g*	Benzene	−29.2	307
IId	*h*	Benzene	−28.4	495
IIIa	*i*		−27.9[d]	
IIIb	*i*		−28.4[d]	
IIIc	*h*	Neat	−30.6	262
IVa	*j*	Neat	−18.0	141
IVb	*j*	Neat	−17.9	155
IVc	*j*	Neat	−17.7	118
IVd	*j*	Neat	−15.6 (−15.5)[d]	92
		Acetonitrile	−15.8	110
IVe	*k*	Neat	−17.7	237
IVf	*l*	Neat	−17.7	253
		Carbon disulfide	−18.0	108
IVg	*j*	Carbon disulfide	−17.9	123

[a] In parts per million relative to boron trifluoride etherate. Estimated error ±0.15 ppm for line widths >100 Hz, ±0.3 ppm for line widths >200 Hz, ±1 ppm for wider lines. [b] At half-height; estimated error ±5%. [c] D. W. Aubrey and M. F. Lappert, *J. Chem. Soc.*, 2927 (1959). [d] H. North and H. Vahrenkamp, *Ber.*, 99, 1049 (1966). [e] M. F. Lappert and H. Pyszora, *J. Chem. Soc.*, 1744 (1963). [f] Reference 5. [g] D. W. Aubrey, W. Gerrard, and E. F. Mooney, *J. Chem. Soc.*, 1786 (1962). [h] M. F. Lappert and M. K. Majumdar, *J. Organometal. Chem.*, 6, 316 (1966). [i] W. Gerrard, M. F. Lappert, and C. A. Pearce, *J. Chem. Soc.*, 381 (1957). [j] W. Gerrard and M. F. Lappert, *ibid.*, 2545 (1951). [k] W. Gerrard and M. F. Lappert, *Chem. Ind. (London)*, 53 (1952). [l] C. R. Kinney, H. T. Thompson, and L. C. Cheney, *J. Amer. Chem. Soc.*, 57, 2396 (1935).

For the monoalkylaminoboranes (series I), as the size of the alkyl group increases from methyl (−24.6 ppm) to ethyl (−23.6 ppm) to *n*-propyl (−23.3 ppm) to isopropyl (−22.4), the boron chemical shift increases. Clearly this is opposite to what might be predicted if steric interactions were important in determining the chemical shift of boron. An increase in the electron density on nitrogen as a result of the inductive effect of the alkyl group will result in greater shielding of boron and therefore explains this apparent anomaly.[11] This explanation is supported by the correlation (correlation coefficient 0.976) obtained by plotting the ^{11}B chemical shifts of Ia–d *vs.* Taft σ^*[12] values (see Figure 1).

(5) J. K. Ruff, *J. Org. Chem.*, **27**, 1020 (1962).
(6) F. A. Davis, M. J. S. Dewar, and R. Jones, *J. Amer. Chem. Soc.*, **90**, 706 (1968).
(7) J. P. Onak, H. Landesman, R. E. Williams, and I. Shapiro, *J. Phys. Chem.*, **63**, 1533 (1959).
(8) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).
(9) A. H. Clark and G. A. Anderson, *Chem. Commun.*, 1082 (1969).
(10) M. J. S. Dewar and P. Rona, *J. Amer. Chem. Soc.*, **91**, 2259 (1969).
(11) It should be noted that this trend is opposite to that observed for the pK_a's of monoalkylamines and has been attributed to steric hindrance to solvation: see H. K. Hall, Jr., *ibid.*, **79**, 5441 (1957).
(12) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956.

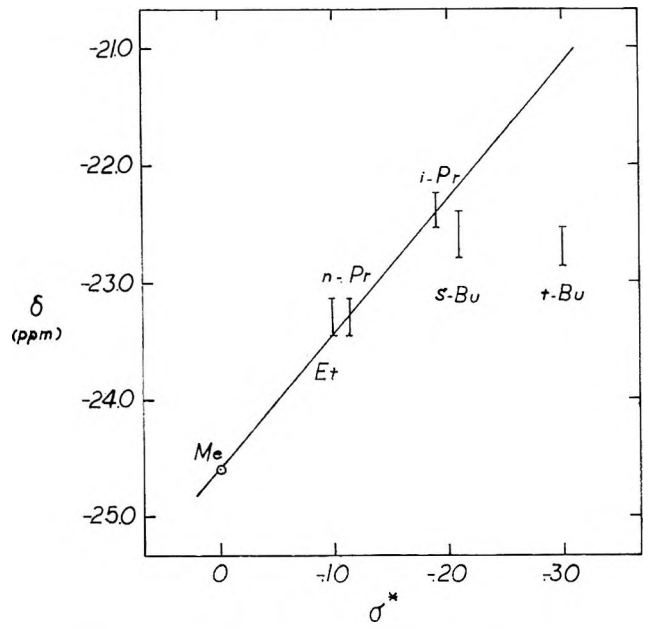

Figure 1.—Plot of the ^{11}B chemical shifts of series I *vs.* σ^*.

Methyl (Ia), ethyl (Ib), *n*-propyl (Ic), and isopropyl (Id) correlate reasonably well, but *sec*-butyl (Ie) and *tert*-butyl (If) do not. Apparently nonbonded interactions between the alkyl groups are important in Ie–f resulting in reduced shielding of boron.

The trisdialkylaminoboranes (series II) have the same chemical shift and are deshielded by 5–6 ppm as compared with series I. This low field shift for series II may be attributed to increased nonbonded interactions which reduce the coplanarity of the nitrogen and boron orbitals. The substantial twist about the B–N bond in IIa[9] is apparently not increased by increasing the size of the alkyl group in this series.

The clearest example of nonbonded interactions affecting the boron chemical shift is observed for series III. Bisdiisopropylaminoboron chloride (IIIc) is approximately 2 ppm deshielded as compared with IIIa and IIIb. Models (Drieding) suggest that there are considerably fewer nonbonded interactions between the alkyl groups in IIIa than in IIIc.

With the exception of *tert*-butyl borate (IVd), the alkyl borates in series IV have identical boron chemical shifts. The effect of nonbonding interactions between the alkyl groups would be expected to have little effect on the chemical shift not only because they are fewer, but because oxygen has two lone pairs of electrons with which to shield boron.

The large shielding of *tert*-butyl borate (IVd), −15.7 ppm, as compared with the rest of the series, −18.0 ppm, is difficult to explain in terms of the inductive effect of the *tert*-butyl group, since *sec*-butyl borate (IVc) shows no increase in shielding. The shielding of IVd as compared with the rest of the series may be explained either in terms of repulsion between the lone pairs of electrons on oxygen or to a diamagnetic shielding effect of the alkyl groups.

It is well known that repulsions between lone pairs of electrons can be important in determining the conformation of molecules.[13] As already pointed out, the most favorable conformation for shielding of boron by an adjacent atom containing lone pairs of electrons is with the lone pair and the orbital on boron being coplanar. In this conformation the lone pairs of electrons will be eclipsed. By twisting about the B–O bond this unfavorable interaction may be relieved but will result in lower chemical shifts for the borates. However, in compound IVd repulsions between the alkyl groups may be more important than repulsion between the lone pairs of electrons, resulting in a more effective B–O π bond and hence great shielding.[14] The greater shielding of IVd may also be due to diamagnetic shielding by the alkyl groups. Models suggest that there is a close proximity between the alkyl groups in IVd and the p_z orbital on boron.

In conclusion, these results indicate that inductive effects and conformation of groups attached to boron have a measurable effect on the ^{11}B chemical shift.

(13) (a) E. L. Eliel, *Accounts Chem. Res.*, **3**, 1 (1970); (b) R. O. Hutchins, L. D. Kopp, and E. L Eliel, *J. Amer. Chem. Soc.*, **90**, 7174 (1968).

Experimental Section

The borates and aminoboranes were prepared according to procedures given in the literature. Purity was checked by glc. ^{11}B nmr chemical shifts were measured with a Varian HR-100 at 32.1 MHz reference against a capillary containing boron trifluoride etherate.

Registry No.—Ia, 7397-44-6; Ib, 4254-92-6; Ic, 28049-70-9; Id, 22238-43-3; Ie, 28049-72-1; If, 18379-73-2; IIa, 4375-83-1; IIb, 867-97-0; IIc, 20708-66-1; IId, 13906-02-5; IIIa, 6562-41-0; IIIb, 868-25-7; IIIc, 28049-80-1; IVa, 688-74-4; IVb, 13195-76-1; IVc, 22238-17-1; IVd, 7397-43-5; IVe, 621-78-3; IVf, 4396-02-5; IVg, 5456-06-4.

Acknowledgment.—We are indebted to Dr. Ben A. Shoulders, University of Texas, for running the boron spectra and to Dr. R. O. Hutchins for helpful discussions.

(14) Nonbonded interactions between the lone pair electrons in aminoboranes I–III undoubtedly occur, but their effect on the boron chemical shift is difficult to determine. The major factor appears to be interaction between the alkyl groups.

Crystal State Photodimerization of Methyl α-(4-Nitrophenyl)acrylate and 4-Nitrostyrene

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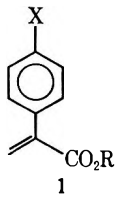
Several reports, especially the elegant studies of Schmidt and coworkers, have shown that cyclobutanes obtained by crystal state photodimerization can be expected to arise by a lattice-controlled stereospecific process.[2,3] Our interest in this topic prompted us to examine the photochemical behavior of some crystalline α-(4-substituted phenyl)acrylic acids and esters.

(1) (a) Abstracted in part from the M.S. Thesis of E. Hertz, Villanova University, May 1968; (b) National Science Foundation Undergraduate Participant, academic year 1966–1967 and summer 1967 (Grant No. GY-41 and GY-2669).

(2) M. Lahav and G. M. J. Schmidt, *J. Chem. Soc., B*, 239 (1967), and preceding papers in that series.

(3) D. J. Trecker in "Organic Photochemistry," Vol. 2, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1969, p 63.

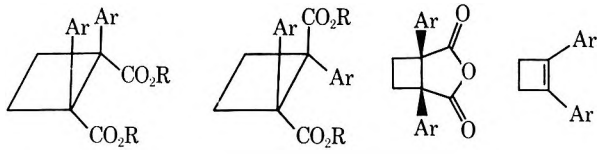
α-Phenylacrylic acid, α-(4-bromophenyl)acrylic acid, and α-(4-nitrophenyl)acrylic acid (**1a–c**) were essentially unaffected by irradiation at wavelengths >260



1

	X	R
a	H	H
b	Br	H
c	NO_2	H
d	NO_2	CH_3
e	NO_2	4-nitrobenzyl
f	Br	4-nitrobenzyl

nm; however, under similar conditions, methyl α-(4-nitrophenyl)acrylate (**1d**) provided a dimer in high yield. The nmr spectrum of this product exhibited a complex symmetrical four proton AA'BB' pattern centered at 2.90 ppm, indicative of cyclobutane structures **2a** or **3a**.[4,5]



2 3 4 5

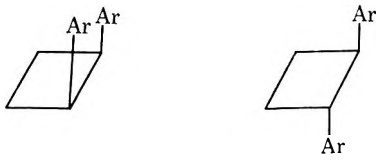
Ar = 4-nitrophenyl
a, R = CH_3; b, R = H; c, R = 4-nitrobenzyl

As expected from the sterically hindered environment of the ester groups, the dimer was quite resistant to acid-catalyzed hydrolysis. It was inert to hot concentrated hydrochloric acid and 4.5 *M* sulfuric acid; however, it was converted to the corresponding diacid upon heating in 97.5% sulfuric acid for an extended time at 70°.[6] Attempts to recrystallize the diacid resulted in a product having infrared absorptions at 5.43 and 5.63 μ, indicative of the formation of a cyclic anhydride.[7,8] The steric requirement for anhydride formation limits the diacid to the cis 1,2 structure **2b**. Conclusive evidence of structure **2b** for the diacid and consequently structure **2a** for the photodimer was obtained by oxidative decarboxylation of the diacid to 1,2-di(4-nitrophenyl)cyclobutene (**5**) by means of lead tetraacetate in benzene–pyridine solution.[9]

The 4-nitrobenzyl ester of α-(4-nitrophenyl)acrylic acid (**1e**) yielded a photodimer having the same configuration as the dimer obtained from the methyl ester **1d**. This correlation was achieved by converting the dimer of **1e** to the anhydride **4**. Attempted photodimerization of the 4-nitrobenzyl ester of α-(4-bromophenyl)acrylic acid (**1f**) resulted in slow polymerization.[10]

The mass spectrum of **2a** shows ring fragmentation to **1d** as the principal feature (in addition to the usual fragmentations expected for the ester and 4-nitrophenyl groups). In contrast, the 4-nitrobenzyl ester **2c** appears to undergo thermal fragmentation, the spectrum observed being essentially that expected for the monomer **1e**.

Irradiation of crystalline 4-nitrostyrene, obtained by rapid freezing of droplets of the liquid, resulted in a 15% yield of dimer. The mass spectrum of this compound exhibited an M − 28 peak (loss of C_2H_4),[11] consistent with either structure **6** or **7**.



6 7

Ar = 4-nitrophenyl

Attempted sublimation of the photodimer of 4-nitrostyrene at 200° *in vacuo* resulted in its conversion to an isomeric cyclobutane plus 4-nitrostyrene in low yield. This result indicates structure **6** for the photoisomer and structure **7** for the thermodynamically stable isomer derived from it. The photodimer **6** was also isomerized to **7** by heating in piperidine solution at 85°. Attempted isomerization of **6** by heating with potassium *tert*-butoxide in dimethoxyethane or with potassium hydroxide in ethanol–water led to tarry materials.[12]

Gross and Wilkins reported significant differences in the mass spectral ring fragmentations of *cis*- and *trans*-1,2-diphenylcyclobutane.[11] They observed that ring cleavage to styrene is more prevalent for the cis isomer; alternate cleavage (loss of C_2H_4) is also preferred for the cis compound. While the mass spectra of **6** and **7** show similar fragments (*m/e* 149, 270), these species do not exhibit the corresponding differences in intensity. Further, the cis isomer exhibits peaks at *m/e* 119, 103, 91, and 77 which are much more intense than those observed for the trans isomer. These peaks apparently arise from consecutive loss of NO and CO and of NO_2 and C_2H_2 from 4-nitrostyrene,[13] formed by thermal fragmentation of dimer in the inlet system [metastable peaks were observed at *m/e* 70 (149 → 103) and 58 (103 → 77)]. In agreement with the relative intensities observed for the 4-nitrostyrene fragments, the cis isomer **6** is expected to be more prone to thermal cleavage than the trans isomer **7**.

(4) K. Griesbaum, W. Naegele, and G. G. Wanless, *J. Amer. Chem. Soc.*, **87**, 3151 (1965).
(5) E. Lustig and R. Moriarty, *ibid.*, **87**, 3252 (1965).
(6) Attempted hydrolysis with potassium hydroxide in methanol gave intractable material.
(7) G. W. Griffin, A. F. Vellture, and K. Furuka, *J. Amer. Chem. Soc.*, **83**, 2725 (1961).
(8) L. H. Klem, K. W. Gopinath, T. J. Dooley, and C. E. Klopfenstein, *J. Org. Chem.*, **31**, 3003 (1966).
(9) Procedure due to C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958).
(10) The methyl esters of **1a** and **1b** are liquids which could not be crystallized, even at −80°.
(11) M. L. Gross and C. L. Wilkins [*Tetrahedron Lett.*, **44**, 3875 (1969)] have observed this type of fragmentation for *cis*- and *trans*-1,2-diphenylcyclobutane.
(12) R. M. Dodson and A. G. Zielske, *J. Org. Chem.*, **32**, 28 (1967), have reported the thermal as well as base-catalyzed (potassium *tert*-butoxide–DMSO) isomerization of *cis*-1,2-diphenylcyclobutane to the trans isomer.
(13) This fragmentation pattern has been observed for nitrobenzene: J. Momigny, *Bull. Soc. Roy. Sci. Liege*, **25**, 93 (1956).

Experimental Section[14]

α-(4-Bromophenyl)acrylic Acid (1b).—Reaction of 4-bromophenylacetylene with nickel carbonyl in acetic acid–ethanol–water[15] provided **1b** which was purified by dissolving in acetone and reprecipitating with water: white powder, 47% yield; mp 107–111°; uv max (CH_3OH) 250 nm (ε 9580); nmr ($CDCl_3$) δ 6.02 and 6.55 (2 d, $J \simeq 1$ Hz, CH_2=C), 7.3 and 7.5 (2 d, $J = 9$ Hz, 4-bromophenyl), and 11.05 (s, CO_2H).

Anal. Calcd for $C_9H_7BrO_2$: C, 47.58; H, 3.11; Br, 35.18. Found: C, 47.48; H, 3.15; Br, 35.35.

Methyl α-(4-Nitrophenyl)acrylate (1d).—A solution of 2.38 g (2.3 mmol) of α-(4-nitrophenyl)acrylic acid (**1c**)[16] in 10 ml of 10% H_2SO_4 in methanol was heated at reflux for 1.5 hr. After cooling, the crystalline ester was removed by suction filtration and dissolved in ether. The ether solution was washed with 10% K_2CO_3 solution and water and dried ($MgSO_4$). Successive evaporation and crystallization of the ether solution yielded 2.12 g (83%) of white needles, **1d**: mp 110.5–111°; nmr ($CDCl_3$) δ 3.85 (s, OCH_3), 6.07 and 6.57 (2 s, $J \simeq 0$ Hz, CH_2=C), and 7.65 and 8.20 (2 d, $J = 9$ Hz, 4-nitrophenyl); uv max (CH_3OH) 275 nm (ε 10,980).

Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.06; H, 4.36; N, 6.62.

Preparation of the 4-Nitrobenzyl Esters 1e, 1f.—These esters were prepared by reaction of the sodium salts of the corresponding acids **1c** and **1b** with 4-nitrobenzyl bromide.[17] Crude **1e** from 12.5 mmol of **1c** was recrystallized from ethanol providing a 26% yield of white solid: mp 118–119°; uv max (CH_3OH) 271 nm (ε 20,300). Crude **1f** from 5 mmol of **1b** was recrystallized from methanol to give a 49% yield of white solid: mp 105.5–108.5°; uv max (CH_3OH) 258 nm (ε 16,480). Microanalyses (C, H, N) for **1e** and **1f** were within 0.3% of theoretical. The nmr spectra were consistent with the assigned structures.

Attempted Photodimerization of the Acrylic Acids (1a–c).—Samples of the acrylic acids **1a**, **1b**, and **1c** were placed as thin layers in 7-cm diameter crystallizing dishes and irradiated (Hanovia arc, Corex filter, 4 in. above samples) for 10 hr. The samples were somewhat discolored; however, nmr analysis indicated only starting material.

Photodimerization of Methyl α-(4-Nitrophenyl)acrylate (1d).[18]—Samples of **1d** (4.82-g total) were spread out as thin layers in three crystallizing dishes (12.5-cm diameter), and each sample was irradiated for 24 hr with a 275-W sunlamp[14] mounted 10 in. above the surface. The samples were cooled by air circulation to avoid melting and were mixed several times.[19] The crude product was dissolved in 150 ml of hot methanol and a small amount of residue removed by filtration. After cooling the filtrate, 3.44 g of dimer was collected by suction filtration. Recrystallization from methanol gave 3.41 g (70.7% yield) of off-white crystals: mp 180–181°; nmr ($CDCl_3$) δ 2.90 (broad sym m, CH_2CH_2), 3.78 (6 H, s, OCH_3), and 7.4 and 7.9 (8 H, 2 d, $J = 9$ Hz, 4-nitrophenyl groups); mass spectrum (50 eV, direct inlet) *m/e* (relative intensity) (high mass scan) 414 (92), 384 (9), 383 (41), 382 (100), 355 (35), 354 (17), 353 (10), 352 (metastable, 414 → 382), 350 (30), 337 (16), 323 (21), 322 (45), 296 (12), 295 (48), 250 (15), 249 (42), 248 (11); (low mass scan) 208 (12), 207 (100), 177 (16), 176 (26), 148 (62), 118 (14), 102 (26), 101 (12), 90 (17), 76 (13), 59 (15).

Anal. Calcd for $C_{10}H_8N_2O_8$: C, 57.97; H, 4.38; N, 6.76; mol wt, 414.4. Found: C, 57.75; H, 4.23; N, 6.93; mol wt, 426 ($CHCl_3$).

