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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 26

DECEMBER 29, 1972

Friedel–Crafts Cyclialkylations of Certain Mono- and Diphenyl-Substituted Alcohols and Alkyl Chlorides[1,2]

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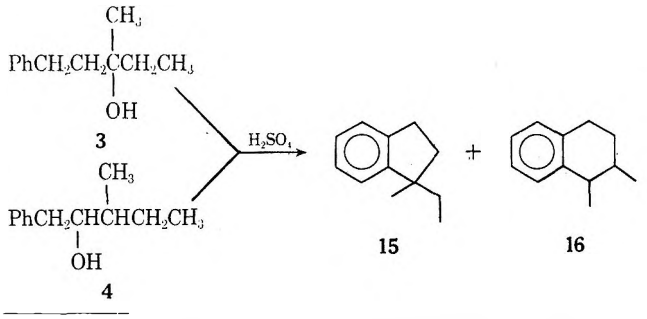
Received May 31, 1972

Compounds 1–14 were prepared and cyclized under Friedel–Crafts conditions. The results of these cyclizations demonstrated that (1) ring closure at secondary carbons to tetralins takes precedence over ring closure at tertiary carbons to both indans and benzosuberanes (compounds 2–6); (2) ring closure at *benzylic* secondary carbon to a benzosuberane takes precedence over ring closure at an ordinary secondary carbon to a tetralin (compound 10); (3) in contrast to intermolecular alkylations with neopentyl systems, which proceed with complete rearrangements, intramolecular alkylations give some nonrearranged products (compound 1); (4) ring closure at tertiary carbons to tetralins is favored over ring closure at tertiary carbons to indans (compounds 7 and 8); (5) ring closures at tertiary carbons to indans are favored over ring closures at tertiary carbons to benzosuberanes (alcohol 13) and similarly cycliacylations to indanones are favored over cycliacylations to benzosuberones (compound 14); and (6) steric interactions in the transition states play significant roles in determining the nature of the final cyclization products (compounds 11, 12, and 13). Mechanisms are suggested for the various processes involved in the formation of the observed products.

In continuation of our exploration of the mechanistic aspects and the synthetic potentialities of Friedel-Crafts cyclialkylation reactions,[4] we have undertaken an investigation of the cyclization of various phenyl-substituted alcohols, alkyl chlorides, and related compounds (**1** through **14**) in the presence of various acid catalysts. The sulfuric acid catalyzed cyclizations of 3-methyl-1-phenyl-3-pentanol (**3**) and 3-methyl-1-phenyl-2-pentanol (**4**) were conducted by Roblin, Davidson, and Bogert.[5] Using fractional distillation as the only means of separation and identification, these authors reported that alcohols **3** and **4** gave product mixtures consisting of 1-ethyl-1-methylindan (**15**) and 1,2-dimethyltetralin (**16**) in 87 and 50% yields, respectively. In these mixtures, the ratio of **15** to **16** was estimated as being 3:1 from alcohol **3** and 1:4 from alcohol **4**. In view of their results with alcohols **3** and **4**, the above workers expressed their belief that similar cyclization of the isomeric 3-methyl-5-phenyl-2-pentanol (**2**) would yield a still larger proportion of 1,2-dimethyltetralin with "little or perhaps none of the 1-ethyl-1-methyltetralin." However, the authors were unable to confirm their prediction because of the failure encountered in the preparation of the desired isomeric alcohol (**2**). With these early results and the latter prediction in mind, it seemed of interest to us to find out, with the help of modern instrumental methods of analysis, whether or not isomeric alcohols such as **2**, **3**, and **4** or **7** and **8** (see Table I), which differ only with respect to the position of the hydroxyl group in the carbon chain, would yield similar cyclization products. It seemed also of interest to examine the cyclizations of the monophenylated alcohols **1**, **5**, and **9** and the diphenylated compounds **10**, **11**, **12**, **13**, and **14**.



Results and Discussion

The conditions and results of the cyclialkylation experiments are presented in Table I. Examination of the data included in Table I shows that the cyclization of the isomeric alcohols **2**, **3**, and **4** as well as of the corresponding chlorides **5** and **6** gave similar product mixtures whose compositions were determined by the type

(1) (a) Part XXVII of the series "New Friedel–Crafts Chemistry." (b) Part XXVI: R. M. Roberts and T. L. Gibson, *J. Amer. Chem. Soc.*, **93**, 7340 (1971).

(2) Generous support of this research, including a postdoctoral fellowship for A. A. Khalaf, by the Robert A. Welch Foundation is gratefully acknowledged.

(3) Chemistry Department, Assiut University, Assiut, Egypt.

(4) R. M. Roberts, G. P. Anderson, Jr., A. A. Khalaf, and C.-E. Low, *J. Org. Chem.*, **36**, 3342 (1971).

(5) R. O. Roblin, D. Davidson, and M. T. Bogert, *J. Amer. Chem. Soc.*, **57**, 151 (1935).

TABLE I

CYCLIALKYLATIONS OF MONO- AND DIPHENYL-SUBSTITUTED ALCOHOLS AND ALKYL CHLORIDES[a]

Alcohol or chloride	Catalyst, solvent	Time, hr	Yield,[b] %	Products[c] (%)
$PhCH_2CH_2C(CH_3)_2CH_2OH$ (1)	H_3PO_4[d]	...	70	**15** (30), **24** (23), *cis*-**16** (8), *trans*-**16** (31), unidentified (9)
	$AlCl_3$ or $AlCl_3$–CH_3NO_2, petroleum ether[e]	4	...	No cyclialkylation products
$PhCH_2CH_2CH(CH_3)CH(OH)CH_3$ (2)	H_2SO_4	3	75	**15** (31), *cis*-**16** (15), *trans*-**16** (54)
	$AlCl_3$–CH_3NO_2, petroleum ether[e]	1	...	**15** (21), **24** (2), *cis*-**16** (7), *trans*-**16** (56), unidentified (14)
		8	70	**15** (20), **24** (14), *cis*-**16** (15), *trans*-**16** (35), unidentified (16)
	$AlCl_3$, petroleum ether[e]	4	66	**15** (27), **24** (38), *cis*-**16** (15), *trans*-**16** (2), unidentified (18)
$PhCH_2CH_2C(CH_3)(OH)CH_2CH_3$ (3)	H_2SO_4	3	73	**15** (34), **24** (tr[f]), *cis*-**16** (10), *trans*-**16** (56)
	$AlCl_3$–CH_3NO_2, petroleum ether[e]	2	...	**15** (19), **24** (tr), *cis*-**16** (11), *trans*-**16** (70)
		8	...	**15** (19), **24** (tr), *cis*-**16** (11), *trans*-**16** (70)
		20	75	**15** (20), **24** (tr), *cis*-**16** (9), *trans*-**16** (71)
	$AlCl_3$, petroleum ether[e]	10	...	**15** (22), **24** (59), *cis*-**16** (10), *trans*-**16** (7), unidentified (2)
		20	57	**15** (23), **24** (54), *cis*-**16** (11), *trans*-**16** (5), unidentified (7)
$PhCH_2CH(CH_3)CH(OH)CH_2CH_3$ (4)	H_2SO_4	3	28	**15** (36), **24** (1), *cis*-**16** (16), *trans*-**16** (47)
	$AlCl_3$–CH_3NO_2, petroleum ether[e]	2	...	**15** (16), *cis*-**16** (12), *trans*-**16** (72)
		8	...	**15** (19), *cis*-**16** (10), *trans*-**16** (7)
		20	75	**15** (17), *cis*-**16** (13), *trans*-**16** (70)
	$AlCl_3$, petroleum ether[e]	10	...	**15** (25), **24** (64), *trans*-**16** (11)
		20	31	**15** (20), **24** (51), *cis*-**16** (18), *trans*-**16** (5), unidentified (5)
$PhCH_2CH_2C(CH_3)(Cl)CH_2CH_3$ (5)	$AlCl_3$–CH_3NO_2, petroleum ether[e]	4	78	**15** (16), **24** (3), *cis*-**16** (7), *trans*-**16** (71), unidentified (3)
	$AlCl_3$, CS_2	4	70	**15** (15), **24** (32), *cis*-**16** (20), *trans*-**16** (27), unidentified (6)
	$AlCl_3$, petroleum ether[e]	4	76	**15** (21), **24** (24), *cis*-**16** (8), *trans*-**16** (34), unidentified (9)
	$AlCl_3$ (0.5 mol), petroleum ether[e]	2	...	**15** (9), **24** (57), *cis*-**16** (13), *trans*-**16** (5), unidentified (16)
		4	57	**15** (8), **24** (59), *cis*-**16** (8), *trans*-**16** (11), unidentified (14)
$PhCH_2CH(CH_3)CH(Cl)CH_2CH_3$ (6)	$AlCl_3$, petroleum ether[e]	4	55	**15** (30), **24** (47), *cis*-**16** (4), *trans*-**16** (3), unidentified (16)
	$AlCl_3$, CS_2	4	60	**15** (24), **24** (25), *cis*-**16** (16), *trans*-**16** (25), unidentified (10)
	$AlCl_3$–CH_3NO_2, petroleum ether[e]	4	50	**15** (19), **24** (2), *cis*-**16** (12), *trans*-**16** (63), unidentified (4)

TABLE I

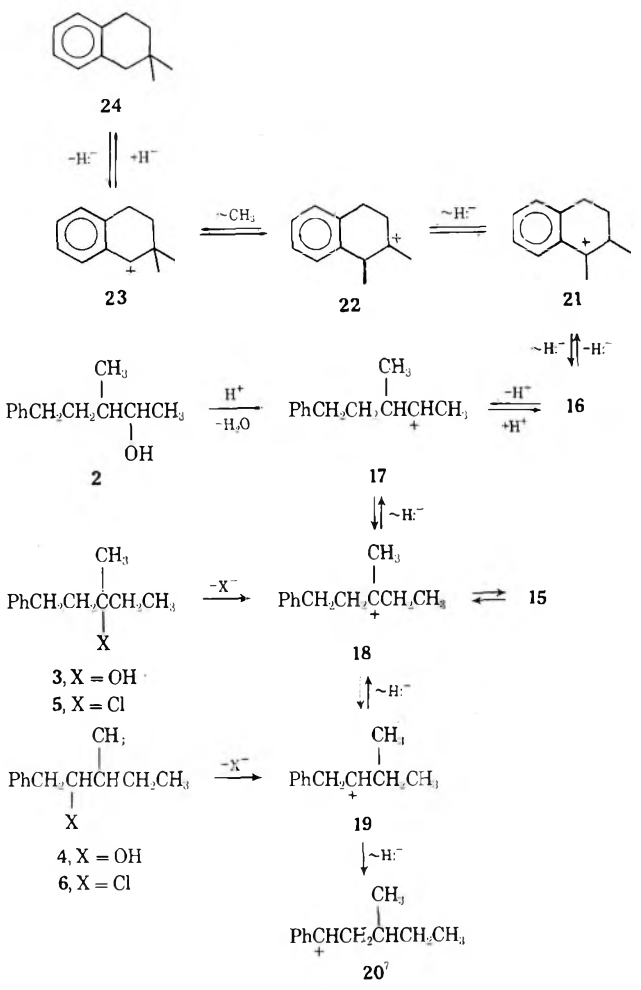
(*Continued*)

Alcohol or chloride	Catalyst, solvent	Time, hr	Yield,[b] %	Products[c] (%)
$PhCH_2CH_2CH(CH_3)C(CH_3)_2OH$ (7)	H_2SO_4	3	60	**45** (100)
	$AlCl_3$–CH_3NO_2, petroleum ether[e]	3	70	**45** (98), **46** (2)
	$AlCl_3$, petroleum ether[e]	3	50	**45** (17), **46** (50), 2 unidentified (32)
$PhCH_2CH_2C(CH_3)_2CHCH_3$ (8) OH	H_2SO_4	3	58	**45** (100)
	$AlCl_3$–CH_3NO_2, petroleum ether[e]	3	65	**45** (100)
	$AlCl_3$, petroleum ether[e]	3	55	**45** (10), **46** (80), unidentified (10)
$Ph(CH_2)_4C(CH_3)_2OH$	H_2SO_4	3	50	**28** (100)
$Ph(CH_2)_4CHPhOH$ (9)	H_2SO_4	3	10	**38** (100)
	$AlCl_3$–CH_3NO_2, petroleum ether[e]	3	15	**38** (100)
	$AlCl_3$, petroleum ether[e]	3	...	**38** (54), benzosuberane (6), tetralin (3), 1-methyltetralin (1), unidentified (36)
$PhCH_2CH_2CH(Ph)CH_2C(CH_3)_2OH$ (11)	H_2SO_4	3	85	**32** (100)
$PhCH_2CH(Ph)CH_2CH{=}CHCH_3$ (12)	H_2SO_4	2.5	60	**36** (87), **37** (13)
$PhCH_2CH(Ph)CH_2C(CH_3){=}CH_2$[g] (13)	H_2SO_4	3	65	1,1-Dimethyl-3-phenyltetralin (100)
$PhCH_2CH_2CH(Ph)CH_2C(=O)Cl$ (14)	$AlCl_3$, petroleum ether[e,h]	2	70	3-(β-Phenylethyl)-1-indanone (100)
	$AlCl_3$–CH_3NO_2, petroleum ether[e]	1	75	3-(β-Phenylethyl)-1-indanone (100)

[a] Unless specified otherwise, all reactions were conducted at room temperature (25°) using reactants in the proportions indicated in the Experimental Section. [b] Total yields were calculated by glpc using 2-phenylhexane as internal standard. [c] The percentage composition of various products was calculated by integration of glpc recordings. These products are listed in order of increasing retention times on all of the following columns: (a) cyanosilicone, (b) Apiezon L, (c) DEGA, (d) Carbowax 20M, and (e) SE-30. [d] Reaction was carried out at 230–240°; see ref 34. [e] Petroleum ether, bp 60–70°. [f] Mol % of distillable hydrocarbons based on original cyclized product. [g] See ref 35. [h] Reaction was conducted at 5–10° using the reactant ratios specified in the Experimental Section. [i] Trace.

of catalyst employed. Thus, while the weak catalysts H_2SO_4 and $AlCl_3$–CH_3NO_2 produced mixtures consisting of 1-ethyl-1-methylindan (**15**) and *cis*- and *trans*-1,2-dimethyltetralin (**16**) with little or none of the isomeric 2,2-dimethyltetralin (**24**) present, the strong catalyst $AlCl_3$ produced mixtures in which the latter isomer predominated. The results from cyclialkylations of compounds **2** through **6** can best be explained in terms of the carbonium ion processes outlined in Scheme I. According to this scheme, treatment of compounds **2** to **6** with the catalyst furnishes the corresponding carbonium ions (or their equivalent complexes with the catalyst) and these subsequently isomerize by 1,2-hydride shifts to produce the possible isomeric ions **17** to **19**. Of these possible ions, **17** will undergo closure at secondary carbon to the six-membered ring product, 1,2-dimethyltetralin (**16**), and **18** will undergo closure at tertiary carbon to the five-membered ring product, 1-ethyl-1-methylindan (**15**). The formation of 2,2-dimethyltetralin (**24**) as the predominant product when $AlCl_3$ was used as cyclialkylation catalyst can reasonably be attributed to the

SCHEME I

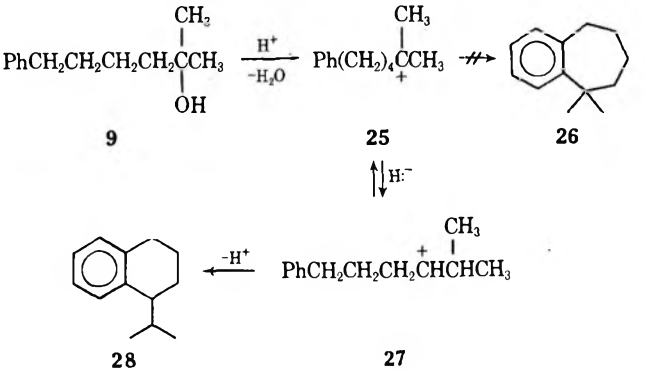


known[6] ability of $AlCl_3$ to abstract hydride ions and thus produce from **16** intermediate ion **21** which, by undergoing successive hydride and methyl shifts, gives carbonium ion **23**; the latter then abstracts a hydride ion to produce **24**. Credibility of the route **16** → **21** → **23** → **24** is found in the following observations: (1) the predominant formation of **24** only when $AlCl_3$ was used as catalyst; (2) the enhanced formation of **24** with increased amount of $AlCl_3$ (see results with compound **5**); and (3) the rapid rearrangement of 1,2-dimethyltetralin (**16**) to 2,2-dimethyltetralin (**24**) in the presence of $AlCl_3$, but not in the presence of the weaker catalysts $AlCl_3$-CH_3NO_2 or H_2SO_4.

In reviewing the results of cyclialkylations of compounds **2** to **6**, two interesting facts should be emphasized: firstly, the preference for closure at secondary carbon to tetralin (**17** → **16**) over closure at tertiary carbon to indan (**18** → **15**), either directly or *via* rearrangement of the tertiary cation **18** to the secondary cation **17**, and, secondly, the preference for closure of **17** to *trans*- rather than to *cis*-1,2-dimethyltetralin. While the latter fact can be attributed to the smaller steric repulsions encountered in closure of **17** to *trans*-1,2-dimethyltetralin, the former fact demonstrates clearly that a six-membered ring forms preferentially to a five-membered ring, even though rearrangement of a tertiary to a secondary carbonium ion must occur.

Another case of tertiary-to-secondary carbonium ion rearrangement was observed during the cyclization of 2-methyl-6-phenyl-2-hexanol (**9**) which upon treatment with H_2SO_4 gave the rearranged product 1-isopropyltetralin (**28**) through the secondary cation **27**, rather than the direct cyclization product **26** through the tertiary cation **25** (see Scheme II). This fact,

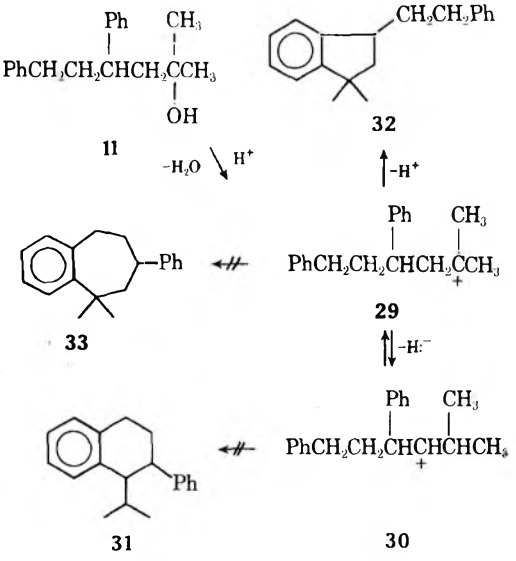
SCHEME II



which has formerly been noted by other workers,[5,8] may also be attributed to the greater driving force for six-membered ring formation than for seven-membered ring formation, in spite of the required tertiary-to-secondary carbonium ion rearrangement.

In light of the above results with alcohol **9**, we expected the H_2SO_4-catalyzed reaction of 2-methyl-4,6-diphenyl-2-hexanol (**11**) to yield a mixture of 1-isopropyl-2-phenyltetralin (**31**) and 1,1-dimethyl-3-(β-phenylethyl)indan (**32**). Far from our expectations, however, alcohol **11** gave exclusively **32** and no **31** (see Scheme III). Explanation for this irregular behavior

SCHEME III



of alcohol **11** can best be given in terms of steric effects. Thus, whereas the developing 1,2 interactions between the bulky phenyl and isopropyl groups would strongly inhibit closure of the rearranged secondary carbonium

(6) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **35**, 3717 (1970).

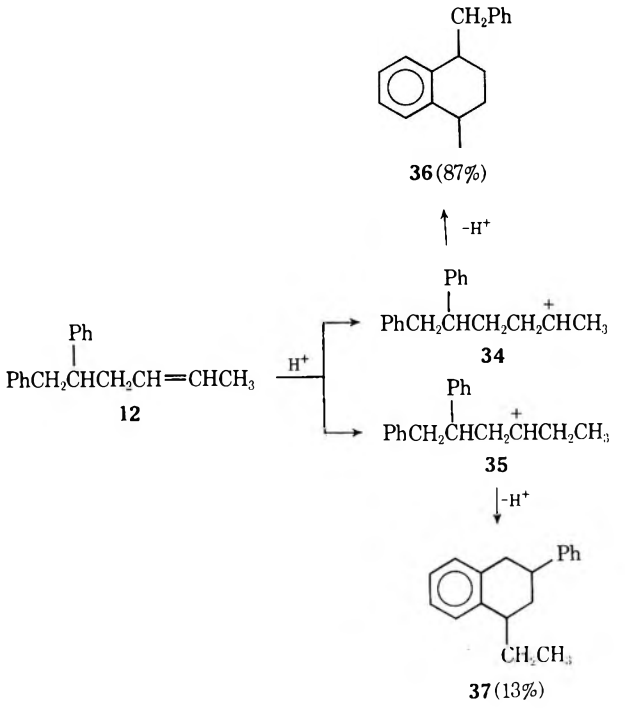
(7) It is to be noted that, as shown in Scheme I, carbonium ion **20** may be formed by carbonium ion rearrangements, but once formed it will lead to the production of polymers.[6]

(8) L. R. C. Barclay, B. A. Ginn, and C. E. Milligan, *Can. J. Chem.*, **42**, 579 (1964).

ion **30** to the disubstituted tetralin **31**, the tertiary carbonium ion **29** would encounter much less steric repulsion to give the trisubstituted indan **32**. None of **33** was produced.

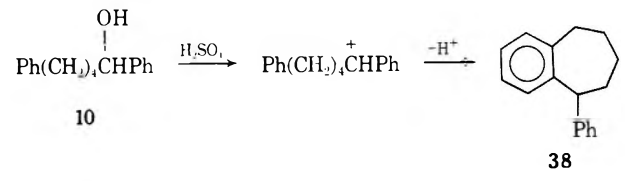
Steric factors also played a determining role in the cyclidehydration of 5,6-diphenyl-2-hexene (**12**). Upon treatment with H_2SO_4, this alkene gave a product consisting of 87% 1-benzyl-4-methyltetralin (**36**) and 13% of the isomeric 1-ethyl-3-phenyltetralin (**37**), as shown in Scheme IV.

SCHEME IV

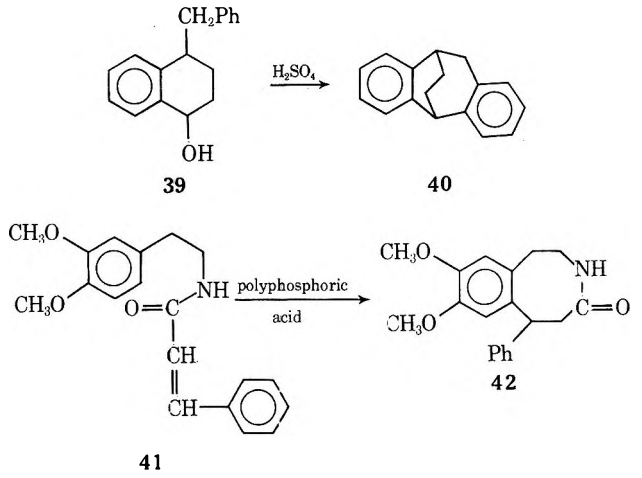


The enhanced production of **36** in the above reaction can hardly be attributed to the small differences in stabilities expected on the basis of the numbers of hyperconjugated hydrogens in these cations (5 H in **34** *vs.* 4 in **35**). The predominant formation of **36**, however, seems well correlated with the large differences in the steric repulsions experienced by both ions during cyclization to the corresponding products; in that respect the developing 1,4 interactions between the benzyl and the methyl groups in going from **34** to **36** are much more favorable than the 1,3 interactions between the ethyl and the phenyl groups in going from **35** to **37**.

We have also seen from our present study of alcohols **9** and **11** that intermediate tertiary carbonium ions do not cyclize to benzosuberane. We thus prepared and examined the cyclization of 1,5-diphenyl-1-pentanol (**10**) to find out if a secondary benzylic carbonium ion would cyclize to a benzosuberane. When **10** was treated with either H_2SO_4 or $AlCl_3$-CH_3NO_2 catalysts, it gave a 10-15% yield of the seven-membered ring product 1-phenylbenzosuberane (**38**) as shown in the following equation.

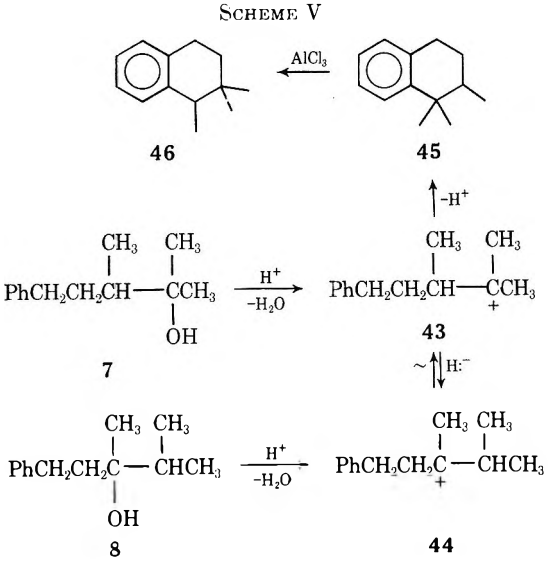


Treatment of **10** with the stronger catalyst $AlCl_3$ resulted in a rather complex product mixture consisting mainly of **38**, together with minor amounts of tetralin, 1-methyltetralin, and benzosuberane, besides a number of unidentified components. We conclude on the basis of the behavior of compound **10** that secondary benzylic carbonium ions can more readily undergo cyclization to seven-membered ring derivatives. Support for this conclusion was found in the report that **39** gave **40** upon treatment with H_2SO_4[9] and that **41** gave **42** upon treatment with polyphosphoric acid,[10] although an eight-membered ring is formed in the latter case.



Since the results for compounds **2** through **6** have shown that ring closure at secondary carbon to tetralin takes precedence over ring closure at tertiary carbon to indan, we decided to examine compounds **7** and **8**, whose cyclodehydration should offer information about competition between ring closure at tertiary carbon to either tetralin or to indan derivatives. The results of cyclodehydration of compounds **7** and **8** are summarized in Table I and in Scheme V. The ready and almost

SCHEME V



exclusive formation of 1,1,2-trimethyltetralin (**45**) from the reactions of both **7** and **8** with either H_2SO_4 or $AlCl_3$-

(9) C.-E. Low, Ph.D. Dissertation, The University of Texas at Austin, 1970.

(10) R. E. Harmon, B. L. Jensen, S. K. Gupta, and J. D. Nelson, *J. Org. Chem.*, **35**, 825 (1970).

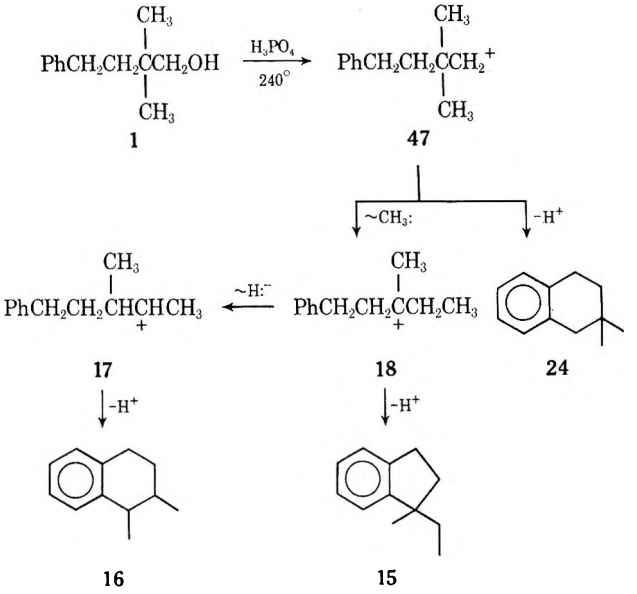
CH_3NO_2 catalysts demonstrates clearly that ring closure of tertiary carbon to tetralin, either directly or *via* rearrangement, is favored over direct or rearranged ring closure to indan. Further support for this fact was obtained when it was found that 2-methyl-4,5-diphenyl-1-pentene (**13**) gave exclusively 1,1-dimethyl-3-phenyltetralin upon treatment with H_2SO_4.[11]

Besides treating compounds **7** and **8** with H_2SO_4 and $AlCl_3$–CH_3NO_2, we also treated these two isomers with the strong catalyst $AlCl_3$ in petroleum ether at room temperature. As expected, this gave a more complex mixture of products consisting mainly of 1,2,2-trimethyltetralin (**46**) together with smaller amounts of 1,1,2-trimethyltetralin (**45**) and other unidentified components. The most logical explanation of this behavior is that **45** was initially formed in the reaction but reacted further with $AlCl_3$ to give **46** and the other unidentified products. Support for this explanation was obtained when it was found that, under the conditions of the reaction, **45** reacted with $AlCl_3$ to give **46** in addition to other products having glpc retention times similar to those of the unidentified components produced during the $AlCl_3$-catalyzed cyclizations of alcohols **7** and **8**.

The cyclialkylation of 2,2-dimethyl-4-phenyl-1-butanol (**1**) presents a case of special interest since, to our knowledge, it provides the first example of intramolecular alkylation with a neopentyl system. A study of the reaction of **1** was chosen to provide more insight into the difference in behavior between inter- and intramolecular alkylations, particularly with regard to the extent of accompanying rearrangements. In intermolecular reactions, it is well established that the formation of neopentyl cation is invariably accompanied by complete rearrangement to *tert*-pentyl cation.[12] For example, *tert*-pentylbenzene was the sole product when benzene was alkylated with neopentyl alcohol and H_2SO_4[13] or BF_3[14] or with neopentyl chloride and $AlCl_3$–CH_3NO_2.[12e] The isolation of neopentylbenzene in alkylations catalyzed by $AlCl_3$ was recently attributed to subsequent isomerization of the initially formed *tert*-pentylbenzene by the strong catalyst $AlCl_3$, first to 2-methyl-3-phenylbutane and then to neopentylbenzene.[12]

It is particularly significant in the present study to note that the intramolecular dehydration of 2,2-dimethyl-4-phenyl-1-butanol (**1**) with H_3PO_4 gave not only the rearranged cyclodehydration products 1,2-dimethyltetralin (**16**) and 1-ethyl-1-methylindan (**15**), but also the nonrearranged (direct) cyclodehydration product 2,2-dimethyltetralin (**24**). The possibility that 2,2-dimethyltetralin (**24**) was formed by subsequent rearrangement of either **15** or **16** rather than by direct closure of **47** was excluded on the ground that treatment of a mixture of the latter two isomers with phosphoric acid under the reaction conditions gave none of the isomeric 2,2-dimethyltetralin (**24**). The above results with alcohol **1** are summarized in Scheme VI. These results give more evidence in confirmation

SCHEME VI



of the fact that intramolecular alkylations are much faster and hence accompanied by fewer rearrangements than the corresponding intermolecular reactions.

We have seen from the results with compound **9** that closure at secondary carbon to tetralin is much more favored than closure at tertiary carbon to benzosuberane, and from the results with compound **11**, that closure at tertiary carbon to indan is much more favored than closure at tertiary carbon to benzosuberane. To provide more insight into five- *vs.* seven-membered ring formation, we decided to examine the cycliacylation of 3,5-diphenylpentanoyl chloride (**14**). Our finding that **14** gives only 3-(β-phenylethyl)-1-indanone upon treatment with either $AlCl_3$ or $AlCl_3$–CH_3NO_2 catalysts adds more support to the conclusion that five-membered ring closure, whenever possible, takes precedence over seven-membered ring closure in both cyclialkylation and cycliacylation reactions.

Experimental Section

The purity (95% or higher) and identity of the starting materials and of the final products were determined by glpc, ir, nmr, and, in many cases, also by mass spectrometric analysis; except where otherwise indicated, yields in each step were not less than 60%.

Synthesis of Starting Materials and Final Products.—Of the required materials 5,6-diphenyl-2-hexene, 1-benzyltetralin, and 1- and 2-phenylbenzosuberane were available from previous work.[4]

2,2-Dimethyl-4-phenyl-1-butanol (1).—2,2-Dimethylsuccinic anhydride was prepared from the acid by refluxing with acetic anhydride according to a method adapted from "Organic Syntheses."[15] The anhydride was obtained in over 90% yield, bp 68–72° (0.11 mm) [lit.[16] bp 223° (atmospheric pressure)]. Reaction of the anhydride with dry benzene in the presence of $AlCl_3$ gave 2,2-dimethyl-3-benzoylpropanoic acid, which was recrystallized from petroleum ether (bp 60–70°), mp 172–175° (lit.[17] mp 173–174°). Reduction of the latter keto acid with hydrogen

(11) See also ref 4.

(12) (a) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 134–136; (b) C. D. Nenitzescu, *Rev. Roum. Chim.*, **7**, 349 (1962); (c) C. D. Nenitzescu, I. Necsoiu, A. Glatz, and M. Zalman, *Chem. Ber.*, **92**, 10 (1959); (d) R. M. Roberts and Y. W. Han, *Tetrahedron Lett.*, **No. 6**, 5 (1959); *J. Amer. Chem. Soc.*, **85**, 1168 (1963); (e) R. M. Roberts and A. A. Khalaf, unpublished results.

(13) H. Pines, L. Schmerling, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **62**, 2901 (1940).

(14) A. Streitwieser, Jr., D. P. Stevenson, and W. D. Schaeffer, *ibid.*, **81**, 1110 (1959).

(15) L. F. Fieser and E. L. Martin, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1955, p 560.

(16) J. B. Conn, G. B. Kistiakowsky, R. M. Roberts, and E. A. Smith, *J. Amer. Chem. Soc.*, **64**, 1749 (1942).

(17) E. N. Marvell and A. O. Geiszler, *ibid.*, **64**, 1259 (1952).

and Pd/C in glacial acetic acid containing a little perchloric acid gave 2,2-dimethyl-4-phenylbutanoic acid which was recrystallized from petroleum ether (bp 60–70°), mp 94–96° (lit.[17,18] mp 98°). Treatment of the latter acid with PCl_3 gave the corresponding acid chloride: bp 68–71° (0.2 mm); $n^{25}D$ 1.5411; ir (film) 5.6 μ (C=O); nmr (CCl_4) δ 7.17 (strong singlet overlapping a weak multiplet at base, 5, aromatic), 2.75–1.70 (m, AA'BB' pattern almost symmetric about 2.22, 4, $PhCH_2CH_2$–), 1.30 ppm (s, 6, *gem*-methyls).

Reduction of the above acid chloride with $LiAlH_4$ in dry ether following standard procedures gave the desired 2,2-dimethyl-4-phenyl-1-butanol (**1**): bp 85–89° (0.4 mm); $n^{25.5}D$ 1.5092; ir (film) 2.98 μ (OH); nmr (CCl_4) δ 7.10 (s, 4, aromatic), 3.69 (s, 1, OH), 3.24 (s, 2, CH_2O), 2.70–1.30 (m, AA'BB' pattern symmetric about 2.00, 4, $PhCH_2CH_2$–), 0.87 ppm (s, 6, *gem*-methyls); mass (calcd for $C_{12}H_{18}O$) 178.169 (found 178.136).

3-Methyl-5-phenyl-2-pentanol (2).—2-Methyl-4-phenylbutanoic acid, prepared by catalytic reduction of 2-methyl-3-benzoylpropanoic acid as described previously,[19] was converted into the corresponding acid chloride by treatment with PCl_3, bp 123° (11 mm) [lit.[20] bp 125° (12 mm)], $n^{24}D$ 1.5112. This acid chloride was transformed into 3-methyl-5-phenyl-2-pentanone by addition to a twofold excess of dimethylcadmium using dry benzene as solvent. This addition took place over a period of 0.5 hr at ice-bath temperature with stirring. When addition was complete, the reaction mixture was stirred at ice-bath temperature for 0.5 hr, at room temperature for 1 hr and at 50° for 0.5 hr. After the usual decomposition, extraction, and drying procedures, the solvent was distilled under atmospheric pressure, and the residue was distilled under vacuum to give 3-methyl-5-phenyl-2-pentanone: bp 90–93° (1.25–1.35 mm); $n^{24}D$ 1.5025; nmr δ 7.12 (s, 5, aromatic), 3.10–2.10 (an apparent quartet superimposed on a multiplet, 3, $PhCH_2$ and >CHCO), 1.98 (s, 3, $COCH_3$), 1.95–1.20 (m, 2, $PhCH_2CH_2$–), 1.04 ppm (d, s, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.81; H, 9.10. Found: C, 81.95; H, 9.13.

Reduction of the above ketone with sodium borohydride followed by careful distillation gave 3-methyl-5-phenyl-2-pentanol (**2**): bp 81° (0.25 mm); $n^{23}D$ 1.5119; nmr δ 7.11 (s, 5, aromatic), 3.82–3.34 (m, 1, >CHOH), 2.68 (s, 1, OH), 2.80–1.20 (complex multiplets, 5, $PhCH_2CH_2CH$–), 1.05 and 1.03 (two partially resolved doublets, 3, J = 6 Hz, diastereomeric $>CHCH_3$), 0.90 ppm [broadened doublet, 3, J = 6 Hz, diastereomeric >CH(OH)CH_3].

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.65; H, 10.14.

A sample of the above alcohol was also prepared by condensing 3-phenyl-2-butylmagnesium chloride with acetaldehyde followed by decomposition with saturated NH_4Cl. This was found to be identical in all respects with that obtained by the former method.

3-Methyl-1-phenyl-3-pentanol (3) and the Corresponding 3-Chloro-3-methyl-1-phenylpentane (5).—Reaction of 4-phenyl-2-butanone with ethylmagnesium iodide and decomposition by saturated ammonium chloride gave compound **3**: bp 94–95° (1.1 mm); $n^{25}D$ 1.5084 [lit.[5] bp 130° (15 mm); n^{25}_{5875} 1.50981]; nmr δ 7.10 (s, 5, aromatic), 2.80–2.48 (m, low-field half of an AA'BB' system, 2, $PhCH_2CH_2$), 1.48 (an apparent quartet, partially superimposed on the latter multiplet, 2, J = 7 Hz, CH_3CH_2), 1.14 (s, 3, CH_3), 0.89 ppm (t, 3, J = 7 Hz, CH_2CH_3).

Treatment of the above alcohol with concentrated hydrochloric acid and anhydrous calcium chloride as described for preparation of *tert*-butyl chloride[21] gave 3-chloro-3-methyl-1-phenylpentane (**5**): bp 85.3° (1.1 mm); $n^{25}D$ 1.5079; nmr (CCl_4) δ 7.13 (s, 5, aromatic), 2.91–1.55 (complex AA'BB' multiplet almost symmetric about 2.30 whose high-field half partly overlaps an apparent quartet with J = 6.5 Hz, 6, $PhCH_2CH_2CCH_2$), 1.47 (s, 3, CH_3), 0.98 ppm (t, 3, J = 6.5 Hz, CH_2CH_3).

Anal. Calcd for $C_{12}H_{17}Cl$: Cl, 17.93. Found: Cl, 17.70.

3-Methyl-1-phenyl-2-pentanol (4) and the Corresponding 2-Chloro-3-methyl-1-phenylpentane (6).—Reaction of phenylacetaldehyde with a 25% excess of *sec*-butylmagnesium bromide followed by decomposition by saturated NH_4Cl gave compound **4**: bp 94–98° (0.85–0.70 mm); $n^{22.5}D$ 1.5088 [lit.[5] bp 132° (15 mm); n^{25}_{5875} 1.50714]; nmr δ 7.10 (s, 5, aromatic), 3.73–3.30 m, 1, >CHOH, 2.70–2.32 (m, $PhCH_2$), 2.08 (s, 1, OH), 2.00–0.60 ppm [complex multiplets, 9, $>CH(CH_3)$-CH_2CH_3]. It is to be noted that the nmr was complicated by the presence of two asymmetric centers in the molecule.

Reaction of the above alcohol with thionyl chloride in pyridine following standard procedures[22] gave a 50% yield of the 2-chloro-3-methyl-1-phenylpentane (**6**): bp 81° (1 mm); nmr (CCl_4) δ 7.10 (s, 5, aromatic), 3.70–1.15 (complex multiplets, 6, $PhCH_2$-$CHCHCH_2$), 1.13–0.70 ppm (an apparent triplet overlapping two apparent doublets, 6, CH_2CH_3 and $CHCH_3$). Again it is to be noted that the nmr spectrum was complicated by the presence of two asymmetric centers in the molecule.

Anal. Calcd for $C_{12}H_{17}Cl$: Cl, 17.93. Found: Cl, 18.01.

2,3-Dimethyl-5-phenyl-2-pentanol (7).—Reaction of the previously prepared 3-methyl-5-phenyl-2-pentanone with a 25% excess of methylmagnesium iodide followed by decomposition with saturated NH_4Cl gave the title compound: bp 77° (0.075 mm); $n^{23}D$ 1.5095; nmr δ 7.10 (s, 5, aromatic), 2.90–1.10 (complex multiplets, 5, $PhCH_2CH_2CH$), 1.30 [s, 6, $>C(CH_3)_2$], 8.80 ppm (d, 3, J = 5.5 Hz, $CHCH_3$).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.17; H, 10.49. Found: C, 8.18; H, 10.53.

2,3-Dimethyl-5-phenyl-3-pentanol (8).—Reaction of methyl isopropyl ketone with a 20% excess of β-phenylethylmagnesium iodide followed by decomposition by saturated NH_4Cl gave the title compound: bp 83–86° (0.15 mm); $n^{23}D$ 1.5096 [lit.[23] 118–119° (3 mm); $n^{25}D$ 1.5083]; nmr δ 7.12 (s, 5, aromatic), 2.85–2.45 (m, low-field half of an AA'BB' system, 2, $PhCH_2CH_2$), 2.30 (s, 1, OH), 2.00–1.30 [complex multiplets including high-field half of the AA'BB' system, 3, $PhCH_2CH_2$– and $-CH(CH_3)_2$], 1.08 (s, 3, $HOCCH_3$), 0.93 and 0.90 ppm [two doublets, 6, J = 7 Hz, diastereomeric methyl groups, $CH(CH_3)_2$].

2-Methyl-6-phenyl-2-hexanol (9).—Reaction of 5-phenylpentanoic acid with methanol–BF_3[24] gave methyl-5-phenylpentanoate, bp 117° (3.65 mm), $n^{24}D$ 1.4965 [lit.[25] bp 173° (35 mm)]. Condensation of the ester with excess methylmagnesium iodide and decomposition by saturated ammonium chloride solution gave 2-methyl-6-phenyl-2-hexanol (**9**): bp 90–91° (0.25 mm); $n^{25.2}D$ 1.5013 [lit.[5] bp 132 (14 mm); n^{25}_{5875} 1.50362]; nmr δ 7.11 (s, 5, aromatic), 2.60 (t, 2, J = 7 Hz, $PhCH_2$), 2.55 (s, 1, superimposed on highest field signal of the latter triplet, OH), 1.90–1.25 [m, 6, $(CH_2)_3$], 1.12 ppm [s, 6, $(CH_3)_2$].

1,5-Diphenyl-1-pentanol (10).—Reaction of benzaldehyde with 20% excess δ-phenylbutylmagnesium chloride (prepared from 4-phenyl-1-chlorobutane and magnesium) followed by decomposition by saturated NH_4Cl gave the title compound: bp 137–139° (0.015 mm); $n^{23}D$ 1.5588; nmr (CCl_4) δ 7.10 (doublet overlapping a weak multiplet at base, 10, aromatic), 4.40 (an apparent triplet, 1, J = 6.5 Hz, PhCHOH), 3.10 (s, 1, OH), 2.48 (an apparent triplet, 2, J = 7 Hz, $PhCH_2$), 1.90–1.15 ppm [m, 6, $(CH_2)_3$].

Anal. Calcd for $C_{17}H_{20}O$: C, 85.00; H, 8.33. Found: C, 84.79; H, 8.34.

2-Methyl-4,6-diphenyl-2-hexanol (11).—Reaction of benzylacetophenone with carbethoxymethylphosphonate anion, $(EtO)_2POCHCOOEt$, in dry 1,2-dimethoxyethane, following essentially the procedure described by Wadsworth and Emmons,[26] with the exception that the reflux period was extended to 2 hr, gave a mixture of *cis*- and *trans*-ethyl 3,5-diphenyl-2-pentenoate (glpc and nmr) consisting chiefly of one of the two isomers: bp 152–154° (0.5 mm); $n^{25.2}D$ 1.5577; mass (calcd for $C_{19}H_{20}O_2$) 280.1463 (found 280.1463).

Reduction of the above ester with hydrogen (60 psi) using 5% Pd/C as catalyst in ethanol as solvent gave ethyl 3,5-diphenylpentanoate: bp 159–161° (1.25 mm); $n^{26.2}D$ 1.5232; nmr (CCl_4) δ 7.30–6.93 (m with sharp singlet at 7.18, 10, aromatic), 3.95 (q, 2, J = 8 Hz, OCH_2), 3.50–1.22 (complex multiplets, 7, $PhCH_2CH_2CHCH_2$–), 1.05 ppm (t, 3, J = 8 Hz, CH_3); mass (calcd for $C_{19}H_{22}O_2$) 282.1620 (found 282.1623).

(18) S. C. Sengupta, *J. Prakt. Chem.*, **151**, 82 (1938).

(19) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **31**, 89 (1966).

(20) G. Schroeter, L. Lichtenstadt, and D. Irinei, *Chem. Ber.*, **51**, 1600 (1818).

(21) J. F. Norris and A. W. Olmsted, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 144.

(22) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., New York, N. Y., 1956, p 384.

(23) D. Price, D. Davidson, and M. T. Bogert, *J. Org. Chem.*, **3**, 540 (1938).

(24) L. Metcalf and A. Schmitz, *Anal. Chem.*, **33**, 363 (1961).

(25) W. Borsche, *Chem. Ber.*, **44**, 2596 (1911).

(26) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

The structure of the above ester was also confirmed by hydrolysis to the known 3,5-diphenylpentanoic acid (see next preparation). Reaction of the ester with methylmagnesium iodide followed by decomposition by saturated NH_4Cl gave 2-methyl-4,6-diphenyl-2-butanol (11) in 95% purity: bp 149–151° (0.6 mm); $n^{26.2}D$ 1.5406; nmr (CCl_4) δ 7.33–6.80 (m, 10, aromatic), 2.90–1.10 (complex multiplets, 8, $PhCH_2CH_2CHCH_2COH$), 0.97 ppm [s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{19}H_{24}O$: C, 85.18; H, 8.95. Found: C, 85.01; H, 9.13.

3,5-Diphenylpentanoyl Chloride (14).—Hydrolysis of ethyl 3,5-diphenylpentanoate, prepared above, by refluxing with a 50% solution of sodium hydroxide in aqueous ethanol gave 3,5-diphenylpentanoic acid: mp 108–110° (lit.[27] mp 109–110°). Reaction of the acid with thionyl chloride folliwing standard procedures gave the title compound: bp 162° (0.75 mm); nmr (CCl_4) δ 7.45–6.83 (m, 10, aromatic), 3.30–2.87 (m, with sharp singlets at 3.05 and 3.02, 3, $PhCHCH_2CO$), 2.60–1.62 ppm (AA'BB' multiplet centered at about 2.13, 4, $PhCH_2CH_2$).

Anal. Calcd for $C_{17}H_{17}OCl$: Cl, 13.00. Found: Cl, 13.17.