Recrystallization of **1d** from a variety of solvents (both above and below room temperature) was carried out in an attempt to obtain polymorphs which could provide photodimers of alternate stereochemistry.[20] In all cases, the same dimer (**2a**) was obtained.

***cis*-1,2-Di(4-nitrophenyl)cyclobutane-1,2-dicarboxylic Acid (2b).**—The diester **2a** (207 mg, 0.5 mmol) was dissolved in 5 ml of 97.5% H_2SO_4 and heated at 70° for 51 hr. The mixture was poured onto 70 g of ice and the resulting white solid was collected by suction filtration, washed with water, and dissolved in 3% aqueous KOH solution. The solution was filtered and the filtrate extracted with ether. The aqueous solution was acidified to pH 1 with concentrated HCl. After cooling (ice bath), the crystalline diacid was removed by suction filtration and dried at room temperature. Repetition of the acid–base purification gave 140 mg (72.5% yield) of **2b**: mp 183.5–184.5°; nmr (acetone-d_6) δ 3.03 (m, CH_2CH_2), 5.87 (s, CO_2H), and 7.60 and 7.95 (8 H, 2 d, $J = 9$ Hz, 4-nitrophenyls).

Anal. Calcd for $C_{18}H_{14}N_2O_8$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.83; H, 3.53; N, 7.24.

The diacid **2b** was slowly reconverted to the methyl ester **2a** with diazomethane in ether (<25% yield after 1 week in the cold).

***cis*-1,2-Di(4-nitrophenyl)cyclobutane-1,2-dicarboxylic Anhydride (4).**—The diacid **2b** (65 mg, 0.168 mmol) was placed in a drying pistol (heated by refluxing toluene) at a pressure of 100 mm. After 42 hr, conversion to the anhydride was complete. Recrystallization from methylene chloride–heptane (Darco G-60) resulted in 22 mg (35.6% yield) of **4**: mp 200.5–202.5°; ir (KBr) 5.43, 5.63 μ (cyclic anhydride); nmr (acetone-d_6) δ 3.33 (sym m, CH_2CH_2) and 7.63 and 8.12 (8 H, 2 d, $J = 9$ Hz, 4-nitrophenyls).

Anal. Calcd for $C_{18}H_{12}N_2O_7$: C, 58.70; H, 3.28; N, 7.61. Found: C, 58.50; H, 3.21; N, 7.51.

1,2-Di(4-nitrophenyl)cyclobutene (5).[9]—Lead tetraacetate (466 mg, 1.05 mmol) was added to a mixture of 386 mg (1 mmol) of **2b**, 200 μl of pyridine, and 15 ml of benzene. This suspension was stirred under reflux for 3.5 hr. After cooling, the solid was removed by suction filtration and washed with benzene. The combined benzene solution was washed with 10% Na_2CO_3, 2 *N* HCl and finally with saturated NaCl solution. After drying (Na_2SO_4) and removal of solvent, the residue was recrystallized from methylene chloride–pentane to give 52 mg (19.6% yield) of bright yellow crystals: mp 204–205°; uv max (CH_3OH) 360 nm (ε 21,300); nmr ($CDCl_3$) δ 2.90 (s, CH_2CH_2) and 7.63 and 8.22 (8 H, 2 d, $J = 9$ Hz, 4-nitrophenyls).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.68; H, 4.05; N, 9.39.

Photodimerization of 4-Nitrobenzyl α-(4-Nitrophenyl)acrylate (1e).—The procedure was the same as that for the dimerization of **1d**, except that a Hanovia arc with Pyrex filter was employed. The crude product that resulted from irradiation of 2.46 g of monomer for 70 hr was dissolved in hot methanol–acetone and filtered. Methanol was then added to the hot filtrate to turbidity and the solution was stored in the cold room for several days. The yield of light tan dimer was 1.25 g (51%):[21] mp 158–160°; nmr ($CDCl_3$) δ 3.0 (m, CH_2CH_2) and 5.25 (4 H, s, CH_2Ar groups) plus absorptions for the two types of 4-nitrophenyl groups.

Anal. Calcd for $C_{32}H_{24}N_4O_{12}$: C, 58.54; H, 3.68; N, 8.53; mol wt, 656.6. Found: C, 58.29; H, 3.68; N, 8.37; mol wt, 670 ($CHCl_3$).

Hydrolysis with 97.5% sulfuric acid followed by dehydration at 140° converted this dimer of **1e** to the anhydride **4** (identity by mixture melting point, ir, and nmr).

Photodimerization of 4-Nitrostyrene.—A 12.5 × 6.5 cm crystallizing dish fitted with a nitrogen inlet tube and covered with transparent polyvinyl chloride (PVC) film (uv cutoff, 275 nm) was cooled by placing it atop a planar surface of Dry Ice. After cooling, the PVC film was removed temporarily and 1.71 g of freshly distilled 4-nitrostyrene was dropped onto the cold surface from a height of 10 in. The droplets froze immediately.[22] The PVC film was replaced and the crystallizing dish was placed on a Dry Ice surface in an insulated container open at the top. The top of the dish was flush with the top of the container.

(14) Irradiations were carried out with a 450-W water-cooled Hanovia mercury arc (Corex or Pyrex filter) or with 275-W sunlamps (Sears, Roebuck and Co.). Nmr spectra were obtained on a Varian A-60 spectrometer using TMS as the internal standard. Mass spectral services were obtained from Morgan-Schaffer Corp., Montreal, Quebec. Ir and uv spectra were obtained on Perkin-Elmer Model 137 and 450 instruments, respectively. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

(15) The conditions employed have been described by E. R. H. Jones, T. H. Shen, and M. C. Whiting [*J. Chem. Soc.*, 230 (1950)] for the preparation of α-phenylacrylic acid from phenylacetylene.

(16) J. H. Schauble and E. Hertz, *J. Org. Chem.*, **35**, 2529 (1970).

(17) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 235.

(18) It should be noted that **1d** was inert to photolysis in methanol solution and that photolysis of the dimer **2a** in methanol solution gave tar.

(19) Nmr analysis indicated 75% conversion to dimer; yields of >90% were obtained by irradiating 100–200-mg samples with the Hanovia arc (Pyrex filter).

(20) This type of behavior is exhibited by the α and β modifications of *trans*-cinnamic acid: M.D. Cohen, G. M. J. Schmidt, and F. I. Sonntag, *J. Chem. Soc.*, 2000 (1964).

(21) Nmr analysis on the crude product indicated a yield of 72%.

(22) Large crystals of 4-nitrostyrene, prepared by slowly cooling of thin layers of the liquid, gave little or no dimer.

Insulation was packed around the sides of the dish and the sample was then irradiated for 20 hr with the Hanovia arc (Pyrex filter) placed 4 in. above the top of the dish. The crude product was dissolved in 20 ml of hot benzene and filtered to remove insoluble tar. Cyclohexane (80 ml) was added, and the solution was heated to boiling, treated with Darco, and again filtered. The filtrate was cooled to room temperature and then overnight at 10° to yield 250 mg (14.6%) of pale yellow crystals. Recrystallization from benzene–cyclohexane gave crystals: mp 185.5–186.5°; nmr ($CDCl_3$) δ 2.57 (m, CH_2CH_2), 4.2 (2 H, m, CHAr), and 7.1 and 7.95 (8 H, 2 d, J = 8.5 Hz, 4-nitrophenyls); mass spectrum (50 eV, direct inlet) m/e (relative intensity) 298 (2.2), 270 (0.5), 150 (9.7) 149 (100), 133 (5.3), 120 (4.5), 119 (43.4), 115 (4.0), 103 (31.9), 102 (9.7), 91 (27.5), 78 (6.0), 77 (52.5), 76 (4.5), 65 (7.5), 63 (3.5), 51 (11.2), 39 (10.2), 30 (6.0).

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39; mol wt, 298.3. Found: C, 64.48; H, 4.85; N, 9.39; mol wt, 303 ($CHCl_3$).

Isomerization of *cis*-1,2-Di(4-nitrophenyl)cyclobutane (6).—A solution of 439 mg of photodimer **6** in 20 ml of piperidine was heated at 85° for 24 hr. After removal of the piperidine *in vacuo*, the residue was taken up in ether. This solution was washed with dilute HCl and water, dried ($MgSO_4$), and evaporated. The residue was recrystallized from benzene–cyclohexane to give 80 mg (18.2%) of pale yellow crystals: mp 86–88°; nmr ($CDCl_3$) δ 2.38 (m, CH_2CH_2), 3.72 (2 H, m, CHAr groups), and 7.40 and 8.15 (8 H, 2 d, J = 9 Hz, 4-nitrophenyls); mass spectrum (50 eV, direct inlet) m/e (relative intensity) 298 (2.2), 270 (0.9), 150 (10.5), 149 (100), 133 (4.5), 119 (23.5), 115 (3.4), 103 (22.1), 102 (5.6), 91 (15.4), 77 (26.5), 74.5 (metastable, 298 → 149^+ + 149), 51 (3.9).

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39; mol wt, 298.3. Found: C, 64.45; H, 4.72; N, 9.33; mol wt, 301 ($CHCl_3$).

Registry No.—**1b**, 28131-17-1; **1d**, 28042-27-5; **1e**, 28042-28-6; **1e** photodimer, 28042-29-7; **1f**, 28042-30-0; **2a**, 28131-18-2; **2b**, 28042-31-1; **4**, 28042-32-2; **5**, 28042-33-3; **6**, 28042-34-4; **7**, 28042-35-5; 4-nitrostyrene, 100-13-0.

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A Simple Method for the Synthesis of Amides[1]

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It has been known for some time that treatment of alcohols with the adduct of triphenylphosphine and bromine (or chlorine) leads to the formation of the corresponding halides in high yield.[2] In this early report,[2] Horner and coworkers also showed that organic acids could be converted to acid chlorides by this method. More recently, Lee[3] and Bestmann and Mott[4] have extended these early observations and shown that treatment of acids or acid anhydrides with the adduct of triphenylphosphine and either bromine[4] or carbon tetrachloride[3] afforded the acid bromide (or chloride). This communication outlines an extension of these methods to a simple, high-yield method for the formation of amide bonds.

Two reaction schemes were used for the preparation of amides. In the first method, triphenylphosphine (**1**) and carbon tetrachloride are refluxed together for 30 min in tetrahydrofuran to form the adduct.[5] The solution is cooled to 5° in an ice–water bath, the carboxylic acid is added, and the mixture is allowed to stand for 10 min to form the triphenylacyloxyphosphonium chloride.[3] The amine (2 equiv) is added and the mixture is heated under reflux for about 45 min. The amine hydrochloride that forms is separated, and the solvent is removed *in vacuo*. The amide is isolated by distillation, or by sublimation, or by extraction of the amide with ethyl ether followed by recrystallization. Some typical yields of amides obtained by this method (method I) are presented in Table I.

TABLE I

PREPARATION OF AMIDES BY METHOD I

Acid	Amine	Yield, %	Method of purification[a]
Acetic	*n*-Butyl	91	A
Acetic	*tert*-Butyl	97	B
Acetic	Benzyl	87	A
Acetic	Diphenyl	85	C
Acetic	Di-*n*-butyl	81	A
Benzoic	*n*-Butyl	85	A
Benzoic	*tert*-Butyl	87	C
Benzoic	Benzyl	83	A
Benzoic	Di-*n*-butyl	95	A
Benzoic	Diphenyl	61	C

[a] A, distillation; B, sublimation; C, extraction with ether and recrystallization.

In the alternative procedure (method II), triphenylphosphine (**1**), bromotrichloromethane, the carboxylic acid, and the amine are refluxed together for 2 hr in tetrahydrofuran. The product **2** is then isolated as in

$$(C_6H_5)_3P + BrCCl_3 + RCO_2H + 2R''R'NH \longrightarrow$$
$$\mathbf{1}$$
$$RC(=O)NR'R'' + (C_6H_5)_3PO + HCCl_3 + R''R'\overset{+}{N}H_2Br^- \downarrow$$
$$\mathbf{2}$$

the first method. Presumably this reaction proceeds through the same intermediates formed when the reagents are added stepwise. A few examples of preparations by this method (method II) are presented in Table II.

TABLE II

PREPARATION OF AMIDES BY METHOD II

Acid	Amine	Yield, %	Method of purification[a]
Acetic	Di-*n*-butyl	92	A
Acetic	Benzyl	89	A
Acetic	*tert*-Butyl	93	B
Acetic	*n*-Butyl	88	A

[a] A, distillation; B, sublimation.

The application of our method to peptide synthesis was also tested. A mixture of triphenylphosphine (**1**), bromotrichloromethane, *N*-benzyloxycarbonyl-L-

(1) Supported by Grant AM-13411 from the U. S. Public Health Service and Grant GB-11781 from the National Science Foundation.

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(3) J. B. Lee, *J. Amer. Chem. Soc.*, **88**, 3440 (1966).

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phenylalanine, ethyl glycinate hydrochloride, and diisopropylethylamine was heated at reflux in 50 ml of tetrahydrofuran for 3 hr. Upon purification, ethyl *N*-benzyloxycarbonyl-L-phenylalanylglycinate was obtained in 85% yield.

Experimental Section

Method I.—The preparation of *N*-*n*-butylacetamide is a typical example of a preparation by method I. A mixture of 13.1 g of triphenylphosphine, 50 ml of CCl_4, and 150 ml of THF was refluxed together for 30 min. The solution was cooled in an ice–water bath to 5° and 2.85 ml of AcOH was added. The mixture was allowed to stand at 5° for 10 min. *n*-Butylamine (9.73 ml) was added, and the mixture was heated at reflux for 45 min. The reaction mixture was cooled to room temperature, and the *n*-butylamine hydrochloride which had precipitated was removed by filtration. The volatile solvents were removed *in vacuo*, and the product was isolated by vacuum distillation, bp 85–87° (0.1 mm), 5.25 g (91%).

Method II.—The preparation of *N*-di-*n*-butylacetamide is a typical example of a preparation by method II. A mixture of 13.1 g of triphenylphosphine, 20.0 g of bromotrichloromethane, 2.85 ml of AcOH, and 16.7 ml of di-*n*-butylamine was refluxed together for 2 hr in 150 ml of THF. The reaction mixture was cooled to room temperature and the di-*n*-butylamine hydrohalide was removed by filtration. The volatile solvents were removed *in vacuo*, and the product was isolated by vacuum distillation, bp 110–112° (11 mm), 7.8 g (92%).

Ethyl *N*-Benzyloxycarbonyl-L-phenylalanylglycinate.—A mixture of 1.31 g (50 mmol) of triphenylphosphine, 1.98 g (100 mmol) of bromotrichloromethane, 1.50 g (50 mmol) of *N*-benzyloxycarbonyl-L-phenylalanine, 0.77 g (55 mmol) of ethyl glycinate hydrochloride, and 1.45 g (112 mmol) of diisopropylethylamine was heated at reflux in 50 ml of THF for 3 hr. The reaction mixture was cooled to room temperature and the diisopropylethylamine hydrohalide was removed by filtration. The volatile solvents were removed *in vacuo*. The peptide was purified by column chromatography upon silicic acid. The product was eluted with ether–methanol (80/20); the yield was 85% after recrystallization from EtOAc–petroleum ether (bp 30–60°), mp 105–106° (lit.[6] mp 106–107°). The optical rotation, $[\alpha]^{25}D$ −16.7° (*c* 2, EtOH), of the product was compared with that of the same peptide prepared by the nitrophenyl ester method,[7] $[\alpha]^{25}D$ −16.8° (c 2, EtOH) [lit.[6] $[\alpha]^{20}D$ −16.6° (c 2, EtOH)].

Registry No.—**1**, 603-35-0; bromotrichloromethane, 75-62-7; *N*-*n*-butylacetamide, 1119-49-9; *N*-di-*n*-butylacetamide, 1563-90-2; ethyl *N*-benzyloxycarbonyl-L-phenylalanylglycinate, 4526-88-9.

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The Reaction of "Activated" Esters with Amidoximes. A Convenient Synthesis of 1,2,4-Oxadiazoles

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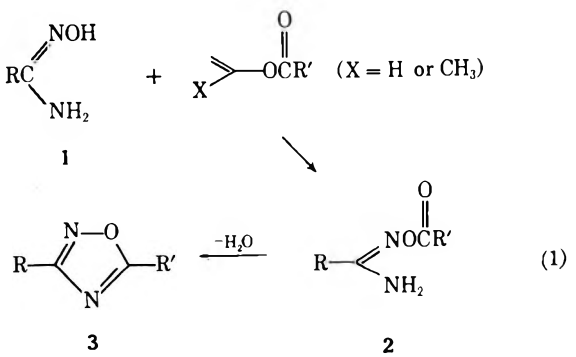
The preparation of 1,2,4-oxadiazoles by the reaction of amidoximes with acylating agents such as acid chlorides and anhydrides has been described frequently.[1,2]

The reaction of esters with amidoximes might be expected to be influenced by the same factors which govern their basic hydrolysis.[3] In considering these parameters it seemed that two of them, the electrophilicity of the carbonyl and the basicity of the anion being displaced, could be particularly important in influencing the ease of reaction of esters which might lead to the types of substituted oxadiazoles which were the object of this work. Thus, simple esters of trichloro- and dichloroacetic acids, and, particularly, enol esters of aliphatic or aromatic acids, have been found to react with amidoximes in a generally straightforward manner to give 1,2,4-oxadiazoles. With aliphatic esters such as ethyl acetate, however, oxadiazoles were not detected.

The reaction of enol (vinyl or isopropenyl) esters with amidoximes offers a convenient, and apparently general, route to 1,2,4-oxadiazoles. This method is particularly useful for the preparation of the lower boiling dialkyl derivatives, *e.g.*, 3,5-dimethyl-1,2,4-oxadiazole, previously prepared by more indirect routes.[4]

The reaction may be carried out either in excess ester or in an inert solvent such as benzene. The use of an inert solvent does not appear to be advantageous in most cases although in some instances, *e.g.*, vinyl trifluoroacetate, a solvent is needed to moderate the initial reaction of the amidoxime with the ester. In the preparation of 5-methyl compounds, isopropenyl acetate appears to be more effective than the vinyl ester, probably because of its higher boiling point.

That the reaction involved an initial O-acylation of the amidoxime[5] is shown by the isolation of *O*-acetylbenzamidoxime (**2**, R = C_6H_5; R′ = CH_3) as well as 5-methyl-3-phenyl-1,2,4-oxadiazole (**3**, R = C_6H_5; R′ = CH_3) from a reaction in which benzamidoxime (**1**, R = C_6H_5) was heated at reflux in vinyl acetate for 8 hr. No evidence of competing O,N-diacylation was observed (eq 1).[5] The general utility of the enol ester–



(1)

amidoxime reaction is illustrated in Table I and the Experimental Section.

The reaction of benzamidoxime (**1**, R = C_6H_5) with excess methyl trichloroacetate at reflux gave chloroform and methanol in addition to a 38% yield of 3-phenyl-5-trichloromethyl-1,2,4-oxadiazole (**3**, R = C_6H_5; R′ = CCl_3). Use of benzene as solvent increased the yield to 66% and only water and methanol were de-

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(3) J. Hine, "Physical Organic Chemistry," 1st ed, McGraw-Hill, New York, N. Y., 1956, p 274.
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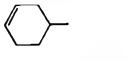
TABLE I

OXADIAZOLES PREPARED *via* VINYL ESTERS

R	R′	Solvent[a]	Yield, %	Bp (mm) or mp, °C
CH_3	CH_3	1	69	118–124[b]
CH_3	C_2H_5	1	62	140.8[c]
C_6H_5	CH_2Cl	2	35	39–40.5[d]
CH_3	CH_2Cl	2	68	80–83 (15)[e]
CH_3	CH_2Cl	1	61	80–83 (15)
C_6H_5	CF_3	4	43	38–39[f]
C_6H_5	H	4	49	73–75 (2)[g]
3-$NO_2C_6H_4$	CH_3[h]	3	21	109–110[i]
	CH_3[h]	3	49	103–109 (10)[j]

[a] 1 is excess ester, 2 is benzene, 3 is xylene, and 4 is toluene. [b] Reference 4 reports bp 124.5°. [c] Reference 10 reports bp 139°. [d] Reference 1b reports mp 38–39°. [e] The infrared spectrum is identical with that of known material (ref 9). [f] Melting point. Calcd for $C_9H_5F_3N_2O$: C, 50.47; H, 2.34. Found: C, 50.77; H, 2.03. [g] Reference 4 reports bp 71–72° (1 mm). [h] Used isopropenyl acetate. [i] From heptane, ref 1b reports mp 109°. [j] Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37. Found: C, 65.88; H, 7.37.

tected as by-products. In similar reactions acetamidoxime gave only minor amounts of 3-methyl-5-trichloromethyl-1,2,4-oxadiazole (**3**, R = CH_3; R′ = CCl_3) together with by-products such as methanol, chloroform, 3,5-dimethyl-1,2,4-oxadiazole, and dimethyl carbonate. The occurrence of 3,5-dimethyloxadiazole may indicate some thermolysis of the acetamidoxime under the reaction conditions.[1a]

Benzamidoxime with excess methyl dichloroacetate gave 52% of 3-phenyl-5-dichloromethyl-1,2,4-oxadiazole (**3**, R = C_6H_5; R′ = $CHCl_2$) while with a stoichiometric amount of ester in benzene a yield of 61% was obtained. Acetamidoxime under similar conditions gave 3-methyl-5-dichloromethyl-1,2,4-oxadiazole (**3**, R = CH_3; R′ = $CHCl_2$) in yields of 33% (slightly impure) and 28%, respectively.

Experimental Section[6]

General Procedure for Reactions Involving Methyl Di- and Trichloroacetate.—A mixture of almost equivalent amounts of ester and amidoxime in 100 ml of solvent (where no solvent was used an excess of ester was employed) was heated at reflux under azeotroping conditions (where excess ester was the solvent, the reaction was carried out under a distillation head at high reflux ratio). When no more volatile materials (methanol, water, chloroform) could be detected by glc in the distillate, the reaction mixture was cooled, filtered to remove any solid, and distilled. In most cases unreacted ester, solvent, and oxadiazole were collected as discrete fractions, whereas by-products such as dimethyl carbonate and dimethyl oxadiazole were detected as components of fractions by combinations of infrared, glc, and mass spectral studies.

Using this procedure a mixture of 27.2 g (0.2 mol) of benzamidoxime and 60 g (0.33 mol) of methyl trichloroacetate was slowly heated to 104° over a period of 7 hr to give 19.5 g (37%) of **3-phenyl-5-trichloromethyl-1,2,4-oxadiazole**, bp 97–104° (0.05–0.15 mm) [lit.[7] mp 26°, bp[8] 95–96° (0.01 mm)]. The infrared spectrum of this product was identical with that of a known material prepared by the method of Sousa, *et al.*[8]

A reaction involving benzamidoxime (13.6 g, 0.1 mol) and methyl dichloroacetate (22 g, 0.15 mol) in 100 ml of benzene carried out according to the general procedure with a reflux period of 20 hr gave 14 g (61%) of **3-phenyl-5-dichloromethyl-1,2,4-oxadiazole**, mp 39–40° (ethanol–water) (lit.[9] 46°). The infrared spectrum of this product was identical with that of a sample prepared by the reaction of benzamidoxime and dichloroacetyl chloride.[8]

Anal. Calcd for $C_9H_6Cl_2N_2O$: N, 12.23. Found: N, 12.19.

The Reaction of Amidoximes with Enol Esters.—The following examples illustrate the general procedure used to prepare the compounds in Table I.

3,5-Dimethyl-1,2,4-oxadiazole (**3**, **R** = **R′** = CH_3).—A suspension of 37 g (0.5 mol) of acetamidoxime in 107 ml (0.5 mol + 50 ml) of isopropenyl acetate was heated at reflux under a distilling head for 5–6 hr during which time acetone was slowly removed at a head temperature of 65°. When acetone removal was essentially complete, the reaction mixture was distilled through an 18-in. Nester-Faust spinning-band column (stainless steel band) to give 39.5 g (81%) of product, bp 118–123° (lit.[5] 124.5°). The infrared spectrum shows a band at 6.34 μ, together with others, characteristic of 3,5-disubstituted 1,2,4-oxadiazoles[10] but showed no bands indicative of a carbonyl-containing impurity. No impurities could be detected by glc.

3-Methyl-5-phenyl-1,2,4-oxadiazole (**3**, **R** = CH_3; **R′** = C_6H_5).—A suspension of 7.4 g (0.1 mol) of acetamidoxime in 22 g (0.15 mol) of vinyl benzoate was heated at a gentle boil under distillation conditions, and acetaldehyde was slowly removed while the suspended solid dissolved. When acetaldehyde evolution was complete, water evolution began (indicative of ring closure); heating was continued for 3 hr to complete cyclization. The reaction mixture was evaporated *in vacuo*, the residue was washed with 10% sodium hydroxide solution, and the insoluble material was taken up in a petroleum ether–hexane mixture with a trace of ethanol added. After drying over sodium sulfate, this solution, upon chilling, gave 8 g (60%) of product, mp 57–58.5° (lit.[1a] 57°), ir 6.34 (μ) (characteristic of 1,2,4-oxadiazoles).

Reaction of Benzamidoxime with Vinyl Acetate. A. In Excess Ester. Preparation of *O*-Acetylbenzamidoxime (**2**, **R** = C_6H_5; **R′** = CH_3) **and 5-Methyl-3-phenyl-1,2,4-oxadiazole** (**3**, **R** = C_6H_5; **R′** = CH_3).—A mixture of 13.6 g (0.1 mol) of benzamidoxime and 30 ml of vinyl acetate was stirred and heated under gentle distillation for 8 hr while acetaldehyde was slowly removed. The cooled reaction mixture was diluted with 200 ml of petroleum ether (bp 30–60°); an oil separated which crystallized upon chilling. When collected and dried this amounted to 11 g (59.5%) of **2** (R = C_6H_5; R′ = CH_3), mp 93–94.5° (lit.[11] mp 96°). The infrared spectrum was completely analogous to that *O*-benzoylbenzamidoxime.[5] The petroleum ether filtrate, upon concentration and charcoal treatment, gave 4 g (24%) of **3** (R = C_6H_5; R′ = CH_3), mp 38–39° (lit.[12] 41°).

B. In Benzene. 5-Methyl-3-phenyl-1,2,4-oxadiazole (**3**, **R** = C_6H_5; **R′** = CH_3).—A mixture of 13.6 g (0.1 mol) of benzamidoxime and 9.8 g (0.1 mol) of vinyl aceate in 60 ml of benzene was heated at reflux under a Dean-Stark trap until 1.6 ml of water was collected (12 hr). The reaction mixture was washed with water, evaporated to 20 ml *in vacuo*, and then diluted with petroleum ether. Chilling produced a solid which was collected and recrystallized from ethanol–water to give the product, 5 g (30%), mp 39° (lit.[11] 41°).

Reaction of Benzamidoxime with Isopropenyl Acetate. 5-Methyl-3-phenyl-1,2,4-oxadiazole (**3**, **R** = C_6H_5; **R′** = CH_3).—A mixture of 6.8 g (0.05 mol) of benzamidoxime and 40 ml of isopropenyl acetate was heated at reflux for 24 hr. The mixture was then evaporated *in vacuo* and the residue was recrystallized from ethanol–water to give 6 g (75%) of product, mp 35–36° (lit.[11] 41°).

Registry No.—**3** (R = C_6H_5; R′ = CF_3), 1736-55-6; **3** (R = cyclohexen-4-yl; R′ = CH_3), 27925-50-4.

(6) The melting points are uncorrected. The infrared spectra were obtained using a Perkin-Elmer 21 infrared spectrophotometer. The glc analyses were carried out on A-90 instrument using a 5-ft 10% silicone on Fluoropak column at 127° and 12.5 psig helium flow. Vinyl and isopropenyl acetate are products of Union Carbide Corp.; the other vinyl esters are also commercially available. Acetamidoxime[4] and benzamidoxime[1a] were prepared from the corresponding nitriles and hydroxylamine.

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Facile Cycloalkylation of Arylacetonitriles in Dimethyl Sulfoxide

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A recent publication on the use of sodium hydroxide–dimethyl sulfoxide in the alkylation of phenylacetonitrile[1] has led us to comment on some of our results using sodium hydride–dimethyl sulfoxide. The α-alkylation reactions of nitriles have been summarized[2,3] and the use of sodium hydride in dimethyl sulfoxide has been described by Bloomfield.[4] We have found that good yields of 1-arylcycloalkanecarbonitriles can be obtained by the addition of a mixture of an arylacetonitrile and an α,ω-dibromoalkane (C_3–C_5) to a cooled (25–35°) suspension of sodium hydride in dimethyl sulfoxide.

This procedure has several advantages over those published. (1) It allows the preparation of halogen-substituted phenylcycloalkanecarbonitriles since the reagents do not react with the aromatic halogens as would the sodium amide conventionally used for cycloalkylation of phenylacetonitrile.[5,6] (2) The reaction is extremely rapid, in comparison to the high dilution techniques recommended when sodium amide is used in an inert solvent. (3) The yields with phenylacetonitrile are either comparable or superior to those reported in the literature.[5,6]

The hydrogen evolution occurs as rapidly as the addition of the phenylacetonitrile and dihalide.[7] This procedure failed with 1,2-dibromoethane and 1,6-dibromohexane. Alkylation of phenylacetonitrile with 1,3-dibromopropane by the procedure described by Taranko and Perry[1] gave a complex mixture of products, which was expected since their procedure was especially useful for monoalkylation. The ready availability of 1-phenylcyclobutanecarbonitrile has led to the discovery of some biologically active derivatives.[8,9]

Yields are based on isolated, analyzed products. The infrared and nmr spectra were consistent with the structures (the latter showed no allyl hydrogens). Some typical examples of this procedure are summarized in Table I.

TABLE I

1-ARYLCYCLOALKYLCARBONITRILES PREPARED BY USING SODIUM HYDRIDE IN DIMETHYL SULFOXIDE

$$2NaH + ArCH_2C{\equiv}N + Br(CH_2)_nBr \longrightarrow Ar\text{-}\underset{(CH_2)_{n-2}}{\overset{}{C}}{\equiv}N$$

Compd	Ar	n	Mp (recrystn solvent) or bp (mm), °C	Yield, % (reported)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Empirical formula
1	C_6H_5[a]	5	138–141 (7)	54 (58[5])	84.28	8.16	7.56	84.48	8.37	7.75	$C_{13}H_{15}N$
2	C_6H_5[a]	4	129–132 (7)	72 (46[5])	84.16	7.65	8.19	84.46	7.86	8.32	$C_{12}H_{13}N$
3	C_6H_5[a]	3	120–122 (7)	58 (15[5])	84.07	7.06	8.87	84.21	7.20	8.92	$C_{11}H_{11}N$
4	2-ClC_6H_4	3	57–59 (hexane)	75	69.01	5.26	7.30	68.90	5.43	7.07	$C_{11}H_{10}ClN$
5	3-ClC_6H_4	3	93–95 (0.75)	53	69.01	5.26	7.30	68.95	5.48	7.04	$C_{11}H_{10}ClN$
6	4-ClC_6H_4	3	168–169 (20)	78	69.01	5.26	7.30	68.93	5.45	7.45	$C_{11}H_{10}ClN$
7	2-BrC_6H_4	3	80–82 (benzene–petroleum ether)	60	55.95	4.27		56.13	4.45		$C_{11}H_{10}BrN$
8	2-FC_6H_4	3	129–130 (8)	40	75.41	5.75	7.99	75.36	5.85	8.09	$C_{11}H_{10}FN$
9	2,6-$DiClC_6H_3$	3	93–95 (methanol)	65	58.43	4.01		58.59	4.16		$C_{11}H_9Cl_2N$
10	2-Thienyl	3	122–125 (10)	58	66.24	5.56		65.93	5.61		C_9H_9NS
11	2-Furyl	3	98–100 (11)	68	73.43	6.16		73.72	6.39		C_9H_9NO
12	C_6H_5	...[b]	140–145 (12)	92 (59[c])	85.24	7.67	7.09	85.30	7.71	7.02	$C_{14}H_{15}N$

[a] These compounds were also converted to the known carboxylic acids and amides as solid derivatives. [b] Using 2 equiv of allyl chloride, 2-allyl-2-phenyl-4-pentenenitrile (12) was prepared. An attempt was made to carry out this reaction using tetrahydrofuran as solvent with *N*-methylaniline as catalyst and also with *tert*-butanol as catalyst; hydrogen was not evolved upon addition of the phenylacetonitrile–allyl chloride mixture. Upon addition of a catalytic (25 ml to 1 l. of THF) amount of dimethyl sulfoxide, hydrogen evolution took place. Completion of the reaction and work-up yielded 74% of the dialkylated product. [c] E. G. Brain, F. P. Doyle, K. Hardy, A. A. W. Long, M. D. Mehta, D. Miller, J. H. C. Nayler, M. J. Soula, E. R. Stove, and G. R. Thomas, *J. Chem. Soc.*, 1445 (1962).

Experimental Section

All reagents were commercially available products and were used without further purification. A typical cycloalkylation reaction is described in the following example.

1-(*o*-Chlorophenyl)cyclobutanecarbonitrile (4).—A 5-l. three-necked flask was equipped with mechanical stirrer, a reflux condenser, thermometer, and a pressure-equalized dropping funnel. The reflux condenser was connected to a Rockwell gas meter[10] to monitor the hydrogen evolution. The flask was charged under N_2 with 2 l. of dimethyl sulfoxide (20–25°) and 211.2 g (4.4 mol) of sodium hydride (50% dispersion in mineral oil). If the mineral oil would interfere with the isolation of the product, it was

(1) L. B. Taranko and R. H. Perry, Jr., *J. Org. Chem.*, **34**, 226 (1969).
(2) A. C. Cope, H. L. Holmes, and H. O. House, *Org. React.*, **9**, 107 (1957).
(3) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 184.
(4) J. J. Bloomfield, *J. Org. Chem.*, **26**, 4112 (1961).
(5) F. H. Case, *J. Amer. Chem. Soc.*, **56**, 715 (1934).
(6) The cyclobutane derivative was obtained in 58% yield compared to the 15% yield reported by Case[5] and 2-phenyl-4-pentenenitrile was not present.
(7) The alkylation occurs at such a rate that highly reactive halides, *e.g.*, allyl chloride, can be used without appreciable reaction with the dimethyl sulfoxide.
(8) D. E. Butler to Parke, Davis and Co., U. S. Patent 3,489,758 (1970).
(9) D. E. Butler to Parke, Davis and Co., U. S. Patent 3,526,656 (1970).
(10) This was a Model S110 dry gas meter calibrated in liters. It was designed for propane, butane, or natural gas and was purchased from Rockwell Manufacturing Co., Pittsburgh, Pa. It was fitted with hose connections after purchase.

washed with toluene and added as a toluene slurry. The flask was immersed in a water bath maintained between 20 and 35°. A solution of 303 g (2.0 mol) of (*o*-chlorophenyl)acetonitrile and 444 g (2.2 mol) of 1,3-dibromopropane in anhydrous diethyl ether (total volume 1 l.) was added at a rapid rate through the dropping funnel with vigorous stirring. Total addition time was determined by the rate of cooling. The temperature was held between 25 and 35° by cooling. The reaction can be worked up immediately or allowed to stir overnight. The mixture was cooled in ice water and 100 ml of 2-propanol was added dropwise, followed by the addition of 1.5 l. of water. The layers were separated and the aqueous layer was extracted four times with 1-l. portions of diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and recrystallized to yield the product. See Table I for yield and physical characteristics.

Registry No.—**1**, 2201-23-2; **2**, 77-57-6; **3**, 14377-68-5; **4**, 28049-59-4; **5**, 28049-60-7; **6**, 28049-61-8; **7**, 28049-62-9; **8**, 28049-63-0; **9**, 28049-64-1; **10**, 28049-65-2; **11**, 28049-66-3; **12**, 28049-67-4.

Nitrogen Inversion in Cyclic *N*-Tosylamines

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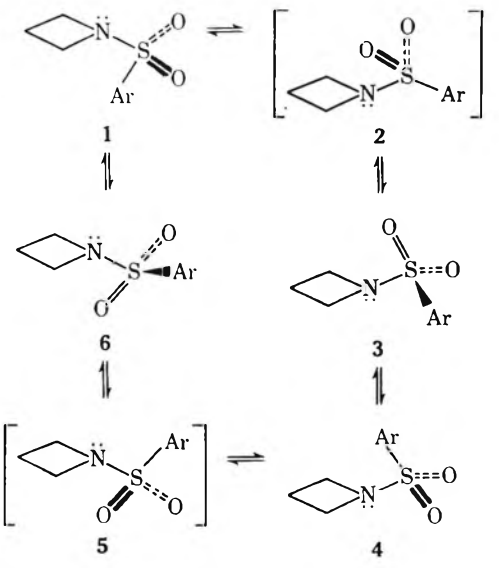
Diastereotopic protons in a sulfonamide of the type $(R)(R'CH_2)NSO_2R''$ may be brought into equivalence by an inversion about nitrogen and a rotation about the N–S bond. The rate-determining step for such a process is not specified by the simple observation of an A_2 to AB change in the spectrum of the indicated methylene protons. Additional evidence, such as the effects of steric bulk, conjugation, or ring size, is needed.[2] Spectral changes for the cyclic sulfonylaziridines have been attributed to hindered nitrogen inversion, but the method used does not unambiguously differentiate inversion from rotation.[3]

In order to clarify the nature of the rate-determining process for interconversions in small-ring sulfonamides, we have compared the free energies of activation for sulfonylaziridines and sulfonylazetidines. There should be little difference between the two systems for a rate-determining bond rotation. If nitrogen inversion is the slow step, however, the observed barrier should be much greater for the more highly strained three-membered rings than for the four-membered rings.[4] The available aziridine data are given in Table I. For the three sulfonylaziridines (I–III), $\Delta G^{\pm}$ is close to 12.5 kcal/mol. Because sulfonylazetidines had not previously been studied,[4] we examined the proton spectrum of *N*-tosylaziridine (VI, *p*-toluenesulfonylaziridine) down to −170°. The α-proton triplet is unchanged to −120°. Below this temperature, the resonance broadens through coalescence to two peaks (T_c = −150°, $\Delta\nu$ = 12 Hz at 90 MHz). The free energy of activation is calculated to be 6.2 ± 1.0 kcal/mol at the coalescence temperature.

The set of processes that must be occurring in VI is depicted in Scheme I. The ground-state form of VI

SCHEME I



is assumed to be **1** (**4**), with the nitrogen lone pair staggered between the two sulfonyl oxygen atoms.[5] Nitrogen inversion converts **1** to **2** through an "sp²" transition state. The eclipsed form **2** then returns to the ground-state form **4** by a torsional process. The pathway **1** → **6** → **5** → **4** represents the same process in the reverse direction. The question to be answered is whether the highest point on the energy surface is the inversion transition state between **1** and **2** with an sp² nitrogen or some point on the rotational itinerary between (and including) **2** and **4**.

At room temperature, the α protons of VI are equivalent, so all processes must be rapid on the nmr time scale. When the temperature is lowered to −170°, the α protons become nonequivalent. So long as only one rotamer is present, it is possible to observe only one set of spectral changes. If the changes in the aziridine II spectrum had been due to a rate-determining N–S rotation, the azetidine VI should have exhibited spectral coalescence with similar kinetics. The difference of over 6 kcal/mol between the barriers for II and VI cannot therefore be explained in terms of a slow torsional process. For a rate-determining nitrogen inversion, a considerably lower barrier is expected of the four-membered ring; *cf.* V *vs.* VIII. The spectral changes for

(1) (a) Alfred P. Sloan Foundation Fellow, 1968–1970. This work was supported by the National Science Foundation (Grant GP-9257), the Advanced Research Projects Agency of the Department of Defense through the Northwestern University Materials Research Center, and the Petroleum Research Fund administered by the American Chemical Society (Grant 2970-A4, 5). (b) National Science Foundation Undergraduate Research Participant, 1969–1970. (c) National Science Foundation Trainee, 1966–1967; National Institutes of Health Fellow, 1968–1970.

(2) M. Raban, G. W. J. Kenney, Jr., J. M. Moldowan, and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **90**, 2985 (1968); M. Raban and F. B. Jones, Jr., *ibid.*, **91**, 2180 (1969).

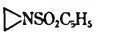
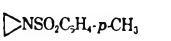
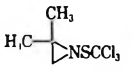
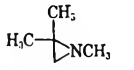
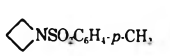
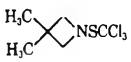
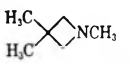
(3) (a) F. A. L. Anet and J. M. Osyany, *ibid.*, **89**, 352 (1967); (b) F. A. L. Anet, R. D. Trepka, and D. J. Cram, *ibid.*, **89**, 357 (1967).