1,1-Dimethyl-3-(β-phenylethyl)indan (32).—Reaction of 3,3-dimethyl-1-indanone[19] with β-phenylethylmagnesium chloride followed by direct reduction of the resulting 1,1-dimethyl-3-(β-phenylethyl)-3-indanol with hydrogen and Pd/C in glacial acetic acid containing a little perchloric acid[28] gave the title compound, which upon recrystallization from cold methanol gave colorless crystals having the following properties: mp 58–59°; nmr (CCl_4) δ 7.13 and 7.03 (both singlets, 9, aromatic), 3.30–1.40 (complex multiplet, 7, all aliphatic methine and methylene protons), 1.33 and 1.13 (two equal singlets, 6, *gem*-methyls).

Anal. Calcd for $C_{19}H_{22}$: C, 91.20; H, 8.80. Found: C, 91.25; H, 8.93.

1-(β-Phenylethyl)indan.—Reaction of β-phenylethylmagnesium chloride with 1-indanone following standard procedures gave 1-(β-phenylethyl)-1-indanol as a thick viscous oil (ir showed OH and no C=O). Reduction of this crude indanol with hydrogen and Pd/C in glacial acetic acid containing a little perchloric acid gave the required 1-(β-phenylethyl)indan: bp 161–163° (2.8 mm); $n^{25}D$ 1.56721; nmr (CCl_4) δ 7.10 and 7.03 (both singlets having an approximate ratio of 5:4, 9, aromatic), 3.33–1.30 ppm (cluster of multiplets, 9, all aliphatic protons).

Anal. Calcd for $C_{17}H_{18}O$: C, 86.44; H, 6.78. Found: C, 86.60; H, 7.01.

The above product was identical in all respects with a sample obtained by catalytic reduction (with hydrogen and Pd/C in glacial acetic acid containing a little perchloric acid)[28] of the 3-(β-phenylethyl)-1-indanone which resulted before upon cyclization of 3,5-diphenylpentanoyl chloride with $AlCl_3$.

1-Isopropyltetralin (28).—Reaction of 1-tetralone with excess isopropylmagnesium bromide gave a product which was shown by glpc and ir analysis to be a mixture of the condensation product 1-hydroxy-1-isopropyltetralin and the starting 1-tetralone. Reduction of this crude mixture using hydrogen and Pd/C in glacial acetic acid containing a little perchloric acid gave a mixture of tetralin and 1-isopropyltetralin. Fractional distillation of the latter mixture gave several fractions consisting of 97–99% 1-isopropyltetralin: bp 100° (7 mm); $n^{26}D$ 1.5279 (lit.[5] bp 247°; n^{25}_{5875} 1.52705); nmr (CCl_4) δ 7.20–6.75 (m, 4, aromatic), 2.90–1.15 [unresolved multiplets, 8, $(CH_2)_3CHCH$], 0.98 and 0.75 ppm [two equal doublets, 6, J = 7 Hz, $(CH_3)_2$]. Based on the starting 1-tetralone, the overall yield of 1-isopropyltetralin was about 20%.

***cis*- and *trans*-1,2-Dimethyltetralin** (16).—Reaction of 2-methyl-1-tetralone, prepared according to the procedure of Alexander and Mudrak,[29] with 1.1 equiv of methylmagnesium iodide gave a mixture of diastereomeric 1,2-dimethyl-1-tetralols. Crystallization of this crude product from methanol gave a 55% yield of a crystalline form of 1,2-dimethyl-1-tetralol with a mp of 65–67° (lit.[20] mp 64–66°) and about 15% yield of a thick oily residue which was obtained from the filtrate by evaporating the solvent under vacuum. Although this oily residue defied crystallization from various solvents, its spectroscopic properties suggested that it was a mixture consisting of about equal proportions of the two diastereomeric forms of 1,2-dimethyl-1-tetralol. This suggestion was further supported by the fact that dehydration of this oily residue by refluxing with 20% H_2SO_4 for 2 hr gave 1,2-dimethyl-3,4-dihydronaphthalene (bp 250–252°; lit.[20] bp 250–251°) which was identical in all respects with the same compound obtained by analogous dehydration of the pure crystalline isomer.

Both the solid and the oily fractions of 1,2-dimethyl-1-tetralol as well as the alkene derived from them were hydrogenated to 1,2-dimethyltetralin. Hydrogenation of the pure crystalline form of 1,2-dimethyl-1-tetralol and of 1,2-dimethyl-3,4-dihydronaphthalene using H_2 and Pd/C in glacial acetic acid containing a little perchloric acid[28] (only in the case of the tetralol) gave similar products which distilled between 234 and 236° and whose glpc and nmr analysis suggested that they consist chiefly of *trans*-1,2-dimethyltetralin[30–32] mixed with not more than 10% of its cis isomer. Purification of this trans isomer was by preparative glpc using an Aerograph Autoprep Model A-700 equipped with a 12 ft × 0.25 in. column packed with cyanosilicone (30%) on 60–80 mesh Chromosorb at 130–140°. The pure isomer had the following properties: $n^{26}D$ 1.5275; nmr (CCl_4, 100 MHz) δ 6.94 (s with weak side signals at 6.90 and 6.98, 4, aromatic), 2.90–1.20 (multiplets, 6, aliphatic ring protons), 1.14 (d, 3, J = 9.5 Hz, CH_3), 1.03 ppm (d, 3, J = 9.5 Hz, CH_3).

Reduction of the oily 1,2-dimethyl-1-tetralol fraction by refluxing for 1 hr with freshly prepared W-2 Raney nickel[33] in ethanol gave a hydrocarbon product which was shown by both glpc and nmr analysis to be a mixture consisting of equal proportions of *cis*- and *trans*-1,2-dimethyltetralin. The 100-MHz nmr spectrum of this mixture in CCl_4 showed the following signals: δ 6.60–7.90 (m, 4, aromatic), 1.40–2.85 (cluster of multiplets, 6, aliphatic ring protons), 1.25, 1.07, 1.02, and 0.96 ppm (all doublets with J = 3 Hz, total, of 6 protons, diastereomeric methyls). It is to be noted that the doublets at 1.07 and 0.96 correspond to the previously described *trans*-1,2-dimethyltetralin and those at 1.25 and 1.02 to its cis isomer.

2,2-Dimethyltetralin (24).—Cyclization of the previously prepared 2,2-dimethyl-4-phenyl-*n*-butanoyl chloride with $AlCl_3$–CH_3NO_2 in the usual manner gave 2,2-dimethyl-1-tetralone: bp 65–68° (0.20–0.15 mm); $n^{25}D$ 1.5411 [lit.[18] bp 150° (27 mm); $n^{24.8}D$ 1.54135]; nmr (CCl_4) δ 8.08–7.85 (m, 1, C-8 aromatic proton), 7.50–7.00 (m centered at 7.25, 3, other aromatic protons), 2.95 (t, 2, J = 6 Hz, benzylic CH_2), 1.93 (t, 2, J = 6 Hz, other CH_2), 1.17 ppm (s, 6, *gem*-methyls). Reduction of the latter tetralone using hydrogen and Pd/C in glacial acetic acid containing a little perchloric acid[28] gave 2,2-dimethyltetralin: bp 50–54° (0.7 mm); $n^{25}D$ 1.5174 [lit.[18] bp 123° (34 mm); $n^{24.1}D$ 1.5185]; nmr (CCl_4) δ 6.97 (s, 4, aromatic), 2.77 (t, 2, J = 7 Hz, $-C_6H_4CH_2CH_2$), 2.50 (s, 2, other benzylic CH_2), 1.55 (t, 2, J = 7 Hz, $-C_6H_4CH_2CH_2$), 0.97 ppm (s, 6, *gem*-methyls).

1-Benzyl-4-methyltetralin (36).—Reaction of benzylmagnesium chloride with 1-tetralone followed by reduction of the intermediate carbinol with H_2 and Pd/C in glacial acetic acid containing a little perchloric acid[28] gave the title compound: bp 158–160° (3 mm); $n^{27}D$ 1.5718; nmr (CCl_4) δ 7.30–6.90 (m, 9, aromatic), 3.28–2.50 (m, 4, benzylic protons), 2.00–1.15 (unresolved, 4, $-CH_2CH_2-$), 1.29 and 1.21 ppm (both doublets in a ratio of 3.4:1, respectively, 3, diastereomeric CH_3); mass (calcd for $C_{18}H_{20}$) 236.1565 (found 236.1572).

It is to be noted that the presence of two methyl doublets in the nmr spectrum of the above compound suggests that it is a mixture of both the cis and the trans isomers. However, various

(27) C. Mannich and A. Butz, *Chem. Ber.*, **62**, 462 (1929).

(28) R. M. Roberts, G. A. Ropp, and O. K. Neville, *J. Amer. Chem. Soc.*, **77**, 1764 (1955).

(29) E. R. Alexander and A. Mudrak, *ibid.*, **72**, 3194 (1950).

(30) The assignment of trans configuration to this isomer was based on two factors: first, the observation made by Siegel[31] and by others[32] that palladium catalysts yield predominantly the more stable trans stereoisomer from 1,2- or 1,4-disubstituted cyclohexenes; and second, examination of the nmr data that indicates that the difference in chemical shifts between the **1** – CH_3 and **2** – CH_3 signals for this isomer (difference between δ 1.07 and 0.96) is smaller than the corresponding difference in the case of its diastereomer (difference between δ 1.25 and 1.02). This observation which suggests that the two methyls of the isomer with less difference are more magnetically similar to each other than those of the other isomer can reasonably be explained by assuming that the two methyls have either a diaxial or diequatorial relationship in the isomer with small chemical shift difference, but an axial–equatorial relationship in the other case.

(31) (a) S. Siegel and G. V. Smith, *J. Amer. Chem. Soc.*, **82**, 6087 (1960); (b) S. Siegel and M. Dunkel, *Advan. Catal. Relat. Subj.*, **9**, 15 (1957).

(32) A. S. Hussey, private communication to S. Siegel mentioned in ref 31a: J.-F. Sauvage, R. H. Baker, and A. S. Hussey, *J. Amer. Chem. Soc.*, **82**, 6090 (1960).

(33) R. Mozingo, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 181.

attempts to separate the isomers using a number of glpc columns were unsuccessful.

1,2,2-Trimethyltetralin (46).—Reaction of methylmagnesium iodide with the above-prepared 2,2-dimethyl-1-tetralone gave 1-hydroxy-1,2,2-trimethyltetralin: ir (film) 2.87 μ (OH); nmr (CCl_4) δ 7.62–7.37 (m centered at 7.50, 1, C-8 aromatic proton), 7.23–6.83 (m, 3, other aromatic protons), 2.97–2.60 (m, 2, benzylic CH_2), 2.23 (s, 1, OH exchangeable with D_2O), 1.85–1.52 (m, 2, other CH_2), 1.33 (s, 3, $HOCCH_3$), 1.00 and 0.93 ppm (two equal singlets, 6, *gem*-methyls). Reduction of the latter tetralol with hydrogen and Pd/C in glacial acetic acid containing a little perchloric acid[28] gave the desired 1,2,2-trimethyltetralin: bp 49–51° (0.5 mm); $n^{26.5}$D 1.5214; nmr (CCl_4) δ 6.98 (s with two weak side signals at 7.06 and 6.93, 4, aromatic), 2.78 (an apparent triplet, 2, J = 6 Hz, benzylic CH_2), 2.47 (q partially superimposed on latter triplet 1, J = 7 Hz benzylic CH), 2.00–1.33 (m, 2, nonbenzylic CH_2), 1.17 (d, 3, J = 7 Hz, CH_3), 0.94 ppm (s, 6, *gem*-methyls).

Anal. Calcd for $C_{13}H_{18}$: C, 89.65; H, 10.35. Found: C, 89.40; H, 10.43.

Cyclization Procedures. (a) Cyclialkylation of Arylalkanols and Arylalkyl Chlorides.—The procedures described before for cyclialkylations of arylalkanol with concentrated sulfuric acid[34] and anhydrous phosphoric acid[34] and of arylalkyl chlorides with $AlCl_3$[19] were essentially followed. However, the following is to be noted. (1) The $AlCl_3$- and $AlCl_3$–CH_3NO_2-catalyzed cyclialkylations were carried out in petroleum ether (bp 60–70°) with alcohols and in petroleum ether (bp 60–70°) or CS_2 with chlorides. (2) In all cases a ratio of solvent (milliliters) to cyclized compound (grams) of *ca.* 4.5 was used. (3) Unless specified otherwise, the molar ratio of $AlCl_3$ to substrate was 1.2 in reactions of alcohols and 0.1 in reactions of chlorides; these ratios were also used in reactions catalyzed by $AlCl_3$–CH_3NO_2, but the $AlCl_3$ was dissolved in 10 equiv of CH_3NO_2 prior to the addition of the substrate.

Details concerning reactants, catalyst, solvent, reaction conditions, and product composition are given in Table I.

(b) Cycliacylation of 3,5-Diphenylpentanoyl Chloride with Aluminum Chloride in Carbon Disulfide and in Nitromethane.—The reactions were carried out in a manner essentially similar to that described before for the cyclialkylation of phenylalkyl chlorides using a ratio of acid chloride (grams)/$AlCl_3$ (grams)/solvent (milliliters) equal to 1:0.6:10 in the case of CS_2 and to 1:0.6:5 in the case of CH_3NO_2. While the reaction in CS_2 was conducted at between 5 and 10° for 2 hr, that in CH_3NO_2 was conducted at 25° for 1 hr. Both the CS_2 and the CH_3NO_2 reactions gave identical products which were shown by glpc to consist only of one compound. A pure sample of this compound showed the following properties: bp 162–163° (0.35 mm); n^{23}D 1.5895; nmr (100 MHz, CCl_4) δ 7.30–6.80 (m, 9, aromatic), 3.20–2.80 (m with sharp singlets at 2.96 and 2.94, 3, benzylic), 2.40–2.18 (an apparent t, 2, $COCH_2$), 1.96–1.54 ppm (m, 2, $PhCH_2CH_2$); mass spectrum (70 eV) m/e (rel intensity) 236 (M, 10), 145 (100), 132 (33), 105 (33), 92 (68), and 91 (49). The above properties suggest that the product of cycliacylation of 3,5-diphenylpentanoyl chloride with $AlCl_3$ and $AlCl_3$–CH_3NO_2 is 3-(β-phenylethyl)-1-indanone. This suggestion was also confirmed by elemental analysis of the compound.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.44; H, 6.78. Found: C, 86.60; H, 7.01.

Treatment of 1,2-Dimethyltetralin (16) and 1,1,2-Trimethyltetralin (45)[35] with $AlCl_3$ in Petroleum Ether (Bp 60–70°).—In both cases the hydrocarbon (1 mol), solvent (5 g/g of hydrocarbon) and $AlCl_3$ (0.5 mol) were stirred at room temperature, and samples were taken, hydrolyzed, and analyzed. It is to be noted that in the case of 1,1,2-trimethyltetralin another batch of catalyst was added to the mixture after 2 hr of reaction.

1,2-Dimethyltetralin gave a mixture consisting of 72% 2,2-dimethyltetralin, 7% *cis*- and 8% *trans*-1,2-dimethyltetralin, and 12% unidentified products after 2 hr of reaction. This composition was almost the same after 4 hr of reaction.

Starting with 1,1,2-trimethyltetralin, the following proportions of 1,1,2-trimethyltetralin/1,2,2-trimethyltetralin/unidentified products were found after the times given: 1 hr, 6:75:19; 2 hr, 8:58:34; 4 hr, 4:40:56; 8 hr, 4:29:67. The unidentified products produced in the above reactions are believed to consist mostly of other trimethyltetralin isomers.

Treatment of a Mixture of 1,2-Dimethyltetralin (16) and 1-Ethyl-1-methylindan (15) with Polyphosphoric Acid.—A 0.2-g sample of the cylization mixture resulting from the reaction of alcohol 2 with H_2SO_4 was refluxed with 2 ml of polyphosphoric acid at 240° for 20 min. After the usual separation procedure, the organic product obtained was shown by glpc and nmr analysis to contain no 2,2-dimethyltetralin.

Registry No.—**1**, 15732-85-1; **2**, 36748-82-0; **3**, 10415-87-9; **4**, 36748-84-2; **5**, 36748-49-9; **6**, 36748-50-2; **7**, 36748-51-3; **8**, 36748-52-4; **9**, 13732-85-9; **10**, 36748-54-6; **11**, 36748-55-7; **12**, 36613-03-3; **13**, 34663-10-0; **14**, 36748-58-0; *cis*-**16**, 36736-25-1; *trans*-**16**, 36736-26-2; **24**, 13556-55-3; **28**, 36748-60-4; **32**, 36748-61-5; *cis*-**36**, 36736-27-3; *trans*-**36**, 36736-28-4; **46**, 1077-80-1; 2,2-dimethyl-4-phenylbutanoyl chloride, 36748-92-2; 3-methyl-5-phenyl-2-pentanone, 5195-30-2; *cis*-ethyl 3,5-diphenyl-2-pentenoate, 36736-29-5; *trans*-ethyl 3,5-diphenyl-2-pentenoate, 36805-43-3; ethyl 3,5-diphenyl-3-pentanoate, 36748-94-4; 1-(β-phenylethyl)-indan, 36748-95-5; 3-(β-phenylethyl)-1-indanone, 21460-83-3.

(34) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **34**, 3571 (1969).

(35) Pure 1,1,2-trimethyltetralin (**45**) was obtained from the cyclization of alcohols **7** and **8** with either H_2SO_4 or $AlCl_3$–CH_3NO_2. The physical properties of this product were shown to be identical with those of the same compound which had previously been obtained by Price, Davidson, and Bogert.[23] Moreover, the nmr and ir data of the compound were consistent with its formulation.

The Reaction of Organolithium Reagents with Allylic Alcohols[1a]

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Allyl alcohol adds a variety of organolithium reagents regiospecifically to give 2-substituted 1-propanols (1). Organolithium intermediate 2 was demonstrated. A similar reaction predominates with 3-buten-1-ol. On the other hand, 2-cyclopentenol undergoes replacement of the hydroxy group by the alkyl group of the organometallic species in a process which was demonstrated to proceed cleanly with double-bond rearrangement. The reactions of other allylic alcohols were similar but much less selective. The synthetic utility and mechanistic aspects of these organometallic transformations are briefly explored.

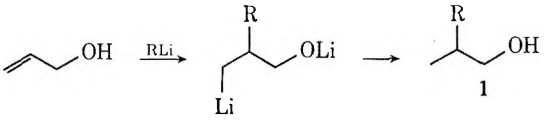
Although the initial observation that organolithium reagents add to nonconjugated olefins appeared some time ago,[2,3] this interesting reaction has not found general synthetic applicability. Thus, whereas ethylene adds secondary or tertiary organolithium reagents cleanly to give the corresponding chain-extended primary reagents,[4] high pressures[2,3] or catalysts such as *N*,*N*,*N'*,*N'*-tetramethylethylenediamine[5] (TMEDA) are required to promote the addition of primary alkyllithiums to this olefin. Under these conditions the initial organolithium product adds to ethylene at a similar rate, leading ultimately to polymeric products. With substituted olefins reaction either does not take place or results in polymers.[2,3,6] However, special instances of synthetically useful additions are observed when particularly stable carbanionic species are formed,[6,7] the starting olefin is strained,[6,8] or the reaction is intramolecular.[8,9]

Allylic ethers react with organolithium reagents by metalation followed by double-bond isomerization to vinyl ethers[10] or by replacement of the alkoxyl group by the organic moiety of the reagent[10,11] in a manner similar to that observed with allylic halides.[12] This substitution reaction appears to proceed with clean double-bond rearrangement probably in a cyclic process from a complex between the ether and the organometallic.[11]

Prior to our preliminary communication[13] and its independent discovery by Felkin and coworkers,[14] the reaction of organolithium reagents with allylic alcohols had not been reported. However, allylic and benzylic Grignard reagents are known to add slowly to both allylic and other unsaturated alcohols.[14,15] These particular Grignard reagents are exceptionally reactive toward double bonds, as shown by their addition to 1-octene as well as ethylene.[16] The present report examines the reaction between organolithium reagents and allylic alcohols as a function of structural change in each of the reaction partners.

Results

Allyl alcohol combines with a variety of organolithium reagents to give 2-substituted 1-propanols (**1**) in



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a, R = *tert*-butyl
b, R = isopropyl
c, R = *n*-butyl
d, R = cyclopentyl
e, R = phenyl
f, R = benzyl

variable yield depending upon the organolithium and the reaction conditions. The isomeric alcohols derived from the alternative mode of addition are not formed.

A study of yields of **1a–c** as a function of temperature and solvent revealed that the yields are at best moderate (20–50%) in hydrocarbon or ethereal solvents, and that raising the reaction temperature did not have a marked effect. However, a significant increase in yield, to 77% was achieved when 0.2 equiv of tetramethylethylenediamine (TMEDA) was used with *n*-butyllithium.[5] Subsequently, allyl alcohol was found to react with cyclopentyl-, phenyl-, and benzyllithium in the presence of TMEDA to give acceptable yields of **1d** (40%), **1e** (40%), and **1f** (52%).

Evidence for the existence of **2** as the organolithium precursor of **1** was obtained by the hydrolysis of reaction mixtures from *tert*-butyllithium and *n*-butyllithium with D_2O. Compounds **1a** and **1c** were ana-

(1) (a) Supported by a research grant from the National Science Foundation. (b) Alfred P. Sloan Fellow, 1968–1970; John Simon Guggenheim Fellow, 1970–1971. (c) National Institutes of Health Predoctoral Fellow, 1969–1970.

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(11) (a) H. Felkin and A. Tambute, *Tetrahedron Lett.*, 821 (1969); (b) R. Quelet, C. Broquet, and J. d'Angelo, *C. R. Acad. Sci., Ser. C*, **264**, 1316 (1967).

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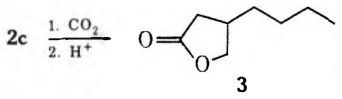
lyzed for deuterium content as the acetate and methyl ether, respectively. The acetate of **1a** did not have a large molecular ion, but the M − CH_3 ion was used for calculation, from which 86% deuterium incorporation was determined, assuming that the fragmentation leading to the M − CH_2D ion was negligible. The methyl ether of **1c** gave 83% deuterium incorporation, using the M − CH_4O ion. Additional evidence for intermediate **2c** was provided by the deuterium magnetic resonance spectrum of **1c** from the heavy water hydrolysis experiment which showed a single, broad resonance centered at δ 0.93, consistent only with deuterium on a methyl group.[17]

Two brief attempts to synthetically utilize **2c** were successful. When a reaction mixture containing **2c** was quenched by the addition of powdered Dry Ice and subsequently stirred with dilute acid, a 23% yield of β-*n*-butyl-γ-butyrolactone (**3**) was obtained in addi-



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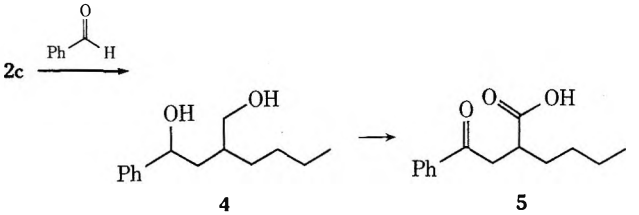
tion to **1c**. Development of this reaction sequence may provide a general synthesis of β-substituted γ-butyrolactones.

The addition of benzaldehyde to a reaction mixture containing **2c** gave a 43% yield of diol **4** as a mixture of diastereomers. This product was characterized by oxidation to keto acid **5**.



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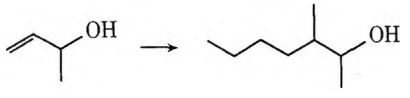
The reaction of 3-buten-2-ol with *n*-butyllithium or benzyllithium in the presence of TMEDA proceeds in a manner similar to that of allyl alcohol. *n*-Butyllithium gave a 66% yield of 3-methyl-2-heptanol (**6**),



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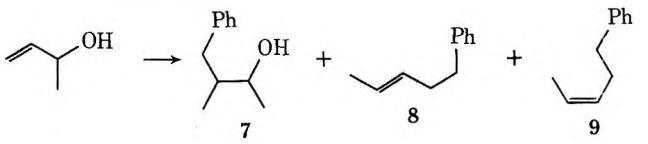
which may be a diastereomeric mixture,[14] but which was a single peak by all glpc methods tried. Benzyllithium afforded minor amounts of *trans*- and *cis*-5-phenyl-2-pentene, **8** and **9**, in addition to the expected product, 3-benzyl-2-butanol (**7**), in a ratio of 7:3:73.



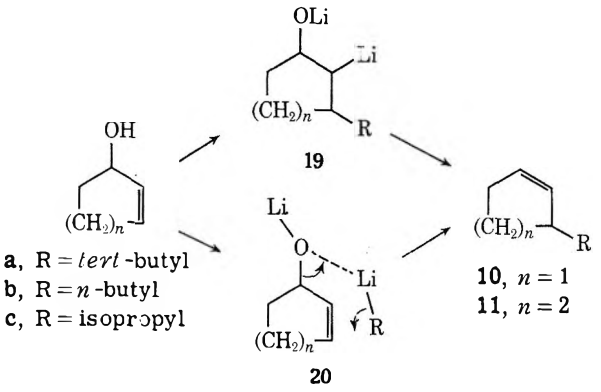
7 8 9

Alcohol **7** was shown by glpc to be a 4.5:1 mixture of threo and erythro isomers.[18] There was less than 0.1% of the isomeric olefin 3-benzyl-1-butene present.

(17) L. K. Montgomery, A. O. Clouse, A. M. Crelier, and L. E. Applegate, *J. Amer. Chem. Soc.*, **89**, 3453 (1967).

(18) Y. Gault and H. Felkin, *Bull. Soc. Chim. Fr.*, 742 (1965).

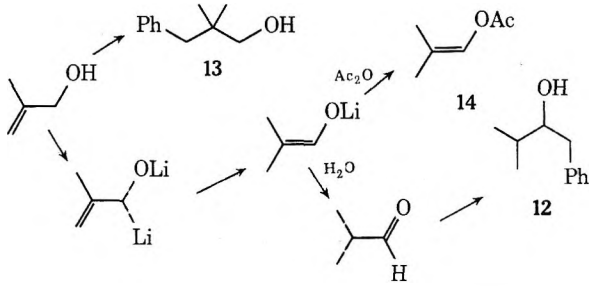
Olefin formation is the predominate reaction of 2-cyclopentenol and 2-cyclohexenol which give 3-alkylcycloalkenes, **10a–c** and **11a,b**, respectively. The best



results were obtained with *n*-butyllithium–TMEDA, which gave a 62% yield of **10b**. The efficacy of TMEDA in promoting reactions did not extend to *tert*-butyllithium; the yield of **10a** dropped from 35% to 10% with TMEDA. The reaction of *n*-butyllithium–TMEDA with 2-cyclohexenol proceeds sluggishly, but under forcing conditions substantial conversion to **11b** can be obtained, albeit accompanied by a number of unidentified by-products.

The mechanism of this reaction has been investigated briefly. The allylic hydroxyl group is requisite for the addition of *tert*-butyllithium to the double bond of 2-cyclopentenol, since neither 3-cyclopentenol nor a mixture of cyclopentene and cyclopentanol reacted with *tert*-butyllithium. Furthermore, treatment of 1-deuterio-2-cyclopentenol with *n*-butyllithium–TMEDA gave **10b**, which retained 98% of its deuterium label. The deuterium magnetic resonance spectrum of **10b** exhibited a single resonance at δ 5.76 indicating olefinic deuterium exclusively.

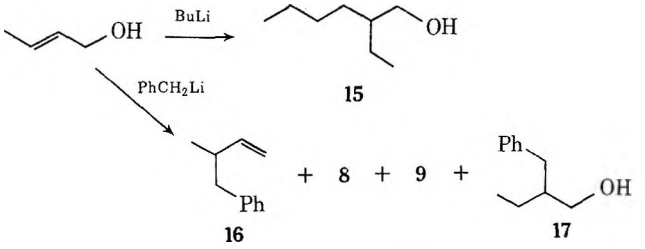
The reactions of 2-methyl-2-propen-1-ol with *n*-butyllithium and benzyllithium take quite different courses. *n*-Butyllithium in the presence of TMEDA led to a rapid darkening of the reaction mixture and formation of a plethora of products, none of which predominated. Benzyllithium, on the other hand, gave 30% of 3-methyl-1-phenyl-2-butanol (**12**) and 37% of 2,2-dimethyl-3-phenyl-1-propanol (**13**). The absence



of 2-methyl-4-phenyl-1-butene and 3-methyl-1-phenyl-2-butene was demonstrated. When the reaction mixture was quenched by the addition of deuterium oxide, the nmr spectrum of **12** revealed that the unique isopropyl hydrogen had been replaced by deuterium. Detailed analysis by dmr showed that extensive deuterium incorporation also occurred at the aromatic and benzylic carbons, and a small amount of deuterium was even seen at the isopropyl methyl positions. Finally,

quenching the reaction mixture with acetic anhydride gave a product mixture in which neither **12** nor its acetate was present. However a new product, enol acetate **14**, was observed along with the acetates of **13** and starting material.

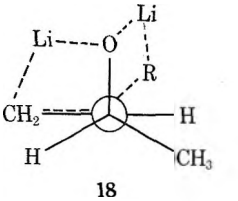
The reactions of *trans*-2-buten-1-ol with *n*-butyllithium and benzyllithium also differ markedly. *n*-Butyllithium–TMEDA reacts to give 2-ethyl-1-hexanol (**15**) as 67% of the volatile products. Glpc analysis revealed at most trace amounts of C_8 olefins. Benzyllithium–TMEDA, however, gives a mixture of olefins **16**, **8**, and **9**, and the addition product, 2-benzyl-



1-butanol, **17**, in a 41:14:14:9 ratio. The product mixture from a similar reaction with *cis*-2-buten-1-ol was a 9:48:41:2 mixture of the same four compounds. However, the overall yields of these reactions were low. Quenching the reaction with acetic anhydride gave no enol acetate and quenching with deuterium oxide gave undeuterated olefins. The reaction of *trans*-1,1-dideuterio-2-buten-1-ol with benzyllithium gave **16** retaining 97% of its deuterium at the terminal vinyl position and a mixture of **8** and **9** retaining 93% of their label at the allylic methylene position. It was further shown that olefin **8** was inert to the reaction conditions, and that, as expected, the saturated alcohol, *n*-butyl alcohol, did not couple with benzyllithium.

Discussion

The regiospecific addition of organolithium reagents to allylic alcohols with unsubstituted vinyl groups appears to be a general and reasonably effective route to **1** proceeding by way of a primary organolithium intermediate **2**, potentially capable of further synthetic transformations. The orientation of the addition is presumably dictated mainly by the greater stability of **2** compared to the secondary organolithium species that would be formed by the alternate mode of addition. Felkin and coworkers[14] have independently witnessed similar reactions and have commented upon the preference for α-substituted allylic alcohols to yield threo alcohols. This is in direct contrast to the addition of allylic Grignard reagents,[15] a reaction which gives preferentially the erythro isomers. The stereochemistry of the organolithium reaction has been explained in terms of a transition state such as **18**, in



18

which the attacking organometallic takes advantage of prior coordination at the lithium alkoxide function in order to add to the double bond by a cyclic mechanism. This explanation accounts for the greater reactivity of allylic alcohols with organolithium reagents as compared to the corresponding simple olefins. Furthermore, the stereochemical preference for threo alcohol is accounted for by the greater stability of transition state **18** over the diastereomeric one with the H and CH_3 groups of the carbinol carbon interchanged. This is apparently because of steric interactions between the CH_3 and the developing organometallic center.

It is well known that both lithium alkoxides and organolithium compounds exist as oligomeric species in hydrocarbons solvents and that mixed aggregates result from a combination of the two.[19] Since the alkoxides of both starting and product alcohols are present during the course of the reaction, the situation is quite complicated. The ability of tertiary amines in general, and TMEDA in particular, to increase the reactivity of organolithium species by breaking up oligomeric structures and polarizing the carbon–metal bond has been observed in a number of instances, and the facilitating effect of the amine can undoubtedly be ascribed to a similar action in the present instance. However, a specific picture of the effect of TMEDA in these complicated systems is less clear. In structure **18** the new carbon–lithium bond is viewed as being generated in concert with the new carbon–carbon linkage so that high-energy carbanionic intermediates are avoided. For simplicity, a lithium originally bound to the reacting oxygen atom is utilized, although the lithium could equally well come from a more remote site in a more complex aggregate or even from a second organolithium species.

The addition reaction with 2-methyl-2-propen-1-ol is also capable of producing a primary organolithium product. However, the presence of a methyl group on the double bond apparently inhibits this reaction with respect to other processes, although reasonable amounts of the expected product were observed with benzyllithium. The competing process here is obviously metalation which results principally in double-bond migration similar to that of allylic ethers[10] to give the enolate of isobutyraldehyde, as indicated by the D_2O quenching experiment, the formation of enol acetate **14** upon quenching with acetic anhydride, and the presence of **12** in hydrolyzed reactions. The latter alcohol results from addition of excess benzyllithium to the aldehyde during the hydrolysis process. The heterogeneity of the reaction mixture undoubtedly contributes to this unusual reaction. Metalation apparently becomes more important in the case of 2-methyl-2-propen-1-ol because of retardation of the addition reaction by the methyl substituent, probably the result of steric interactions.

In the reaction of 3-buten-2-ol with benzyllithium small amounts of olefins **8** and **9** were formed by replacements of the alcohol function by the benzyl group with concomitant double-bond migration. This reaction is the only important one with 2-cyclopentenol and alkyllithium reagents. This substitution process also occurs with clean double-bond migration, as demonstrated by using deuterium-labeled cyclopentenol.

(19) T. L. Brown, J. A. Ladd, and G. N. Newman, *J. Organometal. Chem.*, **3**, 1 (1965).

Two reasonable mechanisms can be visualized for the substitution reaction. The first of these is simply a modification of the addition reaction, which now occurs with the opposite regiospecificity to give intermediate **19**. This species would be expected to undergo ready elimination of lithium oxide to yield the observed olefin.[20] The reversal in regiospecificity in the addition reaction is at least partially accountable for by the fact that a secondary organometallic is necessarily formed by either mode of addition. Furthermore, the rigid cyclic structure may prevent attainment of the optimum geometry required for the addition process indicated by structure **18**. The second mechanism for the substitution reaction involves concerted bond forming and bond breaking as shown in structure **20**. Arguments similar to those given above rationalize the change in reaction pathway with change in substrate. This substitution reaction is analogous to the aforementioned reactions of allylic ethers.[10,11]

Since the 2-buten-1-ols have the same substitution pattern on the double bond as 2-cyclopentenol, a similar reactivity might have been expected for these materials. However, the acyclic compounds behave in a more complex manner. Even the nature of the organolithium appears to be important in determining the course of the reaction. *n*-Butyllithium resulted in predominance of the addition reaction with little, if any, substitution reaction. However, the use of benzyllithium gave only small amounts of the alcohol derived from addition; the major products are the olefins resulting from substitution of the hydroxy function by the benzyl moiety. These materials are formed both with and without double-bond migration in contrast to the very selective cyclopentenol and 3-buten-2-ol reactions, which follow the former course exclusively. Furthermore, the relative proportions of the three olefins varied substantially depending upon whether the cis or trans isomer of the starting alcohol was utilized. Extensive mechanistic study was rendered pointless by the low product yields, but experiments with deuterium-labeled *trans*-2-buten-1-ol ruled out processes involving metalation at the carbinol position, formation of and addition to butadiene, etc. The apparent difference between butyl- and benzyllithium in this reaction raises the possibility of an electron-transfer process[21] being important in the olefin-forming reaction with benzyllithium, but further discussion of this reaction must await more incisive experimentation.

Experimental Section

General.—Infrared spectra (ir) were obtained with Perkin-Elmer Model 137 and 137G Infracord spectrometers as liquid films. Nuclear magnetic resonance spectra (nmr) were obtained with Varian Associates A-60 and HR-100 spectrometers in carbon tetrachloride solution. Deuterium magnetic resonance spectra (dmr) were obtained with a Varian Associates HR-100 spectrometer operating at 15.35 MHz as chloroform solutions with tetramethylsilane-d_3 as an external reference. Mass spectra were recorded with AEI MS-9, Varian MAT CH-7, CEC 21-620, and CEC 21-110b spectrometers at 70 eV. The glpc inlet system of the Varian MAT CH-7 mass spectrometer consisted of a Varian Associates Model 1200 gas chromatograph coupled through a Biemann-Watson separator to the solid probe inlet. A 10 ft × 0.125 in. column packed with 5% Carbowax 20M on Chromosorb P was used with the glpc inlet. Analytical columns were 10 or 20 ft × 0.125 in. of 15 or 20% Carbowax 20M on 60/80 Chromosorb W. Percentage composition data were estimated by peak areas and were uncorrected unless specified otherwise. Preparative gas chromatography was performed on Aerograph Model A-700 and A 90-P3 chromatographs' with 10 or 20 ft × 0.375 in. of 30% Carbowax 20M on Chromosorb W, 10 ft × 0.375 in. of 30% Lac-2-r-446 on Chromosorb W, and 5 ft × 0.375 in. of 30% SE-30 on Chromosorb W. Anhydrous magnesium sulfate was used for all drying operations. Microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind.

All reactions with air-sensitive reagents were run in sealed tubes as described below or in a three-necked, round-bottomed flask equipped with a serum cap and a reflux condenser under a positive pressure of either nitrogen or argon. Prior to the introduction of reactants, the apparatus was dried by heating with a Bunsen burner flame while being flushed with inert gas.

tert-Butyllithium and isopropyllithium were obtained as *ca.* 1.6 and 2.1 *M* pentane solutions from Alfa Inorganics, Inc., Beverly, Mass. Solutions of *ca.* 1.7 *M* methyllithium in ether, *ca.* 1.5 *M* *n*-butyllithium in hexane or pentane, and *ca.* 2.2 *M* cyclopentyllithium in cyclohexane were obtained from Foote Mineral Co., Exton, Pa. Solutions of *n*-butyllithium were generally titrated prior to use.[22] Phenyllithium and benzyllithium were made by the metalation of benzene or toluene with a mixture of *n*-butyllithium and TMEDA.[5]

Sealed-Tube Reactions with Alkyllithiums.—Reactions were performed in Pyrex ampoules which were flushed with nitrogen prior to the addition of reactants (and until just before the ampoules were evacuated and sealed). The alkyllithium solutions were introduced by syringe and cooled to −78° prior to the cautious addition of substrate. The sealed ampoules were generally allowed to warm to room temperature before being placed in a loosely covered steel pot filled with water, maintained at *ca.* 97° by placing the pot in a steam bath. The ampoules were cooled in an ice bath and opened, and the reaction was quenched by the addition of distilled water. The layers were separated, the aqueous layer was extracted with several portions of pentane, and the combined organic extracts were washed with distilled water and dried. For those reactions in which TMEDA was used, the organic layer was washed with dilute hydrochloric acid. (A similar work-up procedure was also used for most organolithium reactions and is referred to as the usual work-up procedure.)

Reaction of *tert*-butyllithium for 7 hr at room temperature gave 17% of **1a**; 3 equiv of TMEDA in a similar experiment resulted in a 25% yield; a reaction at 97° for 2.5 hr gave 22%. The addition of isopropyllithium under the latter conditions gave a 48% yield of **1b**; *n*-butyllithium produced **1c** in only 5% yield. The addition of 9 equiv of either raised the yield of **1c** to 20%, while 0.2 equiv of TMEDA produced 77% of **1c** after 8 hr at room temperature.

Reaction of Allyl Alcohol with *tert*-Butyllithium.—To 36 ml of a 1.5 *M* *tert*-butyllithium solution under nitrogen was added dropwise 1.00 g of allyl alcohol. The reaction mixture was heated to 40° with stirring for 15 hr. Analysis by glpc showed one major product which was identified spectroscopically as 2,3,3-trimethyl-1-butanol (**1a**): ir 3.00, 7.18, 7.34, 9.72 μ; nmr δ 0.88 (s, 9), 0.91 (d, 3), 1.28 (m, 1), 3.45 (eight-line multiplet, 2), 4.00 (s, 1, OH).

Reaction of Allyl Alcohol with Isopropyllithium.—A mixture of 6.2 ml of a 2.1 *M* isopropyllithium solution and 253 mg of allyl alcohol was heated in a sealed tube at 97° for 1.7 hr, allowed to remain at room temperature for 22 hr, and worked up. Glpc analysis revealed three products in a 14:83:3 ratio. The 83% product was identified as 2,3-dimethyl-1-butanol (**1b**) by its ir spectrum.[23] Neither the 14% product, ir 3.73, 5.94, 6.08, 7.12, 7.36, 8.2, 9.6 μ, nor the 3% product was identified.

2-Methyl-1-hexanol (1c).—To an ice-cold solution of 980 mg of lithium hydride and 5.03 g of allyl alcohol in 70 ml of pentane under nitrogen, which had been stirred at room temperature for 30 min, was added 20 g of TMEDA and 123 ml of a 1.4 *M* *n*-butyllithium solution. The reaction mixture was stirred at room temperature for 2 hr and worked up. Distillation gave 7.24 g (72%) of **1c**: bp 166°; ir 3.06, 7.26, 9.64 μ; nmr δ 0.88 (m, 6), 1.38 (m, 7), 3.33 (d, 2), 5.14 (s, 1, OH).

(20) J. K. Crandall and L. C. Lin, *J. Amer. Chem. Soc.*, **89**, 4527 (1967).

(21) (a) W. C. Kossa, T. C. Rees, and H. G. Richey, *Tetrahedron Lett.*, 3455 (1971); (b) J. E. Mulvaney, S. Groen, L. J. Carr, Z. G. Gardlund, and S. L. Gardlund, *J. Amer. Chem. Soc.*, **91**, 388 (1969); (c) G. A. Russell, E. G. Janzen, and E. T. Strom, *ibid.*, **86**, 1807 (1964).

(22) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

(23) Sadtler Index: ir 3432.

Reaction of Cyclopentyllithium with Allyl Alcohol.—To an ice-cold mixture of 54 ml of a 2.2 *M* cyclopentyllithium solution and 2.69 g of TMEDA under nitrogen was added dropwise 2.88 g of allyl alcohol. The reaction mixture was stirred at room temperature for 4 hr, heated to 79° for 1.5 hr, and worked up to give 3.8 g of crude product. Glpc analysis showed four products in the ratio 20:8:4:68. The 68% product was identified spectroscopically as 2-cyclopentyl-1-propanol (**1d**): ir 3.1, 7.24, 9.75 μ; nmr δ 0.90 (d, 3), 1.0–2.0 (m, 10), 3.45 (eight-line multiplet, 2), 4.3 (s, 1, –OH). The 20 and 8% products were shown to be saturated hydrocarbons of molecular weight 180 by their ir, nmr, and mass spectra.

Reaction of Phenyllithium with Allyl Alcohol.—To an ice-cold phenyllithium solution (formed by refluxing a mixture of 100 ml of benzene, 69 ml of a 1.6 *M* *n*-butyllithium solution, and 3.49 g of TMEDA under nitrogen for 1.5 hr) was added 2.88 g of allyl alcohol. The reaction mixture was heated to 61° for 18 hr and worked up. Distillation gave 3.23 g of product, bp 121° (20 mm). Glpc analysis showed three components present in a 3:14:83 ratio. Preparative glpc gave a pure sample of **1e**: ir 3.08, 6.24, 7.25, 9.7, 13.2, 14.4 μ; nmr δ 1.18 (d, 2), 2.75 (sextet, 1), 3.47 (four-line multiplet, 2), 3.98 (s, 1), 7.1 (s, 5). The 14% component was identified as **1c**.

Reaction of Benzyllithium with Allyl Alcohol.—To an ice-cold benzyllithium solution (formed by heating a mixture of 100 ml of toluene, 65 ml of a 1.6 *M* *n*-butyllithium solution, and 3.29 g of TMEDA at 70° with stirring for 2.0 hr under argon) was added 2.54 g of allyl alcohol. The reaction mixture was heated to 65° for 11 hr and worked up. The crude product was distilled to give 4.15 g of 2-benzyl-1-propanol (**1f**): bp 91° (1.65 mm); ir 3.06, 6.24, 7.26, 9.70, 13.6, 14.4 μ; nmr δ 0.86 (d, 3), 1.88 (sextet, 1), 2.53 (eight-line multiplet, 2), 3.40 (d, 2), 4.39 (s, 1, –OH), 7.1 (s, 5). Glpc analysis showed the distilled product to be 83% pure; the remaining 17% was comprised of a dozen minor products, the largest of which was 5%.

1-Acetoxy-2-deuteriomethyl-3,3-dimethylbutane.—To 11 ml of a 1.4 *M* *tert*-butyllithium solution at −78° under nitrogen was added 296 mg of allyl alcohol. The reaction mixture was warmed to room temperature for 8 hr, quenched by the addition of 1 ml of deuterium oxide, and worked up. A mixture of the crude product, 590 mg of isopropenyl acetate, and 1 drop of concentrated sulfuric acid was stirred at 60° for 1 hr, diluted with pentane, and washed with saturated sodium bicarbonate solution. The organic layer was dried, filtered, and concentrated. Glpc analysis showed one major product which was identified spectroscopically as 1-acetoxy-2-deuteriomethyl-3,3-dimethylbutane: ir 4.59, 5.75, 7.22, 7.34, 8.10, 9.70 μ; mass spectrum *m/e* (rel intensity) 144 (0.4), 104 (7), 103 (12), 102 (12), 99 (6), 84 (55), 62 (25), 61 (87), 57 (87), 56 (100), 43 (82), 41 (29). Since there was no molecular ion, the extent of deuteration was calculated using *m/e* 143, 144, and 145. Assuming that the loss of a CH_2D radical from the molecular ion was negligible, it was calculated that the acetate was 86% d_1.

2-Deuteriomethyl-1-methoxyhexane.—To an ice-cold slurry of 48 mg of lithium hydride and 371 mg of allyl alcohol, which had been stirred at room temperature for 1 hr under nitrogen, was added 85 mg of TMEDA and 9 ml of a 1.6 *M* *n*-butyllithium solution. The reaction mixture was stirred at room temperature for 3.5 hr, cooled in an ice bath, quenched by the addition of 4 ml of deuterium oxide, and worked up. Glpc analysis showed one product which was identified spectroscopically as 2-deuteriomethyl-1-hexanol, ir 2.97, 4.57, 7.24, 9.64 μ. The deuterium magnetic resonance spectrum showed a single resonance at δ 0.93.

A solution of 251 mg of 2-deuteriomethyl-1-hexanol and 211 mg of sodium hydride in 20 ml of *N,N*-dimethylformamide was refluxed on a steam bath under nitrogen for 1.25 hr. Approximately 1 ml of methyl iodide was added, and the mixture was refluxed for 15 hr, poured into distilled water, and extracted with pentane. The combined organic extracts were dried, filtered, and concentrated. Preparative glpc gave a pure sample of 2-deuteriomethyl-1-methoxyhexane: mass spectrum *m/e* (rel intensity) 131 (0.6), 99 (30), 85 (18), 71 (20), 70 (26), 69 (14), 57 (43), 56 (49), 45 (100), 44 (45), 43 (60). Because of the small size of the molecular ion, the extent of deuterium incorporation was calculated using the set of ions resulting from the loss of methanol from the molecular ion. Assuming that no loss of deuterated methanol from the molecular ion occurred, an estimate of 83% d_1 was obtained.

β-*n*-Butyl-γ-butyrolactone (3).—To a slurry of 406 mg of lithium hydride in 10 ml of pentane at room temperature under nitrogen was added 2.5 g of allyl alcohol. The mixture was stirred until hydrogen evolution ceased and cooled in an ice bath, and 5 g of TMEDA and 30 ml of 1.4 *M* *n*-butyllithium solution were added. The reaction mixture was stirred at room temperature for 2 hr and quenched by the addition of an excess of freshly crushed Dry Ice. The reaction mixture was stirred for 30 min, acidified with 1 *N* hydrochloric acid, and stirred for an additional 2.5 hr. The layers were separated, and the aqueous layer was saturated with sodium chloride and extracted with pentane. The combined organic layers were dried, filtered, and concentrated, The residue was distilled to give 1.4 g (23%) of **3**: bp 120° (10 mm); ir 5.61, 7.24, 8.54, 9.8 μ; nmr δ 0.90 (t, 3), 1.23 (m, 6), 1.9–2.8 (m, 3), 3.65–4.5 (m, 2); mass spectrum *m/e* (rel intensity) 142 (3), 114 (6), 111 (6), 95 (3), 84 (12), 70 (14), 69 (23), 55 (38), 56 (100), 57 (15), 43 (24), 42 (35), 41 (61), 39 (24).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.89; H, 9.90.

3-Hydroxymethyl-1-phenyl-1-heptanol (4).—To an ice-cold, stirred solution of 1.38 g of TMEDA in 75 ml of a 1.4 *M* *n*-butyllithium solution under argon was added 2.65 g of allyl alcohol. After the reaction mixture had been stirred at room temperature for 7.4 hr, 8.5 ml of benzaldehyde was added. The reaction mixture was stirred at room temperature for 12 hr, quenched by the addition of saturated ammonium chloride solution, and worked up. The crude material was chromatographed on silica gel to give 4.33 g (43%) of **4**: ir 3.05, 6.24, 7.3, 9.65, 13.2, 14.3 μ; nmr δ 0.85 (t, 3), 1.15 (m, 6), 1.6 (m, 3), 3.35 (m, 2), 4.54 (m, 1), 5.35 (m, 2), 7.15 (s, 5).

3-Carboxyheptanophenone (5).—To an ice-cold, stirred solution of 902 mg of 4 in 60 ml of acetone was added dropwise 8 *N* chromic acid until an orange color persisted. The reaction mixture was stirred at room temperature for 15 min and quenched with isopropyl alcohol. The green sludge was dissolved with water and the mixture was extracted with ether. The ether layer was extracted with 10% sodium hydroxide solution and discarded. The basic layer was acidified with 3 *N* hydrochloric acid and extracted with ether. The combined ethereal extracts were washed with water until neutral, dried, filtered, and concentrated to give 721 mg of a viscous residue which was recrystallized from carbon tetrachloride and sublimed (70°, 10^{-2} mm) to give a pure sample of **5**: mp 72.7–73.3°; ir (CCl_4) 3.27, 5.84, 5.90, 6.24, 6.31, 7.33, 14.5 μ; nmr δ 0.90 (t, 3), 1.4 (m, 6), 2.68–3.68 (m, 3), 7.4 (m, 3), 7.86 (m, 2), 12.1 (s, 1); mass spectrum *m/e* (rel intensity) 234 (2), 216 (6), 178 (2), 160 (2), 133 (2), 120 (68), 105 (100), 91 (1), 77 (41), 55 (3), 51 (10).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.95; H, 7.89.

Reaction of 3-Buten-2-ol with *n*-Butyllithium.—To an ice-cold slurry of 5.58 g of 3-buten-2-ol and 895 mg of lithium hydride, which had been warmed to 50° with stirring for 1 hr under argon, was added 80 ml of pentane, 1.71 g of TMEDA, and 100 ml of a 1.6 *M* *n*-butyllithium solution. The reaction mixture was stirred at room temperature for 22 hr and worked up. Distillation of the residue through a 4-in. glass helices column gave 6.7 g (66%) of 3-methyl-2-heptanol (**6**), bp 82–83° (20 mm).[24]

Reaction of 3-Buten-2-ol with Benzyllithium.—To an ice-cold benzyllithium solution (200 ml of toluene, 120 ml of 1.6 *M* *n*-butyllithium solution, and 3.3 g of TMEDA) was added 4.45 g of 3-buten-2-ol. The reaction mixture was warmed to room temperature for 2.5 hr, heated to 70° for 12 hr, and worked up. Glpc analysis of the residue revealed nine products.

Two products, accounting for 13 and 60% of the volatile products, were identified as *erythro*- and *threo*-3-benzyl-2-butanol (**7**): ir 3.0, 6.24, 7.3, 9.25, 13.6, 14.3 μ; nmr δ 0.89 (d, 3), 1.14 (d, 3), 1.75 (m, 1), 2.0–3.1 (eight-line multiplet, 2), 3.47 (s, 1, –OH), 3.60 (pentet, 1). Chromic acid oxidation of **7** gave 3-benzyl-2-butanone: ir 5.85, 6.24, 7.4, 13.3, 13.6, 14.3 μ; nmr δ 1.0 (d, 3), 1.95 (s, 3), 2.17–3.17 (m, 3), 7.12 (s, 5).

Two other products, accounting for 7 and 3% of the volatile products, were identified as *trans*- and *cis*-5-phenyl-2-pentene: ir 6.24, 7.3, 10.37, 13.5, 14.4 μ; nmr δ 1.58 (m, 3), 2.0–2.78 (m, 4), 5.37 (m, 2), 7.07 (s, 5). Glpc analysis showed two additional products (6 and 4%) to be **1c** and bibenzyl. The amount of **16** present was less than 0.1%.

Reaction of 2-Cyclopentenol with *tert*-Butyllithium.—A mixture of 300 mg of 2-cyclopentenol[25] and 7.2 ml of 1.5 *M* *tert*-butyllithium solution in a sealed tube was heated to 97° for 2 hr. Glpc

(24) Sadtler Index: ir 7402, nmr 2844.

(25) K. Alder and F. H. Flock, *Chem. Ber.*, **89**, 1732 (1956).

showed only one product. Preparative glpc afforded 70 mg of 3-*tert*-butylcyclopentene (**10a**): ir 3.24, 6.15, 7.2, 7.35 μ; nmr δ 0.85 (s, 9), 1.3–1.95 (m, 2), 2.05–2.65 (m, 3), 5.66 (m, 2); mass spectrum *m/e* (rel intensity) 124 (5), 109 (12), 68 (12), 67 (43), 66 (48), 57 (100), 41 (25). The ir and nmr spectra were identical with those of an authentic sample of **10a** prepared from the reaction of 3-chlorocyclopentene with *tert*-butyllithium.

Reaction of 2-Cyclopentenol with *tert*-Butyllithium–TMEDA.—A mixture of 51 mg of 2-cyclopentenol, 78 mg of cyclooctane, 210 mg of TMEDA, and 1.2 ml of a 1.5 *M* *tert*-butyllithium solution in a sealed tube was allowed to react at room temperature for 16 hr. Glpc analysis of the product after work-up showed a 10% yield of **10a**. A similar reaction carried out without TMEDA gave a 35% yield of **10a**.

Reaction of *tert*-Butyllithium with a Mixture of Cyclopentene and Cyclopentanol.—A mixture of 157 mg of cyclopentene, 153 mg of cyclopentanol, and 8.2 ml of a 1.5 *M* *tert*-butyllithium solution was heated in a sealed tube at 97° for 2 hr. Glp analysis after work-up showed no appreciable loss of cyclopentene and no products of significance.

Reaction of 2-Cyclopentenol with Isopropyllithium.—A mixture of 300 mg of 2-cyclopentenol and 5 ml of a 2.1 *M* isopropyllithium solution in a sealed tube was heated to 97° for 2 hr. Glpc analysis of the crude product after work-up showed only one product, 3-isopropylcyclopentene (**10c**): ir 3.24, 6.18, 7.21, 7.30, 14.0 μ; nmr δ 0.88 (two overlapping doublets, 6), 1.1–2.6 (m, 6), 5.65 (s, 2).

Reaction of 2-Cyclopentenol with *n*-Butyllithium.—To a stirred solution of 6.79 g of 2-cyclopentenol and 914 mg of TMEDA in 20 ml of pentane at −78° under nitrogen was added by syringe 140 ml of a 1.6 *M* *n*-butyllithium solution over a period of 15 min. The reaction mixture was allowed to warm to room temperature over a period of 3 hr and worked up. Glpc analysis showed two components in a 96:4 ratio. Distillation gave 6.27 g (62%) of 3-*n*-butylcyclopentene (**10b**): bp 137°; ir 3.25, 6.19, 7.26, 7.38, 14.0 μ; nmr δ 0.88 (t, 3), 1.3 (m, 6), 1.65–2.75 (m, 5), 5.60 (s, 2); mass spectrum *m/e* (rel intensity) 124 (10), 95 (4), 82 (12), 67 (100), 41 (11). The spectral properties were identical with those of an authentic sample of **10b** prepared by the reaction of 3-chlorocyclopentene with *n*-butyllithium.

1-Deuterio-2-cyclopentenol.—To an ice-cold, stirred solution of 234 mg of lithium aluminum deuteride in 10 ml of anhydrous ether was added dropwise a solution of 840 mg of 2-cyclopentenone in 10 ml of anhydrous ether. The reaction mixture was stirred at room temperature for 12 hr, cooled in an ice bath, quenched by the addition of water, stirred for 30 min, and filtered. The precipitate was washed with anhydrous ether and the filtrate was dried and concentrated. Preparative glpc afforded 424 mg of 1-deuterio-2-cyclopentenol: ir 4.69 μ; nmr δ 1.37–2.75 (m, 4), 4.61 (s, 1, –OH), 5.75 (m, 2). The deuterium magnetic resonance spectrum showed a single peak at δ 4.84.

Reaction of 1-Deuterio-2-cyclopentenol with *n*-Butyllithium.—To an ice-cold, stirred solution of 211 mg of 1-deuterio-2-cyclopentenol and 887 mg of TMEDA in 10 ml of pentane under nitrogen was added 5 ml of a 1.5 *M* *n*-butyllithium solution. The reaction mixture was stirred at room temperature 2 hr and worked up. Preparative glpc gave a pure sample of 1-deuterio-3-*n*-butylcyclopentene: ir 4.38 μ; nmr (TMS external) δ 0.62 (t, 3), 1.05 (m, 6), 1.4–2.6 (m, 4), 5.37 (s, 1). The deuterium magnetic resonance spectrum contained only one peak centered at δ 5.76. The mass spectrum showed the product to be 98% d_1.

Reaction of 2-Cyclohexenol with *tert*-Butyllithium.—A mixture of 305 mg of 2-cyclohexenol and 6.2 ml of a 1.5 *M* *tert*-butyllithium solution in a sealed tube was heated to 97° for 3 hr. Glpc analysis of the product solution after work-up showed a mixture of about 20 products with three components in the ratio 50:9.4:40 making up the majority of the volatile products. The major product was identified spectroscopically as 3-*tert*-butylcyclohexene (**11a**): ir 3.28, 7.18, 7.32 μ; nmr δ 0.85 (s, 9), 1.1–2.1 (m, 7), 5.65 (s, 2). The next largest component was identified by glpc retention time as starting material. The minor product was not characterized.

Reaction of 2-Cyclohexenol with *n*-Butyllithium.—To a slurry of 2.45 g of 2-cyclohexenol and 251 mg of lithium hydride, which had been stirred at room temperature for 4 hr under nitrogen, was added 3.37 g of TMEDA and 21 ml of a 1.4 *M* *n*-butyllithium solution. The reaction mixture was refluxed for 15 hr and then worked up. Glpc analysis of the product solution showed five components. The major product accounted for 88% of the volatile products and was identified as 3-*n*-butylcyclohexene (**11b**): ir 3.38, 6.06, 7.25, 14.0 μ; nmr δ 0.90 (t, 3), 1.3 (m, 6), 1.4–2.3 (m, 7), 5.54 (s, 2); mass spectrum *m/e* (rel intensity) 138 (21), 123 (0.4), 109 (6), 96 (52), 82 (30), 81 (100), 67 (30), 41 (20), 39 (10). The spectral properties of **11b** were identical with those of a sample prepared by the reaction of 3-bromocyclohexene with *n*-butyllithium.

Reaction of 2-Methyl-2-propen-1-ol with *n*-Butyllithium.—To an ice-cold mixture of 10 ml of a 1.6 *M* *n*-butyllithium solution and 144 mg of TMEDA under nitrogen was added 357 mg of 2-methyl-2-propen-1-ol. The reaction mixture was stirred at room temperature for 19 hr, during which time the color changed from yellow to dark red, and worked up. Glpc analysis showed a plethora of products, none of which were characterized.

Reaction of 2-Methyl-2-propen-1-ol with Benzyllithium.—To an ice-cold benzyllithium solution (200 ml of toluene, 120 ml of 1.5 *M* *n*-butyllithium solution, and 3.36 g of TMEDA) was added 4.45 g of 2-methyl-2-propen-1-ol. The reaction mixture was stirred at 76° for 18 hr and worked up. Glpc analysis showed a dozen products. The major product, accounting for 37% of the volatile products, was identified spectroscopically as 2,2-dimethyl-3-phenyl-1-propanol (**13**): ir 2.9, 6.24, 7.25, 7.37, 9.6, 13.7, 14.2 μ; nmr δ 0.86 (s, 6), 2.55 (s, 2), 3.26 (s, 2), 3.75 (s, 1, –OH), 7.12 (s, 5). Another product, accounting for 30% of the volatile products, was identified spectroscopically as 3-methyl-1-phenyl-2-butanol (**12**): ir 2.93, 6.24, 7.25, 7.35, 9.7, 10.1, 13.5, 14.4 μ; nmr δ 0.89 (d, 3), 1.55 (m, 1), 2.4 (s, 1, –OH), 2.55 (m, 2), 3.36 (doublet of triplets, 1), 7.08 (s, 5); mass spectrum *m/e* (rel intensity) 164 (2), 121 (3), 102 (12), 93 (33), 92 (100), 91 (44), 73 (19), 55 (27), 42 (12). Chromic acid oxidation of **12** gave 3-methyl-1-phenyl-2-butanone.[26] Glpc analysis identified a third product as bibenzyl (16%) and confirmed the absence of 2-methyl-4-phenyl-1-butene and 3-methyl-1-phenyl-2-butene.

Deuterium Oxide Quenching of the Reaction of 2-Methyl-2-propen-1-ol with Benzyllithium.—To a benzyllithium solution (60 ml of toluene, 35 ml of a 1.5 *M* *n*-butyllithium solution, and 985 mg of TMEDA) at room temperature was added 1.01 g of 2-methyl-2-propen-1-ol. The reaction mixture was stirred at 88° for 17 hr, cooled in an ice bath, and quenched by the addition of 4 ml of deuterium oxide. The solution was stirred for an additional 2.5 hr at room temperature and worked up. Glpc analysis showed a 54:14:32 mixture of **12**, **13**, and bibenzyl. The residue was chromatographed on silica gel. Toluene, bibenzyl, and other hydrocarbon impurities were eluted with pentane; and the alcohols were eluted with anhydrous ether. Preparative glpc of the combined alcoholic fractions afforded a sample of **12**: nmr δ 0.90 (s, 5.2), 2.04 (s, 0.8), 2.3–2.85 (m, 1.4), 3.38 (m, 1.0), 7.1 (s, 3.6). The extensive deuterium incorporation which the nmr integration suggests was supported by the dmr spectrum: δ 1.30 (0.3), 1.96 (1.0), 2.85 (1.2), 7.47 (1.0).

Acetic Anhydride Quenching of the Reaction of 2-Methyl-2-propen-1-ol with Benzyllithium.—To a benzyllithium solution (30 ml of toluene, 19 ml of a 1.5 *M* *n*-butyllithium solution, and 503 mg of TMEDA) at room temperature was added 516 mg of 2-methyl-2-propen-1-ol. The reaction mixture was stirred at 80° for 19 hr, cooled to room temperature, quenched by the addition of 4 g of acetic anhydride, stirred at room temperature for 2.5 hr, heated to 80° for 1.5 hr, hydrolyzed, and worked up. Glpc analysis revealed the presence of the acetate of the starting alcohol, **14**, the acetate of **13**, **13**, and bibenzyl in a 17:55:13:1:14 ratio. Neither **12** nor its acetate was present. The residue was chromatographed on silica gel. Toluene, bibenzyl, and other hydrocarbon impurities were eluted with pentane, and the acetates were eluted with ether. Preparative glpc of the combined acetate fractions afforded a sample of **14**, which was spectroscopically identical with an authentic sample.

Reaction of *trans*-2-Buten-1-ol with *n*-Butyllithium.—To an ice-cold mixture of 10 ml of a 1.6 *M* *n*-butyllithium solution and 143 mg of TMEDA under nitrogen was added 368 mg of *trans*-2-buten-ol. The reaction mixture was stirred at room temperature for 50 hr and worked up. Glpc analysis showed at most traces of C_8 olefins and nine major products, one of which made up 67% of the volatile products. Preparative glpc gave 100 mg of the major product, which was identified as 2-ethyl-1-hexanol (**15**).[27]

(26) Sadtler Index: ir 2747.
(27) Sadtler Index: ir 1472, nmr 98.

Reaction of *trans*-2-Buten-1-ol with Benzyllithium.—To an ice-cold, stirred benzyllithium solution (200 ml of toluene, 120 ml of a 1.6 *M* *n*-butyllithium solution, and 3.34 g of TMEDA) was added 4.43 g of *trans*-2-buten-1-ol. The reaction mixture was stirred at 73° for 19 hr and worked up. Glpc analysis showed nine products.

The major product, accounting for 41% of the volatile products, was identified as 3-methyl-4-phenyl-1-butene (**16**): ir 6.10, 6.24, 7.32, 11.0, 13.5, 14.3 μ; nmr δ 0.96 (d, 3), 2.2–2.8 (m, 3), 4.7–5.1 (m, 2), 5.40–6.07 (m, 1), 7.1 (s, 5); mass spectrum *m/e* (rel intensity) 146 (14), 131 (4), 117 (4), 115 (3), 104 (4), 91 (100), 77 (3), 65 (16), 55 (12), 39 (11). Two other products, accounting for 14% each of the volatile products, were identified as **8** and **9**. The nmr spectrum was virtually identical with that of an authentic sample of **8** and the second compound was found to be coincident with the product obtained from the photoisomerization of **8**. (Ozonolysis of a mixture of **8** and **9** in methylene chloride at −78° followed by lithium aluminum hydride reduction of the resulting ozonides gave one major product which was identified unambiguously as 3-phenyl-1-propanol by its characteristic ir and nmr spectra.[28]) A 7% product was identified as bibenzyl and a 9% product as 2-benzyl-1-butanol (**17**): ir 3.03, 6.24, 7.28, 9.6, 13.6, 14.3 μ; nmr δ 0.90 (t, 3), 1.1–1.9 (m, 3), 2.48–2.70 (m, 2), 3.0 (s, 1, –OH), 3.40 (d, 2), 7.10 (s, 5).

In a similar reaction using *sec*-butylbenzene as an internal standard, the yields of **8**, **9**, and **16** were 4.3, 4.9, and 6.7%, respectively. In another reaction in which slightly more than 1 equiv of TMEDA was used per 1 equiv of *n*-butyllithium and the reaction mixture was diluted with hexane to completely dissolve the benzyllithium–TMEDA complex, **8**, **9**, and **16** were obtained in 11, 12, and 2% yield, respectively.

***cis*-2-Buten-1-ol.**—A solution of 7.80 g of *trans*-2-buten-1-ol in 600 ml of benzene was irradiated for 30 hr with a vicor-filtered 450-W Hanovia type L medium-pressure mercury arc in a water-cooled quartz immersion well. Glpc analysis of the reaction mixture showed a 59:41 mixture of *trans*- and *cis*-2-buten-1-ol. The crude reaction mixture was chromatographed on silica gel with anhydrous ether. Preparative glpc gave a pure sample of *cis*-2-buten-1-ol: ir 3.04, 3.35, 6.03, 9.7, 10.24 μ; nmr δ 1.64 (d, 3), 3.78 (s, 1, OH), 4.09 (d, 2), 5.51 (m, 2).

Reaction of *cis*-2-Buten-1-ol with Benzyllithium.—To a benzyllithium solution (5 ml of toluene, 3 ml of a 1.6 *M* solution of *n*-butyllithium, and 113 mg of TMEDA) at room temperature was added a solution of 87 mg of *cis*-2-buten-1-ol in 1 ml of pentane. The reaction mixture was heated to 72° for 14 hr and worked up. Analysis by glpc revealed **16**, **8**, **9**, bibenzyl, and **17** in a 8:44:37:9:2 ratio.

***trans*-5-Phenyl-2-pentene (8).**—To an ice-cold, stirred benzyllithium solution (10 ml of toluene, 5 ml of 1.6 *M* solution of *n*-butyllithium, and 203 mg of TMEDA) was added 229 mg of crotyl chloride. The reaction mixture was heated with stirring to 60° for 15 min, stirred at room temperature for 2 hr, and worked up. Preparative glpc afforded a pure sample of **8**: ir 6.24, 7.3, 10.3, 13.6, 14.4 μ; nmr δ 1.6 (m, 3), 2.0–2.8 (m, 4), 5.4 (m, 2), 7.1 (s, 5).

A solution of 20 mg of **8** in 1.5 ml of spectral-grade benzene in a quartz test tube was irradiated in a Rayonet photochemical reactor at 2537 Å for 5.5 hr. Glpc analysis showed a mixture of 52% trans and 48% cis olefin. The yellow photolysis solution was suction filtered through fluorosil and concentrated. The ir of the residue showed a substantial reduction in the size of the 10.3-μ band. This sample was used for glpc comparison with the reaction products from the reaction of benzyllithium with 3-buten-2-ol and 2-buten-1-ol.

Reaction of 8 with Benzyllithium.—To a stirred benzyllithium solution (5 ml of toluene, 3 ml of 1.6 *M* *n*-butyllithium solution, and 123 mg of TMEDA) at room temperature was added a solution of 31 mg of **8** and 20 mg of decane in 1 ml of pentane. The reaction mixture was stirred at 77° for 19 hr and worked up. Glpc comparison of the starting mixture of trans olefin and decane with the reaction product showed that neither isomerization to the cis olefin nor loss of olefin had taken place.

***trans*-1,1-Dideuterio-2-buten-1-ol.**—To an ice-cold solution of 430 mg of lithium aluminum deuteride in 10 ml of anhydrous ether under a nitrogen atmosphere was added dropwise 1.51 g of methyl-2-butenoate. The reaction mixture was stirred at room temperature for 13 hr, cooled in an ice bath, and quenched by the addition of 1.7 ml of distilled water. Anhydrous magnesium sulfate was added and the resulting suspension was filtered. The precipitate was washed with anhydrous ether, and the dried filtrate was concentrated to give 879 mg (79%) of *trans*-1,1-dideuterio-2-buten-1-ol: nmr δ 1.68 (m, 3), 4.83 (s, 1, OH), 5.55 (m, 2).

Reaction of *trans*-1,1-Dideuterio-2-buten-1-ol with Benzyllithium.—To an ice-cold benzyllithium solution (80 ml of toluene, 45 ml of 1.6 *M* *n*-butyllithium solution, and 1.22 g of TMEDA) was added 879 mg of *trans*-1,1-dideuterio-2-buten-1-ol. The reaction mixture was stirred at 74° for 18 hr. Glpc analysis showed **16**, **8**, **9**, and bibenzyl in a 36:21:23:20 ratio. However, only trace amounts of **17** were observed.

The 36% product was identified as 1,1-dideuterio-3-benzyl-1-butene: nmr δ 0.96 (d, 3), 2.3–2.8 (m, 3), 5.72 (m, 1), 7.08 (s, 5). The relative intensities of the peaks in the molecular ion region of the mass spectrum indicated the composition to be 97% d_2, 3% d_1. The 21 and 23% products were isolated as a mixture and identified as *trans*- and *cis*-4,4-dideuterio-5-phenyl-2-pentene: nmr δ 1.60 (m, 3), 2.62 (m, 2), 5.4 (m, 2), 7.1 (s, 5). The relative intensities of the peaks in the molecular ion region of the mass spectrum indicated the composition to be 93% d_2, 7% d_1.

Deuterium Oxide Quenching of the Reaction of *trans*-2-Buten-1-ol with Benzyllithium.—To an ice-cold benzyllithium solution (100 ml of toluene, 60 ml of a 1.6 *M* *n*-butyllithium solution, and 1.55 g of TMEDA) was added 2.21 g of *trans*-2-buten-1-ol. The reaction mixture was stirred at 78° for 18 hr, cooled in an ice bath, and quenched by the addition of 5 ml of deuterium oxide. Hydrolysis was completed by stirring the solution at room temperature for 2 hr followed by work-up. Glpc analysis showed **16**, **8**, **9**, bibenzyl, and **17** in a 29:24:24:16:7 ratio. The mass spectra of **16** and a mixture of **8** and **9** showed negligible deuterium incorporation.

Acetic Anhydride Quenching of the Reaction of *trans*-2-Buten-1-ol with Benzyllithium.—To an ice-cold benzyllithium solution (30 ml of toluene, 20 ml of 1.4 *M* *n*-butyllithium solution, and 515 mg of TMEDA) was added 501 mg of *trans*-2-buten-1-ol at room temperature. The mixture was stirred at 82° for 18 hr, cooled in an ice bath, and treated with 4 ml of acetic anhydride. The resulting mixture was stirred at room temperature for 3 hr, heated to 75° for 2.5 hr, and quenched by the addition of saturated ammonium chloride solution. Glpc analysis after work-up revealed the presence of 1-acetoxy-1-butene,[29] 1-acetoxy-2-butene, **16**, **8**, and **9** in a 0.4:7:40:26:27 ratio.

Registry No.—**1a**, 36794-64-6; **1c**, 624-22-6; **1d**, 36794-65-7; **1e**, 1123-85-9; **1f**, 7384-80-7; **3**, 22530-99-0; **4**, 36794-69-1; **5**, 36794-70-4; **6**, 31367-46-1; *erythro*-**7**, 1499-64-5; *threo*-**7**, 1499-63-4; **8**, 16091-23-9; **10a**, 6189-88-4; **10b**, 22531-00-6; **10c**, 4276-45-3; **11a**, 14072-87-8; **11b**, 3983-07-1; **12**, 705-58-8; **13**, 13351-61-6; **16**, 1647-06-9; **17**, 3968-87-4; allyl alcohol, 107-18-6; *tert*-butyllithium, 594-19-4; isopropyllithium, 1888-75-1; cyclopentyllithium, 23473-12-3; phenyllithium, 591-51-5; benzyllithium, 766-04-1; 1-acetoxy-2-deuteriomethyl-3,3-dimethylbutane, 36794-81-7; 2-deuteriomethyl-1-hexanol, 36794-82-8; 2-deuteriomethyl-1-methoxyhexane, 36794-83-9; 3-buten-2-ol, 627-27-0; 3-benzyl-2-butanone, 2550-27-8; *trans*-5-phenyl-2-pentene, 16091-23-9; *cis*-5-phenyl-2-pentene, 16487-65-3; 2-cyclopentenol, 3212-60-0; cyclopentene, 142-29-0; cyelopentanol, 96-41-0; 1-deuterio-2-cyclopentenol, 20826-91-9; 1-deuterio-3-*n*-butylcyclopentene, 36794-85-1; 2-cyclohexenol, 822-67-3; 2-methyl-2-propen-1-ol, 513-42-8; *trans*-2-buten-1-ol, 504-61-0; *cis*-2-buten-1-ol, 4088-60-2; *trans*-1,1-dideuterio-2-buten-1-ol, 36807-25-7; 1,1-dideuterio-3-benzyl-1-butene, 36794-86-2; *trans*-4,4-dideuterio-5-phenyl-2-pentene, 36807-26-8; *cis*-4,4-dideuterio-5-phenyl-2-pentene, 36807-27-9; *n*-butyllithium 109-72-8.

(28) Sadtler Index: ir 1651, nmr 116.

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Lithium Amide Catalyzed Amine–Olefin Addition Reactions

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This paper describes the addition of amines to vinyl aromatics and 1,3 dienes catalyzed by lithium amides. The lithium amide is generated *in situ* by adding the desired amount of butyllithium to the reaction mixture containing amine and vinyl aromatic or 1,3 diene. This technique provides a convenient route to alkylalkenyl- and alkylarylamines. High yields are obtained under mild reaction condition.

Reactions of amines with vinylic compounds have been known for some time. The most familiar examples include the host of condensations of acrylates and vinyl ketones with ammonia and amines which result in amino-substituted esters, amides, nitriles, and the like.[1]

The reactions of dienes and vinyl aromatics with amines has not been so widely studied. Aniline, in the presence of 20 g-atom % metallic sodium, is reported[2,3] to condense with butadiene and with isoprene at 120°, giving 79% yields of *N*-crotylanilines in 18 hr. Acid catalysis of aniline–butadiene condensations results[4] in a mixture of ring and N-substitution products at 230–260°.

More closely related to our system is the work of Martirosyan,[5] who claimed the preparation of a series of amines by passing butadiene through ether solutions of alkylamines in the presence of catalytic quantities of sodium metal at 25°. The adducts, obtained in 60–92% yields, appeared to be 1,4 adducts. Wegler and Pieper found that alkylamines add to styrene in the presence of 1–3 wt % sodium metal, give β-phenethylamines in 8–80% yields when refluxed for 3–5 hr.[6]

In our work, we discovered that the reactions of lithium alkylamides, generated *in situ* from alkylamines and butyllithium, in catalytic quantities promote amine–olefin addition reactions, providing a convenient synthetic route to tertiary amines. *n*-Butyllithium and *sec*-butyllithium were used interchangeably.

Results

Addition to Vinyl Aromatic Compounds.—Cyclic and acyclic primary and secondary amines add to vinyl aromatics with the aid of butyllithium in catalytic quantities. The products, substituted β-phenethylamines, are summarized in Table I.

Secondary amines, such as di-*n*-nonylamine and diethylamine, add with ease to styrene, no. 1–5. A slight increase in the rate of reaction is implied when tetrahydrofuran is used in place of cyclohexane as the solvent. The same yield is obtained in tetrahydrofuran with a shorter reaction time, 23 hr compared to 4 hr. Monocyclic and dicyclic amines, piperidine, and 1,3-di(4-azacyclohexyl)propane add to styrene to give high yields, no. 6–8, with shorter reaction times than the aliphatic amines of no. 1–5. This suggests a steric influence on the addition reaction. Primary amines react with 2 equiv of styrene, and no product of monoaddition was detected even with one equivalent of styrene, no. 9–11. Ammonia, however, does not react with styrene under these conditions.

Vinyl aromatics other than styrene may be successfully used in this reaction, as evidenced by the reaction of piperidine with α-methylstyrene, 1,1-diphenylethylene, and *trans*-stilbene, no. 13–16.

Addition to Dienes.—Dienes, such as butadiene and isoprene, react with amines, in the presence of a catalytic amount of butyllithium. The product mixture depends on the solvent employed and the structure of the amine (Table II). In cyclohexane, piperidine adds predominantly 1,4 to 1,3-butadiene, giving 63% trans and 36% cis adduct, no. 1, while 2,6-dimethylpiperidine gives an 80:20 trans–cis product ratio, no. 3, and diethylamine a 20:79 trans–cis product ratio, no. 4. In all three cases, the 1,2-piperidine adduct with 1,3-butadiene is ≤1% of the total product. The isomers were separated by gas chromatography and identified by either uv or nmr spectroscopy.

A change to the polar solvent tetrahydrofuran produces dramatic shifts in adduct stereochemistry. Both piperidine and diethylamine add 1,4 to 1,3-butadiene to give 99% trans adduct, no. 2 and 5. Only traces of other isomers are present. This shift may well be due more to solubility than any other factor. Lithium diethylamide and lithium piperidine, thought to be the initially formed species, are slightly soluble in hydrocarbons; the high cis adduct may thus be a result of a heterogeneous system. Tetrahydrofuran solubilizes both of these lithium salts permitting a homogeneous reaction system. A detailed study of the reaction mechanism(s) was not attempted.

Piperidine and diethylamine add predominantly 4,1 to isoprene, no. 6 and 7. The product with piperidine contains 76% 4,1 adduct accompanied by small amounts of other isomers. Diethylamine gives only the 4,1 adduct.

Discussion

The catalyzed reaction of amines with olefins apparently involves the initial addition of a lithium amide to the olefin, followed by proton transfer from amine to

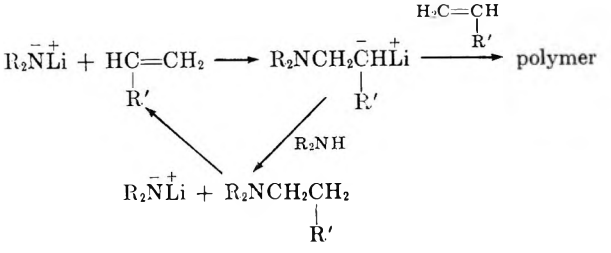

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TABLE I

AMINE ADDITIONS TO VINYL AROMATICS[a]

No.	Amine	Vinyl aromatic	Time, hr	Yield, %	Product	Registry no.
1	$(C_2H_5)_2NH$	$C_6H_5CH{=}CH_2$	23	57	$(C_2H_5)_2NCH_2CH_2C_6H_5$[f,g]	5300-21-0
2	$(C_2H_5)_2NH$	$C_6H_5CH{=}CH_2$	4[b]	58	$(C_2H_5)_2NCH_2CH_2C_6H_5$[f]	
3	$(n\text{-}C_3H_7)_2NH$	$C_6H_5CH{=}CH_2$	16	47	$(n\text{-}C_3H_7)_2NCH_2CH_2C_6H_5$[f-h]	23916-02-1
4	$(n\text{-}C_9H_{19})_2NH$	$C_6H_5CH{=}CH_2$	16	41	$(n\text{-}C_9H_{19})_2NCH_2CH_2C_6H_5$[f,i]	31165-60-3
5	$(CH_3)(n\text{-}C_4H_9)NH$	$C_6H_5CH{=}CH_2$	16	70	$(CH_3)(n\text{-}C_4H_9)NCH_2CH_2C_6H_5$[f,j]	36794-44-2
6	$C_5H_{11}N$ (piperidine)	$C_6H_5CH{=}CH_2$	5	81	$C_5H_{10}NCH_2CH_2C_6H_5$[f,n]	332-14-9
7	$C_5H_{11}N$	$C_6H_5CH{=}CH_2$	5[b]	88	$C_5H_{10}NCH_2CH_2C_6H_5$[f]	
8	$(4\text{-}C_5H_{10}NCH_2)_2CH_2$	$C_6H_5CH{=}CH_2$[c]	8	80	$[C_6H_5CH_2CH(NC_5H_{10}\text{-}4)CH_2]_2CH_2$[f,k]	36794-46-4
9	$n\text{-}C_3H_7NH_2$	$C_6H_5CH{=}CH_2$[c]	16	33	$n\text{-}C_3H_7N(CH_2CH_2C_6H_5)_2$[f,g]	27974-01-2
10	$n\text{-}C_4H_9NH_2$	$C_6H_5CH{=}CH_2$[c]	16	47	$n\text{-}C_4H_9N(CH_2CH_2C_6H_5)_2$[f,l]	24068-19-7
11	$n\text{-}C_5H_{11}NH_2$	$C_6H_5CH{=}CH_2$[c]	16	32	$n\text{-}C_5H_{11}N(CH_2CH_2C_6H_5)_2$[f,m]	36794-49-7
12	NH_3	$C_6H_5CH{=}CH_2$	16[d]	0		
13	$C_5H_{11}N$	$(C_6H_5)(CH_3)C{=}CH_2$	5[b,e]	71	$(C_6H_5)(CH_3)CHCH_2C_5H_{10}N$[f,g]	36794-50-0
14	$C_5H_{11}N$	$(C_6H_5)(CH_3)C{=}CH_2$	6	42	$(C_6H_5)(CH_3)CHCH_2C_5H_{10}N$[f]	
15	$C_5H_{11}N$	$(C_6H_5)_2C{=}CH_2$	48[e]	82	$(C_6H_5)_2CHCH_2C_5H_{10}N$[f,g,o]	36794-51-1
16	$C_5H_{11}N$	*trans*-$C_6H_5CH{=}CHC_6H_5$	48	10	$C_6H_5CH_2CH(C_6H_5)(C_5H_{10}N)$[f,g]	36794-52-2

[a] 13% (w/w) reactants in cyclohexane; 50°; 5 mol % butyllithium, based on the amine; 1 mol of styrene/mol of amine. [b] Solvent, tetrahydrofuran. [c] 2 mol of styrene/mol of amine [d] Room temperature. [e] 2 mol of amine/mol of vinyl aromatic. [f] Identification by ir. [g] Identification by picrate formation and comparison with known sample. [h] *Anal.* Calcd for $C_{14}H_{23}N$: C, 81.95; H, 11.22; N, 6.83. Found: C, 81.80; H, 11.20; N, 7.19. [i] *Anal.* Calcd for $C_{26}H_{47}N$: C, 83.65; H, 12.60; N, 3.75. Found: C, 81.90; H, 13.38; N, 4.75. [j] *Anal.* Calcd for $C_{15}H_{23}N$: C, 81.68; H, 10.99; N, 7.33. Found: C, 81.69; H, 11.10; N, 7.22. [k] *Anal.* Calcd for $C_{29}H_{40}N_2$: C, 83.25; H, 10.05; N, 6.70. Found: C, 83.20; H, 10.16; N, 6.71. [l] *Anal.* Calcd for $C_{20}H_{27}N$: C, 85.40; H, 9.60; N, 4.98. Found: C, 84.11; H, 10.23; N, 5.81. [m] *Anal.* Calcd for $C_{21}H_{29}N$: C, 85.42; H, 9.83; N, 4.75. Found: C, 84.45; H, 10.59; N, 6.16. [n] *Anal.* Calcd for $C_{13}H_{19}N$: C, 82.54; H, 10.05; N, 7.41. Found: C, 81.88; H, 10.07; N, 8.58. [o] *Anal.* Calcd for $C_{19}H_{23}N$: C, 86.04; H, 8.68; N, 5.28. Found: C, 85.57; H, 8.85; N, 5.71.

TABLE II

AMINE ADDITIONS TO 1,3 DIENES[a]

No.	Amine	Solvent	Time, hr	Yield, %	Product[b]	Registry no.
			Additions to 1,3-Butadiene			
1	$C_5H_{11}N$ (piperidine)	CHX[c]	24	83	*cis*-$C_5H_{10}NCH_2CH{=}CHCH_3$ (36%)	36807-51-9
					trans-$C_5H_{10}NCH_2CH{=}CHCH_3$ (63%)	36807-52-0
					$C_5H_{10}NCH_2CH_2CH{=}CH_2$ (1%)	4088-34-0
2	$C_5H_{11}N$	THF[d]	28	58	*trans*-$C_5H_{10}NCH_2CH{=}CHCH_3$	
3	2,6-$(CH_3)_2C_5H_9N$	CHX	17	50	*trans*-2,6-$(CH_3)_2C_5H_8NCH_2CH{=}CHCH_3$ (80%)	36812-99-4
					cis-2,6-$(CH_3)_2C_5H_8NCH_2CH{=}CHCH_3$ (20%)	36813-00-0
4	$(C_2H_5)_2NH$	CHX	24	81	*cis*-$(C_2H_5)_2NCH_2CH{=}CHCH_3$ (79%)	34069-08-4
					trans-$(C_2H_5)_2NCH_2CH{=}CHCH_3$ (20%)	34069-09-5
					$(C_2H_5)_2NCH_2CH_2CH{=}CH_2$ (1%)	15431-05-7
5	$(C_2H_5)_2NH$	THF	24	48	*trans*-$(C_2H_5)_2NCH_2CH{=}CHCH_3$	
			Additions to Isoprene			
6	$C_5H_{11}N$	CHX	24	95	$C_5H_{10}NCH_2CH{=}C(CH_3)_2$ (76%)	36794-55-5
					$(C_5H_{10}NCH_2)(CH_3)C{=}CHCH_3$ (15%)	36794-56-6
					$(C_5H_{10}NCH_2CH_2)(CH_3)C{=}CH_2$ (7%)	36794-57-7
					$(C_5H_{10}NCH_2)(CH_3)CHCH{=}CH_2$ (2%)	36794-58-8
7	$(C_2H_5)_2NH$	CHX	24	57	$(C_2H_5)_2NCH_2CH{=}C(CH_3)_2$[e]	10229-36-4

[a] 13% (w/w) reactants in cyclohexane; 50°; 5 mol % *sec*-butyllithium, based on the amine; 2 mol of amine/mol of 1,3 diene. [b] Gpc separation of isomers; identification by nmr and ir. [c] CHX = cyclohexane. [d] THF = tetrahydrofuran. [e] Identification by picrate formation and comparison with a known sample.

the organolithium intermediate,[7] thereby regenerating amide anions. Schematically, the system is pictured as a competition between olefin and amine for organolithium.

The initial reaction between amide and olefin can only occur if the amide is sufficiently nucleophilic to add to the olefin. Thus, dialkylamides react, while aniline derivatives do not. The olefin itself must be activated to nucleophilic attack, and the greater the activation, the more rapid and complete the reaction. For example, vinyl aromatics add amide quite readily, while dienes react more slowly, and simple aliphatic olefins do not react with amides at all under these conditions.

For the reaction to proceed cleanly to adduct formation, the reaction between the intermediate adduct and the amine must occur very much more rapidly than the potentially competing polymerization reaction. For the 1,3 dienes and vinyl aromatics studied this is apparently the case, since no polymeric material is isolated.

The reaction of secondary amines with a large excess of 1,3-butadiene in cyclohexane in the presence of a catalytic amount of butyllithium produces the monoamine–butadiene adduct coupled with polybutadiene containing one secondary amine residue. The nature of

(7) In amine–styrene reactions the formation of 2-lithiophsnethylamines is indicated by the ultraviolet spectrum of the reaction mixture which shows a strong absorption at the wavelength expected for a benzylic anion (330 mμ).

the termination step of this polymerization is unknown. The microstructure is that expected for normal anionic polymerization, 44% cis 1,4, 48% trans 1,4, and 8% 1,2. Curiously, when an excess of styrene is employed, no polymeric material is isolated.

In summary, vinyl aromatic compounds and 1,3 dienes add amines readily in the presence of small amounts of lithium alkylamides, providing a particularly convenient route to alkylalkenyl- and alkylarylamines.

The yields are higher using milder reaction conditions than the amine–olefin reactions discussed by Wegler and Pieper.[6] For example, they prepared a β-phenethylamine in only 25% yield by reacting di-*n*-butylamine and styrene with 1–2% sodium at 150–200° for 6–8 hr. Compare to our more facile reaction in Table I. Di-*n*-propylamine reacted with styrene with a 47% yield. Martirosyan's[5] yields are also lower in reactions of amines and 1,3 dienes catalyzed by sodium. Diethylamine reacted with 1,3-butadiene at 25° with *ca.* 1% sodium at 25° with a 65% yield (compare to our data in Tables I and II). Diethylamine reacted with 1,3-butadiene catalyzed by butyllithium with an 81% yield (Table II, no. 4).

Experimental Section

sec-Butyllithium was purchased from the Foote Chemical Co. The reactants and solvents were purchased from either the Eastman Kodak Co. or the Aldrich Chemical Co. and were distilled prior to use. The reaction products reported in this paper were characterized by infrared, elemental analysis, nuclear magnetic resonance, and gas chromatography. When possible, comparison of boiling points and picrate melting points with those in the literature were made.

The following five experiments show the general procedures.

Reaction of Diethylamine with Styrene.—Diethylamine (7.3 g, 0.10 mol) was added to 150 ml of nitrogen-degassed cyclohexane in a 12-oz beer bottle. *sec*-Butyllithium (0.32 g, 0.005 mol) was added and allowed to equilibrate for a few minutes at room temperature. Styrene (10.4 g, 0.10 mol) was added, and the mixture was heated at 50° for 23 hr. The solvent was removed by distillation. Distillation of the crude product gave diethylphenethylamine, isolated in a yield of 57%. The infrared spectrum and boiling point were identical with an authentic sample.

Reaction of 1,3-Di(4-azacyclohexyl)propane with Styrene.—1,3-Di(4-azacyclohexyl)propane (21.0 g, 0.10 mol) was added to 150 ml of nitrogen-degassed cyclohexane in a 12-oz beer bottle. *sec*-Butyllithium (0.32 g, 0.005 mol) was added and allowed to equilibrate for a few minutes at room temperature. Styrene (10.4 g, 0.10 mol) was added, and the mixture was heated at 50° for 23 hr.

The reaction mixture was extracted with dilute hydrochloric acid. The aqueous phase was made basic with sodium hydroxide, extracted several times with chloroform, and dried over sodium sulfate. The chloroform was removed by distillation. The product was isolated in a yield of 80%, mp 53–64°.

Anal. Calcd for $C_{29}H_{40}N_2$: C, 83.25; H, 10.05; N, 6.70. Found: C, 83.20; H, 10.16; N, 6.71.

Reaction of Diethylamine with 1,3-Isoprene.—Diethylamine (7.3 g, 0.10 mol) was added to 150 ml of nitrogen-degassed cyclohexane in a 12-oz beer bottle. *sec*-Butyllithium (0.32 g, 0.005 mol) was added and allowed to equilibrate for a few minutes at room temperature. Isoprene (6.8 g, 0.10 mol) was added, and the mixture was heated at 50° for 23 hr. The solvent was removed by distillation. Distillation of the crude product gave 4-diethylamino-2-methyl-2-butene, isolated in a yield of 57%, picrate mp 100–101° (lit.[8] mp 101–102°).

Reaction of Piperidine with Styrene.—Piperidine (8.5 g, 0.10 mol was added to 150 ml of nitrogen-degassed cyclohexane in a 12-oz beer bottle. *sec*-Butyllithium (0.32 g, 0.005 mol) was added and allowed to equilibrate for a few minutes at room temperature. Styrene (10.4 g, 0.10 mol) was added, and the mixture was heated at 50° for 5 hr. The solvent was removed by distillation. Distillation of the crude product gave *N*-phenethylpiperidine, isolated in a yield of 81%. *Anal.* Calcd for $C_{13}H_{19}N$: C, 82.54; H, 10.05; N, 7.41. Found: C, 81.58; H, 10.07; N, 8.58.

Reaction of 1,1-Diphenylethylene with Piperidine.—Piperidine (17.0 g, 0.20 mol) was added to 150 ml of nitrogen-degassed cyclohexane in a 12-oz beer bottle. *sec*-Butyllithium (0.32 g, 0.005 mol) was added and allowed to equilibrate for a few minutes at room temperature. 1,1-Diphenylethylene (26.5 g, 0.10 mol) was added, and the mixture was heated at 50° for 48 hr. The solvent and excess piperidine were removed by distillation. Distillation of the crude product gave *N*-2,2-diphenylethylpiperidine in a yield of 82%. *Anal.* Calcd for $C_{19}H_{23}N$: C, 86.04; H, 8.68; N, 5.28. Found: C, 85.57; H, 8.85; N, 5.71.

Acknowledgment.—The authors would like to express their appreciation to Dr. D. F. Hoeg and Dr. J. F. Pendleton for their encouragement and many suggestions.

(8) L. Spialter and J. A. Pappalardo, "The Acyclic Aliphatic Tertiary Amines," Macmillan, New York, N. Y., 1965, pp 201–202.

Reduction of Epoxides. IV. Lithium Aluminum Hydride Reduction of Cyclohexene Oxides Containing Neighboring Oxygen Groups[1]

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The effects of β-hydroxy and methoxy substituents on the lithium aluminum hydride reduction of cyclohexene oxides have been examined. Contrary to reports in the literature, these reactions in flexible systems exhibit little regioselectivity. Some conformationally rigid epoxy alcohols were also reduced; a small amount of "abnormal" opening product is observed in some instances, presumably formed *via* a boatlike transition state and facilitated by metal–oxygen bridging. *cis*- and *trans*-1,3-cyclohexadiene diepoxides were also subjected to lithium aluminum hydride reduction, and the diol product distributions are analyzed in terms of a two-step reduction mechanism.