(4) The factors that influence the inversion barrier have been discussed by J. B. Lambert, *Top. Stereochem.*, in press; J. M. Lehn, *Fortschr. Chem. Forsch.*, **15**, 311 (1970); A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed. Engl.*, **9**, 400 (1970).

(5) S. Wolfe, A. Rauk, and I. G. Csizmadia, *J. Amer. Chem. Soc.*, **91**, 1567 (1969). Arguments analogous to those presented here would still apply if **3** (**6**) were the stable rotamer.

TABLE I

ACTIVATION PARAMETERS FOR N-SUBSTITUTED AZIRIDINES AND AZETIDINES

	Compd	Solvent	$\Delta G^{\ddagger}$ (T_c), kcal/mol	Process	Source
I		$CDCl_3$	12.4 (−30)[a]	Inversion	*b*
II		$CDCl_3$	12.4 (−30)[a]	Inversion	*b*
III		$CDCl_3$	12.8 (−25)[a]	Inversion	*c*
IV		CH_2Cl_2–$CFCl_3$	9.1 (−87)	Inversion	*d*
V		$CDCl_3$	18.9 (∼+60)	Inversion	*e*
VI		$CHClF_2$	6.2 (−150)	Inversion	This work
VII		CH_2Cl_2	12.1 (−30)	Rotation	*d*
VIII		$CFCl_3$	8.9 (−93)	Inversion	*f*

[a] Calculated from the reported rate data and the equation $\Delta G^{\ddagger} = RT(23.76 + \ln T/k)$. [b] Reference 3b. [c] Reference 3a. [d] Reference 6. [e] M. Jautelat and J. D. Roberts, *J. Amer. Chem. Soc.*, 91, 642 (1969). [f] J. M. Lehn and J. Wagner, *Chem. Commun.*, 148 (1968).

both *N*-tosylamines II and VI may therefore be confidently attributed to a rate-determining nitrogen inversion. The barrier for VI (6.2 kcal/mol) constitutes the lowest value yet measured for nitrogen inversion in a four-membered ring.[4]

A contrasting case is given by the trichloromethylthio compounds IV and VII.[6] Here the aziridine has a lower barrier than the azetidine. The authors consequently assigned the rate-determining step for the three-membered ring to inversion, but for the four-membered ring to bond rotation.[6] When bonded atoms both possess lone pairs, as in the sulfenamides IV and VII, the torsional operation can have a high energy barrier.[2,5] The sulfonamide bond (N—SO_2) is therefore expected to have a much lower torsional barrier, because one atom (sulfur) is devoid of lone-pair electrons.

Scheme I may be unnecessarily complex. The conversion of **1** to **3** may involve only a single maximum on the inversion–rotation energy surface. The transition state would then possess both inversional and rotational character. Our data certainly do not exclude such an operation. Nonetheless, we would conclude that such a transition state between **1** and **3** should still have a larger proportion of inversion character.

The extremely low magnitude of the barrier to nitrogen inversion in VI deserves further comment. Some time ago, Traylor[7] remarked that the barrier in sulfonamides might be lowered by $(p\text{–}d)_\pi$ overlap between the nitrogen lone pair and the empty orbitals on sulfur.[8] The *N*-tosyl compound VI has a barrier approximately 3 kcal/mol lower than the corresponding *N*-methyl compound VIII. Since the electron-withdrawing ability of the sulfonamide group (σ_I = 0.60) would raise the barrier with respect to that of an *N*-methyl compound (σ_I = 0.0),[3b] the observed lowering must be due to a strong conjugative effect.[4] Overlap is strongest at the transition state because the lone pair is p hybridized. Donation of the nitrogen 2p lone pair to empty orbitals on sulfur therefore provides a mechanism for the increased rate of inversion of sulfonamides. Since other proposed examples of $(p\text{–}d)_\pi$ acceleration of atomic inversion could alternatively be explained in terms of an inductive rate enhancement by electropositive substituents,[4] the sulfonamides assume an important position in the question of d-orbital conjugation. It should be noted that the specific acceptor orbitals on sulfur cannot really be determined. The d orbitals are convenient for discussion, but other empty low-lying orbitals may also be important. The present observations with *N*-tosylazetidine are at the limit of the dnmr method. It is therefore expected that hindered nitrogen inversion will not be observed in larger ring sulfonamides without imposing specific constraints.[9]

Experimental Section

Nmr spectra were taken at 90 MHz on a Bruker HFX-10 spectrometer[10] and at 60 MHz on Varian A-60 and T-60 spectrometers.

3-(*p*-Toluenesulfonamido)propyl *p*-toluenesulfonate was prepared from 3-aminopropanol according to the method of Vaughan, *et al.*,[11] mp 117–118° (lit.[11] 116–119°).

***p*-Toluenesulfonylazetidine** (*N*-tosylazetidine, **VI**) was prepared in quantitative yield from the above ditosylate by the method of Vaughan, *et al.*,[11] mp 118–119° (lit.[11] 119.0–121.5°).

Registry No.—VI, 7730-45-2.

(6) J. M. Lehn and J. Wagner, *Chem. Commun.*, 1298 (1968).

(7) T. G. Traylor, *Chem. Ind. (London)*, 649 (1963).

(8) Low inversion barriers for *N*-sulfonyl compounds have also been discussed by K. Murayama and T. Yoshioka, *Tetrahedron Lett.*, 1363 (1968).

(9) W. N. Speckamp, U. K. Pandit, P. K. Kower, P. J. van der Haak, and H. O. Huisman, *Tetrahedron*, **22**, 2413 (1966).

(10) We thank the National Science Foundation for an equipment grant that made possible the purchase of this instrument.

(11) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, **26**, 138 (1961).

The Formation and Isomerization of 6,8-Dioxabicyclo[3.2.1]oct-2-ene and 6,8-Dioxabicyclo[3.2.1]oct-3-ene. A Note on the Course of α Halogenation of Acetals

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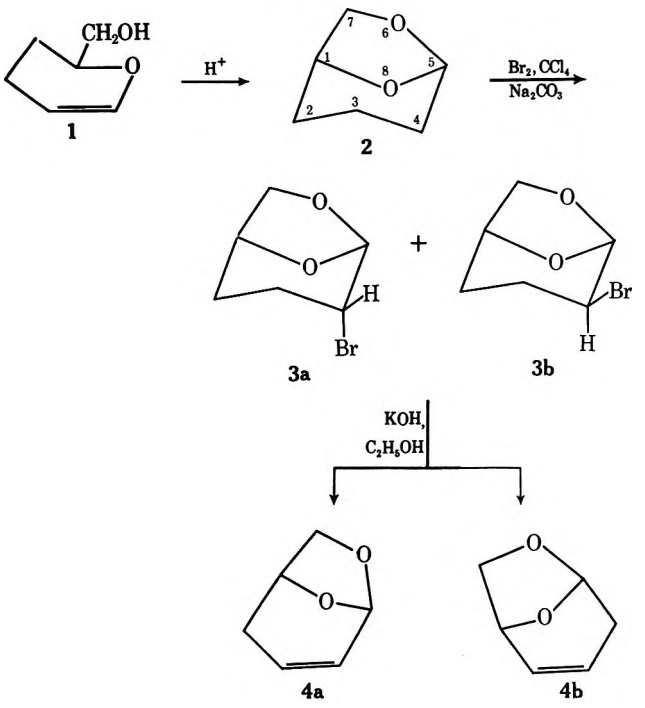
A previous report from this laboratory[2] has described the conversion of 2-hydroxymethyl-3,4-dihydro-2*H*-pyran (**1**) to 6,8-dioxabicyclo[3.2.1]oct-3-ene (**4a**) through the isolable intermediates **2** and **3** as shown in Scheme I. The product obtained from the bromination of 6,8-dioxabicyclo[3.2.1]octane (**2**) was thought to be the single compound *cis*-4-bromo-6,8-dioxabicyclo-[3.2.1]octane (**3b**) because (1) gas–liquid chromatography (glc) of this product showed only one broad symmetrical peak, (2) the proton magnetic resonance (pmr) spectrum showed only one singlet ($W/2$ = 3.5 Hz) in the anomeric proton region, and (3) the low yield (30%) of the olefin **4a** obtained after a 24-hr treatment of **3** with hot ethanolic potassium hydroxide suggested that the bromine atom of the preferred chair conformation of **3** was not in a trans diaxial relationship with a vicinal hydrogen atom. There was no doubt that **4a** was the compound finally obtained[2] since it had been used to prepare 1,6-anhydro-4-deoxy-β-DL-xylohexopyranose[1] as well as DL-chalcose[3] both of which were adequately verified.

SCHEME I



It has been observed in our work[4] that the base-catalyzed dehydrohalogenation of 3-bromo-2-ethoxytetrahydropyran (**5**), when carried out at temperatures above 100°, gave not only the expected 2-ethoxy-5,6-dihydro-2*H*-pyran (**6**), previously reported as the product obtained from the dehydrohalogenation of **5** with hot ethanolic potassium hydroxide,[5] but also 6-ethoxy-5,6-dihydro-2*H*-pyran (**7**). Pure **6** could also be converted partly to **7** by treatment with base, either for an extended period of time or at higher temperatures.[4] Preliminary work in this laboratory had also shown that pure **4a**, heated for 24–72 hr in refluxing ethanolic potassium hydroxide, gave a product which was found to be a mixture of the two olefins **4a** and **4b**.

In view of the potential value of the isomer **4b** in preparing 2-deoxy-DL-hexoses as well as 2,3-, 2,4-, or 3,4-dideoxy-DL-hexoses, we explored means of obtaining **4b** as the major if not the only product of dehydrohalogenation of **3**. The isomerization **4a** ⇌ **4b** was also examined. In addition, the conversion **1** → **2** → **3** was reconsidered with a view to improvement of yields as well as to determine whether both possible isomers **3a** and **3b** were obtained from the bromination of **2**. This paper describes the results of the investigations.

Results and Discussion

Although variable yields of 40–65% have been reported[2] for the preparation of **2** from **1**, it is now found that the adoption of a minor but significant modification of the published precedure[2] provides **2** consistently in yields of 88–94%.

Even though the bromination of **2** has been reported to give **3** in yields of 60[3] and 73%,[2] these results could not be obtained consistently. The procedure in both reports[2,3] is based on that described for the bromination of acetals[6] and utilized finely divided anhydrous sodium carbonate suspended in a carbon tetrachloride solution of **2** to destroy the hydrogen bromide produced. When it became apparent that some hydrogen bromide was still present in the reaction mixture despite the presence of the suspended sodium carbonate, and that α halogenation of the acetals still proceeded well, the necessity for complete elimination of the halogen acid was questioned. Furthermore, the tendency of sodium carbonate to agglomerate prevented adequate dispersal of the reagents during the stirring of the reaction mixture. Accordingly, bromination was carried out in the absence of sodium carbonate, and this gave the monobromo product repeatedly in ~80% yield. Under these conditions, the initial reaction was slow but soon became rapid when the concentration of the evolved hydrogen bromide increased. Most of the halogen acid was eliminated from the carbon tetrachloride solution because of its low solubility. This apparent "induction period" could be eliminated if dry hydrogen bromide was added to the carbon tetrachloride solution of **2** just before the addition of the bromine. Glc of the product on a *freshly prepared* column of 20% butanediol succinate on Chromosorb W showed *two* overlapping peaks in the area ratio of 3:2. It is significant that an old column showed only *one* broad symmetrical peak (*cf.* ref 2). Elemental analysis of this mixture agreed with that required for a monobromo-6,8-dioxabicyclo-[3.2.1]octane; hence it was clear that bromination of **2**

(1) Author to whom correspondence should be directed.
(2) F. Sweet and R. K. Brown, *Can. J. Chem.*, **46**, 2289 (1968).
(3) R. M. Srivastava and R. K. Brown, *ibid.*, **48**, 830 (1970).
(4) F. Sweet, U. Diner, H. Davis, and R. K. Brown, unpublished work.
(5) G. F. Woods and H. Sanders, *J. Amer. Chem. Soc.*, **68**, 2483 (1946).
(6) S. M. McElvain, R. L. Clarke, and G. D. Jones, *ibid.*, **64**, 1966 (1942).

gave a mixture of two isomeric monobromides, considered to be *trans*- and *cis*-4-bromo-6,8-dioxabicyclo-[3.2.1]octane (**3a** and **3b**). These two products could not be separated by glc although ten different columns were tried.

When the mixture of isomers **3a** and **3b** was heated in refluxing ethanolic potassium hydroxide either for 24 hr as previously described[2] or for 1.5 hr, the same yield of olefinic material **4** was obtained, along with some unreacted 4-bromo-6,8-dioxabicyclo[3.2.1]octane. This recovered monobromo material, when analyzed by glc on two different columns, showed only one narrow symmetrical peak coincident in appearance time with the peak of the slower moving and minor component of the mixture **3a** and **3b**. When the recovered monobromo compound was subjected to an additional 24-hr treatment in refluxing ethanolic potassium hydroxide, little change occurred and it could be recovered in at least 83% yield. Only a trace of olefinic product could be detected by glc. The pmr spectrum of this recovered bromide showed a singlet at ($W/2$ = 2.8 Hz) at τ 4.6 in the anomeric proton region [*cf.* the singlet ($W/2$ = 3.5 Hz) at τ 4.6 for the mixture of **3a** and **3b** described previously[2]]. The 100-MHz pmr spectrum of this recovered monobromide permitted a decision that the disposition of the bromination is cis rather than trans to the five-membered ring of the bicyclo structure as indicated by structure **3b**. Signal assignments were readily made by double irradiation spin decoupling. Irradiation of the nuclei of the protons on C-3 giving the high field multiplet centered at τ 7.82 caused loss of a large coupling (~6–7 Hz) in the multiplet at τ 6.02, the position at which the absorption due to the proton on C-4 occurred. Irradiation at τ 6.02 gave a similar loss of coupling at τ 7.82. This large coupling can occur only if the two coupled protons on C-4 and C-3 are trans diaxial, and this requires that the six-membered ring be in the more stable chair conformation as expected. Structure **3b** but not **3a** has, in the chair conformation, the two protons on C-3 and C-4 in a trans diaxial relation. In this more stable conformation, the bromine atom on C-4 and the proton on C-3 of structure **3b** are not trans diaxially oriented, an orientation which is known to facilitate base-catalyzed removal of the halogen acid. On the other hand, in structure **3a** where the bromine atom is trans to the five-membered ring, the lower energy chair form does have the C-4 bromine trans diaxially disposed with respect to a proton on C-3. Hence the monobromo compound **3** which dehydrohalogenates more readily is considered to be **3a**, while that which is more resistant to removal of the halogen acid is believed to be **3b**.[7]

The olefinic material obtained by heating the mixture of **3a** and **3b** in refluxing ethanolic potassium hydroxide, when analyzed by glc on a freshly prepared column of butanediol succinate on Chromosorb W, showed two well-separated peaks in the area ratio of 1:9. These two components were readily separated by glc. A glc analysis of these separated compounds on two different columns gave only one symmetrical narrow peak in each case. The elemental analysis for each agreed with that required for the olefins **4a** and **4b**. A detailed first-order analysis of the 100-MHz pmr spectrum, using double irradiation to assist in identifying signals, agreed completely with the assignment of structure **4a** to the major isomer and **4b** to the minor isomer. A mixture of the two isolated olefins **4a** and **4b** gave a pmr spectrum identical with the spectrum reported[2] to be due to **4a**. The proportion of the two isomeric olefins **4a** and **4b** obtained depended upon the proportion of base to **3** used during dehydrohalogenation. If the molar ratio of base to **3** was 1:1 up to 3:1, only **4a** was obtained. The use of equimolar amounts of sodium hydride and **3** in 1,2-dimethoxyethane containing some ethanol has given **4a** exclusively.[3] Proportions of base to **3** greater than 3:1 gave increased amounts of **4b** relative to **4a**.

When either **4a** or **4b** was heated in a solution of potassium *tert*-butoxide in *tert*-butyl alcohol,[8] there was obtained a 50–65% yield of olefinic product which was found to be a mixture of **4a** and **4b** in the ratio of ~15:85, respectively. Since the isolated yield of olefin was only 50–65%, this proportion 15:85 can be considered at best as only *indicative* of an equilibrium mixture.

Dehydrohalogenation of the mixture of **3a** and **3b** with a hot (80°) solution of potassium *tert*-butoxide in *tert*-butyl alcohol gave in 40–45% yield a mixture of **4a** and **4b** generally in the proportion of 20–15:80–85. The major component **4b** could be separated quite readily by fractional distillation in a spinning-band column.

The exclusive attack of the bromine on the α position of the acetal[6] requires comment. Since (1) the presence of hydrobromic acid apparently increases the rate of bromination of **2**, and (2) it is known that distillation of 2-alkoxytetrahydropyrans in the presence of an acidic species such as phosphorus pentoxide or *p*-toluenesulfonic acid eliminates the alkoxy group and provides a 3,4-dihydro-2*H*-pyran,[9-11] and (3) it is also known that bromination of α,β-unsaturated ethers in alcohol solution containing ammonia[12] or silver carbonate[13] produces α-bromoacetals, the routes A and/or B shown in Scheme II are suggested as reasonable paths by which acetals or ketals are halogenated exclusively in the α position. The key step following the protonation of the acetal **2** is the cleavage of the C-5,O-6 or C-5,O-8 bond to form the oxocarbonium ion **8** and/or **9** which respectively would readily lose a proton to form the α,β-unsaturated ether **10** and/or **1**. The attack by bromine on **10** or **1** would form the β-bromooxocarbonium ion **11** and **12** or the α,β-dibromide **13** and **14**. By an intramolecular reaction involving the hydroxy group, any of the last four species could form the α-bromo acetal **3**. In support of Scheme II we have treated **1** with bromine under the same conditions used to brominate **2** and obtained a 65% yield of an approximately 1:1 mixture of **3a** and **3b**. The relative effectiveness of path a compared to path b is not known. For the moment we prefer route b on the basis of an apparently greater ease of C-5,O-6 bond cleavage in the hydrolysis or alcoholysis

(7) It has been suggested by the referee that the transition state for the dehydrohalogenation might be syn, and if this were the case for both **3a** and **3b** one could account for the greater resistance of **3b** to dehydrohalogenation since this would require the more difficult approach by base to the endo face of **3b** compared to the easier approach of base to the exo face of **3a**.

(8) D. L. Griffith, D. L. Meges, and H. C. Brown, *Chem. Commun.*, 90 (1968).

(9) W. E. Parham and H. E. Holmquist, *J. Amer. Chem. Soc.*, **73**, 913 (1951).