The lithium aluminum hydride reductions of cyclohexene oxides generally yield alcohol products predictable on the basis of trans coplanar (diaxial) opening. In our earlier work,[1] we examined in detail the effects of alkyl substituents attached either at an oxirane position or a more remote carbon; these studies allowed the determinations of the energetic preference for various chair and boat transition states in the reduction, and established some factors which lead to "abnormal" opening of the epoxide ring.

The literature contains a number of reports of hydride reductions of β-oxygen substituted cyclohexene oxides where the substituent appears to play a major role in the direction of oxirane opening[2] An example is found in the work of Fales and Wildman[3] on the alkaloid crimamidine and its *o*-tetrahydropyranyl derivative, where the two materials exhibit different regioselectivity on hydride attack. The epoxide oxygen and the β-hydroxyl group are trans in crimamidine, and reduction *via* initial reaction of the alcohol function and subsequent intramolecular attack by *O*-aluminate may explain the observed selective formation of 1,3-diol. The model system, *trans*-3-hydroxycyclohexene oxide, has been reported by Henbest and Wilson[4] to yield mostly *trans*-1,2-diol, accompanied by some *trans*-1,3-diol, with the latter product presumed to arise by the intramolecular mechanism mentioned above. The corresponding *O*-methyl ether (*trans*-3-methoxycyclohexene oxide) has been reported[5] to give "mainly" *trans*-2-methoxycyclohexanol on $LiAlH_4$ reduction, in apparent agreement with the result obtained with the crimamidine *o*-THP derivative.[3]

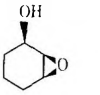
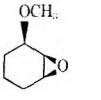
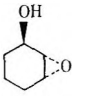
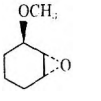
A different feature may arise in the reduction of a *cis*-3-hydroxycyclohexene oxide, namely intramolecular aluminum complex assisted opening. Henbest[4] has reported that the simple model, *cis*-3-hydroxycyclohexene oxide, yields more than 90% of *cis*-1,2-diol on $LiAlH_4$ reduction, and postulated that the product arises from diaxial opening of the half-chair conformer in which the hydroxyl group (or its *O*-metalated derivative) exists in the pseudoequatorial position. On the other hand, a more recent study[6] involving 3α,4α-epoxy-5α-hydroxycholestane (where the 5-hydroxy group is fixed in the pseudoaxial position), indicates similar regioselectivity; the preferred formation of 4α,5α-diol in this instance constitutes a formal violation of the rule of diaxial opening.

Many of the pertinent reactions were carried out prior to the widespread use of vapor phase chromatography, or with materials which did not lend themselves readily to complete analysis of product mixtures. In order to establish more precisely the features leading to regioselectivity in these reductions, and to examine the possibilities of oxidative inversion[7] and syn opening on reduction, we have reexamined some of the earlier work and also made use of fixed conformation derivatives in $LiAlH_4$ reductions.

Results and Discussion

The product distributions obtained on reduction of *cis*- and *trans*-3-hydroxy- and 3-methoxycyclohexene oxides by $LiAlH_4$ in ether solvent are displayed in Table I. These data show clearly that, in these flexible

TABLE I[a]

	Epoxide	cis-1,2	trans-1,2	trans-1,3	cis-1,3
1		60	0	0	40
2		43	0	0.5[b]	57
3		0.3[b]	22	77	0.8[b]
4		0	52	47	1[b]

[a] The products were analyzed as the acetates by vpc. [b] Products attributed to oxidative inversion.[7]

derivatives, neither the hydroxy nor the methoxy substituent exhibits any strong directing influence on the reduction. In fact, the cis compounds **1** and **2** react in

(1) (a) Part III: D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *J. Amer. Chem. Soc.*, **91**, 2649 (1969). (b) Supported in part by grants from the National Science Foundation, GP 9383, and the Petroleum Research Fund, administered by the American Chemical Society (AC-5744).

(2) For a recent excellent review of epoxide chemistry, see H. Z. Sable and J. G. Buchanan in "Selective Organic Transformations," Vol. 2, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1972.

(3) H. M. Fales and W. C. Wildman, *J. Org. Chem.*, **26**, 181 (1961).

(4) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(5) R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Amer. Chem. Soc.*, **80**, 2237 (1958).

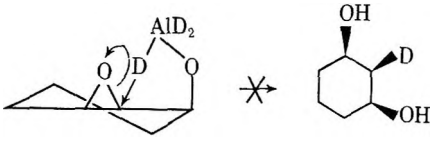
(6) E. Glotter, S. Greenfield, and D. Lavie, *Tetrahedron Lett.*, 5261 (1967).

(7) B. Rickborn and J. Quartucci, *J. Org. Chem.*, **29**, 3185 (1964).

a less regioselectivity manner than *cis*-3-methylcyclohexene oxide, which gives 98% of 2-methylcyclohexanol.[8] The regioselectivity of the trans alcohol **3** is very similar to that observed with *trans*-3-methylcyclohexene oxide.[8] In the cases of the ethers **2** and **4**, the nearly equal amounts of 1,2 and 1,3 products suggests that either steric, polar, and conformational effects are slight, or that a subtle balancing of these effects leads to the observed absence of selectivity.

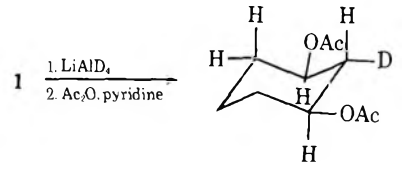
One interesting feature of the data in Table I is the absence or very low level of oxidative inversion[7] which occurs during reaction. It might be argued that, in the alcohols **1** and **3**, initial reaction of $LiAlH_4$ with the hydroxyl group forms some aluminum hydride, which is known to diminish this epimerization process.[7] However, the similar behavior of the ethers **2** and **4** indicates that some other explanation must be involved. In simple alkyl-substituted cyclohexene oxides, oxidative inversion occurs to the extent of *ca.* 10% of overall reduction. Apparently the electronegative oxygen substituent makes the lithium alkoxide (initially generated on reduction of the epoxide) less prone to act as a hydride donor; this view is supported by the observation that electronegative substituents enhance the rate of sodium borohydride reduction of cyclohexanone.[9]

The minor but still significant (40%) product formed on reduction of **1** could conceivably arise by intramolecular syn opening of the oxirane ring through the *O*-aluminate derivative as shown in eq 1. To test this



(1)

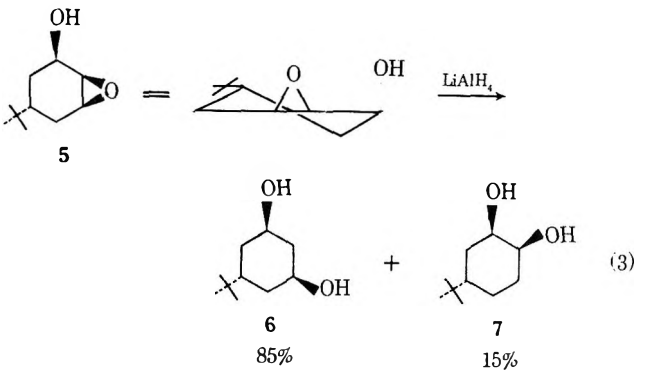
possibility **1** was reduced with lithium aluminum deuteride. The isolated *cis*-1,3-diol was analyzed, as the diacetate, by nmr, which demonstrated that this product contained the 2 deuterium in the trans position, thus ruling out eq 1 as an appreciable pathway (we estimate that $\geq$10–15% would have been detected). The nmr spectrum of the HCOAc protons showed a



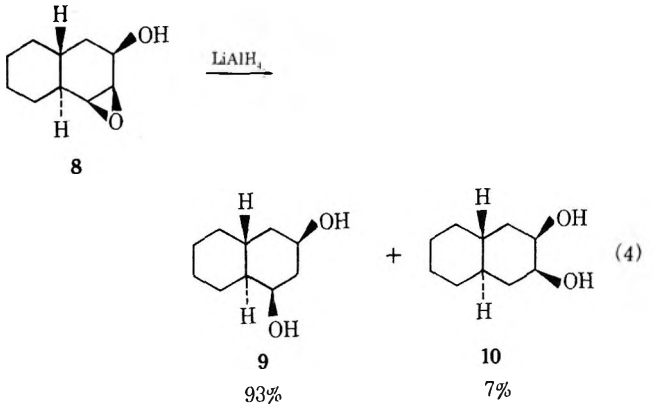
(2)

well-defined triplet (J = 11 Hz) with each line further split into a doublet (J = 4.2 Hz), centered at δ 4.68 ppm, the result of two axial–axial and one axial–equatorial couplings. This product thus most reasonably arises by normal diaxial opening of the half-chair conformer shown in eq 1, but by anti attack by a second molecule of $LiAlH_4$. Note that this implies that the initially formed *O*-aluminate does not have a very large conformational preference.

Fixed conformation model systems were examined to further delineate the effects of pseudoaxial and pseudoequatorial cis hydroxyl groups in the $LiAlH_4$ reduction. Compound **5**, in which the conformational preference of the remote *tert*-butyl group forces the hydroxyl group to assume the pseudoaxial position, gives the product distribution shown in eq 3. The major product 6 is that derived by normal diaxial opening of the oxirane ring. The minor product **7** arises by the abnormal mode involving a boat transition state.[1] Although only 15% of the latter process occurs, this would still be unexpected in the absence of some specific directive effect of the pseudoaxial hydroxyl group, since the parent system, *trans*-4-*tert*-butylcyclohexene oxide, gives >99% of normal diaxial opening.[7] A conformationally analogous system **8** was also subjected to $LiAlH_4$ reduction. The results, shown in eq 4, are comparable to those obtained with **5**; the somewhat greater percentage of normal as compared to abnormal opening in the octalin oxide reduction may be ascribed to the lower flexibility of the bicyclic compound, making the boat transition state process even more unfavorable.

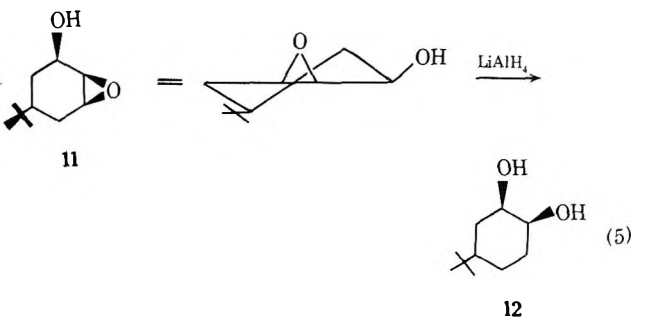


(3)



(4)

When the hydroxyl group is fixed in the pseudoequatorial position, as in compound **11**, the cis epoxide ring is cleaved exclusively (or nearly so; the experimental uncertainty is greater in this case owing to working with a sample containing isomeric impurities) in the normal diaxial mode (eq 5).



(5)

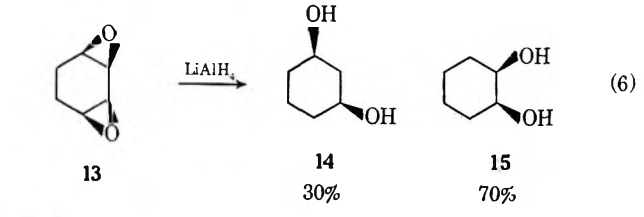
(8) B. Rickborn and W. E. Lamke, II, *J. Org. Chem.*, **32**, 537 (1967).
(9) H. Kwart and T. Takeshita, *J. Amer. Chem. Soc.*, **84**, 2833 (1962).

The data from eq 3 and 4 indicate that the pseudoaxial hydroxyl group does exert an effect on the $LiAlH_4$ reduction process which causes the usually large[1] difference in activation energies between normal (chair) and abnormal (boat) opening to be diminished. Whether the effect has its origin in some kind of specific neighboring group participation (intramolecular complex formation involving either lithium or aluminum) or is simply a polar effect of adjacent alkoxide remains unanswered. It is clear, however, that the effect is not sufficiently large to overcome the preference for normal diaxial (chair) opening in the absence of other (*e.g.*, conformational or steric) influences. Examination of models of the more complex systems where "abnormal" $LiAlH_4$ openings have been reported[3,6] in fact suggests that conformational and remote steric effects are likely the features most responsible for the observed regioselectivity.

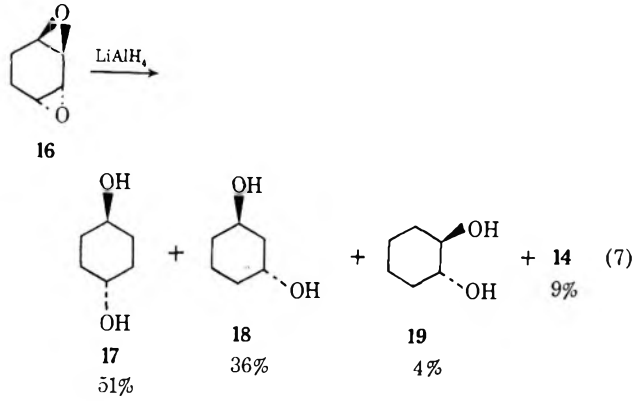
Using the data from the reduction of compounds **5** and **11**, *i.e.*, by assuming that the *tert*-butyl group does not exert some undeterminable effect on the course of reduction, one may calculate that the simple system **1** is reduced *via* 53% of the pseudoequatorial and 47% of the pseudoaxial hydroxyl conformer. Thus regardless of the state of hydroxyl group, whether present as a lithium salt or aluminate derivative, it does not appear to have an energetically large conformational preference.

Although we have not examined conformationally fixed model systems in which the hydroxyl group and oxirane function are trans related, the mixture of diols obtained on reduction of **3** (Table I) can easily be accommodated by assuming that both half-chair conformers contribute appreciably to the reduction process in this flexible compound.

Finally, we have briefly explored the question of selectivity on reduction of *cis*- and *trans*-1,3-cyclohexadiene diepoxides. These data are shown in eq 6 and 7.



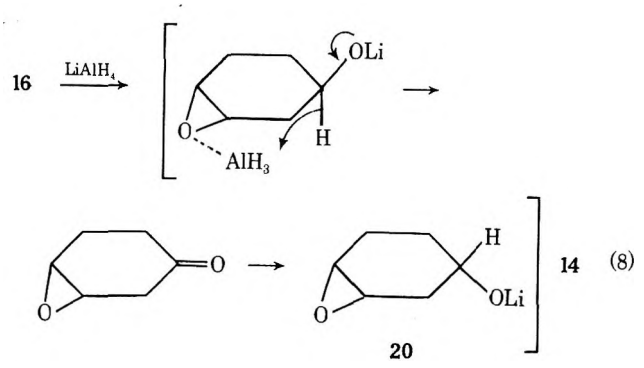
(6)



(7)

These systems are complicated by the fact that a double reduction must occur in two distinct steps; we can refer to attack at either the 1 or 4 (equivalent) positions as "exterior" and at the 2 or 3 position as "interior." Looking first at the cis diepoxide, initial exterior attack will lead to (presumably) the same intermediate as formed in the reduction of **1**, which should in turn be reduced to 60% 1,2-diol (**15**) and 40% 1,3-diol (**14**). This suggests that 50% of the initial hydride attack is exterior and 50% interior, *i.e.*, that the initial reduction of **13** is completely void of regioselectivity. The data in eq 6 further imply that the intermediate formed by initial interior attack must lead exclusively, or nearly so, to 1,3-diol (**14**).[10]

The trans diepoxide, by analogous reasoning, appears to undergo much more regioselective interior initial hydride attack. The small amount of *trans*-1,2-diol (**19**) formed, when viewed in connection with the reduction of compound **3**, implies that little more than 10% of exterior initial hydride attack takes place. The intermediate formed by initial hydride attack is further reduced to **17** and **18**, along with, interestingly, 9% of oxidative inversion product **14** (see eq 7).[10] The formation of this appreciable quantity of *cis*-1,3-diol, considered in connection with the absence of *cis*-1,2- and *cis*-1,4-diol, suggests that some special geometrical feature leads to oxidative inversion in the reduction of **16**. A reasonable explanation is that the epimerization takes place in the initial reduction step, as outlined in eq 8.



(8)

It should be noted that the proposed epimerized intermediate **20** is identical with the initially formed intermediate in the reduction of **13**, which in turn is converted exclusively to **14** (*i.e.*, no *cis*-1,4-diol should be formed, and none is observed).

Experimental Section

All lithium aluminum hydride reductions were carried out in ether solvent using 1 mol of $LiAlH_4$ per mole of substrate. The isolation procedure was that recommended by Fieser and Fieser.[12] The crude alcohol products were converted directly to acetate derivatives for further analysis.

Epoxidation of 3-acetoxycyclohexene with *m*-chloroperbenzoic

(10) We were unable to effect the separation of *cis*-1,3- and *cis*-1,4-cyclohexanediol diacetate by vpc; however, the preparative vpc collected sample of **14** had an ir spectrum identical with that of authentic *cis*-1,3-diol, and different from that of the *cis*-1,4-diol. This observation is somewhat disturbing, since Henbest and Nicholls[11] have reported that the $LiAlH_4$ reduction of *cis*-4-hydroxycyclohexene oxide gives *cis*-1,4-diol; they obtained a recrystallized dibenzoate ascribed to this material. It appears that either Henbest's conclusion is incorrect or our assumption that the intermediate formed from the diepoxide is identical with that obtained from the analogous hydroxy epoxide needs to be modified.

(11) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 4608 (1957).

(12) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1968, p 584.

acid afforded a mixture[13] (68% cis, 32% trans), which was saponified and subjected to spinning band distillation to give pure cis (1), bp 83° (10 Torr), and trans (3) compounds, bp 92° (10 Torr).[14]

Lithium aluminum deuteride reduction of 1 followed by acetylation gave a mixture, separated by preparative vpc, consisting of 67% of *trans-3-d-cis*-2-acetoxycyclohexyl acetate, nmr δ 1.3–2.0 (m, 9 H), 2.01 (s, 6 H), 4.81–5.13 (m, 2 H), and 33% of *trans-2-d-cis*-3-acetoxycyclohexyl acetate, nmr δ 1.0–2.1 (m, 9 H), 2.01 (s, 6 H), 4.68 ppm (d of t, J = 4.2 and 11 Hz, 2 H).

The *cis*- and *trans*-3-methoxycyclohexene oxides (2 and 4) were prepared by the procedure of Bannard and Hawkins.[15]

Authentic samples of the methoxy acetates and diacetates derived from 1–4 by reduction and acylation were available from earlier work.[16]

The procedure of Chamberlain and coworkers was followed to prepare *cis*-2,3-epoxy-*trans*-5-*tert*-butylcyclohexanol (5).[14] The product obtained from one recrystallization of the *p*-nitrobenzoate derivative followed by saponification was contaminated with 2% of the isomeric *trans*-2,3-epoxy-*trans*-5-*tert*-butylcyclohexanol. This material was used directly in the $LiAlH_4$ reduction, giving a mixture of diols which was in turn converted to diacetates for vpc analysis (Carbowax 20M, 150°). The product consisted of 14% of *trans*-5-*tert*-butyl-*cis*-1,2-cyclohexanediol (7),[17] nmr (diacetate) δ 0.85 (s, 9 H), 1.0–2.1 (m, 7 H), 1.93 and 2.04 (s, 3 H each), 4.6–4.8 (m, 1 H), 5.1–5.4 ppm (m, 1 H), further characterized as having the same retention time as the *cis*-1,2-diacetates (not separated under our vpc conditions) derived by applying the Woodward–Brutcher procedure[18] to 4-*tert*-butylcyclohexene; 84% of *trans*-5-*tert*-butyl-*cis*-1,3-cyclohexanediol (6),[19] diacetate having identical properties with those of material obtained by oxymercuration–reduction[19] of *trans*-5-*tert*-butyl-2-cyclohexenol; and 2% of a peak assumed to te *trans*-5-*tert*-butyl-*trans*-1,3-cyclohexanediol (from the isomeric impurity in the starting material).

The sample of *cis*-2,3-epoxy-*cis*-5-*tert*-butylcyclohexanol (11)[14] obtained by epoxidation of 95% pure *cis*-5-*tert*-butyl-2-cyclohexenol (5% trans isomer) contained 4% of *trans*-2,3-epoxy-*cis*-5-*tert*-butylcyclohexanol[14] and 5% of 5. Reduction of this mixture gave *cis*-5-*tert*-butyl-*cis*-1,2-cyclohexanediol (12), 91%, having identical retention time with that of the authentic cis diol derivative obtained by the Woodward–Brutcher procedure as described above, and two other peaks (4 and 5%) attributed to reduction of the isomeric impurities in the starting material.

Epoxidation of *trans*-bicyclo[4.4.0]dec-4-en-*trans*-3-ol[20] with *m*-chloroperbenzoic acid gave a mixture (97:3); the major product, based on analogy with the work of Chamberlain, *et al.*,[14] the reduction data, and other evidence presented below, was *trans*-bicyclo[4.4.0]dec-*trans*-4,5-epoxy-*trans*-3-ol (8), while the 3% contaminant was the isomer in which the hydroxyl group and epoxide were trans related. Reduction of this material gave a mixture, again analyzed as the diacetates, with vpc retention times of 20, 23, and 34 min (relative peak area 6, 3, and 91%, respectively) using a 2M 18% XF-1150 column at 175°. The shortest retention time peak proved to be that of *trans*-decalin-*cis*-2,3-diol (10), by comparison with an authentic sample prepared by the Woodward–Brutcher reaction on *trans*-2-octalin. The minor (3%) productwas *trans*-decalin-*trans*-2,3-diol, demonstrated by comparison with a sample obtained by acid-catalyzed hydration of *trans*-2-octalin oxide.[21] The major product was *trans*-bicyclo[4.4.0]decane-*cis*,*cis*-2,4-diol (9), nmr (diacetate) δ 0.8–2.1 (m, 14 H), 1.96 (two s, separated by 1 Hz, 3 H each, acetates), 4.8–5.1 ppm (m, 2 H), and had identical spectral properties with those of material prepared by oxymercuration–reduction[19] of the starting allylic alcohol.

cis-1,3-Cyclohexadiene diepoxide (13)[22] was prepared by thermal rearrangement of the endoperoxide formed by the reaction of singlet oxygen with 1,3-cyclchexadiene. We found it convenient to simply inject the endoperoxide into a vpc instrument (Carbowax 20M, 150°) and to preparatively collect the effluent of 13 rather than to work with the usual thermal rearrangement mixture.

trans-1,3-Cyclohexadiene diepoxide (16),[23] bp 60° (4 Torr), was obtained in 57% yield by *m*-chloroperbenzoic acid epoxidation of 1,3-cyclohexadiene monoepoxide.[24] The product contained 5% of an impurity having the same retention time and identical ir spectrum with that of the cis diepoxide; in view of the overall yield, a significant pot residue, and the observation that the cis diepoxide appears to be more acid sensitive than the trans material, the stereoselectivity of the epoxidation reaction remains unclear.[13] The trans diepoxide had nmr δ 1.84 (broad s, 4 H), 2.99 (m, 2 H), and 3.17 ppm (d of d, J = 3.2, 1.6 Hz, 2 H); ir 740, 785, 840, 887, 930, 970, 1195, 1245, 1430 cm^{-1}.

Lithium aluminum hydride reduction of 13 gave a mixture of diols in high yield consisting of 29.7% of 15,[10] 70% of 14, and 0.3% of material having the same retention time as that of *trans*-1,3-cyclohexanediol diacetate (oxidative inversion); the major products were characterized by comparison of vpc and spectral properties with those of authentic samples.

Reduction of 16 gave a mixture, analyzed as the diacetates, as shown in eq 7. A sample of commercial *cis*-1,4-cyclohexanediol was converted to the diacetate and proved to have an identical ir spectrum with that of preparatively collected 20 diacetate.[10]

Registry No.—1, 26828-72-8; 2, 2867-30-3; 3, 26828-73-9; 4, 2699-17-4; 7 diacetate, 36736-20-6; 9 diacetate, 36736-21-7; 16, 36736-23-9; *trans-3-d-cis*-2-acetoxycyclohexyl acetate, 36736-22-8; *trans-2-d-cis*-3-acetoxycyclohexyl acetate, 36736-24-0; lithium aluminum hydride, 16853-85-3.

(13) The literature contains conflicting reports regarding the stereospecificity of epoxidation of allylic alcohols. In our hands, 2-cyclohexenol invariably gave a mixture of isomers in which the cis material predominated (*ca.* 90%), but in general the ratio of products depends on the peracid, solvent and other reaction conditions. The acid-catalyzed decomposition of oxiranes is strongly influenced by these same variables and often exhibits considerable stereoselectivity;[8] this subsequent step may in fact be responsible for misleading reports of stereospecificity in epoxidation. The mixture we obtained from epoxidation of 3-acetoxycyclohexene differs substantially from that reported by Chamberlain, Roberts, and Whitham;[14] we have repeated this epoxidation using their conditions and obtain the same ratio of isomers reported by the English group.

(14) P. Chamberlain, M. L. Roberts, and G. H. Whitham, *J. Chem. Soc. B*, 1374 (1970).

(15) R. A. B. Bannard and L. R. Hawkins, *Can. J. Chem.*, **36**, 1241 (1958).

(16) M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **34**, 2781 (1969).

(17) C. W. Davey, E. L. McGinnis, J. M. McKeown, G. D. Meakins, M. W. Pemberton, and R. N. Young, *J. Chem. Soc. C*, 2674 (1968).

(18) R. B. Woodward and F. V. Brutcher, *J. Amer. Chem. Soc.*, **80**, 209 (1958).

(19) P. Chamberlain and G. H. Whitham, *J. Chem. Soc. B*, 1382 (1970).

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

(21) M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 2119 (1958).

(22) K. K. Mashewari, P. DeMayo, and D. Wiegand, *Can. J. Chem.*, **48**, 3265 (1970).

(23) P. Bedox and A. Ruyer, *C. R. Acad. Sci.*, **196**, 625 (1933); these authors proposed the diepoxide structure but proof of stereochemistry was not provided.

(24) J. Staroscik and B. Rickborn, *J. Amer. Chem. Soc.*, **93**, 3046 (1971).

Base-Induced Rearrangement of Epoxides. VI. Diene Monoepoxides[1,2]

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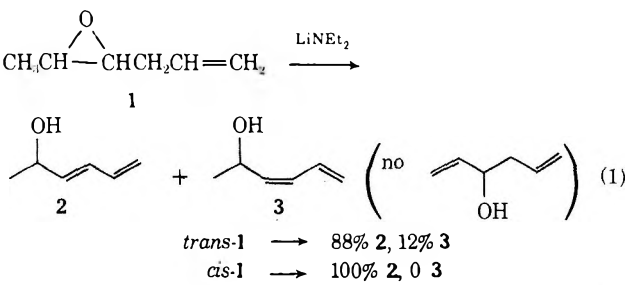
Various diene monoepoxides have been subjected to lithium diethylamide treatment, and the rearrangement products were analyzed. Allylic proton abstraction is strongly preferred in 1,4-diene monoepoxides, with the geometry of the product dependent on the stereochemistry of the starting epoxide. Attempts to form simple arene hydrates gave instead the aromatic systems; an exception was 9,10-epoxy-2-octalin, where the reactive arene hydrate could be isolated. 1,3-Diene monoepoxides undergo 1,4-elimination, preferentially involving abstraction from an alkyl group cis to the oxirane ring. A syn 1,4-elimination mechanism is proposed. The stereoselectivity of these reactions should prove useful for the synthesis of specific dienol isomers and related materials.

Among the marked stereochemical features of the base-induced rearrangement of simple aliphatic epoxides are (a) regiospecific proton abstraction from the least substituted carbon,[3] (b) stereospecific formation of trans double bonds,[3,4] and (c) the operation of a syn-elimination mechanism.[5] Recently we have extended this study to include phenyl-substituted epoxides, where it was found that a β-phenyl group greatly activates the system for rearrangement to allylic alcohol, with the syn-elimination mechanism still strongly preferred.[2] The double bond in the resultant allylic alcohol is exclusively trans when the starting epoxide has the cis stereochemistry (as in *cis*-1-phenyl-2-butene oxide), whereas the analogous trans epoxide gives a product containing small amounts (5–10%) of cis olefin, although the trans product is still preferred. An α-phenyl group also activates the reactant for α-proton abstraction, although in general β-elimination is still preferred if this is an available reaction route.[2]

It was of interest to extend this work to include other activating substituents, and in this paper we describe results obtained with diene monoepoxides.

Results and Discussion

The system 2,3-epoxy-5-hexene (**1**) allows the study of competition for hydrogen abstraction between a primary center and an allylic position. As the results depicted in eq 1 show, only the latter mode of reaction

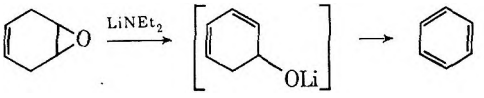


(1)

is observed. The reactions of *trans*-**1** and *cis*-**1** are analogous to those of the corresponding isomers of 1-phenyl-2-butene oxide, in that in both cases the cis isomer gives stereospecific formation of trans olefinic product, whereas the trans epoxide does give some cis olefin as a minor product. The phenyl and vinyl substituents behave analogously in this regard, and stand in contrast to simply alkyl substituents where both cis and trans epoxides lead exclusively to trans olefin.[4,6]

The reactions of both *cis*- and *trans*-**1** with lithium diethylamide occur quite rapidly (complete in less than 4 min under our standard reaction conditions), providing evidence of the acidifying effect of the β-vinyl substituent. This facile removal of the allylic proton accounts for the absence of any product derived from abstraction of a proton from the methyl group, since the latter process in saturated epoxides requires longer times (1–3 hr) for completion. The β-vinyl group is very similar to a β-phenyl substituent[2] in its activating effect for this reaction.

It was of interest to see whether this reaction could be used to generate arene hydrates, and to this end 1,4-cyclohexadiene monoepoxide (**4**) was subjected to lithium diethylamide in ether–hexane solvent. The reaction was effectively instantaneous, leading to a milky precipitate (LiOH or Li_2O) and benzene (eq 2).



(2)

Presumably the lithium salt of benzene hydrate is formed as an intermediate in this reaction, but then undergoes rapid elimination to give the aromatic. It is worth noting that the formally more basic methyllithium reacts with **4** to give benzene hydrate as the major product.[7]

The reaction of 1-methyl-1,2-epoxycyclohex-4-ene (**5**) with lithium diethylamide similarly gives toluene in a rapid, quantitative process (eq 3).

(3)

Somewhat different behavior is exhibited by 9,10-epoxy-2-octalin (**6**), as shown in eq 4. The initial reaction is very rapid, with epoxide fully consumed in less than 1 min; quenching with water at this time leads to the product mixture shown, where the major constituent is the arene hydrate **7**. When longer times elapse before quenching, product **7** is consumed in two ways, one of which is analogous to the "dehydration" in eq 2 and 3, leading to tetralin **8**, and the other in-

(1) Financial support by the Petroleum Research Fund (5744-AC4), administered by the American Chemical Society, is gratefully acknowledged.

(2) Part V: R. P. Thummel and B. Rickborn, *J. Org. Chem.*, **37**, 3919 (1972).

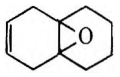
(3) B. Rickborn and R. P. Thummel, *ibid.*, **34**, 3583 (1969).

(4) A. C. Cope and J. K. Heeren, *J. Amer. Chem. Soc.*, **87**, 3125 (1965).

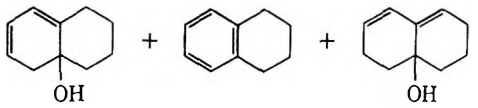
(5) R. P. Thummel and B. Rickborn, *ibid.*, **92**, 2064 (1970).

(6) For a fuller discussion of this behavior see ref 2.

(7) J. Staroscik and B. Rickborn, *J. Amer. Chem. Soc.*, **93**, 3046 (1971).



6



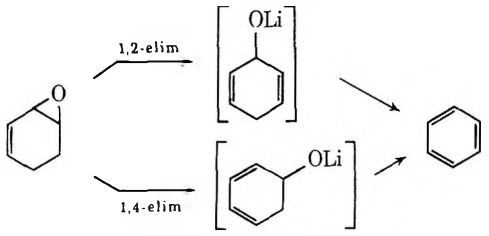
(4)

	7	8	9
1 min	86%	6%	8%
17 min	26%	31%	43%
45 min	13%	42%	45%

volves rearrangement to the more stable diene system of **9**.[8]

The results of eq 4 are noteworthy on two counts. First, although the OLi group in **7** is tertiary, it is lost less readily than the OLi group in **4**, presumably for steric and/or conformational reasons. Second, the rearrangement of **7** to **9** presumably occurs *via* formation of a conjugated dienyl anion, a process which seems to occur particularly rapidly in this system (compared to open-chain analogs). It is likely, as the data in eq 4 suggest, that **9** would eventually be converted to **8** (*via* **7**) on prolonged treatment with lithium diethylamide, but this point was not explored.

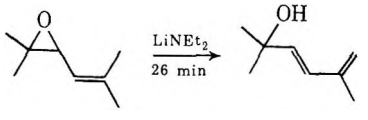
When the vinyl group is present as an α substituent of the epoxide, a number of additional reaction pathways are potentially available (*e.g.*, α-proton abstraction, 1,4-elimination). Treatment of 1,3-cyclohexadiene monoepoxide (**10**) with lithium diethylamide was undertaken to explore this question. As was the case with isomeric compound **4**, a very rapid reaction occurred leading exclusively to benzene. Two possible mechanisms may be considered for the reaction of **10**, as shown in eq 5. The 1,2-elimination pathway does



(5)

not involve the activating influence of the vinyl group, and by analogy with the reaction of cyclohexene oxide, would be expected to require several hours for completion, as opposed to the instantaneous process observed. For this reason and because of evidence provided below, we favor the 1,4-elimination mechanism.

The monoepoxide of 2,5-dimethyl-2,4-hexadiene (**11**) on treatment with lithium diethylamide gives a single product **12** in excellent yield (eq 6). This result is

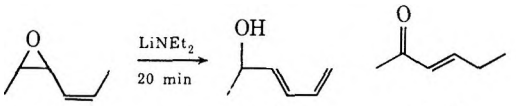


(6)

11 12

especially interesting in that it demonstrates the preference for 1,4-elimination in a system where either 1,2-elimination or α-proton abstraction could compete. The product **12** was homogeneous by vpc and nmr, and both nmr and ir spectra showed it to have the trans geometry about the internal double bond. Two gross mechanistic features of the reaction are not defined by this result. One is the question of which methyl group (cis or trans) acts as the proton source in the 1,4-elimination, if in fact the reaction involves this kind of specificity. The second unanswered question is whether the 1,4-elimination occurs by a syn or anti pathway.

The first of these mechanistic questions was explored through the use of two of the geometric isomers of 2,4-hexadiene monoepoxide. The *cis,cis*-diene monoepoxide **13** was very similar in behavior to compound **11**, *i.e.*, in time required for reaction and in the nature of the product dienol (eq 7). The dienol **2** was isolated

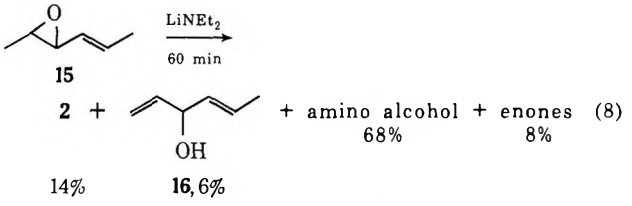


(7)

13 2, 99% 14, 1%

in good yield from this reaction, accompanied by a small amount of the unsaturated ketone **14**. The latter product is thought to arise by rearrangement (on standing prior to analysis) of 4-hexen-2-one formed by α-proton abstraction.

The *trans,trans*-2,4-hexadiene monoepoxide **15** exhibits very different behavior on treatment with lithium diethylamide (eq 8). The reaction is slower and gives a



(8)

15

mixture of dienols in low yield, and the major product is amino alcohol adduct formed by nucleophilic substitution.

Although some dienol **2** is formed from **15**, the process is clearly not as favorable as the analogous reaction of **13**. The formation of some nonconjugated dienol **16** also suggests that **15** possesses unfavorable geometry for 1,4-elimination. Taken together, the results of eq 6, 7, and 8 strongly support the view that 1,4-elimination occurs preferentially (although not necessarily exclusively) *via* abstraction from the alkyl group cis to the oxirane ring. Furthermore, the selective formation of trans internal olefins in these reactions indicates that elimination involves the extended transoid conformation of the diene monoepoxide, since the cisoid conformation (**13c**) would lead to cis internal olefin.

13c

Although we have no direct evidence dealing with the syn,anti-elimination question with diene monoepoxides, we have recently observed[10] that the lithium

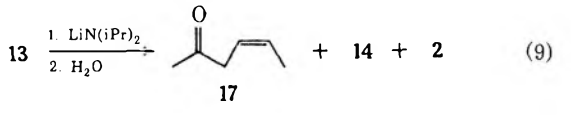
(8) The parent diene system has been equilibrated under basic conditions by Bates and his coworkers,[9] who found that the diene analogous to **7** is relatively unstable (contributing 0% to the equilibrium mixture), while the diene analogous to **9** accounts for 25% of the equilibrium mixture.

(9) R. B. Bates, R. H. Carnighan, and C. E. Staples, *J. Amer. Chem. Soc.*, **85**, 3030 (1963).

(10) Unpublished work with Brian H. Williams.

dialkylamide induced 1,4-elimination of 3-methoxycyclohexene involves abstraction of the cis proton (syn-elimination).

In an effort to cut down the proportion of SN2 product (amino alcohol) obtained from **15** (eq 8), the use of the bulkier base lithium diisopropylamide was explored. The *cis,cis*-diene monoepoxide **13** was similarly treated for comparison purposes, and the course of this reaction is shown in eq 9.

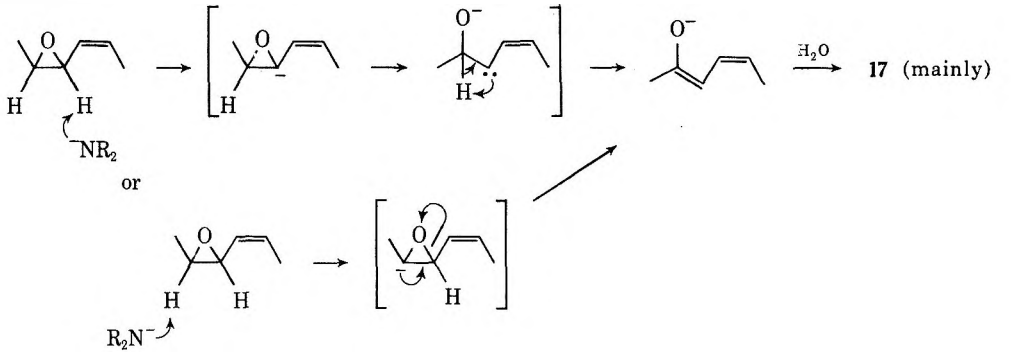


(9)

6 hr[a]	64%	10%	26%
5 days[a]	21%	53%	26%

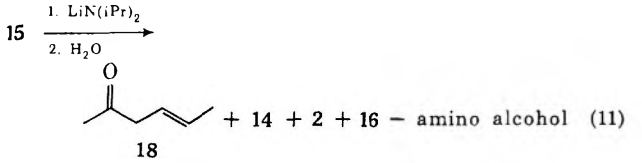
[a] Analysis time.

As anticipated from the results obtained with lithium diethylamide (eq 7), lithium diisopropylamide also gave no adduct with epoxide **13**. However, the dienol **2** yield was diminished at the expense of a new initially formed material **17**, which in turn was slowly rearranged on standing (in ether–hexane solution containing amine) to the more stable conjugated enone **14**. Our previous work[11] demonstrated that increasing the steric bulk of the lithium dialkylamide leads to a preference for α- over β-proton abstraction, and the results of eq 9 show a similar decreased preference for vinylogous β-abstraction. We suggest therefore that compound **17** arises as shown in eq 10.



(10)

The results of treating **15** with lithium diisopropylamide (eq 11) point up the subtle balance of steric and



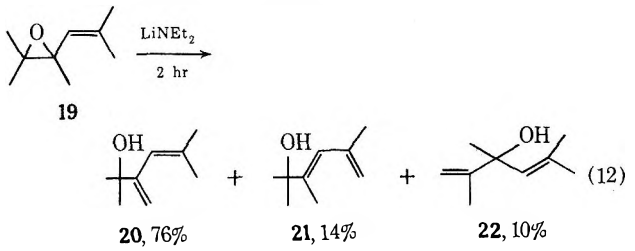
(11)

6 hr[a]	16%	4%	51%	29%	5%
35 days[a]	6%	10%	56%	28%	5%

[a] Analysis time.

electronic factors controlling these reactions. Thus, as anticipated, the yield of amino alcohol adduct is greatly reduced with the bulky base, but in this instance the proportion of dienols increases substantially relative to the enones. The ratio of the two dienols **2** and **16** (1,4- and 1,2-elimination; *cf.* eq 8), however, is not markedly altered by the use of the larger base.

Finally, compound **19** was prepared with the view that the extra methyl group (relative to **11**) might affect the transition-state geometry such as to alter product distribution. This indeed proved to be the case, as the results of eq 12 show.



(12)

The major product **20** was identified by its nmr (equal peak areas for allylic and saturated methyl groups) and mass spectra, which exhibited a major fragment at *m/e* 55 (isobutylene$^+$) but none at *m/e* 41 (propylene$^+$), thus distinguishing it from structure **21**. It appears that conformational distortion due to the extra methyl group causes 1,2-elimination to be preferred over 1,4-elimination leading to **21**; of the two modes of 1,2-elimination, the preference for formation of **20** relative to **22** must be attributed to either an overlap or inductive effect in the transition state favoring the conjugated diene. In the model system 2-methyl-2-butene oxide, we had earlier found[3] that abstraction was roughly that anticipated on the basis of statistical availability of β protons.

It is conceivable that the ratio of **20** to **21** is determined by equilibration; however, aliquots examined during the course of the reaction, including a point taken a few minutes after initiation of the reaction, showed the proportion of all three dienols to be invariant with time. The difficulty in separating other than analytical amounts of **20** prevented direct examination of its possible rearrangement to **21** under the basic reaction conditions, but it is considered doubtful that any such rearrangement would lead to complete equilibration within a few minutes.

Experimental Section

Epoxidations were carried out with peracetic acid following a literature procedure.[12] Lithium dialkylamide solutions were prepared as described previously.[3] The rearrangements in all cases led to high yields of volatile products, as determined by vpc analysis with an inert internal standard. The products were shown to be stable to vpc analytical conditions unless otherwise noted, by collecting and reinjection. Carbowax 6M and 20M columns were used at various temperatures.

trans-**2,3-Epoxy-5-hexene**.—Epoxidation of commercial *trans*-1,4-hexadiene (Chemical Samples Co.) gave distilled *trans*-1

(11) C. Kissel and B. Rickborn, *J. Org. Chem.*, **37**, 2060 (1972).

(12) M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Amer. Chem. Soc.*, **82**, 4328 (1960).

in 60% yield: bp 106°; nmr δ 6.0–4.7 (ABC pattern, 3 H), 2.5 (m, 2 H), 2.15 (t, 2 H), and 1.2 ppm (d, 3 H), J = 5 Hz); ir 2975, 1650, 922, and 868 cm^{-1}. *Anal.*[13] Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.51; H, 10.18.

Lithium diethylamide treatment gave two products in 4 min (vpc yield 85%). The major component (88%) was shown to be *trans*-3,5-hexadien-2-ol (**2**):[14] nmr δ 6.2–4.7 (m, 5 H), 4.08 (quintet, J = 6 Hz, CHOH), 3.2 (s, OH), and 1.15 ppm (d, J = 6 Hz, 3 H); ir 3340, 3080, 1610, 1064, 1009, and 956 cm^{-1}. The minor component (12%) was identified as *cis*-3,5-hexadien-2-ol (**3**): ir 3340, 3090, 1605, 1115, 1073, 1048, and 910 cm^{-1}. Catalytic reduction of the mixture led exclusively to 2-hexanol.

cis-**2,3-Epoxy-5-hexene**.—Epoxidation of diene obtained from Chemical Samples Co. gave a 55% distilled yield of *cis*-**1**: bp 112–114°; nmr δ 6.15–4.9 (ABC pattern, 3 H), 2.85 (m, 2 H), 2.25 (m, CH_2), and 1.25 ppm (d, J = 5 Hz, CH_3); ir 2985, 1645, 990, and 782 cm^{-1}. *Anal.* Found: C, 73.70; H, 10.40.

Rearrangement of this epoxide gave a single product (**2**) in quantitative yield within a few minutes, with no change in composition after 20 min.

1,2-Epoxycyclohex-4-ene (**4**).[15,16]—An instantaneous reaction with formation of a milky white precipitate (Li_2O) was observed on addition of **4** to the lithium diethylamide solution at room temperature. Vpc analysis indicated a quantitative yield of a single volatile product, identified by retention time and nmr as benzene.

1-Methyl-1,2-epoxycyclohex-4-ene (**5**).[16,17]—A similar instantaneous reaction gave toluene (vpc and nmr) in quantitative yield.

4a,8a-Epoxy-1,2,3,4,5,8-hexahydronaphthalene (**6**).[16,18]—When **6** was added to lithium diethylamide solution the mixture immediately turned cloudy and red, and analysis of an aliquot after 1 min showed that all of the epoxide had been consumed. Three volatile products were obtained in essentially quantitative yield, with the ratio varying with time as described in the text. The first vpc peak had an ir spectrum identical with that of authentic tetralin. The second peak was identified as bicyclo[4.4.0]deca-3,5-dien-1-ol (**7**), nmr δ 5.9–5.3 (m, 3 H) and 2.9–1.2 ppm (m, 11 H); addition of formic acid to the nmr tube caused the rapid formation of tetralin. Partial dehydration of **7** to tetralin occurred on vpc analysis, and hence the product ratios reported in the text were determined by combined vpc and nmr analyses of the crude aliquots. The ir of **7** showed bands at 3410, 1495, 849, 746, and 701 cm^{-1}.

The third vpc peak was identified as bicyclo[4.4.0]deca-4,6-dien-1-ol (**9**) by its spectral properties: nmr δ 5.9–5.2 (m, 3 H), and 2.5–1.0 ppm (m, 11 H), addition of formic acid shifts OH singlet out of the upfield multiplet; ir 3300, 1430, 1016, 942, 869, 828, and 758 cm^{-1}; uv λ_{max}^{hexane} 234 mμ (ε 25,100). Of the various possible dienol isomers, these properties in concert are consistent only with structure **9**.

1,2-Epoxycyclohex-3-ene (**10**).[15,16]—The reaction of **10** with lithium diethylamide was identical with that of its isomer **4**, again giving benzene as the product.

2,5-Dimethyl-2,3-epoxy-4-hexene (**11**).—Commercial 2,5-dimethyl-2,4-hexadiene (Eastman) was epoxidized to give 38% of **11**, bp 97–100° (142 Torr) [lit.[19] bp 41–42° (11 Torr)]. When this material was treated with lithium diethylamide for 26 min an essentially quantitative yield of a single product (**12**) was obtained. Analysis on a number of vpc columns indicated the material to be homogeneous, a conclusion borne out by its clean and definitive nmr spectrum: δ 6.1 (d, 1 H, J = 15 Hz), 5.52 (d, 1 H, J = 15 Hz), 4.78 (s, C=CH_2, 2 H), 3.2 (s, OH), 1.74 (s, 3 H, vinyl CH_3), and 1.24 ppm (s, 6 H); ir 3350, 3075, 2970, 1615, 970, 887 cm^{-1}.

cis,cis-**2,3-Epoxy-4-hexene** (**13**).—*cis,cis*-2,4-Hexadiene (Chemical Samples Co.) was epoxidized to give **13** in 78% yield: bp 188–120°; nmr δ 5.8–4.8 (m, 2 H), 3.35 (m, 1 H), 2.95 (quintet, 1 H, J = 5 Hz, –$CHCH_3$), 1.72 (d of d, 3 H, J = 2 and 7 Hz, C=CCH_3), and 1.16 ppm (d, 3 H, J = 5.5 Hz); ir 2990, 1150, 933, and 834 cm^{-1}. *Anal.* Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.86; H, 10.53.

When added to lithium diethylamide solution, **13** was consumed in 20 min to give in 70% yield a mixture consisting of 93% *trans*-3,5-hexadien-2-ol (**2**), 1% unsaturated ketone, and 6% of two unidentified materials having longer retention times.

The reaction of **13** with lithium diisopropylamide was complete in 10 min, giving three volatile products in greater than 70% yield. The ratio of these products changed as described in the text depending on the time elapsed between quenching and vpc analysis. The first peak was identified as *cis*-4-hexen-2-one (**17**):[20] nmr δ 5.5 (m, 2 H), 3.03 (d, 2 H, J = 4.5 Hz), 2.02 (s, 3 H), and 1.61 ppm (d, 3 H, J = 4.5 Hz); ir 3030, 1730, and 1165 cm^{-1}. The second product was *trans*-3-hexen-2-one (**14**):[21] nmr δ 6.65 (d of t, 1 H, J = 6 and 15 Hz), 5.87 (d, 1 H, J = 15 Hz), 2.1 (s, 3 H), 2.1 (quartet, 2 H, J = 7 Hz), and 1.07 ppm (t, 3 H, J = 7 Hz); ir 2960, 1685, 1330, 1375, 1260, and 981 cm^{-1}. The third product was identical in retention time and spectral properties with **2**.

trans,trans-**2,3-Epoxy-4-hexene** (**15**).—Epoxidation of *trans,trans*-2,4-hexadiene (Chemical Samples Co.) gave **15** in 81% yield: bp 114–116°; nmr δ 6.0–5.4 (m, 1 H), 5.2–4.7 (m, 1 H), 2.7 (m, 2 H), 1.65 (d, 3 H, J = 6 Hz), and 1.2 ppm (d, 3 H, J = 5.5 Hz); ir 2960, 1016, 968, 939, 861, and 737 cm^{-1}. *Anal.* Found: C, 73.51; H, 10.39.

On treatment with lithium diethylamide for 60 min, **15** gave a mixture of six products in 80% overall yield: unsaturated ketones (presumably *trans*-4-hexen-2-one and *trans*-3-hexen-2-one), 8%, collected together, ir 1715 and 1680 cm^{-1}; *trans*-1,4-hexadien-3-ol[14] (**16**), 6%, nmr δ 6.0–4.8 (complex m, 5 H), 4.35 (t, J = 4.5 Hz, CHOH), 2.9 (s, OH), and 1.7 ppm (d, 3 H, J = 5.5 Hz); ir 3350, 3080, 1670, 1645, 992, 968, and 925 cm^{-1}; **2** (14%); and two longer retention time materials, 54 and 14%, respectively, both having appropriate nmr, ir, and mass spectral properties for nucleophilic substitution (amino alcohol) products.

The reaction of **15** with lithium diisopropylamide was complete in 30 min, giving four products (75% yield) with ratios changing with time between quenching and analysis as described in the text. The first peak was isolated in fairly pure form and on the basis of its ir spectrum, 2960, 1715, 1675, 1625, 1258, and 970 cm^{-1}, nonidentity with the cis isomer, and rearrangement to **14**, identified as *trans*-4-hexen-2-one (**18**). The second, initially minor component was identical with **14** in retention time and ir spectrum. The third peak was **16** and the last **2**. Trace amounts (<3%) of two longer retention time products (presumably amino alcohols) were also detected but not isolated.

2,3,5-Trimethyl-2,4-hexadiene.—The procedure of Sopov[22] was followed with some modifications. Isopropylmagnesium bromide was treated with freshly distilled mesityl oxide; the resultant tertiary alcohol was not purified but dehydrated directly using iodine as catalyst.[23] The mixture of two olefins obtained in this reaction was steam distilled, and the middle cut (single major peak by vpc) was redistilled to give 23% of pure diene: bp 77–79° (86 Torr); nmr δ 5.5 (s, 1 H) and 1.8–1.5 ppm (m, 15 H); ir 2960, 2920, 2855, 1450, 1380, 1197, 1126, 1062, and 855 cm^{-1}. Epoxidation gave **19** in moderate yield: bp 57–59° (49 Torr); nmr δ 5.1 (s, 1 H), 1.6 (broad s, 9 H), and 1.25 and 1.1 ppm (two s, 3 H each); ir 2990, 1380, 1138, 1064, and 866 cm^{-1}. *Anal.* Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.88; H, 11.75.

When **19** was treated with lithium diethylamide for 2 hr, a 70% yield of three products was obtained. The ratio of products was invariant with time during the reaction, as determined by combined vpc and nmr analysis. The first and major peak (76%) was identified as 2,5-dimethyl-3-methylene-4-hexen-2-ol (**20**): nmr δ 5.80 (s, C=CH), 4.82 and 4.60 (two s, 1 H each, C=CH_2), 2.77 (s, OH), 1.78 (s, 6 H), and 1.29 ppm (s, 6 H); ir 3370, 3080, 2975, 1640, 1180, 965, and 895 cm^{-1}; mass spectrum (10 eV) m/e (rel intensity) 43 (49), 55 (41), 59 (13), 67 (15), 82 (41), 83 (26), 85 (15), 107 (25), 125 (28), and 140 (parent). The other two materials were collected together; the percentage distribution is based on the nmr peak areas at δ 1.28 (s, attributed to the CH_3COH group of **22**) and 1.20 ppm (s, attributed to the

(13) Analyses by C. F. Geiger, 312 E. Yale St., Ontario, Calif.

(14) J. M. Shackelford and L. H. Schwartzman, *J. Org. Chem.*, **27**, 1047 (1962).

(15) M. Tiffeneau and B. Tchoubar, *C. R. Acad. Sci.*, **212**, 581 (1941).

(16) The authors thank James Staroscik for providing this material.

(17) W. Hückel, B. Graf, and D. Munkner, *Justus Liebigs Ann. Chem.*, **614**, 47 (1958).

(18) W. Hückel and U. Worffel, *Chem. Ber.*, **89**, 2098 (1956).

(19) A. C. Day and M. C. Whiting, *J. Chem. Soc.*, 1719 (1966).

(20) H. Morrison, *Tetrahedron Lett.*, 1023 (1964).

(21) W. K. R. Franke and W. Ring, *Angew. Chem.*, **76**, 817 (1964).

(22) N. P. Sopov, *Zh. Org. Khim.*, **1**, 446 (1965).

(23) W. A. Mosher, *J. Amer. Chem. Soc.*, **62**, 552 (1940).

$(CH_3)_2COH$ grouping of 21). The remainder of the spectrum was consistent with these assignments, showing multiplets at 5.5, 5.04, 4.8, and 4.5 (vinyl H) and 1.65 ppm (vinyl CH_3) with appropriate areas.

Registry No.—*cis*-1, 36807-98-4; *trans*-1, 36807-99-5; 13, 36808-00-1; 15, 36808-01-2; 19, 36803-64-2; 20, 36803-65-3; 2,3,5-trimethyl-2,4-hexadiene, 1726-48-3.

The Reaction of Haloaryl Sulfones with Alkali Phenoxides. The Effects of Polyglyme Solvents and Other Variables

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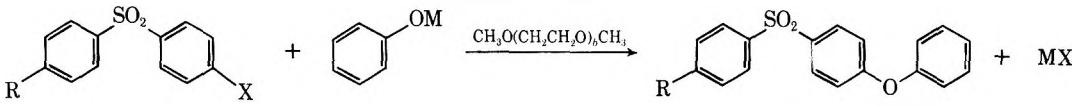
Received May 17, 1972

The reaction of alkali phenoxides with *p*-halophenyl (para-substituted phenyl) sulfones



(M = Na, K, Cs; X = F, Cl, Br; R = H, Cl, OC_6H_5, CH_3; b = 2, 3, 4, ~20)

has been studied in the aprotic dimethyl ether of polyethylene glycol solvents at 160°. This nucleophilic aromatic displacement reaction is first order in halo sulfone and of fractional (~0.5) order in phenoxide ion. The active nucleophile is the monomeric anion which results from a dissociation of the alkali phenoxide aggregate. The ether solvent chain length has a strong influence on the reaction rate: when $b \cong 20$ the reaction is about 25 times faster than when $b = 2$. The reaction rate increases in the order Cl < Br ≪ F, Na ≪ K < Cs; (R) CH_3 < H ~ OC_6H_5 < Cl. When dimethyl sulfoxide is used as solvent in place of these polyethers, a reaction rate enhancement of about 10^3 is found (b = 2, X = Cl, M = K, R = H).

The rates of nucleophilic aromatic displacement reactions[1-3] are strongly accelerated by the nature and number of electron-withdrawing groups attached to the aromatic ring undergoing substitution, by both the nature of the attacking nucleophile and leaving group, by the solvent and cation type, and frequently by the presence of "copper."[4] The combination of dipolar, aprotic solvent,[5] strong electron-withdrawing groups (NO_2, CN, SO_2), a very nucleophilic anion, and a readily polarizable cation (K, Rb, Cs) appears to maximize the rate of halide (F ≫ Cl > Br ~ I) displacement from aromatic rings.[2]

There is evidence that the rates of aliphatic displacement reactions are influenced by the nature and chain length of polyethylene glycol ether-type solvents. Thus, the rate of reaction of potassium or sodium phenoxide with *n*-butyl bromide in dimethyl ether of polyethylene glycol [$CH_3O(CH_2CH_2O)_bCH_3$] increases considerably with increase in b.[6,7] When potassium phenoxide is used and b = 6, then the reaction is about 200 times faster than when b = 1 (also b = 2, rate = 8; b = 3, rate = 51; b = 4, rate = 72). Similar evidence exists for the isomerization of 3-butenylbenzene to 1-butenylbenzene with potassium *tert*-butoxide in these solvents.[8]

One purpose of this investigation was to see whether this effect is also observed in nucleophilic aromatic displacement reactions, in particular on haloaromatic sulfones. A number of other features, *e.g.*, reaction order, impurity effects, solvent and leaving group nature, etc., were also examined.

Results and Discussion

A. Reaction Order and Mechanism.—The reaction of *p*-$ClC_6H_4SO_2C_6H_5$ with potassium phenoxide in diglyme[9] at 160.0°, 1.0 mol phenoxide/1 mol halo sulfone and at about 0.19 mol/l. reagent concentrations, follows a fractional order rate law (k_2 = 0.021 ± 0.001 l./mol min; overall n = 1.41). The order, relative to the haloaromatic sulfone, is 1.0, since the use of a large excess of base (10:1) results in a pseudo-first-order reaction.[10] A variation of the reagent concentrations by a factor of one-half (at 1.0 mol phenoxide/1 mol sulfone) results in no appreciable change in the second-order rate constant (0.019 l./mol min) nor in a deviation from the fractional order nature of the reaction (n = 1.41).

Similar displacement reactions involving charged nucleophiles in aprotic media are frequently of fractional order[6-8,11,12] owing to aggregation of the nucleophile to polymers and because only the monomer appears as the reactive species.[11] Thus, in the reaction of *n*-butyl bromide with alkali phenoxide in glyme solvents, it was found[6] that the reaction order with respect to the phenoxide was "far from unity" and almost zero when sodium phenoxide was used. There also appeared to be an increase in the phenoxide order with

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(2) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York, N. Y., 1968.
(3) J. Sauer and R. Huisgen, *Angew. Chem.*, **72**, 294 (1960).
(4) R. G. R. Bacon and H. A. O. Hill, *Quart. Rev., Chem. Soc.*, **19**, 95 (1965).
(5) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
(6) J. Ugelstad, A. Berge, and H. Liston, *Acta Chem. Scand.*, **19**, 208 (1965).
(7) A. Berge and J. Ugelstad, *ibid.*, **19**, 742 (1965).
(8) J. Ugelstad and O. A. Rokstad, *ibid.*, **18**, 474 (1964).
(9) $CH_3O(CH_2CH_2O)_bCH_3$: b = 2, diglyme; b = 3, triglyme; etc.
(10) Up to at least 85% conversion; the calculated second-order rate constant was 0.042 l./mol min. This is about twice the "normal" k_2 (at 1.0 mol phenoxide/1 mol halo sulfone) of 0.021 l./mol min; the difference may be due to a salt effect. When potassium phenoxide was treated with excess (10:1) *p*-$ClC_6H_4SO_2C_6H_5$ then k_2 = 0.021 l./mol min and n = 0.66. The reason for the deviation from the expected n = 0.4 is not known (duplicate experiments).
(11) R. A. H. Casling, A. G. Evans, and N. H. Rees, *J. Chem. Soc. B*, 519 (1966).
(12) H. Weingarten, *J. Org. Chem.*, **29**, 977, 3624 (1964).

increase in glyme chain length.[13] Similarly, the reaction of potassium phenoxide with bromobenzene (Ullmann condensation) in diglyme showed that the reaction order with respect to the phenoxide was between two and one.[12] Other investigators[11] showed that in the reaction of *tert*-butyllithium with fluorene or diphenylethane, the reaction order with respect to the lithium compound was 0.25. This was ascribed to the tetrameric state of *tert*-butyllithium in benzene (when *n*-butyllithium was used the order was 0.18, *e.g.*, a hexameric polymer).

In all of these cases, as well as the reactions investigated here, a rapid monomer–polymer equilibrium must precede the rate-determining step of the reaction.[14]

The actual $(RM)_1$ (reactive monomer concentration) is therefore dependent upon the equilibrium (eq 1).

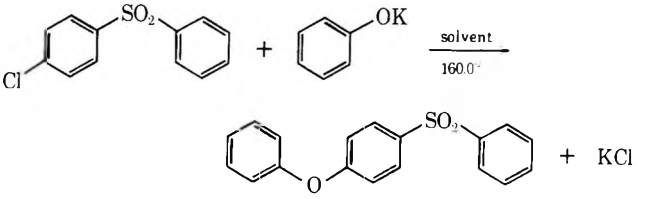
$$(RM)_m \overset{\text{fast}}{\rightleftharpoons} m(RM)_1 \qquad (1)$$

The subsequent step (eq 2) is the displacement of the aromatic halide. The rate order F ≫ Cl ∼ Br (*vide infra*, Table III) suggests that the phenoxide bond formation is the critical step.[3] No colored intermediates[15] suggestive of Meisenheimer-type transients were observed.

$$(RM)_1 + AX \xrightarrow{\text{rate determining}} MX + RA \qquad (2)$$

B. Effect of Solvent Chain Length and Type.—When the chain length of the dimethyl ether of polyethylene glycol is increased a corresponding increase in the reaction rate is observed (Table I). Polyglyme ($b \cong 20$) results in a 25-fold increase in the rate over the rate in diglyme; simultaneously there is a considerable increase in the order of the reaction with respect to the potassium phenoxide. With diglyme the total order is 1.41; with polyglyme this rises to 1.93. This would indicate that the polyglyme causes a shift in the phenoxide monomer–polymer equilibrium to the monomer side.[17] It is unlikely that this glyme series differs appreciably in their dielectric constants;[7] hence a rate enhancement due to a dielectric effect is ruled out. It is most likely that particularly the polyglyme is a far better cation solvating solvent than is diglyme.[20] This is reminiscent of Pedersen's crown ethers,[21] which form stable complexes principally with group I cations.

TABLE I
EFFECT OF SOLVENT NATURE ON THE REACTION[c]



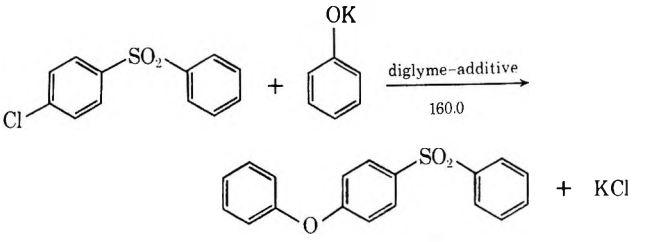
Solvent	Relative rate	k_2, l./mol min	n[a]
$CH_3O(CH_2CH_2O)_2CH_3$ (diglyme)	1.0	0.021 ± 0.001	1.41
$CH_3O(CH_2CH_2O)_3CH_3$ (triglyme)	4.3	0.090 ± 0.01	1.65
$CH_3O(CH_2CH_2O)_4CH_3$ (tetraglyme)	8.8	0.184 ± 0.03	1.68
$CH_3O(CH_2CH_2O)_{20}CH_3$ (polyglyme)	24.8	0.522	1.93
99 wt % diglyme + 1 wt % DMSO[b]	1.4	0.030	1.41
90 wt % diglyme + 10 wt % DMSO	7.6	0.160	1.38
75 wt % diglyme + 25 wt % DMSO	75	1.57	1.58

[a] Total reaction order. [b] Dimethyl sulfoxide. [c] 1 mol of phenoxide/1 mol of halo sulfone; 0.19 mol/l. concentration.

The addition of DMSO to diglyme causes similar reaction rate enhancement. At a 25 wt % level (about 5 mol DMSO/1 mol potassium phenoxide) the reaction is 75 times as fast as in pure diglyme and three times as fast as in polyglyme. The reaction order does not appear to increase; at 25 wt % DMSO, n is only 1.58, far below the 1.93 for pure polyglyme.[22]

C. Impurity Effects.—Table II shows the rate

TABLE II
IMPURITY EFFECTS[a]



Impurity	Concn. mol/mol phenoxide	k_2, l./mol min	Relative rate
None		0.021 ± 0.001	1.00
Ethylene carbonate	0.245	0.026	1.2
$[C_6H_5NCH_2CH_2]_4$[b]	0.045	0.019	0.9
DMSO	1.1	0.030	1.4
Crown-18[c]	0.12	0.031	1.5
CuBr	0.03	0.028	1.3
CuOAc	0.0355	0.021	1.0
$Cu(acac)_2$	0.164	0.024	1.1

[a] The overall reaction orders were 1.4 ± 0.1; 1 mol phenoxide/1 mol halo sulfone; 0.19 mol/l. [b] Models show that the "hole" in this cyclic compound is too small to accommodate a potassium ion. [c] Dibenzo[18]-crown-6.[21]

(13) These authors[6,7] did not consider that these phenoxides could be polymers in solution. Their measurements were correlated *via* the initial reaction rates and the approximately first-order rate constants (1 mol phenoxide per 1 mol RBr). If conversions are low (∼10%) then this treatment is semiquantitatively acceptable.

(14) Potassium phenoxide used here is approximately a trimer in THF (degrees of polymerization = 3.2; 37°, ∼1 wt % concentration, osmometry). The molecular weight decreases to about 200 in boiling diglyme (degree of polymerization = 1.5; 160°, 2.5 wt % concentration, ebullioscopically).

(15) During the reaction of *p,p'*-dichlorodiphenyl sulfone with the disodium salt of 2,2-bis(4-hydroxyphenyl)propane in DMSO at 150°, a transient, vivid orange-yellow color is observed which is discharged on termination of the reaction.[16]

(16) R. N. Johnson, A. G. Farnham, R. A. Clendinning, W. F. Hale, and C. N. Merriam, *J. Polym. Sci., Part A-1*, **5**, 2375 (1967).

(17) Unfortunately, it is not possible to measure the potassium phenoxide molecular weight directly in polyglyme. Ultraviolet or nuclear magnetic resonance techniques might confirm this equilibrium shift.[18,19]

(18) J. Smid, *Angew. Chem.*, **84**, 127 (1972).

(19) J. F. Garst, R. A. Klein, D. Walmsley, and E. R. Zabolotny, *J. Amer. Chem. Soc.*, **87**, 4080 (1965).

(20) In the preparation of polyglyme it was observed that at 25° NaI forms stable solutions at the 23 wt % level (2 mol of NaI/1 mol of polyglyme)

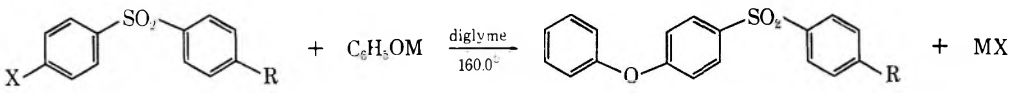
(21) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem.*, **84**, 16 (1972), and previous publications.

(22) In pure DMSO the reaction rate is estimated to be 10^3 times faster than in diglyme (160°). This is in good agreement with others[23] who found the reaction rate of potassium phenoxide with the first chlorine of *p,p*-dichlorodiphenyl sulfone to be about 750 times as fast in DMSO (160°, extrapolated) as *p*-chlorophenyl(phenyl) sulfone and potassium phenoxide react in diglyme (160°).

(23) S. R. Schulz and A. L. Baron, *Advan. Chem. Ser.*, **91**, 692 (1969).

TABLE III

EFFECT OF PHENOXIDE CATION, SULFONE SUBSTITUENTS AND SULFONE HALOGEN[c]



Registry no.	X	R	M	k_2, l./mol min	n	Relative rate
80-00-2	Cl	H	K[d]	0.021 ± 0.001	1.41	(1.00)
312-31-2	F[a]	H	K	1.44		68.7
23038-36-0	Br	H	K	0.068	1.58	3.2
	Cl	H	Na[e]	0.000336	1.08	0.016
	Cl	H	Cs[f]	0.122	1.53	5.8
5184-71-4	Cl	CH_3	K	0.0155	1.42	0.75
80-07-9	Cl[b]	Cl	K	0.054[b]		2.5
36794-63-5	Cl	OC_6H_5	K	0.0235	1.50	1.1

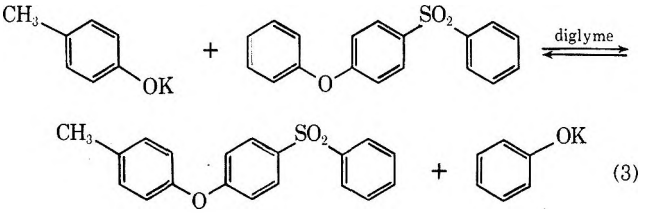
[a] Run competitively against p-$ClC_6H_4SO_2C_6H_5$ with deficient caustic. [b] First chlorine displaced. [c] 1 mol phenoxide/1 mol halo sulfone; 0.19 mol/l. [d] Registry no., 100-67-4. [e] Registry no., 139-02-6. [f] Registry no., 1120-91-8.

changes which took place when relatively small quantities of impurities were added to the displacement reaction. Weingarten[12] found that small quantities of impurities such as ethylene carbonate, in diglyme, greatly accelerated the reaction of bromobenzene with potassium phenoxide. Here this additive seemed to yield no substantial rate acceleration. Neither did *small* quantities of a cyclic amine, the crown-18 ether,[21,24] nor DMSO. The addition of Cu^+ or Cu^{2+} compounds, which acted as catalysts for the Ullmann condensation,[12] caused no appreciable rate change here.

D. Cation, Halogen, and Sulfone Substituent Effects.—Table III summarizes the results which were obtained when the nature of the sulfone halide (leaving group), the phenoxide cation, and the sulfone substituent were varied. As expected,[3,16] the fluoride is considerably more reactive than the chloride (69:1); the bromide is three times as fast as the chloride. The cation effect in this system is remarkable: Cs > K ≫ Na; this is in line with observations in similar systems.[12,16] It is most probable that the highly polarizable potassium and cesium ions interact more effectively with diglyme than does the sodium cation. The total reaction orders n are in the expected direction—1.08 for sodium and 1.4–1.5 for the potassium and cesium ions, respectively. Sodium phenoxide, in this system, must have a fairly high degree of polymerization (~12) and little tendency to be depolymerized and solvated by diglyme.[26]

Substitution para in the other phenyl ring has only a marginal effect on the reaction rate. This is probably due to the inability of the sulfone group to transmit charge by induction or particularly resonance. Others[23] have also observed that the rate difference between the two chlorines in p,p'-chlorodiphenyl sulfone is small (about two); the first chlorine being displaced more readily than the second.

E. Further Reactions.—The reaction of alkali phenoxide with haloaromatic sulfones is essentially quantitative. The products undergo further reaction (eq 3). This represents a cleavage of the C–O bond by



(3)

the nucleophile phenoxide. Relative to the chlorine displacement by phenoxide, this reaction is very slow ($k_2 = 8 \times 10^{-5}$ l./mol min in the direction to the right) and the equilibrium constant is 5.5.[27] Similar reactions[28,29] (eq 4) take place in protic media (the respective alcohols) at high temperatures.

$$(p\text{-}CH_3OC_6H_4)_2SO_2 + 2C_2H_5ONa \xrightarrow[200°,\ 8\ hr]{C_2H_5OH} (p\text{-}C_2H_5OC_6H_4)_2SO_2 + 2CH_3ONa \quad (4)$$

60%

Experimental Section

The solvents diglyme, triglyme, and tetraglyme were purchased from the Aldrich Chemical Co. and fractionally distilled from over a generous quantity of $LiAlH_4$ after 24-hr reflux [diglyme bp 163–164°, triglyme bp 213–214°, tetraglyme bp 165° (14 mm)]. They were stored under N_2. The halo sulfones were purchased or prepared (p-$XArSO_2Cl$ + Ar'H + 4% $FeCl_3$) and crystallized to a constant melting point.

Compd	Mp, °C
p-$FC_6H_4SO_2C_6H_5$	111.5–112.5
p-$ClC_6H_4SO_2C_6H_5$	92.5–93.5
p-$BrC_6H_4SO_2C_6H_5$	108–109
p-$ClC_6H_4SO_2C_6H_4CH_3$-p	123–124
p-$ClC_6H_4SO_2C_6H_4Cl$-p	147–148
p-$ClC_6H_4SO_2C_6H_4OC_6H_5$-$p$	110–112

The metal phenoxides were prepared by mixing an ethanol solution of the phenol with 98% of the theoretical amount of metal hydroxide followed by rigorous and long-term drying of

(24) Various investigators found that the addition of these crown ethers to reactions involving charged nucleophiles results in appreciable rate enhancement; for example, the reaction of potassium phenoxide (0.025 M) with butyl bromide in dioxane is accelerated by a factor of 10^4 when 0.05 M of such a cyclic ether is added.[25]

(25) L. M. Thomassen, T. Ellingsen, and J. Ugelstad, *Acta Chem. Scand.*, **25**, 3024 (1971).

(26) In DMSO the cation effects are apparently not as pronounced,[16,23] since p,p'-dichlorodiphenyl sulfone reacts at high rates with the disodium salts of various biphenols.

(27) No reaction was observed between diphenyl sulfone and potassium phenoxide in diglyme at 160° in 3 days; the sulfone linkage is therefore immune to cleavage under the above reaction conditions.

(28) D. C. Allport, *Chem. Ind. (London)*, 606 (1965).

(29) G. W. Dalman and F. W. Neumann, *J. Amer. Chem. Soc.*, **90**, 1601 (1968).

the resulting powder [110° (0.05 mm), 48 hr; C_6H_6OCs dried 130° (0.05 mm), 96 hr].

Phenoxide	Neut equiv Found	Neut equiv Theory
C_6H_5OK	132.2, 132.2	132.0
C_6H_5ONa	116.5, 116.2	116.0
p-$CH_3C_6H_4ONa$	146.8, 147.2	146.0
C_6H_6OCs	226	226.0

Polyglyme Preparation [$CH_3O(CH_2CH_2O)_{20}CH_3$].—Polyethylene glycol-1000 (a mixture of glycols of C_{18}–C_{24}; 500 g, 0.50 mol) was stirred with 54 g (1.0 mol) of CH_3ONa for 18 hr at 110°. Then low-boiling substances were removed under vacuum [110° (3 hr), 28.2 g liquid, 32 g theory]. To the dark brown, viscous solution CH_3I (206 g, 1.45 mol) was added gradually. The temperature rose to 155° quickly. Refluxing was for 1 hr, yielding a neutral, clear solution. On cooling the product was a clear solution. Of this residue, 310 g in 2000 ml of distilled water was slowly filtered through an Amberlite MB-1 column (450 mequiv, a strong mixed ion exchange resin). Ellution was carried out with 1500 ml of distilled water. The clear, neutral liquors (negative for I^- with $AgNO_3$) were carefully dried to 160° (0.02 mm) for 20 hr.

Anal. Found: C, 54.01; H, 9.11; O, 37.33; ash, 0.0; mol wt (vapor phase osmometer, 37°, THF), 1006 (c = 37.8 mg/g solvent); 934 (c = 14.0 mg/g solvent); nmr (neat, TMS) δ −3.51 (s, CH_2), 3.25 (s, OCH_3); 3.20 ± 0.8 wt % CH_3 (for mol wt 1000, 3.00 wt % CH_3 calcd).

The kinetic reactions were carried out in a dry 250-ml mechanically stirred flask (under N_2) which was immersed in an oil bath (160 ± 0.05°). The accurately weighed metal phenoxide and solvent were placed into the flask (drybox) and the equivalent amount of halophenyl sulfone was placed into a small sealed tube in the reaction flask. All was then thermally equilibrated. At time zero the glass tube was crushed and rapid stirring quickly (<30 sec) resulted in a homogeneous solution (no temperature change). Most kinetic runs were carried out with 1 mol of phenoxide/1 mol of halo sulfone, at 160.0° and at about 0.19 mol/l. concentration. The densities of the solvents were measured at 160°.

From time to time weighed samples were withdrawn (syringe) and titrated with 0.1 N HCl (pH meter) or added to glacial acetic acid for subsequent gas chromatography. An F & M 720 instrument using a 2 m × 0.25 in., 10% OV-1 on Chromosorb column was used.[30] Product studies showed that these reactions resulted in at least 96% product which was free of corresponding isomers.

The kinetic constants were evaluated by the differential method.[31]

The titrated base concentration ([OH] as moles of unreacted phenoxide per liter of solution) was first plotted against time t. Next the logarithms of the slopes ln d[OH]/dt of the smoothed decay curve, at various times t, were then plotted against ln [OH]. This results in a straight line of slope n and an intercept (at ln [OH] = 0) of ln k_2.[32] The empirical reaction order n can be evaluated with a fair degree of accuracy by this method. A plot of $[OH]^{1-k}$ against t (slope k_2) yields a more accurate method for determining the reaction rate constant.

When potassium phenoxide was used in sufficient excess (0.241 mol C_6H_5OH/l. solution) then a first-order plot was obtained (for p-$ClC_6H_4SO_2C_6H_5$ disappearance). The reaction rate constant for p-$FC_6H_4SO_2C_6H_5$ was determined by a competitive experiment with p-$ClC_6H_4SO_2C_6H_5$ using deficient potassium phenoxide (initial concentration of p-$FC_6H_4SO_2C_6H_5$, 0.30 mol/l., C_6H_5OK, 0.24 mol/l., p-$ClC_6H_4SO_2C_6H_5$, 0.0554 mol/l.).[33]

Registry No.—Diglyme, 11-96-3; triglyme, 112-49-2; tetraglyme, 143-24-8; polyglyme, 24991-55-7.

Acknowledgments.—Mr. John Puckhaber carried out a large part of this experimental study. The analyses were performed by the European Research Laboratories, Brussels, Belgium. Miss A. Hammerich carried out the nmr work.

(30) The rate constant calculated from the caustic titration data was the same as that from $ClC_6H_4SO_2C_6H_5$ disappearance, p-$C_6H_5OC_6H_4SO_2C_6H_5$ appearance (gas chromatography), or chloride ion appearance (Ag^+ titration). Ten to twelve samples per run were taken (~80% conversion).

(31) S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill, New York, N. Y., 1960, p 82.

(32) d[OH]/dt = k_2[OH]^k; therefore ln d[OH]/dt = ln k_2 + n ln [OH].

(33) The underlying assumption here is that the reaction order for the chlorophenyl sulfone is the same as that for the fluorophenyl sulfone.

The Reaction of Halothianaphthenes with Metal Amides[1]

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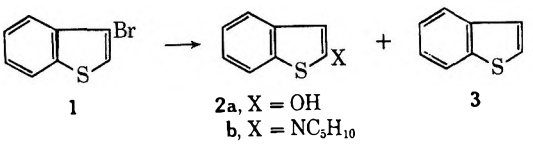
The 2-halothianaphthenes react with metal amides in liquid ammonia to give the 3 isomers, which are stable under the reaction conditions. No amines or polyhalo compounds were detected. 2,3-Dibromothianaphthene is converted to 3-bromothianaphthene either with or without added thianaphthene. The former instance suggests an intermolecular transhalogenation involving carbanions and the latter a dehalogenation *via* $BrNH_2$.

The reaction of haloaromatic compounds with metal amides in liquid ammonia as a potential route to aryne intermediates[2] has been investigated in our laboratories for a variety of thiophenes.[3-6] Although arynes are apparently not implicated in these reactions,[3,4] the related thianaphthene system is reported to react with potassium hydroxide[7] or piperidine[8] to give both dehalogenation and cine substitution[9] (eq 1), the latter process suggesting[11,12] the possible intermediacy of 2,3-dehydrothianaphthene. Since similar processes observed with thiophenes[3-6] and metal



1 2a, X = OH b, X = NC_5H_{10} 3 (1)

(1) Taken from the Master's Thesis of T. A. H., Texas Christian University, 1967.

(2) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Amer. Chem. Soc.*, **78**, 601 (1956).

(3) M. G. Reinecke and H. W. Adickes, *ibid.*, **90**, 511 (1968).

(4) M. G. Reinecke, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14** (2), C68 (1969).

(5) M. G. Reinecke, H. W. Adickes, and C. Pyun, *J. Org. Chem.*, **36**, 2690 (1971).

(6) M. G. Reinecke, H. W. Adickes, and C. Pyun, *ibid.*, **36**, 3820 (1971).

(7) G. Komppa and S. Weckman, *J. Prakt. Chem.*, **138**, 109 (1933).

(8) K. R. Brower and E. D. Amstutz, *J. Org. Chem.*, **19**, 411 (1954).

(9) The reaction of 3-bromothianaphthene and piperidine reported in ref 8 has now been reinvestigated in this laboratory[10] and found to undergo primarily normal and not cine substitution.

(10) W. B. Mohr, Master's Thesis, T. C. U., 1969; manuscript in preparation.

(11) H. J. den Hertog and H. C. van der Plas, *Advan. Heterocycl. Chem.*, **4**, 121 (1965).

(12) T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 543 (1965).

TABLE I

REACTIONS OF HALOTHIANAPHTHENES WITH METAL AMIDES

Reactants	Amide	Time	Products (yield, %)
3-Bromothianaphthene (1)	KNH_2	3 hr	1 (72)
3-Bromothianaphthene (1)	$NaNH_2$	3 hr	1 (65)
2-Bromothianaphthene (4)	KNH_2	15 min	1 (49)
2-Bromothianaphthene (4)	$NaNH_2$	15 min	1 (45)
2-Bromothianaphthene (4)	$NaNH_2$	2 min	1 (39), 4 (23)
3-Iodothianaphthene (7)	KNH_2	3 hr	7 (43)
3-Iodothianaphthene (7)	$NaNH_2$	3 hr	7 (52)
2-Iodothianaphthene (8)	KNH_2	15 min	*a*
2-Iodothianaphthene (8)	$NaNH_2$	15 min	7 (4)
2,3-Dibromothianaphthene (5)[b]	KNH_2	15 min	1 (68), 3 (4)
2-Aminothianaphthene (9) (5 mmol) + 4 (5 mmol)	$NaNH_2$	15 min	1 (47), 9[c] (10)
5 (10.0 mmol) + 3 (11.0 mmol)	$NaNH_2$	15 min	5 (0.3 mmol), 1 (14.1 mmol), 3 (1.8 mmol)
5 (9.4 mmol) + 3 (9.5 mmol)	$NaNH_2$	2 min	5 (1.6 mmol), 4 (0.8 mmol), 3 (1.8 mmol), 1 (9.8 mmol)

[a] No identifiable product. [b] <1% 1 as impurity. [c] Isolated as the acetamide, mp 218–222° (lit.[14] mp 222–226°), and identified by comparison of its ir spectra with that of an authentic sample.

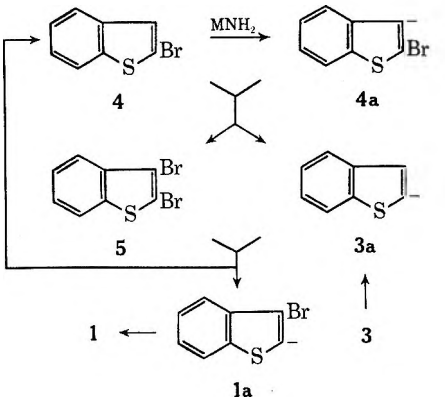
amides proceed *via* a transhalogenation mechanism,[3,4] it was of interest to investigate the nature and mechanism of the reactions of halothianaphthenes with metal amides in liquid ammonia.

In contrast to the previous observations (eq 1), however, 3-bromothianaphthene (**1**) is recovered in 75 and 72% yield when treated with 6 equiv of $NaNH_2$ or KNH_2, respectively, for 3 hr. No traces of either 2- or 3-aminothianaphthene could be detected, although they might have been formed and then decomposed[13,14] during the course of the reaction as indicated by the presence of tars. Under the same conditions 2-bromothianaphthene (**3**) is completely reacted in 15 min to give the 3 isomer **1** in 45 and 49% yield.[15] Once again no amines could be detected, even at reduced reaction times and in spite of the fact that added 2-aminothianaphthene was easily detected (10% recovery) in the reaction mixture. These results are paralleled with the 2- and 3-iodothianaphthenes, although lower yields and more tars are obtained (Table I).

The behavior of the halothianaphthenes toward metal amides is similar to that of the halothiophenes[3] in that the 2 isomers are more reactive than the 3 isomers and in that the former rearrange to the latter. The behavior diverges in that no amino compounds were detected from the thianaphthene systems and no dependence of product composition on concentration[4,16] or nature of the metal amide[4] was observed. Furthermore, it was not possible to detect any polybromothianaphthenes in the reaction mixtures, as would have been expected for a transhalogenation mechanism.[3,4]

Since the absence of polybromo compounds such as 2,3-dibromothianaphthene (**5**) may simply be due to their low concentration and/or high reactivity in the reaction media, a further test of the feasibility of this mechanism was desirable. Consequently, an equimolar mixture of the possible intermediates[3,4] **3** and **5** was subjected to the reaction conditions and 3-bromothianaphthene (**1**) was isolated in 67% yield (based on available thianaphthene rings). At reduced reaction times it was also possible to detect the presence of 2-bromothianaphthene (**4**). Both these results are consistent with an intermolecular transhalogenation mechanism (Scheme I) involving nucleophilic displacements

SCHEME I



by carbanions on halogen and leading eventually to the most stable carbanion **1a**. Analogies for this mechanism are found in the benzene,[17] thiophene,[3,4,18] isothiazole,[19] and imidazole[20] systems, and in the fact that 2,3-dibromothiophene (**5**) undergoes selective halogen–metal interchange at the 2 position with butyllithium.[21]

That another process besides this may be operative, however, is shown by the observation that **5** is debrominated to **1** in 68% yield in the *absence* of any thianaphthene (**3**). Except for a trace of thianaphthene (**3**) as *product* no other compounds could be detected.

In order to explain this result, some nucleophile (Nu) other than the two carbanions **3a** and **4a** in Scheme I

(13) P. Friedländer and A. Laske, *Justus Liebigs Ann. Chem.*, **351**, 412 (1907).

(14) G. W. Stacy, F. W. Villaescusa, and T. E. Wollner, *J. Org. Chem.*, **30**, 4074 (1965).

(15) On subsequent larger scale runs yields as high as 87% have been obtained.[6]

(16) H. W. Adickes, Ph.D. Dissertation, Texas Christian University, 1968.

(17) J. F. Bunnett, *Accounts Chem. Res.*, **5**, 139 (1972).

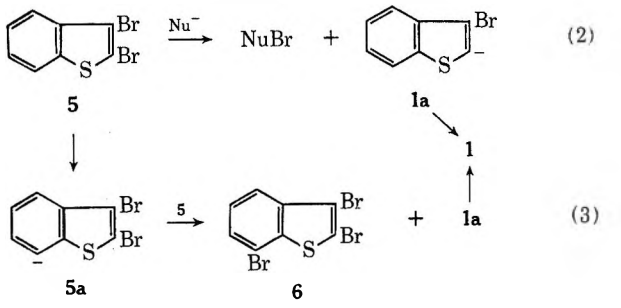
(18) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 75 (1963).

(19) D. A. de Bie and H. C. van der Plas, *Tetrahedron Lett.*, 3905 (1968).

(20) D. A. de Bie and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **88**, 1246 (1969).

(21) W. Reid and H. Bender, *Chem. Ber.*, **88**, 34 (1955).

must be able to carry out the displacement on bromine (eq 2). By analogy with the known reactivity of di-



benzothiophene toward strong bases,[22] one such possibility might be the 7 carbanion **5a**. Disproportionation (eq 3) would lead to the observed product, **1**, and the tribromo compound **6**, which could then undergo the base-catalyzed halogen dance[17] to give still other polybromo compounds and/or amination to give unstable bromo amines.

Another possibility is that the nucleophile in eq 2 is solvent derived (*i.e.*, NH_2^-), as in the case of the DMSO/alkoxide catalyzed debromination of related aryl bromides.[17,23] The expected product in this instance, $BrNH_2$, would react further with amide ion to give hydrazine (eq 4) which would have been unde-

$$NH_2Br + NH_2^- \longrightarrow H_2NNH_2 + Br^- \quad (4)$$

tected by the work-up procedure. In support of this suggestion 1,1′-bipiperidine can be isolated from the reactions of halothiophenes with metal piperidides and piperidine.[24]

The conclusion to be drawn from these results is that the rearrangement of halothianaphthenes with metal amides in liquid ammonia is a further example of the previously observed transhalogenation mechanisms[3,4,17-20] with the added feature that amide ions as well as carbanions may act to remove positive halogen atoms.[25]

(22) H. Gilman and R. L. Bebb, *J. Amer. Chem. Soc.*, **61**, 109 (1939).

(23) J. F. Bunnett and R. R. Victor, *ibid.*, **90**, 810 (1968); J. M. Barker, I. G. C. Coutts, and P. R. Huddleston, *Chem. Commun.*, 615 (1972).

(24) C. Pyun, unpublished results.

(25) A recent independent study[26] on thianaphthene and related heterocycles has led to an identical conclusion and also considered the possible role of $BrNH_2$ as a bromine-transfer agent in these systems.

Experimental Section

Melting points are uncorrected. Infrared spectra of liquids were taken as films on a Beckman IR-10 and solids as KBr discs on a Perkin-Elmer 237 spectrophotometer. Gas chromatographic analyses were carried out on an Aerograph Model A-700 instrument with a 30 ft × 0.25 in. column packed with 10% Carbowax 4000 on Gas-Chrom R.

Starting Materials.—3-Bromothianaphthene (**1**),[27] 2-bromothianaphthene (**4**),[28] 2- and 3-iodothianaphthene,[29] 2,3-dibromothianaphthene (**5**),[21] and 2-aminothianaphthene[14] were prepared by the cited literature procedures and their purity was checked by glc. The monohalothianaphthenes were furthermore purified by glc prior to use.

General Procedure for the Reaction of Halothianaphthenes with Metal Amides.—To a fresh preparation of 0.06 mol of metal amide[30] in 500 ml of liquid NH_3 in a 2-l. Morton flask equipped with a stirrer and a Dry Ice–acetone condenser was rapidly added 0.01 mol of the appropriate halothianaphthene or mixture of thianaphthenes (Table I). After the reaction had proceeded for the desired length of time at −33°, 0.065 mol of NH_4Cl was added, the NH_3 was evaporated under a stream of dry N_2, and a mixture of 100 ml of ether and 200 ml of H_2O was added. The separated water layer was extracted with three 100-ml portions of ether and the combined ether extracts were washed with four 50-ml portions of 1 *N* HCl. The combined acid washes were basified with 50% NaOH and extracted with four 50-ml portions of ether, and 40 ml of Ac_2O was added to the combined ether layers. After 12 hr at room temperature the mixture was taken to dryness on a rotary evaporator and the residue was examined for acetamidothianaphthenes.

The original ether extracts were dried ($CaCl_2$) and fractionally distilled. The products in the distillate were identified by comparing their ir spectra after collection from the glc with those of authentic samples. Quantitative analysis was based on the relative areas of each component in the glc trace taking into account the molar response factor for each compound.

The results of these reactions are summarized in Table I.

Registry No.—**1**, 7342-82-7; **3**, 95-15-8; **4**, 5394-13-8; **5**, 6287-82-7; **7**, 36748-88-6; **8**, 36748-89-7; **9**, 4521-30-6; KNH_2, 17242-52-3; $NaNH_2$, 7782-92-5.

Acknowledgment.—This research was supported by the Robert A. Welch Foundation and the TCU Research Foundation.

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Reductive Dehalogenations by Alkali Metals and Sodium Naphthalenide. Capture of Solvent-Derived Intermediates

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o-Chlorobenzylideneaniline (1) was treated with sodium and lithium in diethyl ether (DEE) and tetrahydrofuran (THF) and with sodium naphthalenide in THF. Dehalogenation occurred, and the intermediate solvent-derived species were captured by the aldimine group of 1 and its chlorine-free analog *N*-benzylideneaniline. The reaction products were isolated, their structures were established, and the reaction was interpreted as proceeding through carbanions formed by removal of the α hydrogen from the ether solvents. Results of experiments performed in mixed solvents support this interpretation.

Recently, the dehalogenation of alkyl and aryl halides has been the subject of considerable discussion.[1-6] Two mechanisms[7] have been advanced for this reaction, both requiring the solvent to supply the proton which replaces the lost halogen. The subsequent solvent-derived species are highly reactive, and their existence has been inferred[8] largely on the basis of their decomposition products.

Our interest in the dehalogenation reaction stems from the possibility of trapping these solvent-derived intermediates before they decompose. If successful, such a reaction would provide direct chemical evidence for the generation of these intermediates and afford a possible access to a variety of reactive intermediates which are not easily accessible[9] even under ideal circumstances.

Drawing upon our earlier study[10] of the reductive dimerization of substituted aryl imines, *N*-(*o*-chlorobenzylidene)aniline (1) was chosen as the aryl halide to be examined. To keep the reaction as simple as possible, the radical anion was generated *in situ* from the imine and sodium metal. Thus 1 not only served as the aryl halide undergoing dehalogenation but also provided the functional group to capture the reactive intermediates arising from the solvent.

Results

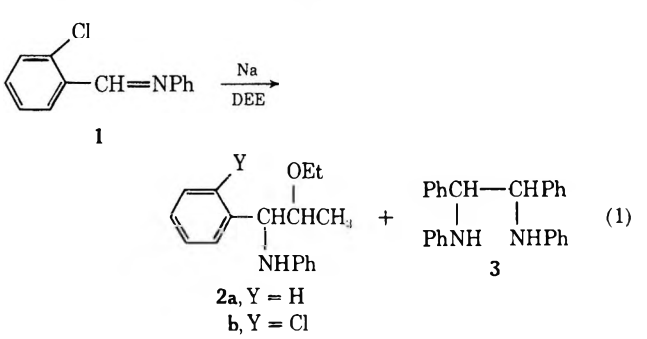
In diethyl ether (DEE), *N*-(*o*-chlorobenzylidene)-aniline (1) reacted slowly with sodium. Titration of aliquot samples of the reaction mixture showed an apparent equilibrium uptake of 1 g-atom of sodium/mol of 1. The nmr spectrum of the crude reaction product indicated clearly the presence of chemically bound solvent in some component of the reaction mixture.