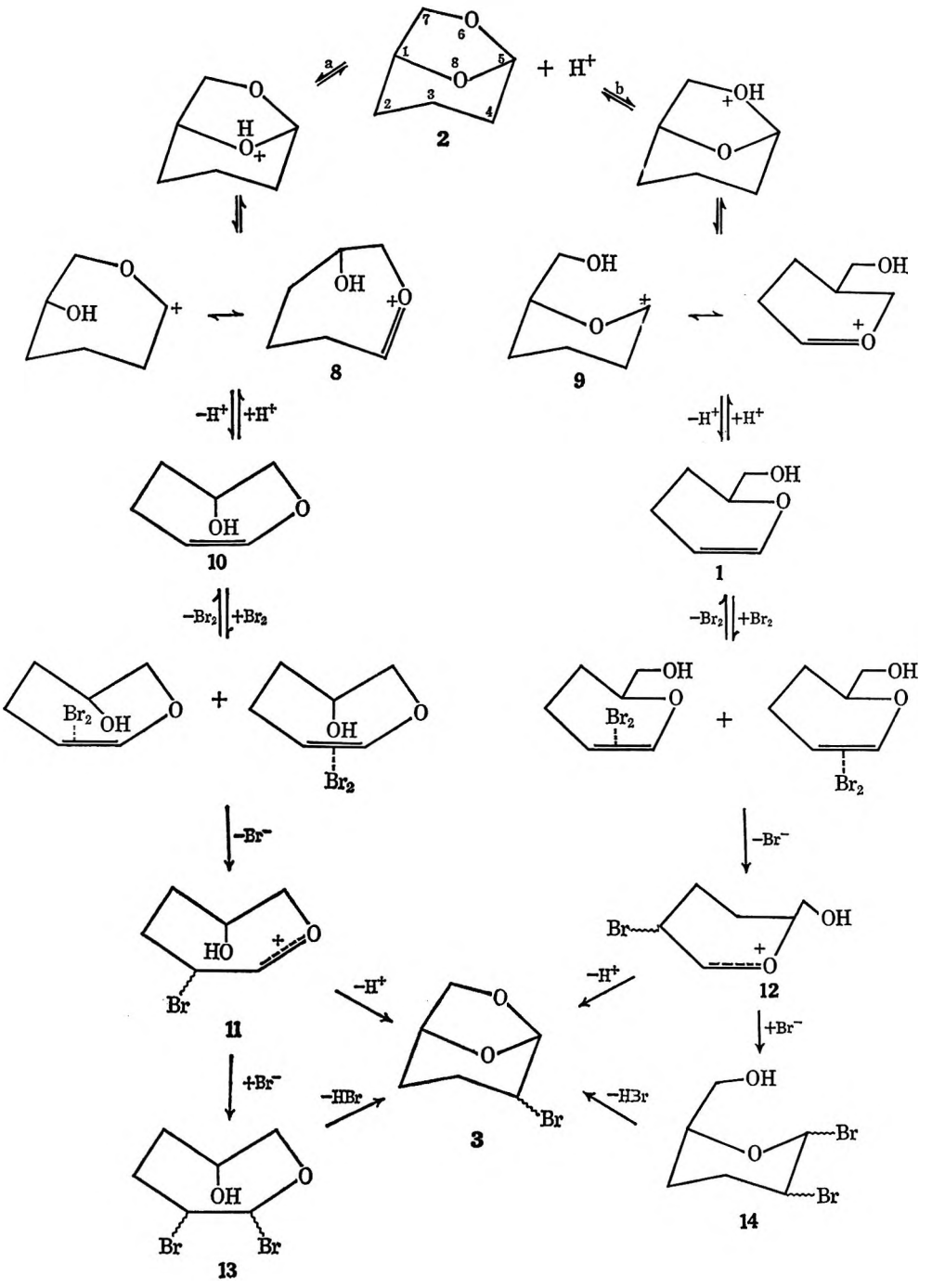
(10) M. Julia and B. Jacquet, *Bull. Soc., Chim. Fr.*, 1983 (1963).

(11) R. M. Srivastava and R. K. Brown, *Can. J. Chem.*, **48**, 2341 (1970).

(12) F. Sweet and R. K. Brown, *ibid.*, **46**, 707 (1968).

(13) R. U. Lemieux and B. Fraser-Reid, *ibid.*, **43**, 1460 (1965).

SCHEME II



of substituted bicyclic structures such as 2 to produce only the substituted pyran structure. However the substituted pyran so obtained may have been the result of accumulation of the thermodynamically more stable product and thus may not support the view that the C-5,O-6 bond cleaves much more readily than does the C-5,O-8 bond.

Experimental Section

All boiling points are uncorrected. Glc analyses were made with an F & M Model 700 chromatograph equipped with a column (1/8 in. × 12 ft) containing either 20% butanediol succinate on Chromosorb W (60–80 mesh) or 10% Reoplex (polypropylene adipate) on 80–100 mesh Chromosorb WAW (DMCS 5750). Helium was the carrier gas. Pmr spectra were taken in $CDCl_3$ and referred to tetramethylsilane.

6,8-Dioxabicyclo[3.2.1]octane (2).—Compound 2 was prepared according to published directions[2] but with the following modification. The amount of sodium methoxide added to the cooled solution of 1 and *p*-toluenesulfonic acid catalyst was doubled to ensure complete neutralization of the acid, thus preventing polymerization with consequent loss of product. The yield of 2 was 88–94%.

4-Bromo-6,8-dioxabicyclo[3.2.1]octane (3). A. From 2.—To a well-stirred solution of 2 (83.3 g, 0.73 mol) in 1.5 l. of dry CCl_4 was added dropwise a solution of bromine (116 g, 0.73 mol) in an equal volume of dry CCl_4. Bromine consumption occurred slowly at first but soon increased in rate as the concentration of evolved hydrogen bromide increased. The rate of bromine addition was adjusted so that the reaction was under control, requiring 1 hr total time for complete addition. When the last of the bromine had been added, the solvent was removed on a rotatory evaporator under vacuum at a *maximum* bath temperature of 30°. The residual light brown oil was distilled under vacuum in an apparatus equipped with a potassium hydroxide trap and afforded 112 g (80%) of 3, bp 60° (0.2 mm) [lit.[2] bp 68° (1 mm)]. Glc analysis on a freshly prepared column containing the butanediol succinate, and on a column packed with

the Reoplex, showed in both cases two overlapping peaks in the area ratio of 3:2 corresponding to **3a** and **3b**, respectively.

B. From 1.—To a stirred solution of 22.8 g (0.20 mol) of 1 in 300 ml of dry carbon tetrachloride at room temperature was added dropwise over a period of 1 hr 32 g (0.20 mol) of bromine dissolved in 50 ml of dry carbon tetrachloride. The reaction mixture became warm (~45°) and evolved hydrogen bromide profusely. When the bromine addition was completed, the mixture was freed from solvent in a rotary evaporator under vacuum during which time the temperature of the mixture was kept below 30°. The light brown oily residue was distilled in an apparatus equipped with two potassium hydroxide traps and gave 14.9 g (65%) of 4-bromo-6,8-dioxabicyclo[3.2.1]octane (**3**) boiling at 64° (0.5 mm). Glc on either or the two columns showed it to be identical in retention time with **3** obtained from 2 above and that it was an approximately 1:1 mixture of **3a** and **3b**.

Dehydrohalogenation of 4-Bromo-6,8-dioxabicyclo[3.2.1]octane (3). A. With a 1 or 2 *M* Excess of Potassium Hydroxide in 95% Ethyl Alcohol.—The published directions[2] were modified as follows. To a stirred solution of 56 g (1.0 mol) of potassium hydroxide in 900 ml of 95% ethyl alcohol was added 96.5 g (0.50 mol) of the cis–trans mixture **3ab**. The resulting solution was heated under reflux for 24 hr and then cooled and filtered. The solvent (700 ml) was removed by fractional distillation at atmospheric pressure. Water (200 ml) was added to the residual dark mass and the mixture was then continuously extracted with ether for 10 hr. The ether extract was dried ($MgSO_4$) and freed from solvent by fractional distillation. The remaining black oil was distilled under reduced pressure and gave 21.8 g (39%) of 6,8-dioxabicyclo[3.2.1]oct-3-ene (**4a**): bp 58° (15 mm); $n^{25}D$ 1.4775 [lit.[3] bp 83–84° (51.5 mm); $n^{22}D$ 1.4795]; 100-MHz pmr τ 4.18 (m, 2, vinyl), 4.52 (m, $W/2 \sim 5$ Hz, 1, anomeric H), 5.35 (m, 1, HCO), 6.06 (t, 1, HCO), 6.33 (d, 1, HCO), 7.22 (d, 1, CH aliphatic), and 8.13 (d, 1, CH aliphatic). Glc on both columns showed only one narrow symmetrical peak.

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.04; H, 7.23.

The recovered bromide **3b** boiled at 71° (1.0 mm): $n^{27}D$ 1.5156 [lit.[2] of mixture **3a–b**, bp 68° (1 mm) or 90° (4.5 mm); $n^{27}D$ 1.5176]; glc analysis on either of the columns used showed only one narrow symmetrical peak; 100-MHz pmr τ 4.61 (s, 1, anomeric), 5.41 (m, 1, HCO), 6.05 (m, 3, CH_2O and HCBr), and 8.10 (m, 4, CH_2). Irradiation at τ 6.02 gave loss of coupling of ~6-7 Hz in the multiplet at τ 7.82 due to the two protons on C-3.

B. **With Potassium *tert*-Butoxide in *tert*-Butyl Alcohol.**—To a stirred solution of 0.75 mol of potassium *tert*-butoxide from 28.6 g of potassium metal slowly added to 750 ml of dry *tert*-butyl alcohol under N_2 was added 48.2 g (0.25 mol) of *cis,trans*-4-bromo-6,8-dioxabicyclo[3.2.1]octane (**3**). The mixture was kept at 80° for 24 hr and then half of the solvent was removed by fractional distillation. The dark residue was cooled and diluted with 250 ml of water. The resulting mixture was continuously extracted with ether for 12 hr. The ether extract was dried ($MgSO_4$) and freed from solvent by fractional distillation, and the residue distilled under vacuum to give 10 g (36%) of a 4:96 mixture (by glc) of the olefins **4a** and **4b**, respectively, bp 58–60° (16 mm), along with 12.3 g of **3b**, bp 72° (1.5 mm). The mixture of **4a** and **4b** was separated by distillation with a spinning-band column (50 cm): bp of **4b** 69–69.5° (41 mm); $n^{22}D$ 1.4750; 100-MHz pmr τ 4.14 (m, 2, vinyl), 4.34 (broad s, 1, anomeric H), 5.4 (t, 1, HCO), 6.02 (d, 1, HCO), 6.28 (t, 1, HCO), 7.47 (d, 1, CH aliphatic), and 8.03 (d, 1, CH aliphatic). Glc on both columns showed only one narrow symmetrical peak.

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.24; 63.99; H, 7.31; 7.22.

One of the repetitions of this experiment gave a yield of 44% of a 21:79 ratio of **4a**:**4b** as the lowest proportion of **4b** obtained.

Isomerization of 4a and 4b. A. With Potassium *tert*-Butoxide in *tert*-Butyl Alcohol.—A solution of potassium *tert*-butoxide in *tert*-butyl alcohol [from 3.13 g (0.08 g-atom) of potassium added to 80 ml of dry *tert*-butyl alcohol] containing 4.88 g (0.04 mol) of **4a** was kept under N_2 at 80° for 24 hr. Subsequent treatment followed that described in B above. There was obtained 2.40 g (49%) of a 20:80 mixture of the olefins **4a** and **4b**, respectively (by glc), bp 59° (15 mm).

When 5.60 g (0.05 mol) of **4b** was treated similarly with 0.051 mol of potassium *tert*-butoxide in *tert*-butyl alcohol, there was obtained 3.50 g (63%) of a 15:85 mixture of the olefins **4a** and **4b**, respectively (by glc).

B. **With Potassium Hydroxide in 95% Ethyl Alcohol.**—A solution of 21 g (0.188 mol) of a 19:1 mixture of **4a** and **4b** and 36.8 g (0.65 mol) of potassium hydroxide in 180 ml of 95% ethyl alcohol was heated under reflux (N_2) for 24 hr. The solvent was then removed by fractional distillation. The residue, diluted with water, was extracted several times with ether. The combined ether extracts were dried (Na_2SO_4) and freed from solvent. Fractional distillation of the residue under vacuum gave 12.6 g (60%) of a colorless liquid, bp 58–62° (9 mm), $n^{23}D$ 1.4775. Glc analysis produced two well-separated narrow peaks which showed this to be a mixture of **4a** and **4b** in the ratio 2:3, respectively.

Registry No.—**4a**, 20583-51-1; **4b**, 27925-22-0.

Acknowledgment.—We thank the National Research Council of Canada for financial assistance in this work.

Conformational Analysis of Sulfur-Containing Heterocycles. A Dipolar Effect[1]

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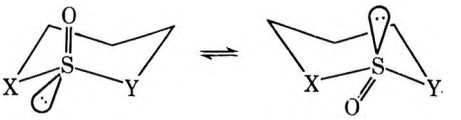
Received May 11, 1970

The conformational preferences for substituents on cyclohexane ring systems are well studied.[3] However, when heteroatoms containing nonbonded lone-pair electrons are present, conformational effects may be altered considerably.[4] The conformational preference for an axial disposition of a sulfoxide oxygen is very small (0.1–0.5 kcal).[5] It is therefore surprising that sulfoxides of the type **1** where X and Y are hetero-



1a, X = Y = O
b, X = O; Y = NH
c, X = Y = CH_2

atoms exhibit a remarkably high axial preference (3–5 kcal/mol).[6] The substitution of a heteroatom for a methylene group in such systems should lower the barrier to chair–chair interconversion by reducing 1–2 rotational interactions.[7] Moreover, Eliel[4a] has demonstrated that sulfur (presumably oxygen as well) with its lone pairs has a smaller space requirement than a methylene group. While there have been several explanations advanced[5] for the small preference for axial S=O in **1c**, the question remains open as to why

(1) Organic Sulfur Chemistry. Part VII. For Part VI, see D. N. Harpp and B. A. Orwig, *Tetrahedron Lett.*, 2691 (1970).

(2) Holder of a NRCC Scholarship, 1968–1970.

(3) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 36–126.

(4) See, for example, (a) E. L. Eliel and R. O. Hutchins, *J. Amer. Chem. Soc.*, **91**, 2703 (1969); (b) H. T. Kalff and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 467 (1966).

(5) (a) N. A. Allinger, J. A. Hirsh, M. A. Miller, and L. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969); (b) J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966).

(6) (a) D. G. Hellier, J. G. Tillett, H. F. van Woerden, and R. F. M. White, *Chem. Ind. (London)*, 1956 (1963); (b) H. F. van Woerden and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **86**, 342 (1967); **86**, 353 (1967); (c) J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, **34**, 175 (1969).

(7) E. B. Wilson, Jr., *Advan. Chem. Phys.*, **2**, 367 (1959).

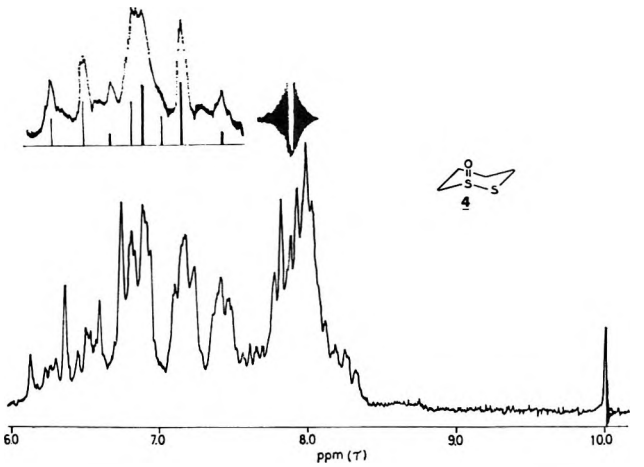
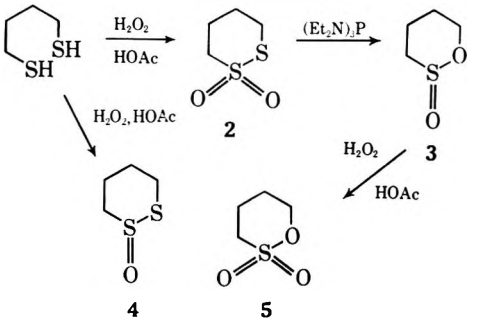


Figure 1.—60-MHz nmr spectrum of 1,2-dithiane 1-oxide (4).

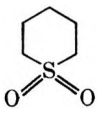
the introduction of the oxygen atoms into the ring (*e.g.*, **1a,b**) so markedly increases this axial preference. As outlined above, these heteroatoms should decrease the conformational stability of such molecules. We felt that further insight might be gained by an analysis of other similar heterocycles.

We have recently developed simple syntheses of some missing members of this series, 1,2-dithane 1,1-dioxide (**2**), 1,2-oxathiane 2-oxide (**3**),[8] its thio analog,



1,2-dithiane 1-oxide (**4**), and 1,2-oxathiane 2,2-dioxide (**5**), and have undertaken a detailed analysis of the nmr spectra of these compounds to further investigate this conformational preference.

The low temperature nmr spectra of both sultone **5** and thiosultone **2** indicated that these compounds undergo very rapid chair–chair interconversion as low as −90°. In contrast, the conformational isomers of thiane 1,1-dioxide (**6**) are observable at −60°.[5b] The



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second heteroatom, as expected, significantly lowers the barrier to chair–chair interconversion.

The spectrum of 1,2-dithiane 1-oxide (**4**) (Figure 1) was extremely complex; however, irradiation of the high-field multiplet caused the collapse of the low-field lines to two AB quartets thus indicating the nonequivalence of the pairs of protons α to the S and S=O groups. While it was not possible to definitively assign the configuration of the S=O bond in this molecule, clearly this ring is not undergoing interconversion.

(8) D. N. Harpp and J. G. Gleason, *Tetrahedron Lett.*, 1447 (1969).

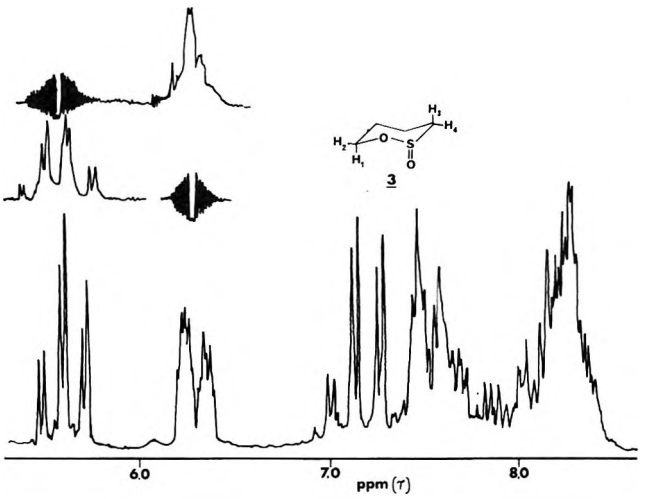


Figure 2.—100-MHz nmr spectrum of 1,2-oxathiane 2-oxide (**3**).

The 100-MHz nmr spectrum of 1,2-oxathiane 2-oxide (**3**) (Figure 2) was interpretable only in terms of a single conformational isomer. The multiplet at τ 5.58 may be assigned to the axial proton H_1 adjacent to the ring oxygen on the basis of the observed 11.5-Hz coupling which is consistent with a trans diaxial relationship to the adjacent proton.[9] The multiplet at τ 6.28 was assigned to the corresponding equatorial proton H_2. This assignment was confirmed by double resonance. Similarly, the multiplet at τ 7.13 was assigned to the axial proton H_3.

This interpretation has placed both axial protons H_1 and H_3 to low field relative to their equatorial counterparts H_2 and H_4. In alicyclic systems, axial protons are normally displaced to high field relative to equatorial protons.[9] Previous studies have shown that protons in a 1,3 diaxial relationship to a sulfinyl oxygen experience a deshielding effect[10] (the so-called syn-axial effect)[10e,f] due to a proximity effect[10f,11] and/or an acetylene-like anisotropy[10,f,g,12] of the S=O bond. Thus, the deshielding of H_1 relative to H_2 would imply that H_1 is in a 1,3 cis-diaxial relationship to the S=O bond as illustrated. In addition, deshielding of proton H_3 relative to H_4 is consistent with that observed for other sulfoxide systems.[13,14]

(9) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 193.

(10) (a) For a review, see J. G. Tillett, *Quart. Rep. Sulfur Chem.*, **2**, 227 (1967); see also (b) C. R. Johnson, and W. O. Sigel, *J. Amer. Chem. Soc.*, **91**, 2796 (1969); (c) E. T. Strom, B. S. Snowden, and P. A. Toldan, *Chem. Commun.*, 50 (1969); (d) C. R. Johnson, *Tetrahedron Lett.*, 1879 (1969); (e) A. B. Foster, J. M. Durbury, T. D. Inch, and J. M. Webber, *Chem. Commun.*, 881 (1967); (f) K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *ibid.*, 759 (1966); (g) J. G. Pritchard and P. C. Lauterbur, *J. Chem. Soc.*, 2105 (1961), and references cited therein.

(11) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Fransico, Calif., 1964, p 51.

(12) R. D. F. Copper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969).

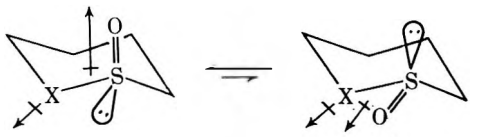
(13) M. Nishio, *Chem. Commun.*, 560 (1969); see also R. S. Edmondson, *Tetrahedron Lett.*, 1349 (1965).