Fortunately, one component crystallized readily from ether, and chemical analyses and mass spectra established the molecular formula as $C_{17}H_{20}NCl$. The presence of an amino group was established by the ir spectrum while the nmr spectrum could only be interpreted as due to *N*-phenyl-1-(*o*-chlorophenyl)-2-ethoxypropylamine (2b). Thus the methyl region consisted of a superimposed doublet and triplet indicating that reaction had occurred at the α position of DEE, while the benzylic proton was a doublet showing that this was the point of attachment of the moiety from DEE. In addition, the mass spectrum showed the principal fragmentation to be the loss of this DEE-derived moiety to give the Cl-isotopic fragment pair *m/e* 218 and 216.

Gas chromatography disclosed the presence of four volatile compounds[11] in the crude reaction mixture with one having a retention time identical with that of the isolated diastereomer of 2b.

On a preparative scale, only the third and fourth peaks were separately isolated, and these proved to be the erythro and threo isomers of 2b. The first and second peaks were collected together, and spectral and analytical data established this as a mixture of the *erythro-* and *threo-N*,1-diphenyl-2-ethoxy-1-propylamines, 2a.

Comparing the nmr spectra of these isolated materials with that of the crude reaction mixture disclosed that the benzylic proton region (δ 4–5 ppm) contained two sharp singlets in addition to the four doublets corresponding to the benzylic protons of erythro and threo 2a and 2b. These singlets had the same chemical shifts[12] as the *N*,*N*′,1,2-tetraphenylethylenediamines (3). The *meso*-3 was isolated from the reaction mixture by means of its DMF complex.[13] Thus the overall



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(10) J. G. Smith and I. Ho, *J. Org. Chem.*, **37**, 653 (1972).

(11) A fifth, *N*-benzylideneaniline, was observed in reactions which were incomplete.

(12) J. G. Smith and C. D. Veach, *Can. J. Chem.*, **44**, 2497 (1966).

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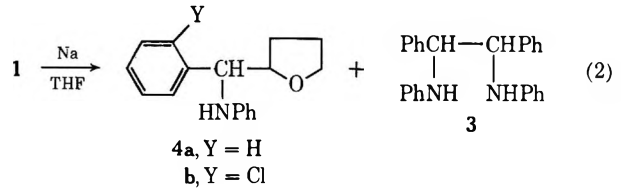
reaction is that shown in eq 1 and integration of the nmr spectrum in the benzylic proton region provided an analysis of the reaction mixture. That this analysis accounted for essentially all the reaction products was supported by the correspondence shown between the ionic chloride formed during the reaction and that calculated from the measured product composition.

In the more basic solvent tetrahydrofuran (THF), the same type of product mixture was formed (see eq 2). However, as expected[10,12,14] the dimer **3** was



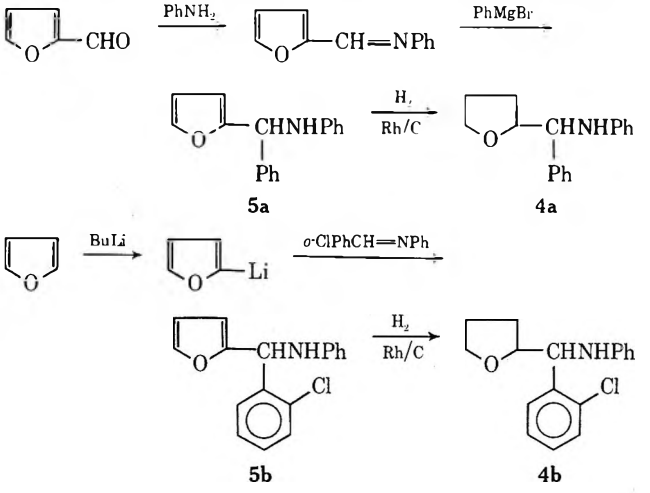
4a, Y = H
b, Y = Cl

chiefly the racemic diastereomer. In this reaction, the products **4** were isolated by column chromatography and had sufficiently complex nmr spectra that their structures were verified by synthesis.

The synthetic routes are shown in Scheme I. Different routes were required for **4a** and **4b** since the

SCHEME I

PREPARATION OF *N*-(ARYLTETRAHYDROFURYLMETHYL)ANILINE

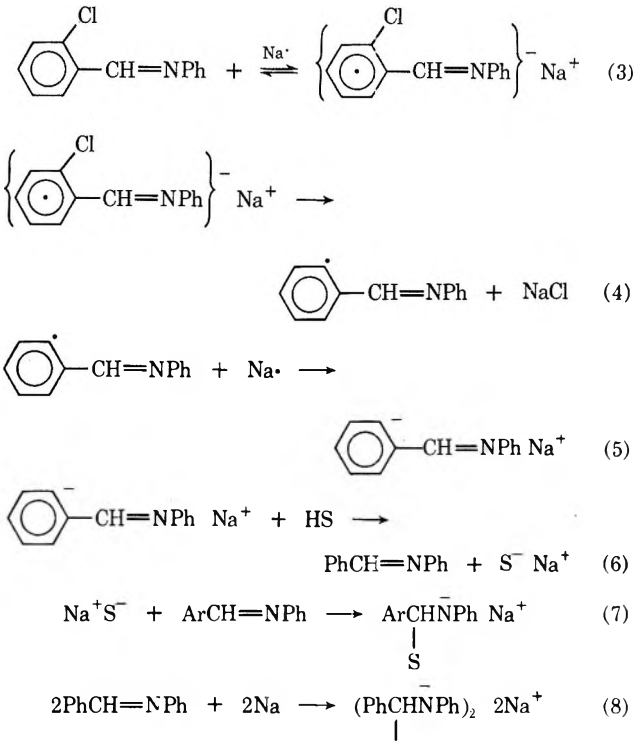


reaction between the Grignard reagent and *N*-(furfurylidene)aniline used in the preparation of **4a** failed when adapted to the preparation of **4b**.

To confirm the original supposition that the reaction between **1** and alkali metals corresponded to that between **1** and the radical anion of naphthalene, the latter reaction was also examined. In THF, the same spectrum of products was produced but the reaction proceeded rapidly even at −60°. Undoubtedly, the reaction was greatly facilitated[15] by the much higher concentration of the reducing agent (sodium naphthalenide) in solution.

Discussion

Sargent[2] has cogently summarized the evidence supporting the suggested mechanisms for the dehalogenation of aryl halides and radical anions. Adapting his conclusions to the present reaction leads to the following sequence. The initially formed radical anion (reaction 3) eliminates a halide ion in the rate-limiting[16a] reaction



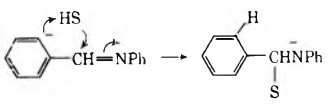
4. The aryl radical so formed is reduced (reaction 5) to an aryl anion by the alkali metal as shown or equally likely by the radical anion formed in reaction 3. Abstraction of an α hydrogen from the ether solvent (HS) generates the chlorine-free Schiff base and the solvent derived anion in reaction 6. This last anion then adds to either of the two Schiff bases present in solution (reaction 7) while the *N*-benzylideneaniline also undergoes a competitive dimerization[10,12,14,16b] (reaction 8).

The extreme rapidity of electron-transfer reactions[17] dictates the formation of anionic intermediates. The fact that the nucleophilic addition reaction 7 successfully competes with reaction 8, also an electron-transfer reaction, is best explained by noting that the solvent anion is formed in the immediate vicinity of the substrate with which it reacts. It is this spatial proximity which permits addition of the solvent anion to compete. Even so, the addition reaction can be completely surpressed by using an excess of the more efficient reducing reagent, sodium naphthalenide (3 mol/mol of **1**). Reaction 8 then becomes dominant over 7 and the reaction products consist only of dimeric dianions.[18]

(14) J. J. Eisch, D. D. Kaska, and C. J. Peterson, *J. Org. Chem.*, **31**, 453 (1966).

(15) J. J. Eisch, *ibid.*, **28**, 707 (1963).

(16) (a) The formation of products from both **1** and *N*-benzylideneaniline is the basis for this. (b) A referee has suggested the attractive possibility that reactions 6 and 7 may be a one-step addition involving a cyclic transition state



This would also explain the successful competition of the addition reaction with reaction 8.

(17) (a) L. M. Dorfman, *Accounts Chem. Res.*, **3**, 224 (1970); (b) J. F. Garst, P. W. Ayers, and R. C. Lamb, *J. Amer. Chem. Soc.*, **88**, 4260 (1966).

(18) In a control experiment, we have qualitatively observed complete dimerization of *N*-benzylideneaniline by sodium naphthalenide in 2 min at −60°. Dimerization has also been effected[14] by the radical anion of diphenyl.

Related reaction conditions have been examined briefly. In DEE, a slower reaction occurred with lithium metal than with sodium to produce **2a**, **2b**, and **3**. In addition, the reaction product always contained unconsumed **1** and also its dimeric reduction product, *N*,*N*′-diphenyl-1,2-bis(*o*-chlorophenyl)ethylenediamine. Thus dimerization of the radical anion of **1** must occur at a rate competitive with its dehalogenation.

With lithium metal and THF, **1** was converted completely into the dimeric diamines **3**; no other products were detected. At the moment, the simplest explanation appears to be that the equilibrium between lithium and **1** (in THF but not in DEE) is considerably more favorable to the radical anion than the corresponding case with sodium. The resulting high concentration of radical anion coupled with the slower rate of addition of the tetrahydrofuryllithium (relative to the sodium analog) permits dimerization of the *N*-benzylideneaniline[10,12,14] to occur as the only detected reaction.[19]

The behavior of the positional isomers of **1** towards alkali metals has also been examined. As already reported,[10] *m*-chlorobenzylideneaniline undergoes normal dimerization. However, the *p*-chloro analog with sodium in THF produced a series of products similar to those from **1** but showed no reaction towards sodium in DEE. The more facile loss of the *o*- and *p*-chloro substituents (relative to the *m*-chloro) undoubtedly reflects the higher charge density found at these positions in the intermediate radical anion. The more rapid elimination of the *o*-chloro substituent relative to the para has also been noted in electrochemical reductions[20] and may reflect a steric effect from the nitrogen anionic center of the intermediate radical anion. This point is being examined further.

In an alternative mechanism Cheng[3] has suggested that the aryl radical produced in reaction 4 could remove the hydrogen atom from the solvent. The resulting solvent radical would be expected to be reduced to the solvent anion. An attempt was made to assess this possibility by conducting the reaction in mixtures of THF and DEE. Should hydrogen removal be effected by radicals then the ratio of solvent containing products would reflect the relative reactivity of the two ethers towards radicals.

In contrast, should anions effect proton removal as shown in eq 6, then the more basic solvent, which would be concentrated near the reaction site by its coordination with the alkali metal counterion, would appear incorporated into the reaction products by a significantly higher factor.

The relative amounts of solvent incorporation into products was assessed by the nmr spectrum of the crude reaction mixture. These results appear in Table II and show that THF reacted four to five times more readily than did DEE. This preferential reaction of THF is more suggestive of proton removal by carbanions[21a,b] than by radicals.[21c]

(19) The possibility that dimerization of the aryl anion formed in reaction 5 might occur with lithium was considered. However, quenching the reaction mixture with D_2O failed to generate ring-deuterated dimers **3**.

(20) (a) T. Kitagama, T. P. Layloff, and R. N. Adams, *Anal. Chem.*, **35**, 1086 (1963); (b) W. C. Danen, T. T. Kensler, J. G. Lawless, M. F. Marcus, and M. D. Hawley, *J. Phys. Chem.*, **73**, 4389 (1969).

(21) (a) H. Gilman, A. H. Haubein, and H. Hartzfeld, *J. Org. Chem.*, **19**, 1034 (1954); (b) H. Gilman and H. A. McNinch, *ibid.*, **27**, 1889 (1962); (c) C. Walling and M. J. Mintz, *J. Amer. Chem. Soc.*, **89**, 1515 (1967).

Experimental Section

Melting points are uncorrected and were determined with a Mel-Temp melting point apparatus. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer and nmr spectra on a Varian T-60 spectrometer. Chemical shifts are in ppm downfield from internal TMS. Analytical and preparative vapor phase chromatography (vpc) were performed on a Varian-Aerograph 1520 instrument. Mass spectra were determined on a Perkin-Elmer RMU-6E single focusing mass spectrometer operated at 70 eV. Silica gel (0.05–0.2 mm) from E. Merck AG was used for column chromatography and Eastman Chromagram 6060 (silica gel) sheets were used for thin layer chromatography (tlc). Analyses were determined by M-H-W laboratories, Garden City, Mich.

All operations with the alkali metal compounds were performed under nitrogen which had been scrubbed by a refluxing solution of benzophenone ketyl in xylene. The solvents (THF and DEE) were purified by distillation from $LiAlH_4$ and stored over and freshly distilled from $LiAlH_4$ immediately before use.

General Procedure.—The preparation and handling of these alkali metal compounds has been described[10] elsewhere. The *N*-(*o*-chlorobenzylidene)aniline (**1**) (2.16 g, 0.01 mol) was dissolved in 75 ± 5 g of solvent and 0.5 g (0.02 g-atom) of freshly cut sodium added. The mixture was shaken 24 hr[22] during which time a precipitate formed and the solution became dark brown. The mixture was drained from the excess metal, cooled to −60°, and quenched by injecting 2.0 ml of methanol.

Product Analysis.—The quenched reaction mixture was diluted with 50 ml of water, and the organic products were isolated by ether extraction. The water layer and washings were diluted to a constant volume, and the ionic chloride was determined gravimetrically (AgCl).

The ether extracts were analyzed by vpc (flame ionization detectors) using a 5 ft × 1/8 in. column packed with 10% Carbowax 20M on 100/120 mesh Chromosorb W at 195° with a He flow rate of 30–40 ml/min. Peaks were identified by "spiking" with authentic samples or by isolation and characterization.

Evaporation of the ether extracts followed by a 24-hr pumping provided the solvent-free reaction mixture. This was analyzed by nmr spectroscopy[23] using the benzylic proton region. These various data are included in Table I for an experiment which titrated as 0.98 g-atom of sodium/mol of initial **1** and showed 59% of the initial chlorine as ionic chloride. Reproducibility of these figures from run to run was ±10%.

In the case of the reactions performed in THF, the benzylic proton region and the α-proton region of the tetrahydrofuryl group overlapped, and an independent nmr analysis was not attempted. By using the vpc analyses and the nmr integrations, an estimate of the content of dimer **3** could be made (see Table I).

Isolation of Reaction Products from DEE Experiments.—Separation of the monomeric products in the reaction mixture was achieved by preparative vpc using a 10 ft × 3/8 in. column packed with 10% Carbowax 20M on 60/80 mesh Chromosorb W operated at 185° (thermal conductivity detector at 220°) with a helium flow rate of 60 ml/min.

The first peak eluting was a nonresolvable mixture of *erythro*- and *threo*-*N*,1-diphenyl-2-ethoxypropylamines (**2a**): ir (max) (KBr) 3440, 2980, 1600, 1500, 1450, 1320, 1090, 1080, 750, 690 cm^{-1}; nmr ($CDCl_3$) δ 0.9–1.3 (m, 6, CH_3), 3.1–3.9 (m, 3, $-CHOCH_2-$), 4.15 (d, 0.67, J = 6 Hz) and 4.47 (d, 0.33, J = 4 Hz) (benzylic H's), 6.4–7.6 (m, 10, aromatic H); *m/e* (rel intensity) 255 (11, M^+), 210 (2, $M^+ - OEt$), 183 (42), 182 (100, $M^+ - C_4H_9O$), 180 (15), 104 (41), 77 (50).

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.95; H, 8.29; N, 5.49. Found: C, 79.85; H, 8.35; N, 5.54.

The second peak, one of the diastereomeric *N*-phenyl-1-(*o*-chlorophenyl)-2-ethoxypropylamines, **2b**, proved to be an oil: ir (max) 3440, 2980, 1600, 1500, 1440, 1310, 1100 (broad), 750, 700 cm^{-1}; nmr ($CDCl_3$) δ 1.02 (t, 3, J = 6 Hz, $-CH_2CH_3$), 1.32 (d, 3, J = 6 Hz, $-CHCH_3$), 2.9–4.0 (m, 3, $-CHOCH_2-$), 4.78 (d, 1, J = 3 Hz, benzylic H), 6.3–7.7 (m, 9, aromatic H); *m/e* (rel intensity) 291 (2, M^+), 289 (5, M^+), 218 (36, $M^+ -$

(22) Preliminary experiments showed that at least a 12-hr reaction time was necessary to obtain an "equilibrium uptake" of 1 g-atom of Na/mol of **1** (determined as NaOH).

(23) We are grateful to Dr. L. W. Reeves of this department for providing the well-resolved spectra (determined on an HA-100 spectrometer) which were used in this determination.

TABLE I
COMPOSITION OF THE REACTION PRODUCTS

	S = MeCHOEt			S = 2-tetrahydrofuryl				
	Na		Li	Na		NaNp		Li
	Vpc[a]	Nmr[b]	Vpc[a,c]	Vpc[a]	Vpc + nmr[d]	Vpc[a]	Vpc + nmr	Nmr
PhCH=NPh	2		13	14	11	8	5	...
PhCHNHPh S	24	9 12 (30)[e]	Trace	25	19	41	27	...
o-ClC$_6$H$_4$CHNHPh S	25	17 (24)[e]	16	38	29	20	13	...
	49	33 (46)[e]	22	22	17	31	21	...
(PhCHNHPh)$_2$ racemic		16			24		34	41
meso		12						59

[a] Normalized peak areas. [b] The nmr analysis indicates a 61% conversion of the chlorine into ionic chloride. [c] 49% of *o*-chlorobenzylideneaniline was also present. Nmr[10] showed that the crude reaction product contained 16% of *N*,*N*-diphenyl-1,2-bis(*o*-chlorophenyl)-ethylenediamine. [d] This combined analysis indicates a 63% conversion of chlorine into ionic chloride (64% was measured). [e] Per cent of total volatile products—for comparison with vpc analysis.

C$_4$H$_9$O), 217 (16), 216 (100, M$^+$ − C$_4$H$_9$O), 181 (12), 180 (15), 104 (13), 77 (21).

Anal. Calcd for C$_{17}$H$_{20}$NOCl: C, 70.46; H, 6.96; N, 4.83; Cl, 12.23. Found: C, 70.41; H, 6.71; N, 4.66; Cl, 12.00.

The third peak, the second diastereomer of **2b**, was a solid and was recrystallized from diethyl ether: mp 121–123°; ir (max) (KBr) 3400, 2990, 1600, 1510, 1380, 1310, 1250, 1100, 760, 740, 690 cm^{-1}; nmr (CDCl$_3$) δ 1.03 (d, J = 7 Hz, –CHCH$_3$) overlapping 1.22 (t, J = 7 Hz, –CH$_2$CH$_3$) (total 6 H), 3.62 (q, 2, J = 7 Hz, –CH$_2$CH$_3$), 3.8–4.2 (m, 1, –CHCH$_3$), 5.05 (d, 1, J = 4 Hz, benzylic H), 6.4–7.7 (m, 9, aromatic H); *m/e* (rel intensity) 291 (2, M$^+$), 289 (7, M$^+$), 218 (70, M$^+$ − C$_4$H$_9$O), 217 (43), 216 (100, M$^+$ − C$_4$H$_9$O), 180 (10), 104 (22), 77 (39).

Anal. Found: C, 70.50; H, 7.21; N, 4.91; Cl, 12.05.

This last compound was directly isolated by treating the crude reaction product with a small amount of ether. The crystalline material which separated was recrystallized and proved identical in all aspects with that isolated by preparative vpc.

Treatment of the crude reaction product with warm *N*,*N*-dimethylformamide produced, on standing, the crystalline DMF complex[13] of *meso*-**3**. Recrystallization from ethyl acetate–ethanol regenerated *meso*-**3** which was identified by mixture melting point and spectral comparison with authentic material.

Isolation of Reaction Products from THF Experiments.—The reaction products (7.3 g) from 0.03 mol of **1** were chromatographed on 120 g of silica gel using benzene as an eluting agent. Four major fractions were collected. The first, 2.3 g (42%), was *rac*-**3**, mp and mmp with an authentic sample 152–154°.

The second fraction was distilled to give 0.93 g (11%) of a pale yellow viscous oil, bp 167–170° (0.35 mm). Vpc retention times showed it to be a mixture of *erythro*- and *threo*-**4b**. The ir was identical with the authentic reference mixture, and the nmr differed only in the areas of the two benzylic proton doublets. The isolated sample contained 67% of the major isomer while the synthetic sample contained 80%.

The third fraction was distilled, 1.9 g (25%) of a pale yellow oil, bp 155–156° (0.25 mm). This proved to be a mixture of the diastereomeric *N*-(phenyltetrahydrofurylmethyl)anilines, **4a**, whose ir spectrum was identical with that of the authentic mixture of diastereomeric **4a**. The benzylic proton region of the nmr spectrum showed a larger amount of the crystalline diastereomeric **4a** to be present in this isolated mixture than in the synthesized product, but in other respects the nmr spectrum was identical with that of the reference mixture.

The fourth fraction crystallized, and recrystallization from methanol gave 1.2 g (16%), mp 48–50°, undepressed on mixing with the synthetic crystalline **4a** and having identical ir and nmr spectra.

Reaction in THF–DEE Mixed Solvents.—The procedure was identical with that described earlier, the solvent composition being determined by weighing the reaction vessel after each solvent was distilled in. The isolated mixture of reaction products was pumped under a vacuum of at least 0.1 mm for 24 hr and analyzed by nmr spectroscopy. The ratio of the two solvents incorporated into reaction products was determined by the integrated peak areas of the methyl protons of the DEE-containing products (δ 0.8–1.4) and of the β-tetrahydrofuryl protons of the THF-containing products (δ 1.5–2.0). An additional 24-hr pumping and a second nmr analysis established that the solvent had been completely removed from the reaction products. Table II summarizes these results.

TABLE II
ANALYSIS OF THE MIXED-SOLVENT REACTIONS

Mole ratio, DEE/THF	Mole ratio, 2/4	Relative reactivity, THF/DEE
12.3	2.41	5.1
5.2	1.07	4.9
2.7	0.73	3.7

Reaction of 1 with Sodium Naphthalenide.—Sodium naphthalenide (0.01 or 0.015 mol) was prepared by shaking a mixture of excess sodium, naphthalene, and THF in a Schlenk tube for 24 hr. After draining from excess metal, the solution was cooled to −60° and **1** (0.005 mol) dissolved in THF was injected through a septum into the stirred solution. After 24 hr at room temperature, the mixture was diluted with water and the reactions products isolated by ether extraction. Analyses were conducted as described with the results shown in Table I.

When 0.010 mol of sodium naphthalenide was treated with 0.010 mol of *N*-benzylideneaniline the reaction product consisted entirely of *meso*- and *rac*-**3**. When the quenching procedure described above was used, the product contained 11% *meso*-**3**. When quenching was performed at −60°, either 2 min or 2 hr after mixing, the product contained 27% *meso*-**3**.

Reference Compounds.—*N*-(**Phenylfurylmethyl**)**aniline** (**5a**) was prepared from 17.1 g (0.1 mol) of *N*-furfuralaniline[24] and 0.15 mol of phenylmagnesium bromide in diethyl ether. Distillation of the crude product provided 20.0 g (80% yield) of **5a**, bp 154–155° (0.2 mm), which crystallized on standing. Recrystallization from ethanol provided an analytical sample: mp 53–55°; ir (max) 3440, 1600, 1500, 1320, 1020, 750, 700 cm^{-1}; nmr (CDCl$_3$) δ 4.2 (broad s, 1, NH exchanges with D$_2$O), 5.6 (s, 1, benzylic H), 6.0–7.5 (m, 13, aromatic and furyl H's).

Anal. Calcd for C$_{17}$H$_{15}$NO: C, 81.91; H, 6.07; N, 5.62. Found: C, 81.74; H, 6.12; N, 5.41.

N-(**Phenyltetrahydrofurylmethyl**)**aniline** (**4a**) was prepared by hydrogenation of **5a** (5.0 g, 0.02 mol) at 22° in ethanol (120 ml) using 5% rhodium-on-carbon (0.5 g) catalyst[25] and 50 psi of hydrogen pressure for 24 hr. Chromatography of the crude product on 80 g of silica gel with benzene as eluent partially separated the two diastereomers of **4a**. The first fraction eluting was distilled: 2.3 g; bp 155–157° (0.2 mm); ir (max) 3420, 3000, 2900, 1600, 1500, 1320, 1070, 750, 700 cm^{-1}; nmr (CDCl$_3$) δ 1.6–2.1 (m, 4, tetrahydrofuryl β-H), 3.6–4.5 (m, 4, tetrahydrofuryl α-H and benzylic H), 6.4–7.6 (m, 10, aromatic H); *m/e* (rel intensity) 253 (8, M$^+$), 183 (22), 182 (100, M$^+$ − C$_4$H$_7$O), 104 (12), 77 (19).

Anal. Calcd for C$_{17}$H$_{19}$NO: C, 80.61; H, 7.56; N, 5.53. Found: C, 80.41; H, 7.58; N, 5.52.

The second fraction which eluted was a solid and recrystallized gave 1.22 g: mp 48.5–49.5°, ir (max) (KBr) 3410, 1600, 1500, 1310, 1060, 1040, 730, 685, 675 cm^{-1}; nmr (CDCl$_3$) δ 1.4–2.0 (m, 4,

(24) T. F. West, *J. Soc. Chem. Ind., London*, **61**, 158 (1942).

(25) Hydrogenation with 5% Pd on carbon provided complex reaction mixtures due, in part, to hydrogenolysis.

tetrahydrofuryl β-H), 3.6–4.5 (m, 4, tetrahydrofuryl α-H and benzyl H), 6.4–7.5 (m, 10, aromatic H's); *m/e* (rel intensity) 253 (8, M^+), 183 (31), 182 (100, $M^+ - C_4H_7O$), 104 (21), 77 (33).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.61; H, 7.56; N, 5.53. Found: C, 80.60; H, 7.36; N, 5.50.

The spectral properties of these two diastereomers were very similar. The most obvious difference was in the chemical shift of the benzylic proton doublet. In the solid isomer this was δ 4.41 (J = 5 Hz) while in the "liquid isomer" this was δ 4.20 (J = 5 Hz). This latter material was a mixture of the two isomers as indicated by the nmr spectra (30% solid isomer).

N-(*o*-Chlorophenylfurylmethyl)aniline (**5b**) was prepared by the addition of 2-furyllithium[26] (0.15 mol) to *N*-(*o*-chlorobenzylideneaniline (21.6 g, 0.1 mol) in *n*-hexane (30 ml). The crude product was distilled to give 26.1 g of viscous oil, bp 155–156° (0.2 mm). The nmr spectrum of this product showed the presence of 10% of the starting material. While the bulk of this product was used in the next step, an analytical sample was isolated by preparative vpc using a 5 ft × 1/4 in. column containing 10% Carbowax 20M on Chromosorb W and operated at 195° with a He flow rate of 50 ml/min: ir (max) 3420, 3060, 1600, 1500, 1320, 1250, 1010, 745, 690 cm^{-1}; nmr ($CDCl_3$) δ 6.04 (s, benzylic H), 6.1–7.6 (m, aromatic and furyl H's).

Anal. Calcd for $C_{17}H_{14}NOCl$: C, 71.95; H, 4.97; N, 4.94; Cl, 12.49. Found: C, 71.97; H, 4.91; N, 4.97; Cl, 12.71.

(26) W. E. Truce and E. Wellisch, *J. Amer. Chem. Soc.*, **74**, 5177 (1952). We were unable to effect a successful reaction between *o*-chlorophenylmagnesium bromide and *N*-furfurylideneaniline

N-(*o*-Chlorophenyltetrahydrofurylmethyl)aniline (**4b**) was obtained by hydrogenation of 9.5 g (0.034 mol) of **5b** with 1.0 g of 5% rhodium on carbon in 150 ml of ethanol at 50 psi of hydrogen and 50° for 24 hr. The crude product was chromatographed on 80 g of silica gel with benzene as eluent. The first fraction (5.8 g) was **5b** while the second fraction was distilled to give 2.8 g, bp 175–176° (0.5 mm) of the diastereomeric mixture of **4b**: ir (max) 3400, 1600, 1500, 1310, 1055, 1025, 740, 680 cm^{-1}; nmr ($CDCl_3$) δ 1.5–2.1 (m, 4, β-tetrahydrofuryl H), 3.6–4.5 (m, α-tetrahydrofuryl H), 4.92 (d, 0.2, J = 5 Hz) and 5.07 (d, 0.8, J = 4 Hz) (benzylic H of the two isomers), 6.4–7.6 (m, 9, aromatic H); *m/e* (rel intensity) 289 (2, M^+), 287 (6, M^+), 218 (41, $M^+ - C_4H_7O$), 217 (19), 216 (100, $M^+ - C_4H_7O$), 180 (15), 104 (16), 77 (32), 71 (16).

Anal. Calcd for $C_{17}H_{18}NOCl$: C, 71.11; H, 6.32; N, 4.88; Cl, 12.35. Found: C, 71.15; H, 6.43; N, 4.80; Cl, 12.54.

Registry No.—**1**, 5877-49-6; *erythro*-**2a**, 36736-41-1; *threo*-**2a**, 36736-42-2; *erythro*-**2b**, 36736-43-3; *threo*-**2b**, 36736-44-4; (±)-**3**, 5297-98-3; *meso*-**3**, 6135-06-4, *erythro*-**4a**, 36736-45-5; *threo*-**4a**, 36736-46-6; *erythro*-**4b**, 36736-47-7; *threo*-**4b**, 36736-48-8; **5a**, 36749-19-6; **5b**, 36749-20-9; sodium, 7440-23-5; lithium, 7439-93-2; sodium naphthalenide, 3481-12-7.

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The Diels–Alder Reaction of Polymethylnaphthalenes with Maleic Anhydride

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The effect of polymethyl substitution has been studied in the Diels–Alder reaction with maleic anhydride and eight polymethylnaphthalenes: 1,4-dimethyl- (**1**), 2,3-dimethyl- (**2**), 1,2,3,4-tetramethyl- (**3**), 1,4,5,8-tetramethyl- (**4**), 1,4,6,7-tetramethyl- (**5**), 1,2,3,4,5,8-hexamethyl- (**6**), 1,2,3,4,6,7-hexamethyl- (**7**), and octamethylnaphthalene (**8**). The reaction rates (in chloroform) were in the order of **6** (rel rate 40) > **8** (10) > **7** (3) > **3** (1) > **4** (0.4) > **5** > **2** > **1**. Nmr analysis of the products showed that **1** and **7** gave two structural isomers (1,4 and 5,8 adducts), **2**, **3**, **4**, and **6** gave only 1,4 adducts, and **5** gave the 5,8 adduct exclusively. The endo/exo isomer ratio of the adducts indicated a preferred configuration of the endo isomer (anhydride ring, anti to the benzene nucleus) for the naphthalenes bearing methyl groups on the reacting position while the exo isomer was preferred for the naphthalenes bearing no methyl group on that position. Examination of the reversibility of the reaction showed that the endo isomer is kinetically preferred while the exo isomer is thermodynamically more stable. A structural preference rule is discussed.

The Diels–Alder reaction of naphthalene with benzynes, acetylene dicarboxylates, and maleic anhydride exhibits only limited yields.[1] However, naphthalenes with alkyl substituents show enhanced reactivity towards dienophiles.[2] When methyl groups are in peri positions or even vicinal to each other, they may be shifted from their normal positions to out-of-plane positions and may complicate the diene system. This assumption is supported by X-ray analysis of octamethylnaphthalene by Donaldson and Robertson,[3] who mention that the methyl groups in this molecule are significantly displaced from the plane of the ring, but they gave little comment concerning the distortion of the naphthalene nucleus. Similarly, Gafner and Herbstein[4] have suggested a double-bladed propeller structure for octachloronaphthalenes. The possibility exists that the naphthalene nucleus itself loses its coplanarity, and the diminution of a planar geometry, if any, will change the electronic structure of the nucleus and may be reflected in the dienoid character of the ring halves.

In relation to the chemistry of octamethylnaphthalene,[1,5] we examined the Diels–Alder reaction of maleic anhydride with symmetrically substituted polymethylnaphthalenes with the purpose of obtaining further information on the effect of multialkyl substitution, especially in peri positions. In the present study it has been found that the reacting position in the naphthalene nucleus is influenced by varying positions of methyl substitution regardless of the number of methyl groups on the reacting ring, and that the endo/exo isomer distribution in the products depends on the position of methyl substituents as well. The peri interaction was also evidenced not only by the rate enhancement but in the high yields of thermally stable adducts for highly substituted polymethylnaphthalenes.

(1) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. III, Part B, Elsevier, Amsterdam, 1956, p 1361.

(2) M. C. Kloetzel, R. P. Dayton, and H. L. Herzog, *J. Amer. Chem. Soc.*, **72**, 273 (1950); M. C. Kloetzel and H. L. Herzog, *ibid.*, **72**, 1991 (1950).

(3) D. M. Donaldson and J. M. Robertson, *J. Chem. Soc.*, 17 (1953).

(4) G. Gafner and F. H. Herbstein, *Nature (London)*, **200**, 130 (1963).

(5) H. Hart and A. Oku, *J. Chem. Soc. D*, 254 (1972).

TABLE I
NMR CHEMICAL SHIFTS OF POLYMETHYLNAPHTHALENES[c]

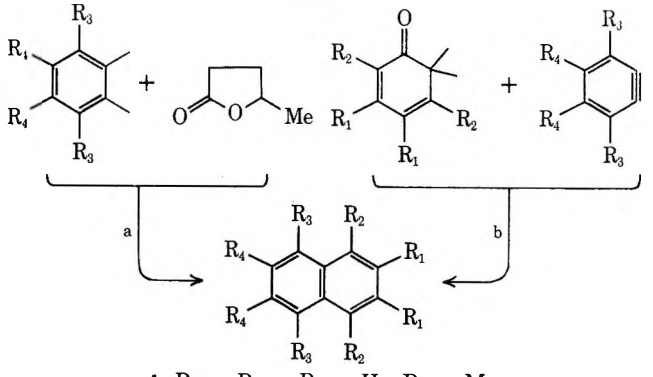
Polymethyl-naphthalene	Ring proton[a] 2,3	1,4	5,8	6,7	Methyl proton[a] 2,3	1,4	5,8	6,7
1	2.80		2.02[b]	2.50[b]		7.33		
2		2.44	2.31[b]	2.66[b]	7.60			
3			2.00[b]	2.60[b]	7.58	7.38		
4	2.82			2.82		7.19	7.19	
5	2.82		2.20			7.42		7.59
6				2.85	7.66	7.42	7.32	
7			2.16		7.63	7.43		7.58
8					7.68	7.51	7.51	7.68

[a] Singlet, unless otherwise mentioned. [b] Quartet: $J_1 = 7$, $J_2 = 3$ Hz. [c] In τ units, in $CDCl_3$, 100 MHz.

Results and Discussion

Preparation of Polymethylnaphthalenes and Their Spectra.—The introduction of methyl groups on a given position of the ring by a direct methylation of naphthalene is usually difficult. Mosby's method,[6] however, enabled us to prepare some naphthalenes bearing at least 1,4-dimethyl substituents (Scheme I, a). Also some highly substituted naphthalenes were prepared by treating benzyne adducts of hexamethyl-2,4-cyclohexadienone with methylsulfinylcarbinyl anion in dimethyl sulfoxide solution (Scheme I, b).[7]

SCHEME I



1, $R_1 = R_3 = R_4 = H$; $R_2 = Me$
2, $R_2 = R_3 = R_4 = H$; $R_1 = Me$
3, $R_3 = R_4 = H$; $R_1 = R_2 = Me$
4, $R_1 = R_4 = H$; $R_2 = R_3 = Me$
5, $R_1 = R_3 = H$; $R_2 = R_4 = Me$
6, $R_4 = H$; $R_1 = R_2 = R_3 = Me$
7, $R_3 = H$; $R_1 = R_2 = R_4 = Me$
8, $R_1 = R_2 = R_3 = R_4 = Me$

In spite of the extensive collection of nmr spectra catalogs, no systematic comparison of nmr spectra of polymethylnaphthalenes has been available. Comparative data obtained in the present study are listed in Table I.

Ultraviolet spectra of the polymethylnaphthalene system have been studied by a number of workers.[8,9] Dannenbergs[10] suggested that an additive value of +3 nm per one methyl group can be given to the bathochromic shift of the E_1 absorption band of this system. This value, however, does not fit the higher homologs than tetramethylnaphthalenes. A list of uv spectra (E_2 band) of the eight naphthalenes obtained in the present study is shown in Table II. Comparing the first three naphthalenes substituted on one half of the nucleus without steric hindrance, one can obtain the additive values of +14 and +4 nm bathochromic shift per one 1,4-dimethyl and 2,3-dimethyl substitution, respectively. The calculated wavelength according to eq 1 showed a comparatively good agreement with

$$\text{uv max (nm)} = 275 + 14a + 4b \quad (1)$$

those observed except for **4**. So far as the minor difference between the calculated and the observed values for the E_2 band is concerned, one can hardly expect any appreciable perturbation of the electronic structure of the ring, which might be caused by losing the planarity of the ring.

TABLE II
ULTRAVIOLET SPECTRA OF POLYMETHYLNAPHTHALENES (E_2 BAND, IN ETHANOL)

Polymethyl-naphthalene	λ max, nm (log ϵ) Obsd	Calcd[a]	Obsd − Calcd
Naphthalene	275 (3.72)		(0)[b]
1	289 (3.79)		(0)[b]
2	279 (3.67)		(0)[b]
3	293 (3.76)	293	0
4	297 (3.87)	303	−6
5	291 (3.78)	293	−2
6	307 (3.82)	307	0
7	295 (3.71)	297	−2
8	311 (3.77)	311	0

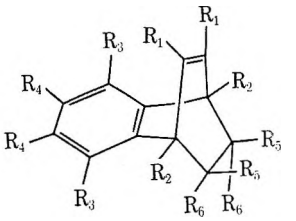
[a] Calculated λ max (nm) = 275 + 14*a* + 4*b* (*a*, number of 1,4-Me_2 substitution; *b*, number of 2,3-Me_2 substitution). [b] Used as the standard of bathochromic shifts.

Diels–Alder Reaction of Polymethylnaphthalenes with Maleic Anhydride.—In spite of the earlier study[11] in which naphthalene itself had reacted with much difficulty, our previous study suggested that maleic anhydride could be a reactive dienophile toward polymethylnaphthalenes. The reaction was carried out at 110° in the molten state without solvent. When a powdered mixture of naphthalene and maleic anhydride melted in a sealed tube, the immediate appearance of a red color was observed, probably due to the formation of charge-transfer complex. The most typical example was exhibited by **6**, which melted and formed a red solution which solidified as a colorless solid in 5 min. The other mixtures remained as a red or orange solution through the heating period. The reaction was followed up by measuring the uv spectra of naph-

(6) W. L. Mosby, *J. Amer. Chem. Soc.*, **74**, 2564 (1952).
(7) A. Oku, T. Kakihana, and H. Hart, *ibid.*, **89**, 4554 (1967).
(8) E. Heilbronner, U. Frolicher, and P. A. Plattner, *Helv. Chim. Acta*, **32**, 2479 (1949).
(9) W. L. Mosby, *J. Amer. Chem. Soc.*, **75**, 3348 (1953).
(10) H. Dannenberg and D. Dannenberg, *Chem. Ber.*, **89**, 1316, 1326 (1956).
(11) K. Takeda, K. Kitahonoki, M. Sugiura, and Y. Takao, *Chem. Ber.*, **95**, 2344 (1962).

TABLE III
STRUCTURES OF THE DIELS–ALDER ADDUCTS AND THEIR NMR SPECTRA[a]

endo $\begin{cases} R_5 = (\text{-COOCO-})/2 \\ R_6 = H \end{cases}$
exo $\begin{cases} R_5 = H \\ R_6 = (\text{-COOCO-})/2 \end{cases}$

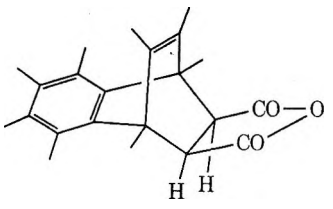


Polymethylnaphthalene	Adduct structure	^{1}H Chemical shifts[a] R_5	R_6	R_7	R_1	R_3	R_4
1	1,4 endo	*b*	H 7.03	Me 7.98	H 3.69	H 2.7	H 2.7
	exo	H 6.75		Me 8.00	H 3.65	H 2.7	H 2.7
	5,8 endo		H 6.80	H 5.25	H 3.33	Me 7.62	H 3.1
	exo	H 6.63		H 5.25	H 3.33	Me 7.69	H 3.1
2	1,4 endo		H 6.77[c]	H 5.84[c]	Me 8.22	H 2.8	H 2.8
	exo	H 6.61[c]		H 5.98[c]	Me 8.19	H 2.8	H 2.8
3	1,4 endo		H 7.13	Me 7.97	Me 8.27	H 2.7	H 2.7
	exo	H 6.95		Me 8.05	Me 8.25	H 2.7	H 2.7
4	1,4 endo		H 6.99	Me 7.84	H 3.82	Me 7.45	H 3.23
	exo	H 6.97		Me 7.80	H 3.80	Me 7.54	H 3.23
5	5,8 endo		H 6.82[d]	H 5.60[e]	Me 8.22	Me 7.62	H 3.14
	exo	H 6.61[d]		H 5.60[e]	Me 8.19	Me 7.69	H 3.14
6	1,4 endo		H 7.02	Me 7.79	Me 8.22	Me 7.50	H 3.22
7	1,4 endo		H 7.17	Me 8.01	Me 8.30	H 2.94	Me 7.73
	exo	H 6.93		Me 8.10	Me 8.20	H 2.74	Me 7.85
	5,8 endo		H 6.83[f]	H 5.52[f]	Me 8.23	Me 7.66	Me 7.80
	exo	H 6.65[f]		H 5.52[f]	Me 8.20	Me 7.72	Me 7.80
8	1,4 endo		H 7.05	Me 7.84	Me 8.23	Me 7.59	Me 7.75
	exo	H 6.89		Me 7.78	Me 8.26	Me 7.48	Me 7.76

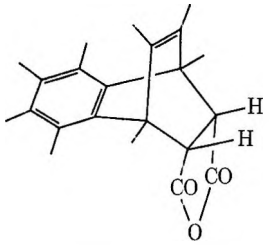
[a] Singlet, except ring protons. [b] (-COOCO-)/2. [c] Triplet: $J_1 = J_2 = 1.3$–1.5 Hz for both isomers. [d] Unclear triplet: $J_1 = J_2 = 1$ Hz. [e] Multiplet. [f] Unclear triplet: $J_1 = J_2 = 1$–1.5 Hz. [g] In τ units, in $CDCl_3$, 100 MHz.

thalenes and nmr spectra of the corresponding products. After heating for 6 hr at 110° all reactions seemed to have reached an equilibrium since no further decrease in naphthalene concentration nor the increase of products (by nmr) were detected. In some cases, prolonged heating caused the decomposition of products.

The structural determination of the Diels–Alder adducts was carried out on the basis of the nmr analysis of the products. Results are summarized in Table III. The endo and exo structures were assigned on the assumption that the methine proton which is on the α carbon to the carbonyl and anti to the benzene ring (exo isomer, **9**) should be relatively more deshielded



endo **10**



exo **9**

than the syn methine proton of the corresponding endo isomer, **10**, in which the proton lies closer to the shielding region of the ring current.[12,13]

(12) *Cf.* C. D. verNooy and C. S. Rondestvedt, Jr., *J. Amer. Chem. Soc.*, **77**, 3583 (1955).

(13) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution NMR Spectroscopy," Vol. 1, Pergamon Press, Elmsford, N. Y., 1965, p 140. According to the equation by Johnson and Bovey, the chemical shift difference between exo and endo methine protons of a naphthalene–MA adduct was *ca.* 0.2 ppm, being consistent with the observed values. See Table III.

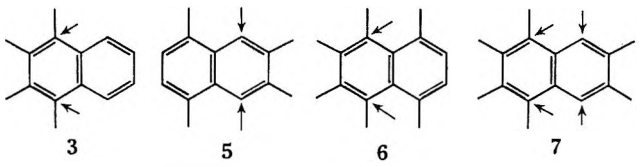
As illustrated in Tables III and IV, it is of interest that the position of methyl substituents affects not

TABLE IV
ADDITION OF MALEIC ANHYDRIDE TO POLYMETHYLNAPHTHALENES[a]

Polymethylnaphthalene	Adduct structure[b]	Yield, % 1,4 Adduct	Yield, % 5,8 Adduct	exo/endo Ratio[c] 1,4 Adduct	exo/endo Ratio[c] 5,8 Adduct
1	1,4 5,8	0.4	0.7	0.9	0.7
2	1,4	10		0.6	
3	1,4	82		0.05	
4	1,4	34		0.05	
5	5,8		20		0.55
6	1,4	100		0	
7	1,4 5,8	60	30	0.05	0.55
8	1,4	91		0.14	

[a] At 110°, [MA]/[naphthalene] = 1.0. Heated for 24 hr in sealed tubes without solvent. [b] 1,4 and 5,8 mean the adding position of maleic anhydride onto the ring based on the original numbering of the polymethylnaphthalenes. [c] Determined by nmr.

only the reaction rates (see Table VI) but also the positions to which maleic anhydride adds. Generally, the dienophile attacks a ring with a larger number of methyl substituents, as was first observed by Kloetzel and coworkers.[2] In the present study, however, some irregular addition occurred on the ring bearing a smaller number of methyl group (5,8 addition) as well as on the methyl-rich ring (1,4 addition) as illustrated by **1** and **7**. Moreover, an exclusive 5,8 addition was observed for **5**. Taking into account the significant



3 5 6 7

difference in reactivity between **1** and **2** as seen in Table IV, a general rule can be proposed as follows: (i) 1,4-dimethyl substitution somewhat disfavors 1,4 addition but favors 5,8 addition to some extent; (ii) 2,3-dimethyl substitution strongly favors 1,4 addition but disfavors 5,8 addition. A qualitative application of this empirical rule, which is also compatible with the results found by German workers,[14] to the other highly substituted homologs results in a comparatively good agreement with the reaction behaviors observed.[15] This rule presents a clear contrast to the reactive position of methyl-substituted nonaromatic 1,3-butadiene systems where, it has been known, trans 1- and/or 4-methyl substituents facilitate the 1,4 addition of a dienophile more effectively than 2- and/or 3-methyls.[16]

The preliminary uv and nmr analysis of the reaction mixtures showed that the substrate concentration reached a constant at 160° after 1 hr. Analogously to the earlier study,[2] it indicates a possible formation of an equilibrium and, therefore, the thermal dissociation of the isolated adducts was examined. Thermal reversibility of the reaction was demonstrated by the results shown in Table V. Thus, essentially the same equilibrium mixture was established in the following two cases: (a) a 1:1 mixture of an adduct and maleic anhydride; (b) a 1:2 mixture of a naphthalene and maleic anhydride. It is also shown that in the equilibrium dissociation is more facilitated at 155° than at 110° (see Table IV).

TABLE V
EQUILIBRATED THERMAL DISSOCIATION OF THE DIELS–ALDER ADDUCTS[a]

Starting adduct[b]	Equilibrated composition (%) Naphthalene	Adduct[c]	Adduct structure	exo/endo Ratio[d] 1,4 Adduct	5,8 Adduct
2-MA (2′)	90	10 (7)	1,4	0.6	
3-MA (3′)	60	40 (36)	1,4	0.5	
4-MA (4′)	77	23 (14)	1,4	0.13	
5-MA (5′)[e]	86	14 (14)	5,8		1.0
6-MA (6′)	0	100 (100)	1,4	0.0	
7-MA (7′)	30	70 (50)	1,4 and 5,8 (4:3)	0.3	0.7
8-MA (8′)	20	80 (60)	1,4	0.23	

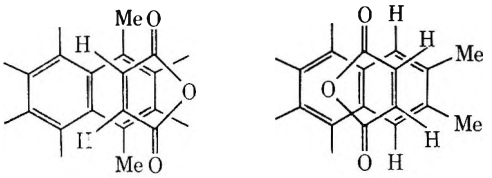
[a] At 155°, [MA]/[adduct] = 1.0. Heated for 6 hr in sealed tubes. Maleic anhydride (MA) was mixed with the adduct to obtain an instant solution at the temperature. [b] Endo 1,4 adduct, unless otherwise stated. [c] Isomeric mixture (exo/endo = 0.55). [d] Determined by nmr with the data in Table III for comparison. [e] Values in parentheses are the yields of adducts obtained in the reaction at 160° with reactant ratio [MA]/[naphthalene] = 2.0.

(14) H. Plieninger, D. Wild, and J. Westphal, *Tetrahedron*, **25**, 5561 (1969).

(15) Mr. T. Hino of our group performed some extended LCAO–MO calculations on the polymethylnaphthalene systems. The result shows that the bond-order density and the atomic orbital population are higher at the 5,8 position for **1**, 1,4 for **2**, 1,4 for **3**, 5,8 for **5**, and 5,8 for **7**, than the other position. This result seems to account well for the reacting positions in these systems. We are indebted to Professor T. Yonezawa for allowing us to use his programming for the calculation.

(16) T. Inukai, *J. Syn. Org. Chem. Jap.*, **29**, 353 (1971).

The influence of the reaction temperature as well as of methyl substitution on the endo–exo orientation of the adduct is noticeable (compare Tables IV and V). The exo/endo ratios show that the exo isomer tends to increase as the temperature rises. This indicates that the exo form is thermodynamically more stable than the endo. The only exception was that the endo isomer obtained from **6** did not isomerize in the temperature range examined. On the other hand, the preferred formation of endo adduct at the lower temperature (110°) qualitatively indicates the kinetic preference of the endo form to the exo, and suggests that Alder's rule is applicable so that the maximum π accumulation is attained[17] between maleic anhydride and the one half of the naphthalene, as illustrated by the transition state A.[18] The ease of this thermodynamically con-



A B

trolled endo–exo isomerization also depends on the mode of methyl substitution. Thus, in case of **4**, **6**, **7**, and **8** where addition occurs to the 1,4-dimethyl-substituted position, the endo isomer predominates even at 155° (refer to the transition state A), whereas such systems as **2**, **5**, and **7** where no methyl group exists on the reacting position increase the amount of exo isomer (refer to the transition state B).

A kinetic study[19] on five naphthalenes (**3**, **4**, **6**, **7**, **8**) showed that their reaction rates with maleic anhydride are in the order of **6** (rel rate 40) > **8** (10) > **7** (3) > **3** (1) > **4** (0.4). (See Table VI.) The rates of the other three naphthalenes were incapable of being measured in this experiment. Interesting results are that **6** reacted four times faster than **8**, which is also four times faster than **7**, and that **4** showed a lower reactivity than **3**. Although the result shows some rate enhancement in the peri-substituted naphthalenes, the observed values are somewhat against our original expectation; that is, peri-substituted naphthalenes would react much faster than the other homologs where nonbonded methyl interaction does not exist, since the peri interaction would be released in the transition state where the atomic arrangement is rather close to that of the product in which no more appreciable interaction is likely to exist.[20] The peri dialkyl interaction in the naphthalene system has been known well,[21] and the acid-catalyzed isomerization of **6** into **7** as well as the

(17) E. W. Butz and J. W. Butz, *J. Org. Chem.*, **7**, 199 (1942).

(18) This bimolecular orientation may be close to that of the corresponding CT complex. The CT bands of the complexes appear around 400 nm (maximum at 425 for **8**). A study of the CT equilibrium in connection with the naphthalene structure is under way.

(19) The rates were measured by two methods: (a) disappearance of the naphthalene by uv, (b) appearance of the adduct by nmr. Both methods agreed within the experimental error. Since Beer's Law is applicable (10^{-4}–10^{-6} mol/l. in $CHCl_3$) and the equilibrium constant for the formation of CT complex was very small in the above concentration range, only the result by a is presented here. In addition, no exo isomer was detected in this reaction by b.

(20) According to this assumption, the reactivity should have been in the order of **8** > **6** > **7** > **4** . . .

(21) For a review, see V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

TABLE VI

REACTION RATES OF POLYMETHYLNAPHTHALENES WITH MALEIC ANHYDRIDE IN CHLOROFORM[a]

Polymethylnaphthalene	Temp, °C	$k_2 \times 10^{-4}$, l./mol sec[b]
6	60 ± 0.5	4.45
	40 ± 0.5	1.14
8	60 ± 0.5	1.11
7	60 ± 0.1	0.31
3	60 ± 0.1	0.12
4	60 ± 0.1	0.04

[a] Concentration, 0.05 mol/l. for each reactant. Rates were determined by measuring the decrease in the strength of the E_2 band (uv) of naphthalenes. See also footnote 21. [b] Second-order rate constant for the equimolar reaction.

electrophilic oxidation of **8**[22,23] are also accounted for by this interaction. This discrepancy, however, could partly be rationalized by applying the general rule mentioned above. Thus, the methyl substitution on the 6,7 position of **6** should lower the reactivity of its 1,4 position down to a level somewhat higher than that of **7**. Similarly, the lower reactivity of **7** at its 1,4 position than that of **8** can be interpreted as the result of losing the 5,8-dimethyl group (which would activate the 1,4 position) from **8**.

To get a clearer view of this reaction, more experimental data and some theoretical treatment of polymethylnaphthalene systems[15] will be required.

Experimental Section

Nmr spectra were recorded on a LEOL 4H-100 spectrometer (100 MHz) and chemical shifts are given in τ units. These data are tabulated in Table III. Ultraviolet and ir spectra were taken on a Hitachi spectrophotometer Model 124 and JASCO IRA-1, respectively. Melting points are uncorrected.[24] Combustion analysis was performed by the Microanalytical Laboratory of Kyoto University. Product yields and isomer ratios are listed in Table IV.

Polymethylnaphthalenes.—The preparation of 1,4-dimethyl- and 1,4,5,8- and 1,4,6,7-tetramethylnaphthalenes has been reported by Mosby.[6] The purification of 1,4-dimethylnaphthalene (liquid) was achieved by forming the corresponding picrate. 2,3-Dimethylnaphthalene was commercially available. The other naphthalenes, 1,2,3,4-tetramethyl-, 1,2,3,4,5,8- and 1,2,3,4,6,7-hexamethyl-, and octamethylnaphthalene, were synthesized[1] from the Diels–Alder reaction of hexamethyl-2,4-cyclohexadienone with methyl-substituted benzynes.

Octamethylnaphthalene–Maleic Anhydride (MA) Adduct (8′).—In a sealed tube of 8 mm diameter × 80 mm length was charged a mixture of octamethylnaphthalene (0.242 g, 1 mmol) and MA (0.098 g, 1 mmol) under nitrogen. The tube was immersed in a bath controlled at 110 = 2°. After 24 hr, the mixture was chromatographed (silica gel) with alcohol-free chloroform eluent. The first fraction contained the unreacted naphthalene (20 mg, 93% conversion) and the second fraction consisted of the isomeric mixture of the adduct (287 mg, 91%). Unreacted MA remained in the column. The adduct **8′**, *i.e.*, 1,4,5,6-tetramethyl-7,8-(tetramethylbenzo)bicyclo[2.2.2]octa-5,7-diene-2,3-dicarboxylic anhydride, consisted mainly of the endo isomer (7 parts) with a small amount of the exo isomer (1 part). The isomeric mixture had mp 153–160°; ir 1855, 1765 cm^{-1} (C=O, acid anhydride); uv max (chloroform) 280 nm (log ϵ 3.26).

Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.75. Found: C, 77.98; H, 7.68.

The pure endo isomer was separated by recrystallization from chloroform, mp 162°.

Similar experimental procedures were used for the reactions of MA with the other polymethylnaphthalenes.

1,2,3,4,6,7-Hexamethylnaphthalene–MA Adduct (7′).—Two structural isomers (1,4 and 5,8 adducts) were separated by recrystallizing the total isomeric mixture in chloroform. The major fraction (60%), mp 172–174°, was the endo 1,4 adduct and the minor fraction (30%), mp 175–185°, was a mixture of endo (2 parts) and exo (1 part) 5,8 adducts. The structural isomeric mixture had ir 1860, 1825, 1775 cm^{-1} (C=O); uv max (chloroform) 280 nm (log ϵ 3.16), 271 (3.14).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.29; H, 7.15.

1,2,3,4,5,8-Hexamethylnaphthalene–MA Adduct (6′).—The adduct, with quantitative yield, was composed exclusively of the *endo* 1,4 adduct (**6′**): mp 212–214°; ir 1860, 1825, 1772 cm^{-1} (C=O); uv max (chloroform) 283 nm (log ϵ 3.23), 275 (3.25).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.65; H, 7.08.

1,4,6,7-Tetramethylnaphthalene–MA Adduct (5′).—The isolated solid adduct was a mixture of endo and exo 5,8 adducts: mp 163–165°; ir 1855, 1825, 1775 cm^{-1} (C=O); uv max (chloroform) 279 nm (log ϵ 2.76), 270 (2.77).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.08; H, 6.45.

1,4,5,8-Tetramethylnaphthalene–MA Adduct (4′).—The isolated product was a mixture of endo (more than 95 parts) and exo (less than 5 parts) adducts. The pure endo isomer was obtained by recrystallization from chloroform: mp 168–169°; ir 1855, 1825, 1765 cm^{-1} (C=O); uv max (chloroform) 283 nm (log ϵ 2.99), 275 (2.97).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.53; H, 6.36.

1,2,3,4-Tetramethylnaphthalene–MA Adduct (3′).—The adduct was an isomeric mixture of endo (95 parts) and exo (5 parts) 1,4 adducts (not separated): mp 166–167°; ir 1850, 1820, 1765 cm^{-1} (C=O); uv max (chloroform) 272 nm (log ϵ 2.59), 265 (2.70).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.27; H, 6.46.

2,3-Dimethylnaphthalene–MA Adduct (2′).—The isolated product was a mixture of endo (1 part) and exo (0.6 part) 1,4 adducts: mp 173–182°; ir 1858, 1835, 1770 cm^{-1} (C=O); uv max (chloroform) 273 nm (log ϵ 2.68), 266 (2.73), 259 (2.65).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.60; H, 5.64.

Recrystallization from carbon tetrachloride gave the endo isomer, mp 196°.

1,4-Dimethylnaphthalene–MA Adduct (1′).—Because of the lower reactivity of this liquid naphthalene, the reaction was carried out in 50-mmol scale. Only a small amount of the isomeric mixture (1,4 and 5,8 adducts) was obtained: mp 115–122°; ir 1855, 1775 cm^{-1} (C=O); uv max (chloroform) 281 nm (log ϵ 2.78), 272 (2.78).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 74.98; H, 5.97.

Kinetic Study.—A chloroform solution of a polymethylnaphthalene (100 mmol $l.^{-1}$) was mixed with an equal volume of a chloroform solution of MA (100 mmol $l.^{-1}$) under cooling. Immediately after the mixing, every 1.0 ml of the mixed solution (50 mmol $l.^{-1}$ for each reagent) was charged in a sealed tube, and the tubes were immersed in a bath (60 or 40 ± 0.2°). After every 75 min a tube was taken out and cooled to 0°, and the solution was diluted with chloroform for uv measurement. Simultaneously, every 5 ml of the kinetic solution was cooled down to 0° and quickly evaporated *in vacuo* to dryness, and the residue was diluted with deuteriochloroform for nmr measurement.

Retro Diels–Alder Reaction of the Isolated Adducts.—An equimolar mixture of an adduct (*ca.* 0.1–0.2 mmol) and MA was placed in a sealed tube, which was immersed in a bath (155 ± 2°) and shaken vigorously for 5 min until a clear solution was obtained. At this moment the immediate appearance of a color (yellow-red) was observed. After heating for 6 hr, the tube was quickly cooled down to 0° and the mixture was dissolved in deuteriochloroform for nmr analysis (see Table V).

(22) Unpublished data. A quantitative isomerization of **6** to **7** was observed in a warm mixture of zinc cyanide and hydrogen chloride.

(23) H. Hart and A. Oku, *J. Org. Chem.*, **37**, 4274 (1972).

(24) By the capillary technique. The glass-plate technique, on the other hand, gave the higher melting point: **1′**, 115–125°; **2′**-endo, 220°; **3′**, 175–177°; **4′**-endo, 180–182°; **5′**, 176–179°; **6′**-endo, 234–235°; **7′**-1,4-endo, 178–180°; **7′**-5,8-, 210–220°; **8′**-endo, 163°. It seems difficult to get the precise melting point of these dissociable adducts.

Registry No.—1, 571-58-4; 2, 581-40-8; 3, 3031-15-0; 4, 2717-39-7; 5, 13764-18-6; 6, 36230-30-5; 7, 17384-76-8; 8, 18623-61-5; maleic anhydride, 108-31-6.

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Synthesis and Chemistry of Octamethylnaphthalene

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A five-step synthesis of octamethylnaphthalene (1) from hexamethylbenzene, overall yield 51%, is described. Addition of 3,6-dimethylbenzyne to hexamethyl-2,4-cyclohexadienone (2) gave adduct 3 which with dimsyl sodium eliminated butyric acid to give 1,2,3,4,5,8-hexamethylnaphthalene (4). Bischloromethylation of 4, followed by lithium aluminum hydride reduction, gave 1. Octamethylnaphthalene gave 1,4 adducts with maleic anhydride, dimethyl acetylenedicarboxylate, benzyne, and 4,5-dimethylbenzyne. Tetracyanoethylene gave a deep blue color with 1 in nonpolar solvents, and singlet oxygen reacted with 1 to give a stable 1,4-endoperoxide (13). With dibromocarbene, 1 gave a homoannular bis adduct 14 and a benzomethylenecycloheptatriene 15, the latter from rearrangement and HBr elimination from the monoadduct. Octamethylnaphthalene is protonated at an α position by trifluoracetic acid at room temperature to give a long-lived arenonium ion.

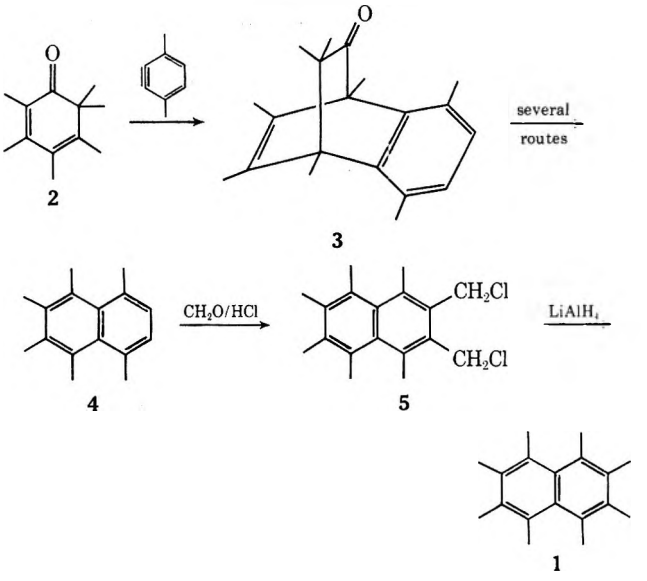
Octamethylnaphthalene (1) is not planar, owing mainly to strong interactions between the peri methyl groups.[1] An early structure determination[2] showed that the α-methyl carbon atoms are displaced about 0.73 Å from the mean molecular plane; the β-methyls are also displaced, but only by one-third that distance. Adjacent α and β methyl groups are displaced in the same sense, whereas adjacent α,β pairs are alternatively displaced above and below the mean molecular plane.[3,4] It seems likely that the aromatic ring carbon atoms themselves are also distorted from the mean molecular plane. This twisting should alter the π overlap from that in naphthalene itself, and might be reflected in the reactivity of 1 toward electrophiles.

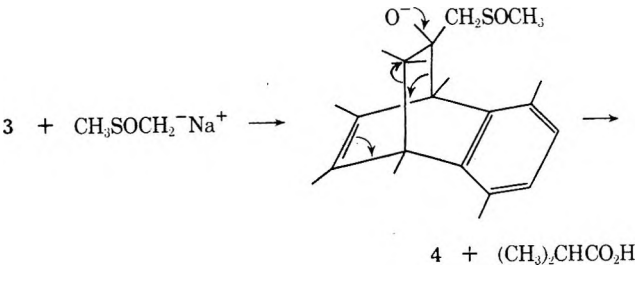
The original synthesis of 1[6] unfortunately required many steps and was unattractive if 1 was to serve as the starting point for other investigations. Consequently, we developed and describe here a simple, high-yield synthesis of 1.[7] We also describe here and in the following paper several reactions of octamethylnaphthalene.

Synthesis of Octamethylnaphthalene (1).—In the synthesis which we devised (Scheme I), the step which produces both peri interactions also introduces aromaticity into the second ring, thus providing a strong driving force for the reaction. The last two methyl groups are added in the final steps, *via* chloromethylation and reduction, at the less hindered β positions.

Reaction of hexamethyl-2,4-cyclohexadienone (2)[8] with 3,6-dimethylbenzyne[9] afforded the adduct 3 in 76% yield. The adduct was converted to 1,2,3,4,5,8-hexamethylnaphthalene by three routes. The best of these, which was essentially quantitative, involved the reaction of 3 with dimsyl sodium.[10] Pyrolysis of 3 also gave 4 (and dimethylketene) but conversions at

SCHEME I





(1) For a review on peri interactions in naphthalenes, see V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

(2) D. M. Donaldson and J. M. Robertson, *J. Chem. Soc.*, 17 (1953).

(3) G. Gafner and F. H. Herbstein, *Nature (London)*, **200**, 130 (1963).

(4) In the abstract of the paper on the X-ray structure of octamethylnaphthalene,[2] the methyls are said to alternate in their up-and-down displacement around the ring. However, the original structure was based only on a two-dimensional X-ray analysis. A three-dimensional X-ray analysis of octa*chloro*naphthalene[3] showed that the chlorines at C-1, -2, -5, and -6 are displaced in one sense from the mean molecular plane and those at C-3, -4, -7, and -8 are displaced in the opposite sense. A recent reexamination of the octamethylnaphthalene structure[5] shows that its structure is analogous to that of the octachloro derivative.

(5) Private communication from Professor Iain C. Paul.

(6) B. J. Abadir, J. W. Cook, and D. T. Gibson, *J. Chem. Soc.*, 8 (1953).

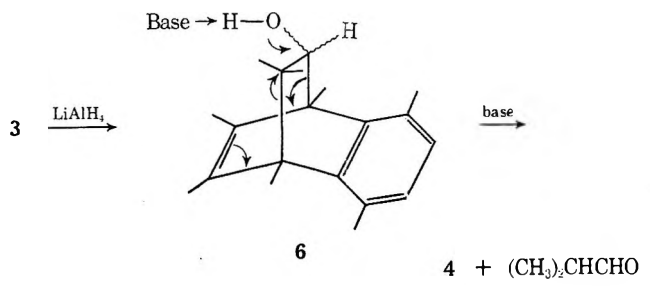
(7) For a preliminary report, see A. Oku, T. Kakihana, and H. Hart, *J. Amer. Chem. Soc.*, **89**, 4554 (1967). We are indebted to Dr. Tsuyoshi Kakihana for his contributions to the early phases of this work.

(8) H. Hart, P. M. Collins, and A. J. Waring, *J. Amer. Chem. Soc.*, **88**, 1005 (1966).

(9) Produced from the corresponding diazonium carboxylate hydrochloride, using the procedure of Professor L. Friedman (private communication).

(10) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

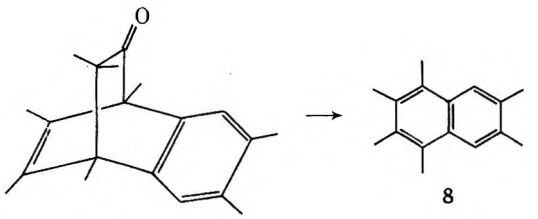
moderate residence times were only modest (~20%), even at 450°. Reduction of **3** with lithium aluminum hydride gave a mixture of epimeric alcohols **6** which,



when refluxed with sodium hydride in DMSO, gave **4** (overall yield from **3**, 95%).

The hexamethylnaphthalene **4** was readily bischloromethylated to give **5**, which was reduced without purification to give **1**. The overall yield from hexamethylbenzene to octamethylnaphthalene (five steps) was 51%, and further work on the final reduction could probably improve this to 70%.

The importance of introducing the peri methyl groups in a step (**3** → **4**) which also involves the formation of an aromatic ring is seen from the following results. Addition of 4,5-dimethylbenzyne to **2** gave the adduct **7** (76%), which could be converted to **8** in good yield.

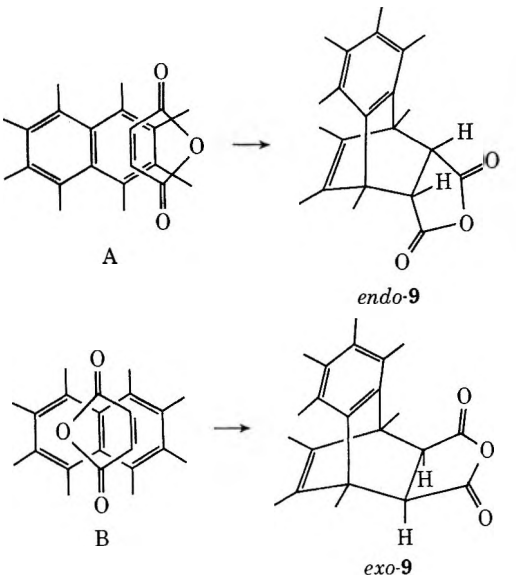


However, chloromethylation and reduction of **8** gave only very low yields of heptamethylnaphthalene (~6%) and octamethylnaphthalene (~3%), even under rather forcing conditions.

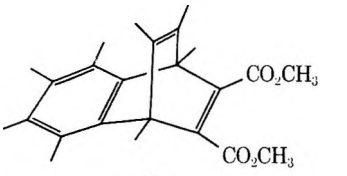
Diels–Alder Additions of Octamethylnaphthalene.—Octamethylnaphthalene is more reactive than naphthalene itself toward dienophiles. This may be because the ring framework is distorted from planarity, thus making the compound somewhat less aromatic and more diene-like.

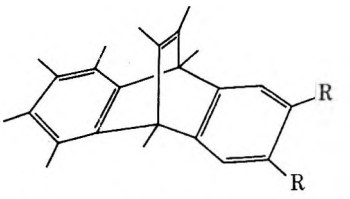
Maleic anhydride, when heated at 132° for several hours with **1**, gave an 83% yield of the endo and exo adducts *endo*-**9** and *exo*-**9**, in a ratio of 2:1 in accord with the Alder rules.[11] The isomers were not separated, but were readily distinguished by their nmr spectra, and the mixture was analyzed in that way. The transition state A, with the anhydride ring oriented away from the second ring of the naphthalene, is preferred.

(11) Kinetic measurements [A. Oku, Y. Ohnishi, and F. Mashio, *J. Org. Chem.*, **37**, 4264 (1972)], show that **1** reacts with maleic anhydride in chloroform at 60° ten times faster than does 1,2,3,4-tetramethylnaphthalene; under these conditions naphthalene itself reacts at a rate too slow to measure.



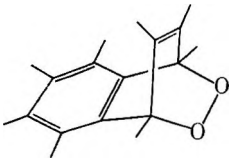
Reaction of **1** with dimethyl acetylenedicarboxylate and with the appropriate arynes gave adducts **10**–**12**





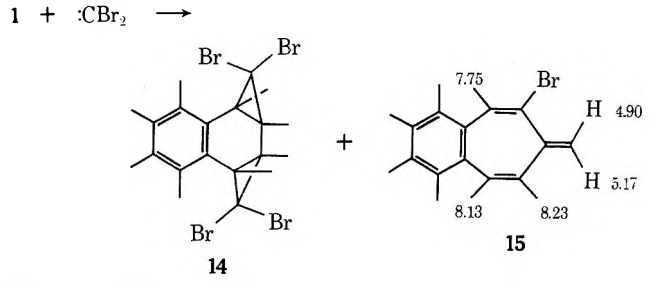
in fair yield. 3,6-Dimethylbenzyne was apparently too hindered to react with **1**. The structures of the adducts were clear from nmr and other spectral data. Tetracyanoethylene produces a deep blue color with octamethylnaphthalene in nonpolar solvents such as benzene, chloroform, or hexane, but no color is produced in ethanol. The color can be discharged from the nonpolar solutions by adding a little alcohol. All attempts to isolate a simple adduct from the blue solutions were unsuccessful; some crystalline products which contained both moieties were isolated, but they contained considerable amounts of oxygen and did not correspond to the 1:1 adduct; their structures are as yet undetermined.

Octamethylnaphthalene readily adds 1 mol of oxygen, either on direct or dye-sensitized irradiation, to form the stable crystalline 1,4-endoperoxide **13**. The reaction



involves singlet oxygen, and can be reversed by refluxing **13** in di-*n*-butyl ether.[12]

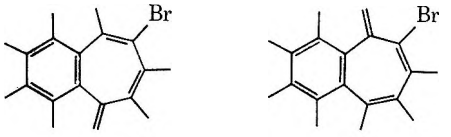
Addition of Dibromocarbene to Octamethylnaphthalene.—Dibromocarbene, generated from bromoform and potassium *tert*-butoxide in benzene at room temperature, gave two products with octamethylnaphthalene, assigned structures **14** and **15**. The yields of



14 **15**

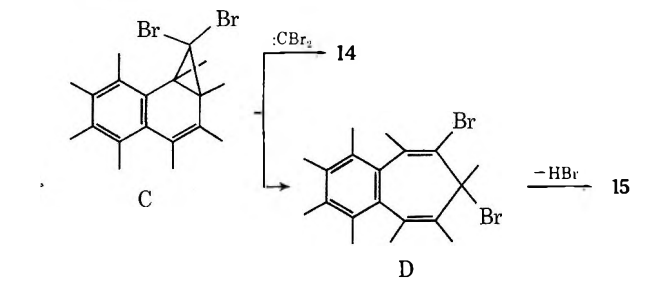
pure, crystalline material were 30 and 59%, respectively. Compound **14** gave the correct analysis for a bis adduct, and its nmr spectrum consisted of four equal singlets, two in the region of aromatic methyls (τ 7.74, 7.80) and two in the region of aliphatic methyls (τ 8.33, 8.65). These data are consistent with either a cis or a trans bis adduct. The trans geometry seems the more likely of the two possibilities, since nonbonded interactions between two bromine atoms would be very severe in the cis structure.

The second product, **15**, analyzed correctly for a monocarbene adduct minus the elements of HBr. The infrared spectrum showed a strong terminal methylene absorption at 918 cm^{-1}; the uv spectrum had an intense maximum at 245 nm (log ϵ 4.67) and shoulders at 267 (4.30) and 270 (3.95), indicative of the extensive conjugation present. The nmr spectrum had a broad singlet for the four aromatic methyl groups at τ 7.88 and other bands as shown in the formula. The peak at τ 7.75 was a sharp singlet, whereas those at τ 8.13 and 8.23 were mutually coupled (J = 0.8 Hz), as were the two vinyl protons (J = 1.8 Hz). The mechanistically accessible fully conjugated alternative structures **15a** and **15b** appear to be less likely from these data.



15a **15b**

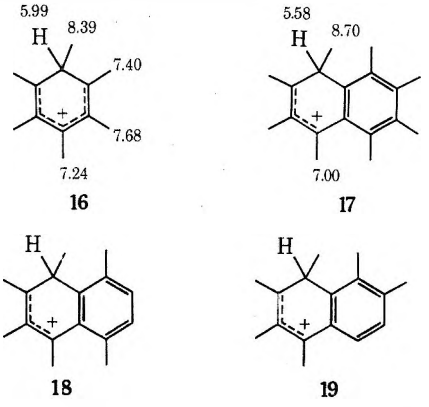
The mechanism presumably involves the formation of a monoadduct C, which can either react with a second carbene to give **14** or ring open to D which eliminates HBr to give **15**. The monoadduct was not isolated.



(12) For a preliminary account of this endoperoxide, see H. Hart and A. Oku, *J. Chem. Soc. D*, 254 (1972).

The formation of **15** is analogous to the formation of chlorobenzotropones from methoxynaphthalenes and dihalocarbenes.[13]

Protonation of Octamethylnaphthalene.—It was of interest to compare the basicities of octamethylnaphthalene and hexamethylbenzene. The behavior of all the methylbenzenes in strong acids has been studied, and the nmr spectra of the benzenonium ions which result from their protonation are recorded.[14] In trifluoroacetic acid containing boron fluoride, or in 96% sulfuric acid at 20°, the protons of all six methyl groups of hexamethylbenzene appear as a single sharp peak at τ 7.65[15] (shifted only 0.15 ppm downfield from its position in carbon tetrachloride). Under these conditions, proton exchange is so rapid that the spectrum of the hexamethylbenzenonium ion **16** is not seen. However, in HF + BF_3 at −80° this ion is clearly seen, with a quartet at τ 5.99 and a doublet at 8.39 (J = 6.8 Hz), and the para methyl shifted 0.41 ppm downfield from its position in trifluoroacetic acid. When this solution is warmed above −20° the detail of this spectrum is lost owing to rapid exchange.



16 **17**

18 **19**

In sharp contrast with hexamethylbenzene, octamethylnaphthalene is fully protonated on an α carbon at room temperature in trifluoroacetic acid.[16] The spectrum is stable indefinitely. Although an absolute assignment of all the chemical shifts is not yet possible, there is good evidence that protonation occurs at an α-ring position (**17**). Both 1,2,3,4,5,8- and 1,2,3,4,5,6-hexamethylnaphthalene behaved similarly to give **18** and **19**, respectively. The nmr spectra of the three ions are compared in the Experimental Section. Under identical conditions 1,2,3,4-tetramethylnaphthalene gives an nmr spectrum virtually identical with that obtained in carbon tetrachloride. The relief of strain resulting from nonbonded peri interactions clearly must provide a strong driving force for protonation; consequently octamethylnaphthalene and other methylnaphthalenes with peri interactions are very much more basic than is hexamethylbenzene.

Conclusions

The facile addition of a variety of dienophiles, singlet oxygen, carbenes, and a proton by octamethylnaph-

(13) W. E. Parham, D. A. Bolon, and E. E. Schweizer, *J. Amer. Chem. Soc.*, **83**, 603 (1961).

(14) For a review, see D. M. Brouwer, E. L. Mackor, and C. MacLean in "Carbonium Ions," Vol II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, pp 837–897.

(15) Tetramethylammonium tetrafluoroborate is taken as reference, at τ 6.87.

(16) We are indebted to George M. Love for obtaining several spectra of the protonated naphthalenes.

thalene is contrasted with the difficulty or absence of these reactions under comparable conditions with either naphthalene itself or with hexamethylbenzene. The severe peri methyl interactions in octamethylnaphthalene apparently distort the π-electron system and enhance its reactivity toward dienophiles and electrophiles. This effect is likely to be general, and we are exploring this possibility with other strained aromatic systems.

Experimental Section[17]

3,6-Dimethylbenzenediazonium-2-carboxylate Hydrochloride (20).—To a suspension of 16.8 g (0.1 mol) of 3,6-dimethylanthranilic acid[18] in 270 ml of ethanol at 0° was added slowly 10 ml of concentrated hydrochloric acid. The resulting clear solution was kept below 8° as 25 ml of isoamyl nitrite was added dropwise (15 min). After the solution was stirred at 4° for 1 hr, 300 ml of ether was added, and the mixture was stirred for another hour at 0°, during which a slightly brown precipitate of 20 separated. The product was rinsed with ether and dried under vacuum at room temperature, yield 17.1 g (81%), mp 88° (with explosion[19]).

1,3,3,4,7,8-Hexamethyl-5,6-(3,6-dimethylbenzo)bicyclo[2.2.2]-octa-5,7-dien-2-one (3).—A stirred mixture of 8.5 g (0.04 mol) of **20**, 7.1 g (0.04 mol) of **2**,[8] and 12 ml (0.16 mol) of propylene oxide in 100 ml of ethylene dichloride was gradually warmed. As gas evolution commenced, the temperature was controlled to prevent vigorous foaming. After 10 min of gas evolution the solution became clear. It was heated under reflux for 1 hr, solvent was removed under vacuum, and the brown liquid residue was taken up in ether, washed with aqueous sodium hydroxide and water, and dried ($MgSO_4$). Evaporation of the solvent gave a reddish-brown liquid which solidified on standing. Recrystallization from methanol gave 8.6 g (76%) of **3** as colorless crystals: mp 103.5–104°; ir $\nu_{C=O}$ 1705, other major peaks at 1460–1480 (br), 1395, 1360, 1265, 1180, 1100, 1075, 1065, and 1030 cm^{-1}; nmr τ 9.28 (3, s, C-3 methyl syn to the aromatic ring), 9.01 (3, s, C-3 methyl anti to the aromatic ring), 8.17, 8.21, 8.24 (12, m, vinyl and bridgehead methyls), 7.52 (3, s, aromatic methyl), 7.47 (3, s, aromatic methyl), 3.33 (2, s, aromatic protons).

Anal. Calcd for $C_{20}H_{26}O$: C, 85.05; H, 9.28. Found: C, 85.10; H, 9.30.

Alternative Preparation of 3.—To a refluxing methylene chloride (60 ml) solution of **2** (4.09 g, 0.023 mol) and isoamyl nitrite (3.9 g, 0.033 mol) there was added over 80 min a solution of 4.95 g (0.03 mol) of 3,6-dimethylanthranilic acid in 110 ml of acetone. After an additional 2 hr reflux, solvent was removed under vacuum, and the oily residue was taken up in ether, washed with aqueous sodium hydroxide and water, dried (Na_2SO_4), and distilled (40–70°, 0.1 Torr) to give 2.5 g of unreacted **2** and an undistillable residue. Chromatography of the latter [activated alumina, petroleum ether (bp 30–60°) eluent] gave 1.7 g (28%) of colorless crystals of **3**, mp 103–104°. Although this procedure eliminates the need to convert the anthranilic acid to its diazoniumcarboxylate hydrochloride, the overall yield is lower and the work-up procedure is more tedious.

1,2,3,4,5,8-Hexamethylnaphthalene (4).—This is the preferred procedure. The sodium salt of dimethyl sulfoxide was prepared from 200 ml of DMSO and 10 g of sodium hydride (50% dispersion in mineral oil).[10] To this clear solution was added at 50° during 15 min 27.5 g (0.097 mol) of **3**. The mixture was stirred at 50–70° for 3 hr, then poured into ice water. The white solid which separated was collected, dissolved in ether, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave 22 g (about 100%) of **4** as white crystals, mp 42.5–43°. This material was sufficiently pure for further reactions, but further purification could be achieved by column chromatography (silica gel, petroleum ether eluent) to give product with mp 43.5–44.0° (lit.[20] mp 62–63.5°); ir 1820 (w), 1630 (w), 1590 (m), 1350 (s), 1060 (m), 1040 (m), 1010 cm^{-1} (m); nmr τ 7.72 (6, s, C-2 and C-3 methyls), 7.48 (6, s, C-1 and C-4 methyls), 7.37 (6, s, C-5 and C-8 methyls), 3.13 (2, s, aromatic protons).

The aqueous filtrate from the initial separation of the hexamethylnaphthalene was strongly acidified with concentrated hydrochloric acid and extracted with ether. Evaporation of the ether gave an oily residue (0.35 g) which was analyzed by vpc (Apiezon L column, 163°). Comparison with authentic material showed that the oil contained 0.12 g (43%) of isobutyric acid.

Analogous attempts to convert **3** to **4** with other bases such as sodium methoxide in methanol, or sodium hydride, were unsuccessful.

1,2,3,4,5,8-Hexamethylbenzene (4) from the Pyrolysis of 3.—**3** was recovered unchanged when heated in hexylcarbitol (bp 260°) for 25 hr, and when heated neat for 10 hr at 300°. Molten **3** (2.7 g) was dropped through a quartz pyrolysis tube at 450° over 30 min under mild vacuum in a nitrogen atmosphere; the pyrolysate was collected and the exit gases were passed through a trap which contained a carbon tetrachloride solution of aniline. Vpc analysis of the pyrolyzate (Apiezon L column, 250°) showed it to contain a 17.8% yield of **4**, and unchanged **3**. Work-up of the aniline trap contents gave 0.28 g of colorless crystals which on recrystallization from benzene gave isobutyroyl anilide, mp 101–101.5° (lit.[21] mp 105°), in 17.9% yield.

Alternate Preparation of 1,2,3,4,5,8-Hexamethylnaphthalene (4) from 3 *via* 6.—To a suspension of 2.0 g of lithium aluminum hydride in 100 ml of absolute ether was added at 0° over 30 min a solution of 7.4 g (0.0262 mol) of **3** in 50 ml of ether. After the mixture was stirred at room temperature for 16 hr, work-up gave a colorless oil which had a ν_{OH} at 3650 cm^{-1} and contained no carbonyl absorption. To a solution of this crude product **6** in 50 ml of dimethyl sulfoxide was added 3.5 g of sodium hydride (50% dispersion in oil), and the mixture was heated for 17 hr at 40–45°. Work-up gave 5.3 g (95.5% overall) of 1,2,3,4,5,8-hexamethylnaphthalene, mp 42.5–43.0°.

Octamethylnaphthalene (1).—Dry hydrogen chloride was bubbled through a suspension of 27 g (0.9 mol) of paraformaldehyde in 200 ml of glacial acetic acid for 2 hr, when the solution became clear. 1,2,3,4,5,8-Hexamethylnaphthalene (17.9 g, 0.084 mol) was added in one batch and the mixture was stirred for 2 hr at 35° and 1 hr at 40–45°. The mixture became green to dark blue. Hydrolysis in ice water gave a light brown solid which was collected, dissolved in ether, washed with aqueous sodium bicarbonate and water, and dried ($CaCl_2$). Evaporation of the solvent gave 25.2 g (97%) of crude 6,7-bischloromethyl-1,2,3,4,5,8-hexamethylnaphthalene (**5**). This compound decomposed on attempts at purification and was immediately reduced as follows.

To a suspension of lithium aluminum hydride (15 g, 0.4 mol) in 150 ml of anhydrous ether was added at 0–5° over 30 min a solution of crude **5** from above in 650 ml of anhydrous ether. After being stirred for 6 hr at room temperature the mixture was hydrolyzed, extracted with ether, and dried ($MgSO_4$). Evaporation of the ether left a yellow solid which was chromatographed through silica gel using petroleum ether as eluent. Fine, colorless crystals of octamethylnaphthalene (11.8 g, 64%) were obtained: mp 181–181.5° (lit.[6] mp 174°); ir 1585 (m), 1480 (s), 1450 (s), 1393 (s), 1345 (m), 1220 (w), 1140 (w), 1090 (m), 1070 (m), 1000 cm^{-1} (m); nmr τ 7.75, 7.59 (sharp singlets, equal in area); λ_{max}^{EtOH} 308 nm (log ϵ 3.76), 251 (4.70).

1,3,3,4,7,8-Hexamethyl-5,6-(4,5-dimethylbenzo)bicyclo[2.2.2]-octa-5,7-dien-2-one (7).—4,5-Dimethylbenzenediazonium-2-carboxylate hydrochloride, mp 132–133°, was prepared in 89% yield from the corresponding anthranilic acid[18] by a procedure analogous to that described above for the 3,6 isomer. A mixture of 7.5 g (0.035 mol) of the diazoniumcarboxylate hydrochloride, 6.2 g (0.035 mol) of 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (**2**), 10 ml of propylene oxide, and 100 ml of ethylene chloride was stirred and heated at reflux for 3 hr. After gas evolution

(17) Analyses were by Spang Microanalytical Laboratories, Ann Arbor, Mich. 48106. Melting points are uncorrected. Infrared and nmr spectra were taken in carbon tetrachloride solution unless otherwise stated, and are calibrated against polystyrene film and tetramethylsilane, respectively. All nmr chemical shifts are in τ units.

(18) B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, **17**, 149 (1952).

(19) The compound is stable at room temperature and can be kept for considerable time periods, though the yields of dienone–aryne adducts are somewhat improved if freshly prepared diazoniumcarboxylate hydrochloride is used.

(20) This value, reported by W. L. Mosby, *J. Amer. Chem. Soc.*, **74**, 2564 (1952), is probably in error; we have checked our value in numerous preparations.

(21) "Handbook of Tables for Organic Compound Identification," 3rd ed, compiled by Z. Rappoport, Chemical Rubber Co., Cleveland, Ohio, 1967, p 190.

ceased the mixture became homogeneous. Work-up as in the preparation of **3** gave 11.6 g of an oil which on vacuum distillation gave 1.3 g of unreacted **2**. The distillation residue was chromatographed (alumina, petroleum ether eluent) to give 7.5 g (76%) of **7**: mp 131–132° from methanol; ir $\nu_{C=O}$ 1708, other bands at 1500, 1460 (broad), 1390 (broad), 1294, 1240, 1175, 1130, 1100, 1078, 1025, 1015, 920, 890, 830 cm^{-1}; nmr τ 9.52 and 8.98 (3 each, s, *gem*-dimethyl), 8.44 (6, s, bridgehead methyls), 8.32, 8.25 (3 each, s, allylic methyls), 7.78 (6, s, aromatic methyls) 3.15 (2, s, aromatic). The compound was not analyzed, since its structure is certain from the method of synthesis and from its conversion to the known **8**. The alternative preparation from 4,5-dimethylanthranilic acid (analogous to the alternate preparation of **3**) gave **7** in 27% yield.

1,2,3,4,6,7-Hexamethylnaphthalene (8).—To a suspension of lithium aluminum hydride (0.38 g, 0.01 mol) in 30 ml of anhydrous ether at 0° was added over 60 min a solution of **7** (2.0 g, 0.0071 mol) in 20 ml of ether. After 5 hr of stirring at 0°, work-up gave 2.14 g of a colorless, viscous oil with no carbonyl and a strong hydroxyl absorption in the infrared. The mixture of epimeric alcohols was used directly in the next step.

The mineral oil was removed from 2.0 g of sodium hydride (50% dispersion) with petroleum ether, 30 ml of dimethyl sulfoxide was added followed by the epimeric alcohols from the reduction of **7**, and the mixture waa stirred at room temperature for 22 hr. The mixture was poured into ice water and the white precipitate was collected and chromatographed (silica gel, petroleum ether eluent) to give 1.22 g (77%) of 1,2,3,4,6,7-hexamethylnaphthalene (**8**): mp 145–145.5° (lit.[6] mp 145°); nmr τ 7.70 (6, s, C-2 and C-3 methyls), 7.62 (6, s, C-6 and C-7 methyls), 7.49 (6, s, C-1 and C-4 methyls), 2.39 (2, s, aromatic).

Chloromethylation of 1,2,3,4,6,7-Hexamethylnaphthalene.—The same procedure used to bischloromethylate **4**, but with somewhat longer reaction times, gave, after lithium aluminum hydride reduction, predominantly recovered **8**, with some (~30%) 1,2,3,4,5,6,7-heptamethylnaphthalene (aromatic proton at τ 2.55). The following more vigorous chloromethylation procedure was then tried.

A mixture of 0.90 g of **8**, 3 ml of chloromethyl methyl ether, 3 ml of carbon disulfide, and 0.1 ml of stannic chloride was heated at 40° for 15 hr. The resulting dark brown solid was reduced with 0.7 g of lithium aluminum hydride in 25 ml of ether for 48 hr to give, after work-up, 0.82 g of crude product. Chromatography on silica gel with petroleum ether eluent gave recovered **8**, but careful analysis of the nmr spectrum showed the presence of 27 mg (2.7%) of octamethylnaphthalene and 63 mg (6.2%) of 1,2,3,4,5,6,7-heptamethylnaphthalene.

Maleic Anhydride Adducts of Octamethylnaphthalene (*endo*-**9** and *exo*-**9**).—A mixture of 0.48 g (0.002 mol) of octamethylnaphthalene, 0.196 g (0.002 mol) of maleic anhydride, and 2 ml of chlorobenzene was heated at 132° for 13.5 hr. After removal of the solvent, the residue was chromatographic (silica gel, benzene eluent) to give some recovered **1** and 0.34 g (50.3%; 83% based on consumed **1**) of adducts *endo*-**9** and *exo*-**9**, mp 151–153° from benzene and 161–162° from carbon tetrachloride. The two isomers were not separated, but analysis of the nmr spectrum (in $CDCl_3$) showed that the ratio of *endo*-**9**, to *exo*-**9**, was 2 and permitted the following nmr assignments: *endo*-**9**, τ 8.22 (6, s), 7.83 (6, s), 7.75 (6, s), 7.58 (6, s), 7.03 (2, s); *exo*-**9**, τ 8.25 (6, s), 7.78 (6, s), 7.76 (6 s), 7.48 (6, s), 6.90 (2, s).[22]

Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.75. Found: C, 77.91; H, 7.60.

1,2,3,4-Tetramethyl-5,6-dicarbomethoxy-7,8-tetramethylbenzobicyclo[2.2.2]octa-2,5,7-triene (10).—A solution of 0.37 g (0.0016 mol) of octamethylnaphthalene and 0.33 g (0.0023 mol) of dimethyl acetylenedicarboxylate in 5 ml of chlorobenzene was heated at 130° for 20 hr. Removal of the solvent by vacuum distillation left a brown solid which was extracted with hot methanol (most of the unreacted **1** is not extracted by this solvent). Evaporation of the methanol and chromatography of the residue (silica gel, benzene eluent) gave some recovered **1** and 0.10 g (36% based on consumed **1**) of adduct **10**: mp 170–171° from cyclohexane; nmr τ 8.27 (6, s, allylic methyls), 7.93 (6, s, bridgehead methyls), 7.91 and 7.61 (6 each, s, aromatic methyls) and 6.42 (6, s, methoxyls).

Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.48; H, 8.04.

(22) These assignments are clear from a study of the maleic anhydride adducts of eight different polymethylnaphthalenes: A. Oku, Y. Ohnishi, and F. Mashio, *J. Org. Chem.*, **37**, 4264 (1972).

1,2,3,4-Tetramethyl-5,6-benzo-7,8-tetramethylbenzobicyclo[2.2.2]octa-2,5,7-triene (11).—A stirred suspension of 0.36 g (0.0015 mol) of octamethylnaphthalene, 0.64 g (0.0030 mol) of benzenediazoniumcarboxylate hydrochloride, 0.60 g (0.01 mol) of propylene oxide, and 5 ml of chlorobenzene was gradually heated until gas evolution occurred. After 1 hr, the volatile solvents were removed by vacuum distillation. The solid residue was dissolved in ether, washed with cold 2% sodium hydroxide and water, and dried ($CaCl_2$). The brown residue which remained after the solvent was evaporated was chromatographed (silica gel, carbon tetrachloride eluent). The first fraction was a solid, mp 115–130°, 0.35 g; a second, slowly eluting oily fraction was not examined further. Rechromatography (silica gel, cyclohexane eluent) gave recovered **1** and 0.14 g (30%) of the benzyne adduct **11**: mp 188.5–189° from cyclohexane; ir 1480 (s), 1460 (s), 1395 (s), 1090 (m), 1070 (m), 1045 (m), 880 cm^{-1} (s); λ_{max}^{EtOH} 269.5 nm (log ϵ 3.49), 262 (3.48), 228 (4.29); nmr τ 8.27 (6, s, allylic methyls), 7.97 (6, s, bridgehead methyls), 7.71 and 7.59 (6 each, s, aromatic methyls), 2.7–3.2 (4, m, aromatic).