(14) This deshielding of H_3 relative to H_4 is not, however, consistent with assumed acetylenic anisotropy of the S=O bond.[10g] Using an anisotropy constant as -22.6×10^{-30} cm^3 molecule^{-1}, in good agreement with that calculated for an S=O bond in sulfites[10g] and acetylenes,[12] and applying the McConnell point dipole approximation[15] predicts that the signal for H_3 should occur 0.66 ppm upfield from H_4. Such is not the case; the resonance for H_3 is 0.4 ppm *downfield* from H_4. The shift difference of −0.4 ppm is much closer to that which would be expected if the S=O bond anisotropy resembled that of a carbonyl bond and not an acetylenic bone, an assumption for which there is some precedent.[12] However, a more quantitative description of this anisotropy should take into account contributions resulting from the presence of other heteroatoms and bonds in the molecule.

(15) H. M. McConnell, *J. Chem. Phys.*, **37**, 226 (1957).

Since the nmr spectra of both **3a** and **4** are unchanged over a wide temperature range (−90 to +150°), it may be concluded that both these compounds are conformationally pure. Thus **3** (and presumably **4**) adopt the same axial sulfoxide conformation as do the sulfites. Since only one isomer is observed at room temperature for sulfite **1a**, the oxides of oxathiane **3**, oxathiazine **1b**, and dithiane **4** under conditions where less than 5% of the minor isomer would be detectable, a conformational barrier in excess of 2000 cal exists for these compounds. This is more than 1800 cal greater than the barrier observed for sulfoxide **1c** (X = Y = CH_2).

We suggest that this strong preference for an axial S=O configuration results from a dipolar interaction analogous to the anomeric effect observed in carbohydrate systems.[16] The conformation in which the S=O bond is in an equatorial position possesses an unfavorable dipolar arrangement, since the net dipole resulting

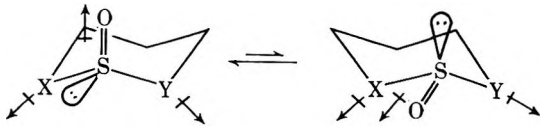


a b

3, X = O
4, X = S

from the nonbonded lone-pair electrons of oxygen is nearly parallel to that of the S=O bond. This unfavorable arrangement is relieved with the S=O bond adopting an axial configuration. Such a dipolar effect has been used to explain the conformational preference (500 cal) of the trans-diaxial conformation of *trans*-1,2-dibromocyclohexane over the corresponding diequatorial isomer.[17] For methyl glycosides, the dipolar or anomeric effect is approximately 1.5 kcal;[18] for a highly polar group as a sulfoxide, this effect should be even greater.

A similar argument may be advanced for the conformational preference of an axial S=O bond in sulfite **1a** and the oxathiazine oxide **1b**. Thus, in all of



1a, X = Y = O
b, X = O; Y = NH

these cases **1a**, **1b**, **3**, and **4**, the sulfoxide bond is adjacent to at least one heteroatom bearing lone-pair electrons and therefore should experience an electrostatic dipole repulsion when the S=O bond is in an equatorial conformation.[19]

(16) Reference 3, p 375.

(17) W. Kwestroo, F. A. Meijer, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **73**, 717 (1954).

(18) R. U. Lemieux and N. J. Chu, Abstracts, 133rd National Meeting of the American Chemical Society, New York, N. Y., 1958, 31N.

(19) Müller has recently carried out semiempirical calculations on analogous heterocyclic systems which indicate that diaxial lone-pair repulsions are also significant (5–6 kcal/mol): K. Müller, *Helv. Chim. Acta*, **53**, 1112 (1970).

Experimental Section

1,2-Dithiane, 1,1-Dioxide (2).—This compound was prepared as previously described,[20] mp 54–56°.

1,2-Oxathiane 2-Oxide (3).—Substance **3** was formed by desulfurization with tris(diethylamino)phosphine[21] as described in an earlier publication,[20] bp 60–61° (0.5 mm).

1,2-Oxathiane 2,2-Dioxide (5).—To a solution of 100 mg (0.84 mmol) of 1,2-oxathiane 2-oxide (**3**) in 5 ml of water was added an aqueous potassium permanganate solution until the permanganate color persisted. The solution was filtered and acidified with concentrated hydrochloric acid, and the solvent removed under vacuum; the residue was dissolved in ether and dried, and the ether removed under vacuum to provide a clear oil identical in its ir and nmr spectrum with an authentic sample.

1,2-Dithiane 1-Oxide (4).—A solution of 10.0 g (82 mmol) of 1,4-butanedithiol in 200 ml of acetic acid was cooled to 10° and 17 ml (175 mmol) of a 35% hydrogen peroxide solution was slowly added. To maintain solution, 25–40 ml of methylene chloride was added as necessary. After this stirred for 24 hr, the solvent was removed under vacuum, the residue diluted with water, extracted with ether, washed with water, and dried, and the solvent removed under vacuum to afford a viscous oil which on distillation provided a fraction, bp 100–105° (0.1 mm), which crystallized on cooling to yield 0.6 g (5%) of a wax-like material, mp 67–74°. This material could be sublimed *in vacuo* [70–90° (0.1 mm)] to provide pure product, mp 74–76°. This material was homogeneous by vpc analysis, ir (KBr) 1060 cm^{-1} (S=O). The mass spectrum of this material exhibits a parent ion at *m/e* 136.0007 (calcd for $C_4H_8OS_2$, *m/e* 136.0016).

Registry No.—**2**, 18321-15-8; **3**, 24308-29-0; **4**, 7153-76-6; **5**, 1633-83-6.

Acknowledgment.—We wish to thank the National Research Council of Canada for financial support of this work and Professors J. T. Edward and A. S. Perlin for helpful discussions.

(20) D. N. Harpp, J. G. Gleason, and D. K. Ash, *J. Org. Chem.*, **36**, 322 (1971).

(21) This phosphine has been used to desulfurize a wide variety of organosulfur compounds: see D. N. Harpp, J. G. Gleason, and J. P. Snyder, *J. Amer. Chem. Soc.*, **90**, 4181 (1968); D. N. Harpp and B. A. Orwig, *Tetrahedron Lett.*, 2691 (1970); D. N. Harpp and D. K. Ash, *Chem. Commun.*, 811 (1970).

Formation and Transannular Reactions of Cyclopropane Half-Cage Alcohols[1a]

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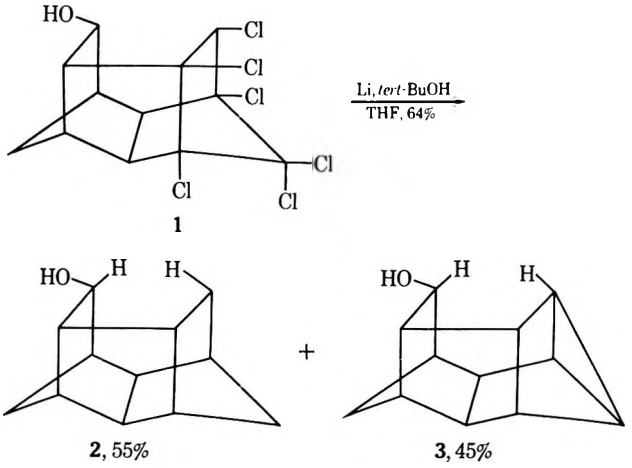
Dechlorination of hexachloro half-cage alcohol **1** with lithium and *tert*-butyl alcohol in tetrahydrofuran[2] gave a solid alcohol mixture that consisted of 55% of the known[2,3] half-cage alcohol **2** and 45% of a new alcohol, cyclopropane half-cage alcohol **3**. In the nmr spec-

(1) (a) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967. (b) Address inquiries to this author. (c) Deceased Nov 23, 1969.

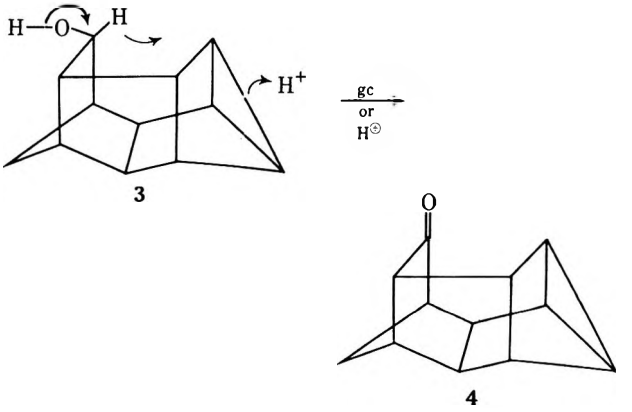
(2) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960).

(3) L. de Vries and S. Winstein, *J. Amer. Chem. Soc.*, **82**, 5363 (1960).

trum the α protons of the two alcohols appeared as slightly broadened singlets at τ 5.41 and 5.59, respectively. Both signals are at unusually low field due to strong deshielding that arises from severe steric congestion[4,5] of the α protons with the opposed transannular hydrogen atoms. This deshielding in half-cage alcohols has been discussed previously.[5]

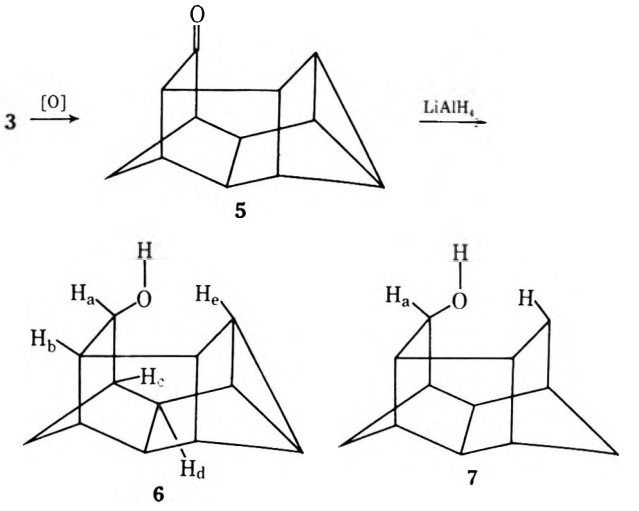


Alcohol **3** could not be isolated in pure form either by alumina chromatography, fractional crystallization, or preparative gas chromatography. The mixture of alcohols decolorized bromine in carbon tetrachloride but did not react with potassium permanganate in acetone, indicative of the presence of the cyclopropane ring in **3**. Pure **2** does not decolorize bromine in carbon tetrachloride. Attempted gas chromatographic separation of the alcohol mixture led to conversion of **3** to half-cage ketone **4** as determined by infrared spectra of the two materials, **2** and **4**, collected from the gas chromatograph. This conversion also occurred quantitatively within a few hours when an ether solution of the alcohol mixture was stirred with dilute sulfuric acid. From a 55:45 mixture of alcohols there was obtained a 55:45 mixture of half-cage alcohol **2** and half-cage ketone **4**.



The quantitative conversion of **3** to **4** is consistent only with the proposed cyclopropane half-cage alcohol structure. The acid-catalyzed cyclopropane ring opening occurs in the direction of the least strained structure; cleavage of either of the other two cyclopropane ring bonds would lead to a highly strained structure containing a cyclobutane ring. The hydride shift may possibly be concerted with and may facilitate the ring opening.

Oxidation of a 53:47 mixture of the two alcohols with chromium trioxide in pyridine gave a 57:43 mixture of the corresponding ketones in 78% yield. A pure sample of the cyclopropane half-cage ketone **5** was obtained by gas chromatographic purification. The carbon–hydrogen analysis of this ketone was consistent with an empirical formula of $C_{12}H_{12}O$. The ketone instantly decolorized bromine in carbon tetrachloride but did not react with potassium permanganate in acetone, as expected for the presence of the cyclopropane ring. Furthermore, the infrared spectrum exhibited cyclopropane C–H stretching at 3067 and 3040 cm^{-1} and a carbonyl frequency of 1746 cm^{-1}, exactly the same as that of **4**. Lack of a methylene group adjacent to the carbonyl was indicated by the lack of absorption at 1410–1420 cm^{-1}, an absorption that is characteristic[6] of α-methylene ketones.



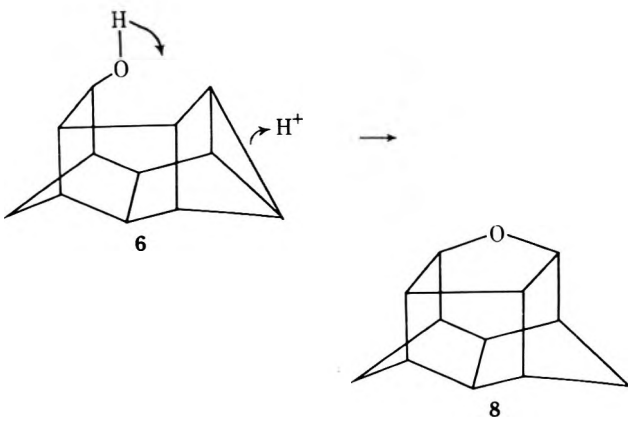
Reduction of **5** with lithium aluminum hydride in ether followed by a work-up that involved no trace of acid gave the oxygen-inside cyclopropane half-cage alcohol **6** in 91% yield. In the nmr spectrum ($CDCl_3$) the α-proton signal appeared at τ 6.02 as a doublet, J = 8.5 Hz, with both components of the doublet split into triplets, with an apparent J of 2 Hz. The major splitting is due to coupling of the α proton with the eclipsed H_b proton. Additional small coupling of the α proton with H_c and long-range coupling with H_d result in the 2-Hz splitting. The severely congested transannular hydrogen atom H_e is strongly deshielded and appeared as a broad signal at τ 6.96. In the nmr spectrum (CCl_4) of oxygen-inside half-cage alcohol **7**, the α-proton signal appeared at τ 6.08, and the strongly deshielded transannular hydrogen atom signal appeared at τ 6.45.[5]

After the chloroform-*d* solution of **6** was allowed to stand overnight, the nmr spectrum of the solution revealed very nearly complete conversion of **6** to cage ether **8**. Removal of the solvent gave impure cage ether; after purification the solid had an infrared spectrum, gas chromatographic retention time, and melting point which were identical with those of authentic **8**.[4] Chloroform-*d* usually contains traces of acid. The

(4) D. Kivelson, S. Winstein, P. Bruck, and R. L. Hansen, *J. Amer. Chem. Soc.*, **83**, 2938 (1961).

(5) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *ibid.*, **87**, 5247 (1965).

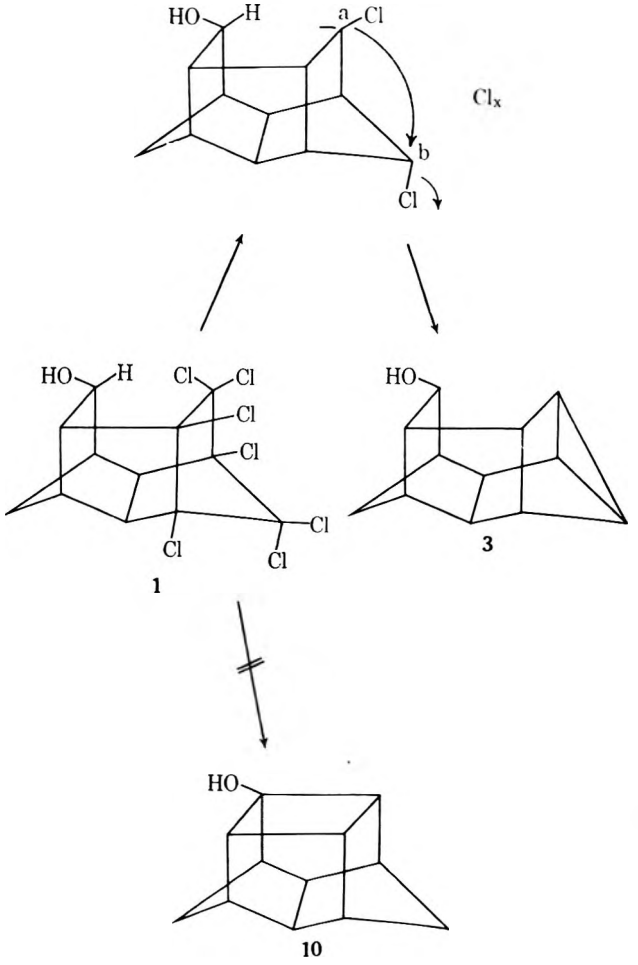
(6) S. A. Francis, *J. Chem. Phys.*, **19**, 942 (1951).



6 8

conversion of **6** to **8** probably occurred by acid-catalyzed cyclopropane ring opening, possibly with oxygen participation, and ring closure to the ether. This conversion further supports the structural assignments for the two cyclopropane alcohols and the ketone **5**.

Formation of **3** from hexachloro half-cage alcohol **1** could occur either by a carbene mechanism or by an internal carbanion displacement of chlorine. The carbene mechanism would involve abstraction of the hydrogen α to chlorine at C_a by lithium *tert*-butoxide formed in the dechlorination, followed by α elimination of chloride anion to form a carbene. Insertion of the carbene into the proximate C_b–Cl bond or the C_b–H bond formed in the dechlorination would ultimately



1 3 10

give rise to **3**. If the carbene mechanism were operative, insertion into the opposed transannular carbon–hydrogen bond to give bird-cage alcohol **10**[7] might be expected also. In fact, there is less than 0.3% bird-cage alcohol in the crude product mixture from dechlorination. It thus appears that the carbanion displacement of chlorine is responsible for the cyclopropane ring formation. The only chlorine atom in a suitable stereochemical position for displacement is the *anti*-chlorine atom on C_b.[8] Carbanion formation at C_a could occur either by proton abstraction by lithium *tert*-butoxide or by exchange of the chlorine atom with lithium.

Experimental Section

Melting points are corrected. Infrared spectra were determined with a Perkin-Elmer Model 421 spectrometer; frequencies are accurate to within ± 2 cm^{-1}. Nmr spectra were determined with a Varian A-60 spectrometer.

3. Dechlorination of 1.—To a magnetically stirred solution of 28.5 g of pure hexachloro half-cage alcohol **1**, mp 203–203.5° (lit.[9] mp 204°), and 158 g of *tert*-butyl alcohol in 500 ml of tetrahydrofuran under dry nitrogen was added 30 g of lithium wire cut into 0.25-in. lengths so that the freshly cut pieces fell directly into the 3-l. flask. After a few minutes a vigorous, exothermic reaction began that required cooling with an ice bath. The mixture was allowed to reflux spontaneously with stirring until the reaction subsided (90 min). The mixture was held at reflux on a steam bath for an additional hour. The hot reaction mixture was poured through a wire screen to remove residual lithium. Ice and then 2 l. of water were added. The mixture was extracted with 500 ml of ether and then with two 250-ml portions of ether. The ether layers were combined, extracted with three 200-ml portions of saturated sodium chloride solution, dried (Na_2SO_4), and concentrated to an oil. The oil was heated several minutes on a steam bath under aspirator vacuum. Upon cooling, the oil solidified. Gc analysis (1/8 in. × 5 ft column of 25% SE-30 at 155°) indicated that the mixture consisted of 93% **2** and **3**, with less than 0.3% bird-cage alcohol **10** (none detected). The solid, 12 g, exhibited α-proton signals at τ 5.41 (55%) and 5.59 (45%) in the nmr spectrum ($CDCl_3$ solvent).

Repeated attempts to crystallize the sample from hexane and from aqueous ethanol were unsuccessful. In each case the material separated as an oil. After removal of the solvent, the material was chromatographed on a 2.5 × 40 cm column of activity III alumina. The first 250 ml of eluate (20% ether in pentane) yielded an oil. The next 1250 ml of eluate yielded 7.1 g (54% yield) of a mixture of 55% **2** and 45% **3** (nmr analysis). Elution with 50% ether in pentane and then 100% ether yielded more oil. The combined oils were rechromatographed on a 2.5 × 37 cm column of activity III alumina with 15% ether in pentane. An additional 1.3 g (10% yield) of a 65:35 mixture of **2** and **3** was obtained. Fractional crystallization of 6.2 g of the 55:45 mixture of alcohols from hexane and then aqueous ethanol gave 1.07 g of pure **2**, mp 130–131° (lit.[3] 130–131°), and a 40:60 mixture, constant mp 124–125°, of **2** and **3**. Both the 55:45 and 40:60 mixtures of **2** and **3** decolorized bromine in carbon tetrachloride and did not react with potassium permanganate in acetone. Pure **2** did not decolorize bromine in carbon tetrachloride.

Acid Treatment of 3.—A solution of 6.0 g of a 55:45 mixture of **2** and **3** in 100 ml of ether and a solution prepared from 10 ml of concentrated sulfuric acid and 90 ml of water were stirred together for 8 hr. The aqueous layer was extracted with two 50-ml portions of ether. The ether layers were combined, extracted with three 50-ml portions of saturated sodium bicarbonate solution and 100 ml of water, and dried (Na_2SO_4). The solvent was distilled off through a Vigreux column. Gc analysis (0.25 in. × 2 m column of 20% Apiezon L at 170°) and ir analysis indicated the product mixture to consist of 55% of **2** and 45% of **4**.

The mixture was chromatographed on a 2.5 × 28 cm column of activity I alumina. The ketone, 2.2 g (37% yield), was eluted

(7) P. Carter, R. Howe, and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 914 (1965).

(8) The facile replacement of this chlorine atom by hydrogen *via* alkoxide attack on halogen in a number of similar compounds has been reported: C. H. M. Adams and K. Mackenzie, *J. Chem. Soc. C*, 180 (1969).

(9) C. W. Bird, R. C. Cookson, and E. Crundwell, *ibid.*, 4809 (1961).

with 20% ether in pentane. Sublimation at 85° (0.05 mm) gave 1.87 g of 4, mp 165–167° (lit.[10] 167–169°). The infrared spectrum of this solid was identical with that of authentic 4.[10] Elution of the alumina column with 100% ether gave 3.25 g (54% yield) of 2.

In a control experiment, a solution of 50 mg of 2 in 10 ml of ether was stirred 4 hr with an acid solution prepared from 1.0 ml of concentrated sulfuric acid and 9.0 ml of water. Work-up yielded 47 mg of solid; the infrared spectrum of this material showed it to be pure 2 with no trace of carbonyl absorption.

Cyclopropane Half-Cage Ketone 5.—A 1.0-g sample of a 53:47 mixture of 2 and 3 was added to 2.0 g of CrO_3 in 11 ml of pyridine. The mixture was stirred for 11 hr. Then water was added, and the mixture was extracted three times with pentane. The pentane extracts were combined, washed well with water, dried (Na_2SO_4), and concentrated to 0.77 g (78% yield) of ketone mixture that consisted of 57% of 4 and 43% of 5 (gc analysis on 2-m column of 20% XF-1150 at 180°). A small amount of 5 was purified by gas chromatography and then was sublimed at 80° (0.03 mm) to give 20 mg of pure 5: mp 176–177°; positive test with Br_2–CCl_4; negative test with $KMnO_4$–acetone; ir (CCl_4) 3067 (m), 3040 (m), 2965 (s), 2875 (m), 1746 (s) cm^{-1}, no absorption at 1400–1440 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.77; H, 7.12.

6. Rearrangement of 6 to 8.—A 59-mg sample of 5, mp 173–175°, that contained 0.8% of 4, was treated with a large excess of lithium aluminum hydride in ether After 30 min the reaction mixture was cooled in ice water, and excess hydride was decomposed by dropwise addition of water. Then 30 ml of water was added and the mixture was allowed to stand 1.5 hr. The layers were separated and the aqueous layer was extracted with two 25-ml portions of ether. The ether layers were combined, washed twice with water, dried (Na_2SO_4), and concentrated under vacuum to give 53.5 mg of 6, mp 199–201°, with softening at 191°. This material instantly decolorized bromine in carbon tetrachloride.

The nmr spectrum of a solution of 51 mg of 6 in $CDCl_3$ was taken immediately after preparation of the solution: τ 6.02 (dt, 1, J = 8.5 Hz, J = 2 Hz, HCOH), 6.71 (s, 1, OH), 6.96 (m, 1, transannular H), 7.08–8.8 (m, 11). The solution was allowed to stand 17 hr at room temperature, and another nmr spectrum was taken; this spectrum was identical in all respects with that of authentic cage ether except for trace signals at τ 8.8 and 9.15. There was <5% of 6 (none detected) as judged from complete absence of the α-proton signal of 6. Removal of the solvent and sublimation of the residue at 70° (0.03 mm) gave 23 mg of cage ether, mp 165–175°. The infrared spectrum of this material was identical in all respects with that of authentic cage ether except for an extremely weak hydroxyl absorption and an extremely weak carbonyl absorption. A pure sample of cage ether, mp 191.5–192.5° (sealed capillary; authentic cage ether[4,11] has mp 191–193°), was obtained by gas chromatography on an XF-1150 column. The retention time of the sample was identical with that of authentic cage ether.

Registry No.—5, 28229-16-5; 6, 28229-17-6.

(10) R. Howe and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 915 (1965).
(11) P. Bruck, private communication.

Metalation Reactions. VIII. Evidence for the Sequence of Reactions of Dilithiophenyl-1-propyne

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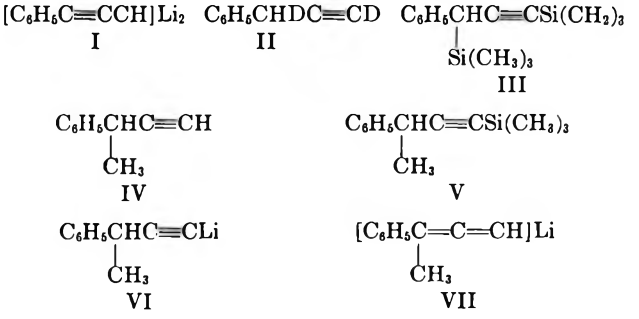
Received August 26, 1970

We have found recently[1] that the reactions of dilithiophenyl-1-propyne (I) with deuterium oxide or trimethylsilyl chloride are accompanied by a rearrangement and give respectively II and III. It was inferred indirectly that the observed hydrogen shift occurred after the first step that was supposed to be an attack on the carbon next to the phenyl group.

We now report reactions proving the attack on the benzylic carbon of I as the first step and present further examples of this rearrangement. The dilithio derivative I reacted with excess methyl bromide for 20 min and then with water yielding 3-phenylbut-1-yne (IV). When the addition of methyl bromide was followed by that of trimethylsilyl chloride, the product obtained was V. The intermediate acetylide VI was apparently slow to react with methyl bromide but reacted rapidly with trimethylsilyl chloride. This acetylide was obtained on rearrangement of the initial product of the reaction (VII).



The reaction of trilithiophenylpropyne[1,2] (VIII) with methyl bromide for 20 min and subsequent treatment with water gave 3-methyl-3-phenylbut-1-yne (IX); the addition of trimethylsilyl chloride 20 min after the addition of methyl bromide to VIII gave X. The structures of the products were supported by their analyses and spectra.

IV showed infrared bands at 3275 and 2100 cm^{-1} supporting the presence of a terminal acetylene group; λ_{max} 242 nm (ϵ 720) shows lack of direct conjugation between the phenyl group and the triple bond. The nmr spectrum showed a doublet at τ 8.53 for the methyl with a coupling of 7 Hz. The benzylic proton at τ 6.37 appeared as an octet and the acetylenic proton at τ 7.91 was a doublet with a coupling constant of 2 Hz.

V did exhibit an acetylenic band at 2170 cm^{-1} but no ≡CH stretching. The lack of conjugation was supported by its uv spectrum with maxima at 252 nm (ϵ 240), 258 (260), and 264 (205). The methyl group appeared in the nmr at τ 8.52 as a doublet with a coupling constant of 7 Hz. The benzylic proton was found at τ 6.28 as a quartet and the trimethylsilyl protons at τ 9.80 (s).

The infrared absorption of IX was similar to that of IV with bands at 3285 and 2110 cm^{-1}, λ_{max} 252 nm (ϵ 220) and 266 (180), and two singlets in the nmr at τ 8.47 (6 H) and 7.85 (1 H) confirmed this structure.

The spectral properties of X were similar to those of IX with differences resulting from the substitution of a trimethylsilyl group for an ethynyl hydrogen: λ_{max}

(1) J. Klein and S. Brenner, *Tetrahedron*, **26**, 2345 (1970).
(2) J. E. Mulvaney, T. L. Folk, and D. J. Newton, *J. Org. Chem.*, **32**, 1674 (1967).

252 nm (ε 760), 257 (740); nmr τ 8.46 (s, 6 H) and 9.82 (s, 9 H).

Experimental Section

3-Phenylbut-1-yne (IV).—A solution of dilithio-1-phenylpropyne was prepared as reported[1] from 1 g of 1-phenylpropyne and 14.5 ml of 1.2 *F* butyllithium in ether. This solution was cooled in an acetone–Dry Ice bath and gaseous methyl bromide was bubbled through it during 15 min. The reaction mixture was allowed to reach room temperature and poured on ice, and the ether layer separated. The reaction product, containing 80% of IV and 20% of 1-phenylpropyne, was separated into its components by glpc.

Anal. Calcd for $C_{10}H_{10}$: C, 92.31; H, 7.69. Found: C, 92.42; H, 7.81.

1-Trimethylsilyl-3-phenylbut-1-yne (V) was prepared as above but trimethylchlorosilane was added after the product of reaction with methyl bromide reached room temperature. The solution was left overnight and poured on water and the product in the ether layer purified by glpc on Apiezon L on Chromosorb, yield 80%.

Anal. Calcd for $C_{13}H_{18}Si$: C, 77.23; H, 8.91. Found: C, 77.38; H, 8.93.

3-Methyl-3-phenylbut-1-yne (IX).—A solution of trilithiophenylpropyne VIII was prepared[1,2] from 1 g of 1-phenylpropyne and a sixfold mole ratio of 1.2 *F* butyllithium in ether. This solution was treated with methyl bromide and worked up as in the preparation of IV. The product IX was obtained in 90% yield and was purified by glpc on polydiethyleneglycol succinate.

Anal. Calcd for $C_{11}H_{12}$: C, 91.67; H, 8.33. Found: 92.05; H, 8.39.

1-Trimethylsilyl-3-methyl-3-phenylbut-1-yne (X) was prepared as above but trimethylchlorosilane was added after methyl bromide. The product X was obtained in 90% yield and purified by glpc on Apiezon L.

Anal. Calcd for $C_{14}H_{20}Si$: C, 77.78; H, 9.26. Found: C, 77.96; H, 9.09.

Registry No.—I, 28129-02-4; IV, 4544-28-9; V, 28129-04-6; IX, 28129-05-7; X, 28129-06-8.

An Efficient and Convenient Synthesis of 1-Methylcyclopropene[1a]

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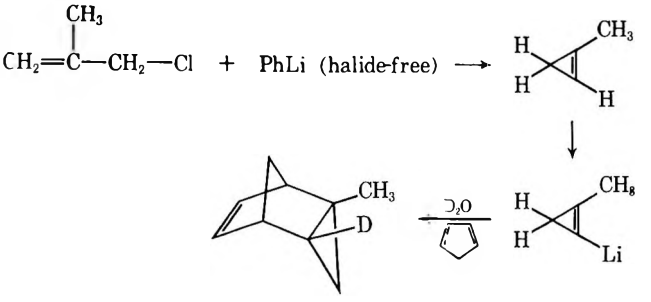
Several syntheses for cyclopropene and its simple derivatives have been reported, by far the most useful of which is the sodium amide induced α elimination of an allylic chloride.[2] This method, however, suffers from the relatively low yields, the difficultly purified product, and the necessity of performing the reaction each time a fresh sample of the cyclopropene is required.

In the course of our mechanistic study of the reaction between phenyllithium and allyl chloride, we demonstrated that α elimination is a major process and that the cyclopropene thus produced undergoes either of two subsequent reactions to roughly equal extents: addition of phenyllithium across the double bond, eventually producing phenylcyclopropane, and abstraction of an olefinic proton yielding 1-lithiocyclopropene.[3] Since the yield of cyclopropene was considerably higher than that in the Closs and Krantz procedure,[2b] we decided to investigate the action of phenyllithium on other allylic chlorides. We now describe a procedure which not only leads to 1-methylcyclopropene in consistently high yields, but which also produces it as a stable derivative which can be stored apparently indefinitely.

When β-methylallyl chloride is allowed to react with phenyllithium prepared in the conventional manner (bromobenzene and lithium), both the coupling product and 1-methylcyclopropene (detected as its Diels–Alder adduct with cyclopentadiene) are formed, normally in comparable amounts but in rather unreproducible yields. It was soon discovered that the presence of either lithium bromide or nonphenyllithium base (such as lithium alkoxide) is a major factor in inhibiting cyclopropene formation. In fact, when an ether solution of crystalline phenyllithium, prepared from iodobenzene and *n*-butyllithium,[4] is employed in this reaction, the yield of coupling product is dramatically reduced and 1-methylcyclopropene is formed in yields typically in the 60–80% range. In and of itself, this is only a modest improvement over the yield claimed by Fisher and Applequist.[2a] The distinct advantages of this new method lies in the following observations.

1. Unlike the parent compound, 1-methylcyclopropene undergoes no detectable addition of phenyllithium across the double bond; instead, complete loss of the olefinic proton occurs, as demonstrated by the formation of totally monodeuterated Diels–Alder adduct when deuterium oxide is used in the neutralization.



2. This lithiocyclopropene can be quenched under conditions such that 1-methylcyclopropene either remains in the reaction vessel or is driven over into a suitable trap (see Experimental Section).

3. Most important, the lithiocyclopropene in ether solution is stable in the freezer for at least 3 months; work-up at this time with deuterium oxide generates the same amount of completely monodeuterated 1-methylcyclopropene as had been present immediately after its synthesis. Thus, one can prepare and store large quantities of the stable organolithium in solution, aliquots of which can then be neutralized to produce the desired quantity of 1-methylcyclopropene.

Although the enormous advantage gained by excluding extraneous lithium salts from the starting material is not understood, it should be noted that other

(1) (a) Partial support of this work by the Robert A. Welch Foundation is gratefully acknowledged as is the assistance of the National Science Foundation in the purchase of a Varian Associates A-56/60A spectrometer; (b) to whom inquiries should be addressed at the Department of Chemistry, The University of Tennessee, Knoxville, Tenn. 37916; (c) National Science Foundation Undergraduate Research Participant, 1968–1969.

(2) (a) F. Fisher and D. A. Applequist, *J. Org. Chem.*, **30**, 2089 (1965); (b) G. L. Closs and K. D. Krantz, *ibid.*, **31**, 638 (1966); (c) R. Köster, S. Arora, and P. Binger, *Angew. Chem., Int. Ed. Engl.*, **8**, 205 (1969).

(3) R. M. Magid and J. G. Welch, *J. Amer. Chem. Soc.*, **90**, 5211 (1968).

(4) M. Schlosser and V. Ladenberger, *J. Organometal. Chem.*, **8**, 193 (1967).

sources of halide-free phenyllithium (such as the commercial material or that prepared from chlorobenzene and lithium shot) give similarly high yields of the stable lithium derivative.

Experimental Section

Instruments.—Analytical glpc was performed on a Perkin-Elmer Model 800 gas chromatograph (flame ionization detector). Product yields were determined by quantitative glpc using the internal standard method; peak areas were measured with a Disc integrator and the response ratios for all products and standards were determined Preparative glpc was performed on a Varian Aerograph Model 202-1B gas chromatograph (thermal conductivity detector). Nmr spectra were obtained on a Varian Associates A-56/60A spectrometer.

Materials.—β-Methylallyl chloride was obtained from Matheson Coleman and Bell and was distilled at atmospheric pressure before use. Iodobenzene was purchased from either Matheson Coleman and Bell or J. T. Baker Chemical Co.; the former gave by far the better and more consistent results. Phenyllithium in benzene–ether was obtained from Alfa Inorganics, Inc., and *n*-butyllithium in hexane from Foote Mineral Co. Lithium shot was prepared from lithium rod by the method of Worden and Burgstahler.[5] Organolithium reagents were analyzed for carbon-bound lithium by either "double titration"[6a] or the triphenylmethane method[6b] (see below); analysis for inorganic halide was done by Volhard titration. All reactions involving lithium reagents were run under an argon atmosphere.

Preparation of Crystalline Phenyllithium.—The procedure of Scholosser and Ladenberger[4] gave phenyllithium yields of the order of 60%, as judged by titration of an aliquot either by the "double titration" method[6a] using 1,2-dibromoethane or, more conveniently, by the addition of a two- to threefold excess of triphenylmethane in tetrahydrofuran followed by titration of the blood-red solution to a pale yellow end point with ethanol in benzene.[6b] Volhard titration of the aqueous layer from the neutralization of an aliquot of solution showed the absence of halide ion.

Synthesis of 1-Methylcyclopropene.—A solution of 2.75 g (0.030 mol) of β-methylallyl chloride in 50 ml of ether (dried over sodium) was added over *ca.* 30 min at room temperature to a stirred solution of a two- to threefold excess of phenyllithium (crystalline) in ether containing cyclooctane as an internal standard. The mixture was stirred for an additional 30 min. An aliquot was quenched with water and quantitatively analyzed by glpc (20 ft × 1/8 in., Hi-Pak silicone rubber W98 column) for β-methylallylbenzene for which a total yield of 0.051 g (1.4%) was calculated. A second aliquot was treated with cyclopentadiene and water. Analysis on the same column for *endo*-2-methyltricyclo[3.2.1.$0^{2,4}$]oct-6-ene, the Diels–Alder adduct of 1-methylcyclopropene, gave a total yield of 2.92 g (80%); the structure was confirmed by comparison of glpc retention time and nmr spectrum with that of an authentic sample.[2a] Small amounts of β-methylallyl chloride could be detected, indicating that the yield of products may be even higher. In other runs, the yield of coupling product was in the range of 1.8–3.2% and that of Diels–Alder adduct from 54 to 73%.

The remainder of the reaction mixture was placed in the freezer for 3 months. Aliquots were then removed and analyzed as described above giving calculated yields for β-methylallylbenzene and Diels–Alder adduct of 4.5 and 76%, respectively. The remainder of this material was quenched with deuterium oxide and cyclopentadiene. The aqueous layer was extracted several times with ether, and the combined organic phases were washed with saturated NaCl, dried over $MgSO_4$, and concentrated with a rotary evaporator. Preparative glpc (10 ft × 3/8 in., XF-1150 column) gave the completely monodeuterated Diels–Alder adduct (total absence of nmr absorption at δ 1.0); mass spectral analysis confirmed that the sample was better than 95% monodeuterated.

For the purpose of further reaction, 1-methylcyclopropene may either be generated by aqueous neutralization of the lithiocyclopropene and used in the original reaction vessel, or generated and driven into a suitable trap, as illustrated for formation of its Diels–Alder adduct, where the reaction vessel was fitted with a condenser which was connected by a length of Tygon tubing to an ice-cooled gas-washing tower containing cyclopentadiene, pentane, and cyclooctane (internal standard). The reaction vessel was cooled (ice bath) while absolute ethyl alcohol was slowly added; a stream of argon was swept through the flask and into the trap. Upon completion of the neutralization, the reaction flask was slowly warmed until ethanol began to reflux, and gentle reflux was maintained for 2.5 hr. Quantitative glpc analysis for the Diels–Alder adduct indicated that 84% of the methylcyclopropene originally present in the reaction flask had been driven over and converted into the Diels–Alder adduct.

Registry No.—1-Methylcyclopropene, 3100-04-7.

(5) L. R. Worden and A. W. Burgstahler, *J. Chem. Educ.*, **45**, 425 (1968).

(6) (a) H. Gilman and F. K. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964); (b) R. M. Magid, S. E. Wilson, T. C. Clarke, and C. D. Duncan, unpublished results.

1,2,3,4-Tetrahydroquinoline 8-Sulfones[1,2]

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Sulfuric acid has been known to cause rearrangement or hydrolysis[3] of arylsulfonanilides. The utilization of the rearrangement technique as a synthetic route to difficultly accessible sulfones has received little attention. Hydrolysis is the predominant reaction for sulfonamides, while either hydrolysis or rearrangement, depending on acid concentration, is possible for the N-substituted sulfonanilides. In their original investigations, Witt and Uermenyi[3] found that high acid concentration with sulfonanilides led primarily to the formation of *o*-amino sulfones rather than the expected hydrolytic products.

Additional work by Witt[4] and later by Halberkamm[5] defined several of the parameters which favored the rearrangement reaction. Where the *N*-alkylaniline was either unsubstituted or possessed *p*-methyl, *p*-methoxy, or *p*-chloro substituents, ortho rearrangement predominated. If, however, the para substituents were amino, nitro, or sulfonic acid, virtually no sulfone was formed and only hydrolytic products were observed. One case of a para rearrangement was reported by Witt[3] in which *N*-ethyl-*p*-toluenesulfono-*o*-toluidide resulted from the rearrangement of *N*-ethyl-4-(*p*-toluenesulfonyl)-*o*-toluidine. Halberkamm, however, observed only ortho rearrangement.

Thus, the rearrangement is generally ortho and appears to be favored by electron-donating groups on the aniline moiety and suppressed by electron-withdrawing groups.

Recently, this reaction has been reinvestigated in this laboratory with a view toward expanding its utility as a synthetic tool. Instead of employing sulfonanilides, the amines were selected such that the amino nitrogen was incorporated in a heterocyclic ring. Thus the heterocyclic sulfonamide **1** would give rise to an aromatic sulfone **2a**. Initially, the rearrangement

(1) Supported by a grant (MH 11489) from the National Institutes for Mental Health.

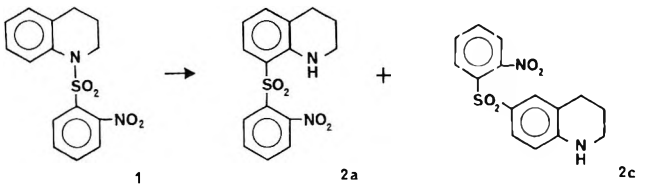
(2) Presented at the 5th Middle Atlantic Regional Meeting of the American Chemical Society, Newark, Del., April 1, 1970.

(3) O. N. Witt and D. Uermenyi, *Ber.*, **46**, 296 (1913).

(4) O. N. Witt and H. Truttwin, *ibid.*, **47**, 2786 (1914).

(5) (a) J. Halberkamm, *ibid.*, **54**, 1665, 1833 (1921); (b) *ibid.*, **55**, 3074 (1922).

of the *o*-nitrobenzenesulfonamide of 1,2,3,4-tetrahydroquinoline (**1**) was studied. In 98% sulfuric acid **1** gave a mixture of isomers (**2a** and **2c**) which was not easily separated. One of the isomers was obtained in a reasonably pure state by continuous extraction of the reaction product with ether, leaving the alternate isomer. The individual isomers were then amenable to purification by crystallization.



1 2a 2c

In order to assign a structure to the two isomers, the 8-sulfone was synthesized unequivocally from 1,2,3,4-tetrahydroquinoline-8-thiol, obtained by the method of Konig[6] and, through interaction with *o*-nitrochlorobenzene in alkali, formed the thioether which was then oxidized to the sulfone **2a**. Comparison of infrared spectra ascertained which of the two isomers was the 8-sulfone, and it was further verified by nmr spectroscopy. The predicted first-order patterns for the protons in the 5, 6, and 7 positions were observed. Splitting patterns for the aromatic protons of the high-melting isomer confirmed the 6-sulfone as the other rearrangement product.

To avoid the formation of a mixture of isomers during rearrangement, further work was done using 6-substituted 1,2,3,4-tetrahydroquinolines. These compounds were converted to the sulfonamides by a modified Hinsberg procedure.

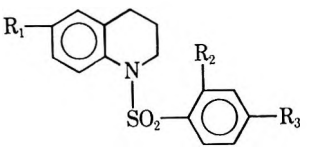
Sulfonamides with a 6-chloro or 6-methyl substituent rearranged smoothly and in good yield. The 6-methoxy compound, however, rearranged with demethylation, contrary to the comparable rearrangement of the sulfonamide of *p*-anisidine in which rearrangement is not accompanied by demethylation.

For the *o*-nitrobenzenesulfonamides, concentrated sulfuric acid at room temperature for from 5 to 60 min was usually sufficient to effect rearrangement, while the unsubstituted benzenesulfonamides required heating at 100° for 1 hr or more. Transient green and blue colors were evident on mixing the reactants, and the sulfuric acid solution of the rearranged material was usually an intense red. Attempted rearrangement of 2,4-dinitrobenzenesulfonamides of tetrahydroquinoline or of indoline gave products which have resisted purification, and thus identification. The synthetic results are summarized in Tables I and II.

Mechanistically, the rearrangement remains to be fully elucidated. The reaction has been compared with the rearrangement of phenylsulfamic acids,[7] and several intramolecular schemes are proposed. One suggested mechanism for the ortho rearrangement postulates the formation of an intermediate (**4**) with subsequent loss of a proton to give the observed product (**2**). A variation of this scheme predicates a preliminary rearrangement to a sulfitoamine (**3**),

(6) W. Konig, W. Kleist, and J. Gotze, *Ber.*, **64B**, 1664 (1931).
(7) C. K. Ingold, "Structure & Mechanism of Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953.

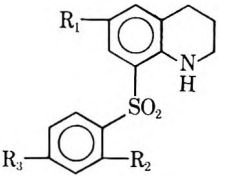
TABLE I



Compd[a,c]	R_1	R_2	R_3	Yield, %	Mp, °C
1[b]	H	H	H	...	67
1a	H	NO_2	H	63	131–132
1b	H	NO_2	NO_2	38	165–166
1c	Cl	H	H	50	91–93
1d	Cl	NO_2	H	56	124–126
1e	Cl	NO_2	NO_2	10	201–202
1f	CH_3O	H	H	80	111–112
1g	CH_3O	NO_2	H	46	121–122
1h	CH_3	NO_2	H	48	112–114
1i	Cl	NO_2	Cl	18	104
1j	CH_3	NO_2	Cl	48	87–88

[c] Synthetic method A was employed for all amides except compound **1**. [b] Mp 67°: C. Schotten and H. Schlomann, *Ber.*, **24**, 3695 (1891). [c] Satisfactory analytical values (±0.3% for C, H, and N) were reported for compounds **1a–j**: Ed.

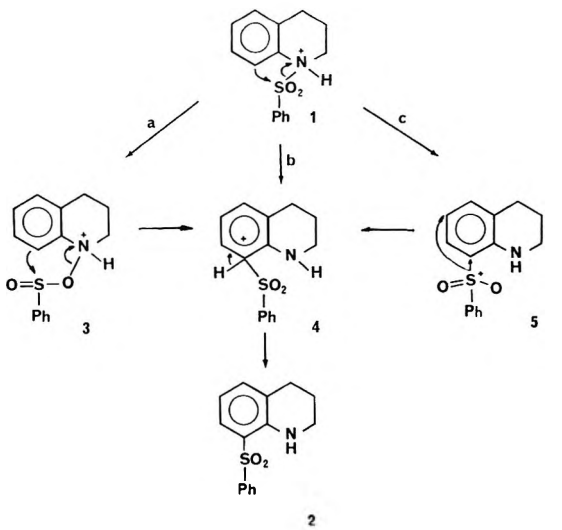
TABLE II



Compd[a]	R_1	R_2	R_3	Yield, %	Mp, °C
2	H	H	H	50	115–116
2a[b]	H	NO_2	H	38	103–106
2b	Cl	H	H	77	147–148
2d[c]	HO	NO_2	H	10	215 dec
2e	CH_3	NO_2	H	50	136–138
2f	H	NO_2	NO_2	...	170–171
2g	Cl	NO_2	H	50	141–142
2h	CH_3	NO_2	Cl	37	109
2i[d]	Cl	NO_2	Cl	10	115

[a] Satisfactory analytical values (±0.3% for C, H, and N) were reported for compounds **2a–h**, inclusive. [b] The 6-sulfone (**2c**) is also formed in this reaction. [c] Formed from **3g** which demethylates upon rearrangement. [d] Confirmed by ir and nmr.

followed by rearrangement to the protonated sulfone (**4**), thence to the product. While these reaction

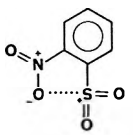


1 3 4 5 2

courses satisfactorily justify the effect of substituents on the amine portion of the sulfonamide, they fail to explain the activating effect of the *o*-nitro group on the sulfonic acid segment. The formation of the para isomer (6-sulfone, in the case of tetrahydroquinoline) rules out a single overall route to the observed products, especially one which is predicated on an intramolecular rearrangement.

More recent work[8] on amine hydrochloride catalyzed rearrangement and transamidation reactions of arylalkylsulfonamides suggests a bimolecular mechanism. A benzenesulfonylonium species, **5** or **6**, separates and can then attack either position, ortho or para to the nitrogen atom. This mechanism rationalizes the origin of the para sulfone, but fails to fully explain why ortho rearranged products generally predominate.

Recently, Sullivan and White[9] studied the rearrangement of the benzenesulfonamides of para-substituted *N*-methylanilines. In an attempted "cross-over" experiment, using radioactively labeled compounds, no mixed products were observed. These authors concluded that the rearrangment was, therefore, intramolecular. None of their compounds contained a group ortho to the sulfonyl group (such as nitro) which could possibly stabilize the sulfonylonium species 6.



6

From our work several conclusions are evident. An *o*-nitro group causes both increased rate of rearrangement and the formation of a para isomer. Some intramolecular cyclic-intermediate mechanism (route a or b) operates in the "normal" or ortho rearrangement. However, if a stabilizing group (*e.g.*, nitro) is ortho to the sulfonyl group, lending stability to an intermediate sulfonylonium ion, then step c is the possible route. This stability originates from a dipole–dipole interaction, as in **6**, and is in apparent contradiction to the generally accepted electron-withdrawing tendencies of a nitro group. Kwart[10] has interpreted the anomalous behavior during the chlorination of *o*-nitrobenzenesulfenyl halides as due to this type of influence.

Experimental Section

Formation of 6- and 8-(*o*-Nitrobenzenesulfonyl)-1,2,3,4-tetrahydroquinoline.—A mixture of 20 g of 1-(*o*-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroquinoline (0.13 mol) and concentrated sulfuric acid (40 ml) was heated on a boiling-water bath for 30 min. Complete solution occurred and the reaction mixture turned an intense red. The cooled solution was poured over cracked ice and brownish-yellow solid precipitated, which was collected, thoroughly washed, and air-dried to give 17 g of crude product. The product was mixed thoroughly with an equal volume of diatomaceous earth and continuously extracted with ether for 30 hr. The ether extract, after removal of solvent, yielded several grams of a yellow solid which was recrystallized from ethanol to give the pure 8-sulfone **2a**, mp 103–106°.

The extraction residue was then reextracted with glacial acetic acid to give a solid which, although sparingly soluble in hot glacial acetic acid, was recrystallized from this solvent. This compound was shown to be the 6-sulfone **2c**, mp 256–257°.

Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80; S, 10.07. Found: C, 56.88; H, 4.30; N, 8.72; S, 10.30.

Synthesis of Arylsulfonanilides. Method A.—A solution of *o*-nitrobenzenesulfonyl chloride (67 g, 0.3 mol) in 400 ml of anhydrous ether was added gradually with stirring to a cooled solution of 1,2,3,4-tetrahydroquinoline (80 g, 0.6 mol) in 120 ml of anhydrous ether. After the addition was complete, the cooling bath was removed and the mixture refluxed for 1 hr. The cooled reaction mixture was filtered and the precipitate washed with hot water to remove the amine hydrochloride. The residue was combined with the ether filtrate and the solvent stripped to give approximately 50 g of crude product. The product was dissolved in ethanol, decolorized, and recrystallized to give 43 g (47%) of **1a**, a pale yellow solid, mp 131–132°.

Method B.—A mixture of 3 g (0.04 mol) of 1,2,3,4-tetrahydroquinoline, benzenesulfonyl chloride (5 g, 0.04 mol), and 20 ml of 10% aqueous sodium hydroxide was stirred until the initial exothermic reaction subsided and then warmed to 50° for a few minutes. The supernatant liquid was decanted; the gummy mass was washed with water and triturated with a small quantity of methanol, whereupon it was converted to a white powdery solid. Crystallization from methanol gave 4 g (36%) of **1**, white crystals, mp 59–61°.

Rearrangement of Arylsulfonanilides. 8-(Phenylsulfonyl)-1,2,3,4-tetrahydroquinoline (2).—A mixture of 2 g of **3** with 6 ml of concentrated sulfuric acid gradually colored, and when complete solution occurred it was heated in a steam bath for 45 min, cooled, and poured over ice. A pale gummy solid precipitated, which was isolated, washed thoroughly with water, and recrystallized from ethanol to give pale yellow needles 1 g (50%) of **2**.

Although rearrangement of the methoxy derivative **1g** was performed at 0° for 10 min, the demethylated sulfone **1d** was formed.

Alternate Synthesis of 2a. 2-Acetylimino-5,6-dihydro-2*H*,4*H*-thiazolo[5,4,3-*ij*]quinoline (7).—The unacetylated imine was prepared by the method of Konig,[6] but, because of a paucity of confirmatory analytical information, some of the imine was converted to the acetyl derivative **7** by warming with acetic anhydride: mp 161–162°, from alcohol and then benzene. *Anal.* Calcd for $C_{12}H_{12}N_2OS$: C, 62.02; H, 5.20; N, 12.08; S, 13.80. Found: C, 62.03; H, 5.09; N, 11.83; S, 13.75.

8-(*o*-Nitrophenylthio)-1,2,3,4-tetrahydroquinoline (8).[6]—Hydrolysis of 1 g (5.25 mmol) of 5,6-dihydro-2*H*,4*H*-thiazolo-[5,4,3-*ij*]quinolin-2-one with alcoholic KOH[11] followed by immediate treatment of the reaction mixture with 0.83 g of *o*-nitrochlorobenzene gave 1.15 g of crude **8**. Repeated crystallization from acetic acid yielded reddish orange crystals, mp 154.5°. The best analytical sample gave the following results. *Anal.* Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.91; H, 4.92. Found: C, 63.35; H, 5.02.

Acetyl Derivative of 8.—Acetylation of 0.8 g (2.8 mmol) of **8** with acetic anhydride yielded 0.50 g (56%) of 1-acetyl-8-(*o*-nitrophenyl)-1,2,3,4-tetrahydroquinoline (**9**), mp 134–5°. *Anal.* Calcd for $C_{17}H_{16}N_2O_3S$: C, 62.10; H, 4.87. Found: C, 62.21; H, 4.86.

Oxidation of 9.—A mixture of 0.48 g of **9** (1.55 mmol), 3 ml of acetic acid, 2 ml of 30% hydrogen peroxide, and a trace of ammonium molybdate was refluxed 2 hr and poured into water to give pale yellow needles of the acetylated sulfone **10**, mp 179.5° (ethanol). *Anal.* Calcd for $C_{17}H_{16}N_2O_5S$: C, 59.31; H, 4.65. Found: C, 59.39; H, 4.72. Hydrolysis of **10**, with 1:1 ethanolic HCl gave **2a**, as determined by mixture melting point and infrared spectra.

Registry No.—**1a**, 24223-38-9; **1b**, 28228-88-8; **1c**, 28228-89-9; **1d**, 28228-90-2; **1e**, 28228-91-3; **1f**, 794-15-0; **1g**, 28228-93-5; **1h**, 28228-94-6; **1i**, 28228-95-7; **1j**, 28228-96-8; **2**, 28228-97-9; **2a**, 28228-98-0; **2b**, 28228-99-1; **2c**, 28229-00-7; **2d**, 28229-01-8; **2e**, 28229-02-9; **2f**, 28229-03-0; **2g**, 28229-04-1; **2h**, 28312-65-4; **2i**, 28229-05-2; **7**, 28229-06-3; **8**, 28312-66-5; **9**, 28229-07-4; **10**, 28229-08-5.

(8) D. Klamann and G. Hofbauer, *Justus Liebigs Ann. Chem.*, **581**, 182 (1953).

(9) J. Sullivan and W. N. White, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. S83.

(10) E. N. Givens and H. Kwart, *J. Amer. Chem. Soc.*, **90**, 386 (1968).

(11) I. K. Ushenko, *Ukr. Khim. Zh.*, **21**, 744 (1955); *Chem. Abstr.*, **50**, 16753*f* (1956).

Acknowledgment.—The authors wish to acknowledge the assistance of Pamela Strong and Robert Balchunis in conducting a portion of the experimental procedure.

A Precautionary Note on the Synthesis of Thiete Sulfone[1]

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Received November 4, 1970

In the original description[2] of the synthesis of thiete sulfone (thiete 1,1-dioxide), the procedure for the preparation of 3-thietanol 1,1-dioxide called for evaporation to dryness of the solution remaining after oxidation of the sulfide to the sulfone.[3] Since several researchers have reported to us that explosions had occurred during this step, we wish to emphasize that the evaporation must be done in an evaporating dish open to the atmosphere and that under no circumstances must the peroxide-containing solution be concentrated in a closed system. Therefore, the following procedure should be followed for the synthesis of 3-hydroxythietane 1,1-dioxide.

(1) The work on small ring sulfur chemistry has been supported by the National Science Foundation, and the synthesis reported in this note was developed with aid from Grant GP-726.

(2) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961).

(3) A synthesis of thiete sulfone which does not involve an oxidation step has been reported recently: P. Chang and D. C. Dittmer, *ibid.*, **34**, 2791 (1969).

Experimental Section

3-Hydroxythietane 1,1-Dioxide.—3-Hydroxythietane (45 g, 0.50 mol) is mixed with 105 ml of glacial acetic acid in a 500-ml three-necked flask fitted with an addition funnel, thermometer, condenser, and a magnetic stirring bar. The flask is cooled in an ice bath, and, with stirring, hydrogen peroxide (116 g, 30%) is added dropwise, the reaction temperature not being allowed to rise above 20°.[4] After the addition of hydrogen peroxide the reaction mixture is kept in the ice bath for 1 hr, the stirring is stopped, and the mixture is allowed to stand at room temperature overnight.[5] It is diluted with 800 ml of distilled water in a 9- to 10-in. evaporating dish, and water and acetic acid are evaporated on a steam bath.[6] The colorless oil is cooled to a white, crystalline mass which is crushed in the evaporating dish and air-dried. The nearly dry solid is recrystallized from 100 ml of ethyl acetate.[7] After two recrystallizations from ethyl acetate, 38–40 g (62.3–65.6%) of 3-hydroxythietane 1,1-dioxide, mp 100°, is obtained.

Registry No.—3-Hydroxythietane 1,1-dioxide, 22524-35-2.

(4) Considerable heat is evolved during the first half of the addition of hydrogen peroxide and the addition must be slow. The reaction becomes more moderate and the last half of the peroxide may be added more rapidly.

(5) The flask is kept in a bath of tap water. A precipitate may appear at this point.

(6) This evaporation is crucial. Evaporation must be stopped at the first indication of a yellow color seen around the edge of the liquid in the dish. Yields are much lower if the heating is prolonged beyond this stage. *Do not evaporate in a closed system. Explosions have occurred when this was done.* The final volume of oily product and the slight amount of trapped solvent is usually about 100 ml.

(7) A fluffy, insoluble material is removed by filtration.

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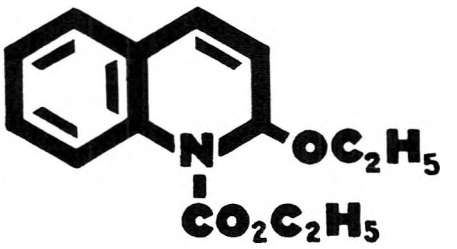

We sell just about every peptide reagent, were the first to offer DCC (and remember with a slight shudder the 39 complaints we received because our material was a waxy solid; the first literature reference had stated that it was a liquid which would not crystallize!) and have even sold thousands of bottles of Woodward's Reagent K, despite its relatively high price. However, no peptide reagent has excited our imagination quite as much as EEDQ.[1,2] Not only because it is also a most interesting pharmacologic tool[3] for the study of both the central and peripheral adrenergic nervous system but because it really appears to be the *ideal* peptide reagent: peptide formation in high yields at room-temperature with practically no *racemization*. For instance, in two peptide syntheses[4], Woodward's Reagent K gave after 24 hours 72 and 95% yields and 1.7 and 1.8% racemization. EEDQ gave after 7 hours yields of the same peptides of 91 and 97% with 0.2% racemization. Probably that racemization was due only to the tertiary amines used; Professor Belleau recommends that EEDQ be used without tertiary amines. Also, EEDQ is so inexpensive that it will become a general reagent for amide formation. Its advantages over DCC are obvious: it is not a skin-irritant, yields are generally higher, and all the reaction byproducts are volatile, leaving the peptide as the only solid residue.

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EEDQ is licensed under U.S. Patent No. 3389142.

(1) B. Belleau and G. Malek, *J. Am. Chem. Soc.*, 90, 1651 (1968).
(2) B. Belleau, *ibid*, 90, 823 (1968).
(3) R. Martel, R. Berman and B. Belleau, *Can. J. Physiol. Pharmacol.* 47, 909 (1969).
(4) N. Izumiya and M. Muraoka, *J. Am. Chem. Soc.*, 91, 2391, (1969).

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