Anal. Calcd for $C_{24}H_{28}$: C, 91.09; H, 8.91. Found: C, 91.10; H, 8.86.

1,2,3,4-Tetramethyl-5,6-(4,5-dimethylbenzo)-7,8-tetramethylbenzobicyclo[2.2.2]octa-2,5,7-triene (12).—The procedure was analogous to that used to prepare **11**. From identical amounts of starting materials there was obtained, after chromatography, 0.14 g (27%) of adduct **12**: mp 220–225° from cyclohexane; ir 1085, 1070, 1005, 895 cm^{-1}; nmr τ 8.27 (6, s, allylic methyls), 7.95 (6, s, bridgehead methyls), 7.83, 7.70, 7.57 (6 each, s, aromatic methyls), 3.08 (2, s, aromatic protons).

Anal. Calcd for $C_{26}H_{32}$: C, 90.64; H, 9.36. Found: C, 90.75; H, 9.27.

When the chlorobenzene was replaced with ethylene chloride and the mole ratio of diazoniumcarboxylate hydrochloride to octamethylnaphthalene was raised to 3, the yield of **12** was increased to 42%.

Attempted Synthesis of the 3,6-Dimethylbenzyne Adduct of Octamethylnaphthalene.—Replacement of 4,5-dimethylbenzenediazonium-2-carboxylate hydrochloride in the above procedure of the preparation of **12** by the 3,6-dimethyl isomer failed to give an aryne adduct. Solvent changes (ethylene chloride, diglyme), an increase in the mole ratio of aryne precursor to **1** of 4:1, and a change from propylene oxide to styrene oxide were to no avail.

Octamethylnaphthalene-1,4-endoperoxide (13).—A solution of 1.20 g (0.005 mol) of octamethylnaphthalene in 400 ml of purified hexane was irradiated (Hanovia Type L, 450-W lamp) at 20° in a Pyrex reactor with a stream of dry air continuously passing through the solution. After 2.5 hr the solution was filtered to remove a small amount of hexane-insoluble material. Evaporation of the solvent left a white residue (mp 115–120°) whose ir spectrum showed $\nu_{C=O}$ at 1700 cm^{-1}. Chromatography through silica gel (chloroform eluent) gave three fractions: 0.10 g of unreacted **1**, 0.94 g (70%) of **13**, mp 139–140° from cyclohexane, and a yellow oil which showed a strong carbonyl absorption and was not examined further. The endoperoxide had the following properties: ir 1440–1480 (broad), 1390, 1315, 1275, 1210, 1165, 1090, 1065, 1010, 690 cm^{-1}; nmr τ 8.23 (6, s), 8.21 (6, s), 7.84 and 7.67 (6 each, s, aromatic methyls). Iodine formed instantly when hydriodic acid (57%) was added to an acetic acid solution of **13**.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.51; H, 9.05.

A solution of **13** in di-*n*-butyl ether, refluxed briefly, gave a quantitative yield of **1**.

Reaction of Octamethylnaphthalene with Dibromocarbene.—Bromoform (3.1 g, 0.012 mol) was added at 0° over 10 min to a slurry of freshly prepared potassium *tert*-butoxide (1.4 g, 0.012 mol) in 60 ml of benzene containing 2.4 g (0.01 mol) of octamethylnaphthalene. The mixture was stirred at room temperature for 4 hr, during which the color changed to yellow. Cold water (50 ml) was added, the organic layer was washed twice with water, and the aqueous layer was extracted twice with benzene. The combined organic layers were dried ($MgSO_4$) and solvent was evaporated to leave a yellow solid which showed two spots on tlc (silica gel H, cyclohexane). Washing the solid with cyclohexane left a cyclohexane-insoluble product assigned structure **14**: 1.55 g (30%); mp 267–268°; ir 1465 (s), 1390 (vs), 1090 (m), 940 (m), 910 (w), 890 (w), 850 cm^{-1} (m); nmr τ 8.65 (6, s), 8.33 (6, s), 7.80 and 7.74 (6 each, s, aromatic methyls). There was no uv maximum in ethanol above 225 nm.

TABLE I

17	18	19
8.70 (3, d, J = 8.0 Hz)	8.58 (3, d, J = 7.0 Hz)	8.62 (3, d, J = 7.5 Hz)
7.72 (3, s)	7.70 (3, s)	7.73 (3, s)
7.68 (3, s)		
7.58 (6, s)	7.50 (3, s)	7.57 (3, s)
7.42 (6, s)	7.35 (3, s)	7.48 (3, s)
	7.23 (3, s)	7.32 (3, s)
7.00 (3, br s)	6.92 (3, br s)	6.98 (3, br s)
5.58 (1, q, J = 8.0 Hz)	5.53 (1, br q)	5.50 (1, br q)
	2.43 (2, q, J = 6 Hz)	2.43 (1, m)
		1.72 (1, m)

Anal. Calcd for $C_{20}H_{24}Br_4$: C, 41.13; H, 4.14. Found: C, 41.37; H, 4.20.

The cyclohexane solution obtained after the removal of **14** was chromatographed on silica gel with cyclohexane eluent to give 1.95 g (59%) of **15**: mp 121.5–122.5° from petroleum ether; ir 1645 (m), 1610 (m), 1460 (s), 1380 (m), 918 (vs), 680 cm^{-1} (s); λ_{max}^{hexane} 270 nm (sh, log ϵ 3.95), 267 (sh, 4.30), 245 (4.67), 218 (sh, 4.20); nmr τ 8.23 (3, d, J = 0.8 Hz), 8.13 (3, d, J = 0.8 Hz), 7.88 (12, br s), 7.75 (3, s), 5.17 (1, d, J = 1.8 Hz), 4.90 (1, d, J = 1.8 Hz).

Anal. Calcd for $C_{19}H_{23}Br$: C, 68.88; H, 6.99. Found: C, 68.91; H, 6.93.

Protonation of Octamethylnaphthalene.[16]—The nmr spectra of ions **17**–**19** derived from octamethylnaphthalene and the 1,2,3,4,5,8- and 1,2,3,4,5,6-hexamethylnaphthalenes in trifluoroacetic acid are shown in Table I.

The reference compound was tetramethylammonium tetrafluoroborate, assigned τ 6.87. The spectrum of **17** was unchanged after 24 hr, but that of **18** and **19** broadened and became complex after 1.5 hr at room temperature. When solutions containing ions **17**–**19** were quenched (the last two within 30 min) the parent hydrocarbons were recovered unchanged. The nmr spectrum of 1,2,3,4-tetramethylnaphthalene in trifluoroacetic acid, even after standing overnight, was identical with that obtained in carbon tetrachloride, except for a slight solvent shift.

Registry No.—**1**, 18623-61-5; **3**, 17384-74-6; **4**, 36230-30-5; **7**, 17384-75-7; **8**, 17384-76-8; *endo*-**9**, 36744-72-6; *exo*-**9**, 36744-73-7; **10**, 36870-60-7; **11**, 36794-90-8; **12**, 36900-85-3; **13**, 36230-32-7; **14**, 36807-30-4; **15**, 36794-92-0; **17**, 36812-96-1; **18**, 36863-00-0; **19**, 36863-01-0; **20**, 36794-93-1; dibromocarbene, 4371-77-1.

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Electrophilic Oxidation of Octamethylnaphthalene

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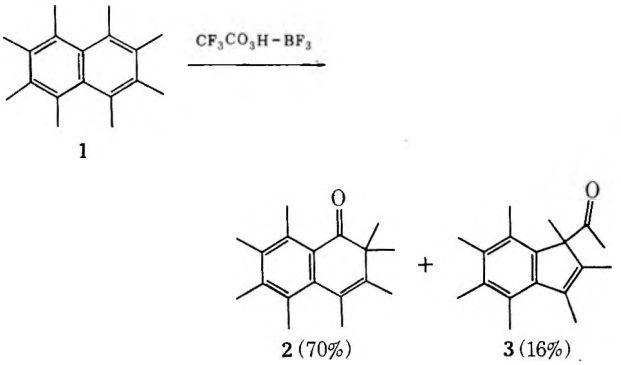
Oxidation of octamethylnaphthalene (**1**) with peroxytrifluoroacetic anhydride–boron fluoride occurred exclusively at the α position, to give 2,2,3,4,5,6,7,8-octamethyl-1(2*H*)naphthalenone (**2**, 70%) and 1-acetyl-1,2,3,4,5,6,7-heptamethylindene (**3**, 16%), formed as a result of methyl and aryl migration, respectively.

In the preceding paper[1] we described a five-step synthesis of octamethylnaphthalene (**1**) from hexamethylbenzene, in an overall yield over 50%. This synthesis made possible a study of the electrophilic oxidation of **1** with peroxytrifluoroacetic acid–boron fluoride,[2] done for the purpose of comparing the reactivity of **1** with that of hexamethylbenzene[3] and 1,2,3,4-tetramethylnaphthalene.[4] It was anticipated that **1** would be highly susceptible to electrophilic oxidation not only because of the electron-donating effect of the methyl groups, but because the peri methyl interactions might distort the aromatic π system. The oxidation did have several unusual features, including the ring contraction of the naphthalene ring system to an indene.



Results

Treatment of **1** with peroxytrifluoroacetic acid–boron fluoride gave one major and one minor product, assigned structures **2** and **3**, respectively. A third product, isolated in 14% yield, is the result of reaction of a second mole of oxidant with one of the primary products, and its structure will be discussed separately below.

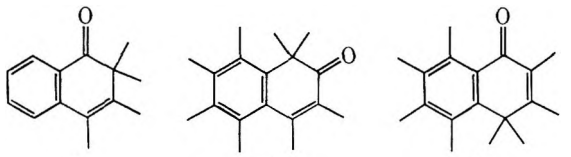
The major product (**2**) had ir and uv spectra which are characteristic of an unsaturated ketone and similar to those of **4**, the principal electrophilic oxidation product of 1,2,3,4-tetramethylnaphthalene.[4] The nmr spectrum of **2** had a sharp singlet for the *gem*-dimethyl group at τ 8.88, two homoallylically coupled methyl signals at τ 8.21 and 8.02 (J = 1.1 Hz), three aromatic methyl protons in a broad singlet at τ 7.78, and one sharp aromatic methyl singlet at τ 7.70, consistent with the assigned structure. The alternative structure **5** (a possible product of β electrophilic attack, the analog of which was a minor oxidation product of 1,2,3,4-tetramethylnaphthalene[4]) and **6** (a possible

(1) A. Oku, T. Kakihana, and H. Hart, *J. Amer. Chem. Soc.*, **89**, 4554 (1967); H. Hart and A. Oku, *J. Org. Chem.*, **37**, 4269 (1972).

(2) For a review of oxidations with this reagent, see H. Hart, *Accounts Chem. Res.*, **4**, 337 (1971).

(3) H. Hart, P. M. Collins, and A. J. Waring, *J. Amer. Chem. Soc.*, **88**, 1005 (1966).

(4) H. Hart and R. K. Murray, Jr., *J. Org. Chem.*, **32**, 2448 (1967).



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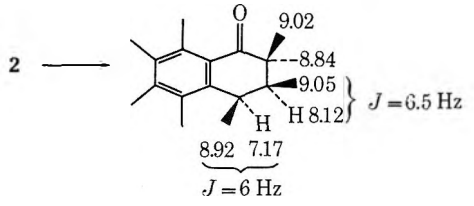
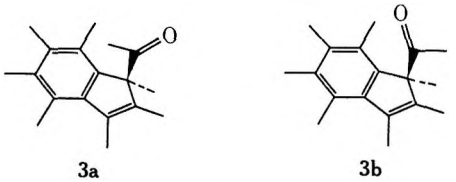
product of α electrophilic attack followed by an overall 1,4-methyl shift) were excluded by the observation that **2** did not undergo any hydrogen–deuterium exchange on prolonged reflux with sodium methoxide in CH_3OD. If the structure were either **5** or **6**, the methyl protons at the terminus of the α,β-unsaturated ketone moiety would have been exchanged. Finally, catalytic hydrogenation of **2** gave a dihydro compound whose nmr spectrum is consistent with the expected structure **7**.



7

The ir spectrum of the minor oxidation product of octamethylnaphthalene had a $\nu_{C=O}$ at 1695 cm^{-1}, a little low for a simple ketone, possibly suggesting some homoconjugation. The uv spectrum showed that there was no direct conjugation of the carbonyl group. The nmr spectrum had bands at τ 8.30 and 7.73 for two homoallylically coupled methyl groups (J = 1.1 Hz), four singlets corresponding to aromatic methyl groups at τ 7.93, 7.84, 7.82, and 7.53, and two sharp aliphatic methyl singlets at τ 8.73 and 8.57. The latter signal was completely eliminated when **3** was refluxed with sodium methoxide in CH_3OD; no other change in the nmr spectrum of **3** resulted from this treatment. This result requires that the singlet at τ 8.57 be due to an acetyl group, despite its high chemical shift.

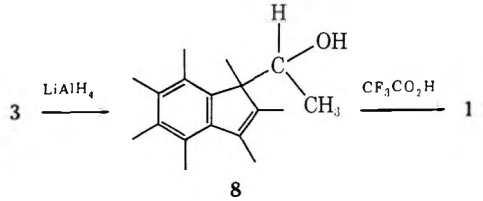
These data cannot be accommodated by any reasonable alternative structure to **3**. The high chemical shift of the acetyl methyl suggests that the favored conformation may be **3a**, not **3b**; the methyl is then placed



3a **3b**

in the shielding region of the indene ring system. Consistent with this notion, catalytic hydrogenation of **3** gave a dihydro derivative in which the acetyl methyl group was shifted downfield to a more normal region (τ 8.10). Alternative rationalizations of the high acetyl methyl shift in **3** are possible.

Reduction of **3** with lithium aluminum hydride gave a secondary alcohol **8** which, when treated with trifluoroacetic acid, dehydrated with rearrangement to give octamethylnaphthalene, as well as some other products which were not investigated.



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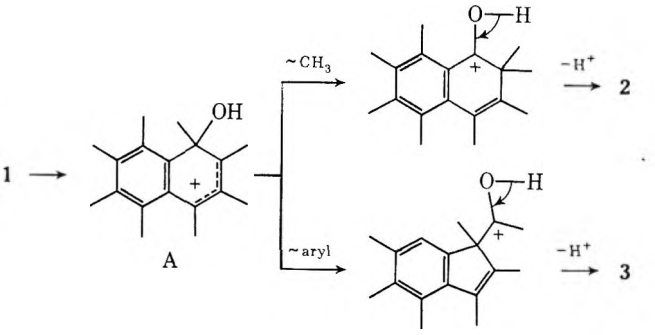
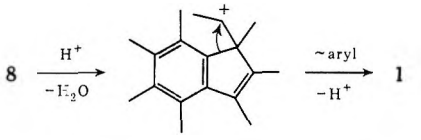
The formation of **2** and **3** as the major monooxidation products of octamethylnaphthalene can be rationalized



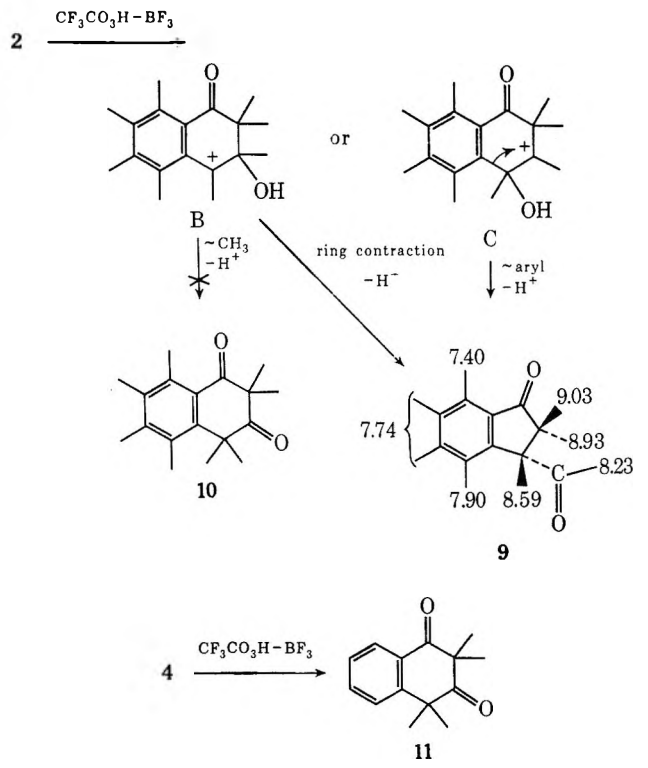
by an electrophilic attack at a peri position followed by methyl or aryl migration, respectively. We believe that this is the first example of conversion of a naphthalene to an indene on electrophilic attack. The analogous reaction was not observed during the oxidation of 1,2,3,4-tetramethylnaphthalene,[4] which suggests that one driving force may be the additional relief from the second peri interaction that is obtained when one of the rings is contracted. However the driving force for rearomatization can overcome the peri interactions, as shown by the conversion of **8** to **1** in acid. Finally,



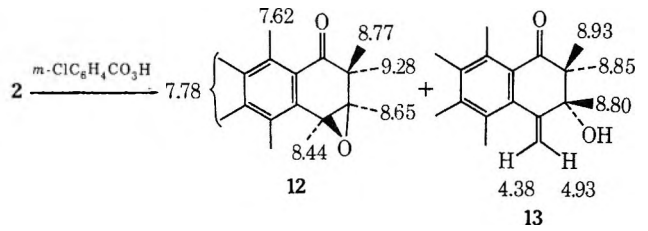
in contrast with 1,2,3,4-tetramethylnaphthalene, no oxidation product was obtained from **1** corresponding to β attack by the electrophile. Such attack would not give any relief from the peri interactions such as is experienced in the intermediate benzenonium ion A.

The overoxidation product of **1** contained one more oxygen atom than **2** or **3**. Its uv spectrum was similar to that of indanone, and the ir spectrum had a $\nu_{C=O}$ at 1700 cm^{-1} but no C=C absorption. The nmr spectrum showed four aromatic methyl groups [τ 7.90, 7.74 (6 H), and 7.40] and four additional sharp methyl singlets at τ 9.03, 8.93, 8.59, and 8.23. The only change brought about by treatment with sodium methoxide in CH_3OD was the complete removal of the τ 8.23 signal, suggesting the presence of one acetyl group, and this was confirmed by a positive iodoform test. Finally, oxidation of **2** with peroxytrifluoroacetic acid–boron fluoride gave the same overoxidation product in good yield. These data suggest that the structure of this product is **9**. This product could arise from intermediates such as B or C. In the tetramethylnaphthalene series, the sole overoxidation product of **4** (the analog of **2**) was the dione **11**.[4] The corresponding reaction of **2** to give **10** was not observed in the octamethyl series, possibly because of the severe repulsion which would exist between the *gem*-dimethyl group and the adjacent aromatic methyl group in **10**. If **9** is formed *via* the less likely nonbenzylic intermediate C, then aryl migration wins out over methyl migration, which would lead to a strained and unobserved 1,4-dione.

In an attempt to synthesize **9** more directly, the primary oxidation product **2** was treated at room tempera-



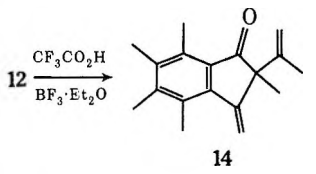
ture with *m*-chloroperbenzoic acid. Two products were obtained; the yield of each depended very sensitively on the reaction conditions. The structures tentatively assigned to these products are **12** and **13**, which could



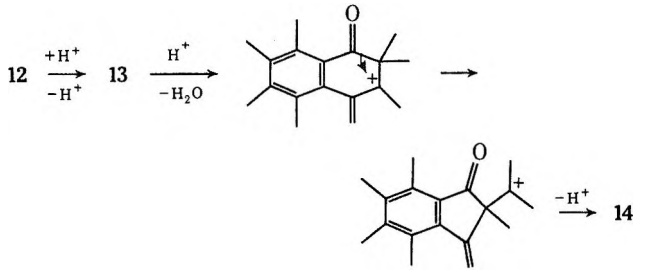
be obtained in yields as high as 83 and 70%, respectively. The structures are assigned from spectral data and mechanistic considerations. The epoxy ketone **12** had a $\nu_{C=O}$ at 1692 cm^{-1} and λ_{max} at 300 nm (log ϵ 3.20), 261 (3.91), and 222 (4.26), showing considerably less conjugation than **2**. The hydroxy ketone **13**, on the other hand, had a $\nu_{C=O}$ at 1678 cm^{-1} and λ_{max} at 324 nm (log ϵ 3.38), 272 (4.09), and 240 (4.42), as well as a ν_{OH} at 3680 cm^{-1} and a strong terminal methylene band at 925 cm^{-1}. The nmr spectra, as shown in the formulas, are consistent with the assigned structures. The nmr spectrum of **13** had signals at τ 7.79 (3 H), 7.73 (3 H), and 7.58 (6 H) for the aromatic methyl groups.

It seems likely that **13** arises from **12** by proton loss from the intermediate ion B. Apparently under the less acidic conditions used for this oxidation, compared with those used to oxidize **1**, proton loss occurs faster than the ring contraction which gave **9**.

The epoxy ketone was treated briefly at room temperature with a little trifluoroacetic acid and boron fluoride etherate, with the hope of obtaining **9**. Although the crude product had some nmr peaks corresponding to **9**, the major product (85%) was yet another unsaturated ketone to which we tentatively assign structure **14**.



The uv spectrum showed considerable conjugation, with λ_{max} at 335 nm (log ϵ 3.41), 268 (4.11), 244 (4.56), and 206 (3.93), but the $\nu_{C=O}$ at 1700 cm^{-1} suggests that the carbonyl group is in a five-membered ring. Bands for the terminal methylene groups appeared at 930 and 905 cm^{-1}. The nmr spectrum of **14** had signals for four vinyl protons at τ 4.96 (2 H), 4.70, and 4.21, two aliphatic methyls at τ 8.69 and 8.50, and four aromatic methyl singlets at τ 7.72, 7.65, 7.45, and 7.34. A possible route to **14** is shown. Acyl migration and the



relief of strain which comes from the ring contraction are apparently preferable to alternative rearrangements, which one can readily envision. It appears that the course taken during the rearrangements of these systems is delicately balanced among many alternatives, and depends very much on the reaction conditions, particularly the acidity or basicity of the reaction medium. Further work is needed to unequivocally establish the structures of **13** and **14**.

In conclusion, electrophilic oxidation of octamethylnaphthalene occurs exclusively at an α position, and involves both alkyl migration to give **2** and aryl migration with ring contraction to give **3**. This is in contrast with the behavior of 1,2,3,4-tetramethylnaphthalene, which is oxidized at the α and β positions of the substituted ring. This difference, as well as others which occur when the primary oxidation products of **1** are further oxidized, is ascribed to efforts to relieve the strain associated with peri methyl interactions.

Experimental Section[5]

Oxidation of Octamethylnaphthalene with Peroxytrifluoroacetic Acid–Boron Fluoride.—To a solution of 2.40 g (0.01 mol) of octamethylnaphthalene in 40 ml of methylene chloride at −20° was added during 15 min a methylene chloride (8 ml) solution of peroxytrifluoroacetic acid prepared from 2.31 g (0.011 mol) of trifluoroacetic anhydride and 0.35 g (0.0102 mol) of 98% hydrogen peroxide. Boron fluoride etherate (47%, 3.08 g, 0.0102 mol) was added concurrently. After addition, stirring was continued at −20° for 25 min, 50 ml of water was added, and the organic layer was washed with water (50 ml), 3% sodium hydroxide (2 × 50 ml), and water (3 × 50 ml) and dried ($MgSO_4$). Evaporation of the solvent gave 2.38 g of a yellow solid which showed four spots on tlc (silica gel G, chloroform eluent). The mixture was chromatographed through silica gel (21 × 500 mm column) using carbon tetrachloride, which gave as the first fraction 0.81 g (34%) of recovered octamethylnaphthalene. A change in the eluent to chloroform gave three additional fractions.

(5) Melting points are uncorrected. Ir and nmr spectra were recorded in CCl_4 solution, calibrated against polystyrene and tetramethylsilane, respectively. Chemical shifts are in τ units. Analysis were by Spang Microanalytical Laboratories, Ann Arbor, Mich.

The first was identified as **2,2,3,4,5,6,7,8-octamethyl-1(2*H*)-naphthalenone** (**2**), 1.20 g (71%), mp 89–90° from petroleum ether (bp 30–60°). The second was **1-acetyl-1,2,3,4,5,6,7-heptamethylindene** (**3**), 0.28 g (16%), mp 140–140.5° after recrystallization from petroleum ether, then methanol. The third, which was eluted from the column much more slowly, is thought to be **3-acetyl-2,2,4,5,6,7,8-heptamethyl-1-indanone** (**9**), 0.27 g (14%), mp 123.5–124.5° from methanol. Only traces of tars were produced during the oxidation. When the mole ratio of oxidant to octamethylnaphthalene was doubled, the amount of unreacted octamethylnaphthalene dropped to 0.24 g, the yield of **2** decreased to 0.54 g, the yield of **3** was unchanged, and the yield of **9** increased to 1.57 g.

Structural Evidence for Compound 2.—Compound **2** had the following properties: ir 1685 (vs), 1624 (w), 1563 (m), 1465 and 1455 (s, br), 1385 (m), 1360 (w), 1320 (w), 1295 (m), 1270 (w), 1118 (m), 1090 (s), 1005 (m), 950 (m), 870 cm^{-1} (m); λ_{max}^{EtOH} 353 nm (log ϵ 3.02), 280 (3.27), 250 (4.54), 212 (4.14); nmr τ 8.88 (6, s, *gem*-dimethyl), 8.21 (3, d, J = 1.1 Hz, C-3 methyl), 8.02 (3, d, J = 1.1 Hz, C-4 methyl), 7.78 (9, br s, C-5, C-6, and C-7 methyls), 7.70 (3, s, C-8 methyl). This nmr spectrum was unchanged when 0.23 g of **2** was refluxed with a solution of 0.02 g of sodium in 4.4 g of CH_3OD for 42 hr.

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.17; H, 9.34.

Catalytic hydrogenation of 0.128 g of **2** in 25 ml of absolute ethanol using 0.128 g of 5% Pd/C catalyst resulted in the uptake of 91% of theory for 1 mol of hydrogen and gave a nearly quantitative yield of **7**: mp 63–65° (not sharp); *m/e* 258; nmr τ 9.05 (3, d, J = 6.5 Hz, C-3 methyl), 9.02 and 8.84 (3 each, s, *gem*-dimethyls at C-2), 8.92 (3, d, J = 6.0 Hz, C-4 methyl), 7.83 (9, br s, C-5, C-6, and C-7 methyls), 7.77 (3, s, C-8 methyl), 8.12 (1, q, J = 6.5 Hz, methine at C-3), 7.17 (1, q, J = 6.0 Hz, methine at C-4).

Structural Evidence for Compound 3.—Compound **3** had the following properties: ir 1695 (vs), 1455 (br m), 1392 (w), 1370 (w), 1355 (m), 1090 (m), 1015 cm^{-1} (m); λ_{max}^{EtOH} 267 nm (log ϵ 3.96), 222 (4.39); nmr τ 8.73 (3, s, C-1 methyl), 8.57 (3, s, acetyl methyl), 8.30 (3, q, J = 1.1 Hz, C-2 methyl), 7.93 (3, s, C-7 methyl), 7.84 and 7.82 (3 each, s, C-5 and C-6 methyl), 7.73 (3, q, J = 1.1 Hz, C-3 methyl), 7.53 (3, s, C-4 methyl).

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.32; H, 9.45.

A solution of 45 mg of **3** in 4 ml of CH_3OD containing 0.01 g of dissolved sodium was refluxed for 22 hr. Work-up gave recovered **3**, whose nmr spectrum was unchanged except that the singlet at τ 8.57 was absent. Compound **3** absorbed bromine (in CCl_4) rapidly, but there was no change in $\nu_{C=O}$, showing that the double bond is not conjugated with the carbonyl group.

A solution of **3** (100 mg) in 23.5 ml of ethanol containing 50 mg of 5% palladium on charcoal was hydrogenated at 5-atm pressure for 3.5 hr, at which time no further hydrogen was absorbed. Work-up gave dihydro-**3** with the following nmr spectrum: τ 9.04 (3, d, J = 7.5 Hz, C-2 or C-3 methyl), 8.94 (3, d, J = 7.5 Hz, C-2 or C-3 methyl), 8.60 (3, s, C-1 methyl), 8.10 (3, s, acetyl methyl), 7.99 (3, s, aromatic methyl), 7.85 (6, s, aromatic methyls), 7.78 (3, s, aromatic methyl). The methine protons appeared as a complex multiplet in the region of τ 8.0.

To a suspension of lithium aluminum hydride (30 mg) in 6 ml of anhydrous ether was added a solution of **3** (50 mg) in 6 ml of ether, and the mixture was stirred at room temperature for 3 hr. The usual work-up gave **1-(1-hydroxyethyl)heptamethylindene** (**8**): mp 125–126.5° from benzene; ir 3680 (m), 1630 (w), 1455 (s, br), 1390 (m), 1375 (m), 1265 (m), 1100–1140 (s, br), 930 (m), 910 cm^{-1} (m); λ_{max}^{EtOH} 270 nm (log ϵ 4.04), 228 (4.20); nmr τ 9.20 (3, d, J = 6.5 Hz, $-CHCH_3$), 8.67 (3, s, C-1 methyl), 8.19 (3, br s, C-2 methyl), 7.82 (9, br s, C-3 C-5, and C-6 methyls), 7.58 (6, s, C-4 and C-7 methyls), 5.92 [1, m, $-CH(OH)CH_3$]. A solution of **8** (17 mg) and 1 drop of trifluoroacetic acid in 2 ml of methylene chloride was allowed to stand at room temperature for 5 hr. Cyclohexane (10 ml) was added, and the organic layer was washed with 5% aqueous sodium hydroxide and water and dried ($MgSO_4$). Tlc on silica gel afforded a few milligrams of octamethylnaphthalene.

Structural Evidence for Compound 9.—Compound **9** had the following properties: ir 1700 (vs), 1570, 1470–1450 (br m), 1385 (m), 1375 (m), 1355 (m), 1310 (m), 1280 (w), 1265 (w), 1220 (m), 1180 (w), 1145 (w), 1110 (s), 1080 (m), 995 (m), 895 cm^{-1} (w); λ_{max}^{EtOH} 310 nm (log ϵ 3.29), 265 (4.18), 218 (4.46); nmr τ 9.03, 8.93 (3 each, s, *gem*-dimethyl), 8.59 (3, s, C-3 methyl), 8.23 (3, s, acetyl methyl), 7.90, 7.74, and 7.40 (3, 6 and 3, s, aromatic methyls). When a solution of **9** (50 mg) in 5 ml of CH_3OD containing 10 mg of sodium metal was refluxed for 20 hr, **9** was recovered unchanged except that the singlet at τ 8.23 was missing from its nmr spectrum. Compound **9** also gave a positive iodoform test.[6] Compound **9** absorbed bromine only gradually and did not absorb any hydrogen when treated with 5% Pd/C in ethanol at room temperature and 5 atm of hydrogen. Compound **9** was recovered unchanged after 5.5 hr reflux with acetic acid in benzene and after 2 days at room temperature with boron fluoride etherate in methylene chloride (that is, an epoxide moiety is not present).

Oxidation of 2 with Peroxytrifluoroacetic Acid–Boron Fluoride.—To a solution of **2** (0.80 g, 0.0031 mol) in 15 ml of methylene chloride was added at −23 to −25° over 15 min 0.96 g (0.0032 mol) of 47% boron fluoride etherate and a solution of peroxytrifluoroacetic acid prepared from 0.72 g (0.0034 mol) of trifluoroacetic anhydride, 0.11 g (0.0032 mol) of 98% hydrogen peroxide, and 3 ml of methylene chloride. After 1.5 hr at −23 to −5°, the mixture was worked up as in the oxidation of **1**. The crude product (0.78 g) was chromatographed (silica gel, chloroform eluent) to give only recovered **2** (a few milligrams) and **9** (0.88 g, 81%), identical (melting point, ir, nmr) with the same product isolated from the oxidation of octamethylnaphthalene.

Oxidation of 2 with *m*-Chloroperbenzoic Acid.—To a solution of **2** (0.195 g, 0.76 mmol) in 15 ml of benzene cooled in an ice bath was added a solution of 0.165 g of 87% *m*-chloroperbenzoic acid in 10 ml of benzene. After 1.5 hr, the solution was washed with 5% sodium carbonate and water and dried ($MgSO_4$). Evaporation of the solvent gave a white solid (0.198 g) which, on recrystallization from methanol, gave 0.170 g (83%) of the epoxide **12**: mp 145–149°; ir 1692 (vs), 1475 (m), 1385 (m), 1370 (w), 1320 (m), 1280 (w), 1225 (w), 1170 (w), 1130 (w), 1105 (m), 1095 (s), 945 (m), 890 cm^{-1} (m); λ_{max}^{EtOH} 300 nm (log ϵ 3.20), 261 (3.91), 222 (4.26); nmr τ 9.28, 8.77 (3 each, s, *gem*-dimethyls), 8.65, 8.44 (3 each, s, epoxide methyls), 7.78, 7.62 (9 and 3, s, aromatic methyls).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.41; H, 8.93.

To a solution of **2** (0.10 g, 0.37 mmol) in 8 ml of methylene chloride was added 0.080 g of *m*-chloroperbenzoic acid in 7 ml of methylene chloride. After 6 min, work-up showed that only 50% of **2** was oxidized. The mixture of starting material and product was redissolved in methylene chloride and 0.07 g of *m*-chloroperbenzoic acid was added. After 20 min the reaction was worked up to give 0.075 g (70%) of alcohol **13**: mp 125–127° from methanol; ir 3680 (w), 1678 (vs), 1470–1460 (s, br), 1420 (w), 1395 (s), 1380 (s), 1298 (s), 1120 (s, br), 1080 (m), 1040 (w), 1010 (w), 950 (m), 925 cm^{-1} (vs); λ_{max}^{EtOH} 324 nm (log ϵ 3.38), 272 (4.08), 240 (4.42); nmr τ 8.93, 8.85 (3 each, s, *gem*-dimethyl), 8.80 (3, s), 7.79, 7.73, 7.58 (3, 3, and 6, s, aromatic methyls), 4.93 (1, d, J = 1.5 Hz), 4.38 (1, d, J = 1.5 Hz).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.28; H, 8.96.

Another oxidation of **2** in methylene chloride at room temperature for 1 hr gave a mixture of **12** and **13**; the former crystallized from methanol; and the latter was obtained from the mother liquors of this crystallization by adding cyclohexane.

Rearrangement and Dehydration of Epoxy Ketone 12 in Acid.—Two drops each of trifluoroacetic acid and 47% boron fluoride etherate were added to a solution of **12** (0.060 g, 0.22 mmol) in methylene chloride (6 ml). After 10 min at room temperature the mixture was washed with 5% sodium carbonate and water, and dried ($MgSO_4$). Evaporation of the solvent left a yellow solid, the nmr spectrum of which showed the presence of traces of **9**. However, the major component (0.048 g, 85%), isolated by chromatography on alumina with cyclohexane and chloroform as eluents, was a yellow, crystalline, unsaturated ketone **14**: mp 119–122° after recrystallization from 75% aqueous ethanol; ir 1700 (vs), 1638 (w), 1630 (m), 1575 (w), 1455 (m), 1380 (m), 1310 (m), 1275 (w), 1100 (w), 930 (m), 905 cm^{-1} (s); λ_{max}^{EtOH} 335 nm (log ϵ 3.41), 268 (4.11), 244 (4.56), 206 (3.93); nmr τ 8.69 (3, s, C-2 methyl), 8.50 (3, s, allylic methyl), 7.72, 7.65, 7.45, 7.34 (3 each, s, aromatic methyls), 4.96 (2, br s, methylene protons), 4.70 and 4.21 (1 each, slightly split, methylene protons).

Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.98; H, 8.70.

(6) R. Shriner, R. C. Fuson, and D. V. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964.

Registry No.—1, 18623-61-5; 2, 36794-95-3; 3, 36794-96-4; 7, 36807-48-4; 8, 36794-97-5; 9, 36870-64-1; 12, 36807-49-5; 13, 36794-98-6; 14, 36870-65-2.

Acknowledgment.—We thank the National Institutes of Health and the National Science Foundation for financial support.

Fundamental Studies of Substituted Ferrocene Systems. VI. Electronic Effects in the Alkylferrocenes

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The 220-MHz proton magnetic resonance spectra of methyl-, ethyl-, isopropyl-, and *tert*-butylferrocene are reported. The improved resolution allows differentiation of resonances in all but isopropylferrocene, thus allowing investigation of chemical shift trends for the various protons involved. Spectra were also obtained for the specifically deuterated molecules necessary to establish the identity of the various resonances. Of interest is the predominant shielding effect experienced at the 3,4-position protons contrary to previous predictions and assignments.

Proton magnetic resonance spectroscopy has proven to be a valuable tool in the analysis of ferrocenes, both for the determination of structure and for the investigation of the modes of transmission of electronic effects. A complete spectral analysis of the alkylferrocenes has been absent from the literature because of the failure of the 60- and 100-MHz instruments to resolve the weakly perturbed ring proton resonances. We wish to report here the 220-MHz spectra of methyl-, ethyl-, isopropyl-, and *tert*-butylferrocene along with the appropriately deuterated molecules necessary to unambiguously assign the various resonances.

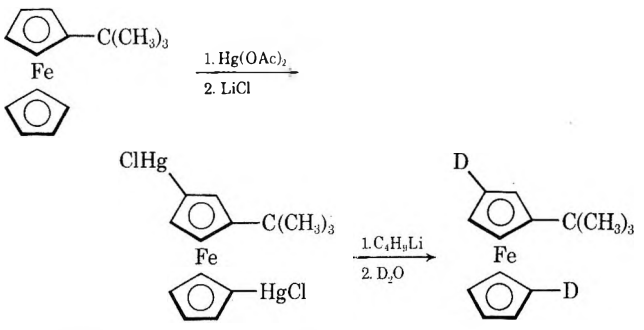
The 60- and 100-MHz spectra of this series of alkylferrocenes have been reported by a number of research groups. Benkeser and coworkers[1,2] observed ring proton resonances for methylferrocene at δ 3.99 and 3.94 and on the basis of integration alone assigned the downfield resonance to the 1′- and 3,4-position protons and the upfield resonance to the 2,5-position protons. Resolution was not sufficient to separate the homoannular ring resonances of the other alkylferrocenes. In contrast, Rausch and Siegel[3] reported that the pmr spectrum of 2,5-dideuteriomethylferrocene exhibited a partial decrease in absorption for the upfield resonance, concluding that this resonance in the undeuterated molecule was in fact due to both the 2,5- and 3,4-position protons. Similarly, Nesmeyanov and coworkers[4] have reported the spectra of this same series of compounds and claimed to have obtained sufficient resolution to partially resolve the upfield resonance in both methyl- and *tert*-butylferrocene. Citing Benkeser, *et al.*,[1,2] and a paper by Levenberg and Richards,[5] they assigned the upfield resonance to the 2,5-position protons. These inconsistencies are mainly the result of insufficient resolution afforded by the 60- and 100-MHz spectrometers, which prohibits reliable assignment of the homoannular ring resonances and hence meaningful assessment of electronic effects of the substituents.

Recent results from this laboratory have demonstrated that for strong electron-donating substituents an upfield shift is experienced predominately by the 3,4-position protons.[6] Since alkyl groups are weak electron donors, a distinct possibility of a parallel electronic effect was seen to exist between these two systems such that the homoannular ring assignments of Benkeser, *et al.*,[1,2] and Nesmeyanov, *et al.*,[4] would need to be reversed.

Results and Discussion

The 220-MHz spectral data for these alkylferrocenes are summarized in Table I along with "corrected" chemical shift data of the previous authors. Assignments of the substituted ring resonances were made on the basis of comparison to the spectra of specifically deuterated molecules. 2-Deuteriomethylferrocene and 2,5-dideuterioethylferrocene were prepared *via* routes involving lithiation–deuteration procedures on *N*,*N*-dimethylaminomethylferrocene[7] and *N*,*N*-dimethylaminoethylferrocene,[8] respectively, in which the metalation has been demonstrated unequivocally to occur at the 2 position. 3,1′-Dideuterio-*tert*-butylferrocene was prepared by the sequence of reactions shown in Scheme I.

SCHEME I



(1) R. A. Benkeser, Y. Nagai, and J. Hooz, *Bull. Chem. Soc. Jap.*, **36**, 482 (1963).

(2) T. Nagai, J. Hooz, and R. A. Benkeser, *ibid.*, **37**, 53 (1964).

(3) M. D. Rausch and A. Siegel, *J. Organometal. Chem.*, **17**, 117 (1969).

(4) A. N. Nesmeyanov, W. I. Fedin, O. U. Nogina, N. S. Kochetkova, V. A. Dubovitsky, and P. V. Petrovsky, *Tetrahedron, Suppl. 8*, Part II, 389 (1966).

(5) M. I. Levenberg and J. H. Richards, *J. Amer. Chem. Soc.*, **86**, 2634 (1964).

(6) (a) D. W. Slocum, P. S. Shenkin, and T. R. Engelmann, Abstracts, 4th International Conference on Organometallic Chemistry, Bristol, England, July 1969, Paper G-5. (b) C. R. Ernst, P. Shenkin, T. R. Engelmann, and D. W. Slocum, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Inorganic Section, Paper 82. (c) D. W. Slocum, P. S. Shenkin, T. R. Engelmann, and C. R. Ernst, *Tetrahedron Lett.*, 4429 (1971).

(7) D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 1241 (1965).

(8) D. W. Slocum, C. A. Jennings, T. R. Engelmann, C. R. Hauser, and B. W. Rockett, *J. Org. Chem.*, **36**, 377 (1971).

TABLE I
CHEMICAL SHIFT DATA FOR ALKYL FERROCENES DETERMINED AT 220 MHz[a]

Registry no.	Substituent	$H_{1'}$	$H_{2,5}$	$H_{3,4}$	α[b]	β[c]
1271-44-9	Methyl	3.964	3.932	3.895	1.877	
		(3.95, 3.99)	(3.92, 3.99)	(3.89, 3.94)	(—, 1.96)	
1273-89-8	Ethyl	3.977	3.936	3.927	2.31	1.18
		(3.98, 4.01)	(3.94, 3.97)	(3.94, 3.97)	(2.30, 2.29)	(1.15, —)
12126-81-7	Isopropyl	3.991	3.927	3.927	2.57	1.18
		(3.97, 4.02)	(3.92, 3.96)	(3.92, 3.96)	(2.58, 2.59)	(1.15, —)
1316-98-9	*tert*-Butyl	4.018	3.945	3.909		1.21
		(4.02, 4.02)	(3.95, 3.92)	(3.89, 3.92)		(1.20, —)

[a] In parts per million. Values in parenthesis are those reported by Nesmeyanov[4] and Benkeser,[1,2] respectively. Assignments have been reversed to coincide with our revised data. [b] Chemical shifts of the protons of the alkyl group located on the carbon atom attached to the ferrocene ring. [c] Chemical shift of the protons of the alkyl group located on the carbon atoms other than those attached to the ferrocene ring.

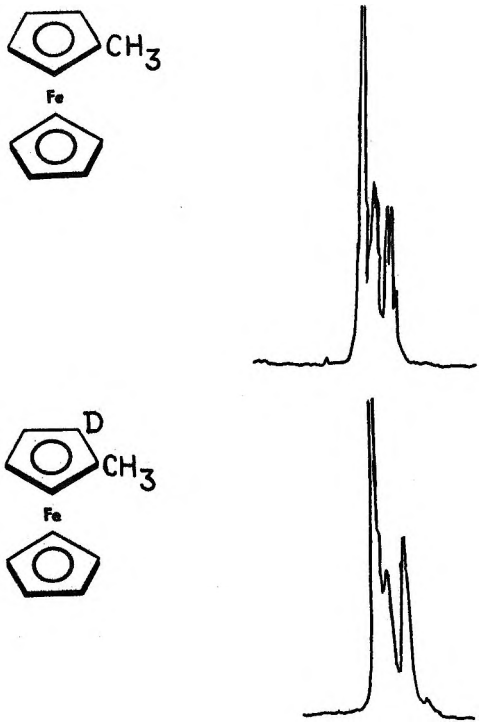


Figure 1.—Pmr spectra of methyl- and 2-deuteriomethylferrocene at 220 MHz.

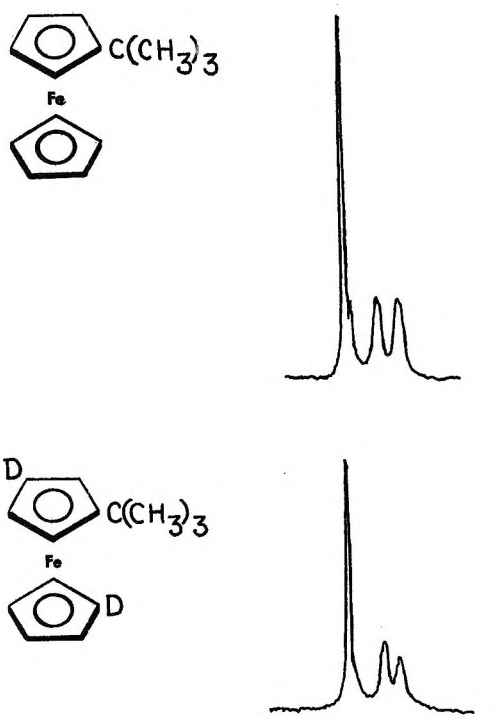


Figure 2.—Pmr spectra of *tert*-butyl- and 3,1′-dideuterio-*tert*-butylferrocene at 220 MHz.

Chloromercuration of *tert*-butylferrocene yielded an intermediate primarily consisting of 3,1′-dichloromercuri-*tert*-butylferrocene. The assumption was made that little or no 2- or 2,1′-dichloromercuri compound would be formed because of the bulk of the *tert*-butyl group. This material was converted to the corresponding dilithio intermediate by reaction with *n*-butyllithium in ether. Condensation of this solution with deuterium oxide yielded 3,1′-dideuterio-*tert*-butylferrocene containing 1.53 atoms of deuterium per molecule as determined by mass spectral analysis. Although the orientation of the product of chloromercuration of *tert*-butylferrocene has not been established, previous electrophilic substitution reactions on this molecule have been shown to occur predominantly at the 3 and 1′ positions.[9]

Comparative pmr spectra of the deuterated and undeuterated methyl- and *tert*-butylferrocene are shown in Figures 1 and 2. The ring proton resonances in the spectra of the undeuterated molecules were clearly resolved in all but isopropylferrocene, which exhibited singlets for both the substituted and unsubstituted rings. In each of the remaining molecules the 3,4-position protons appeared upfield with respect to the 2,5- and 1′-position proton resonances. The observed relative shielding orders are contrary to the assignments previously suggested and are indicative of a predominantly resonance mode of interaction of the alkyl groups with the ferrocene ring. The transmission of this effect primarily to the 3,4 positions is also established.

The improved resolution obtained has revealed some interesting chemical-shift trends for the various positions in this series of alkylferrocenes. Figure 3 is a graphical representation of the ortho, meta, and para protons for the series methyl- through *tert*-butylbenzene.[10] Figure 4 is a similar representation of the 2,5- and 3,4-position protons for the series methyl- through *tert*-butylferrocene. We note that there is a fairly similar trend in the plots of the para benzene

(9) R. A. Benkeser, Y. Nagai, and J. Hooz, *J. Amer. Chem. Soc.*, **86**, 3742 (1964).

(10) F. A. Vobey, F. P. Hood, III, E. Pier, and H. E. Weaver, *ibid.*, **87**, 2060 (1965).

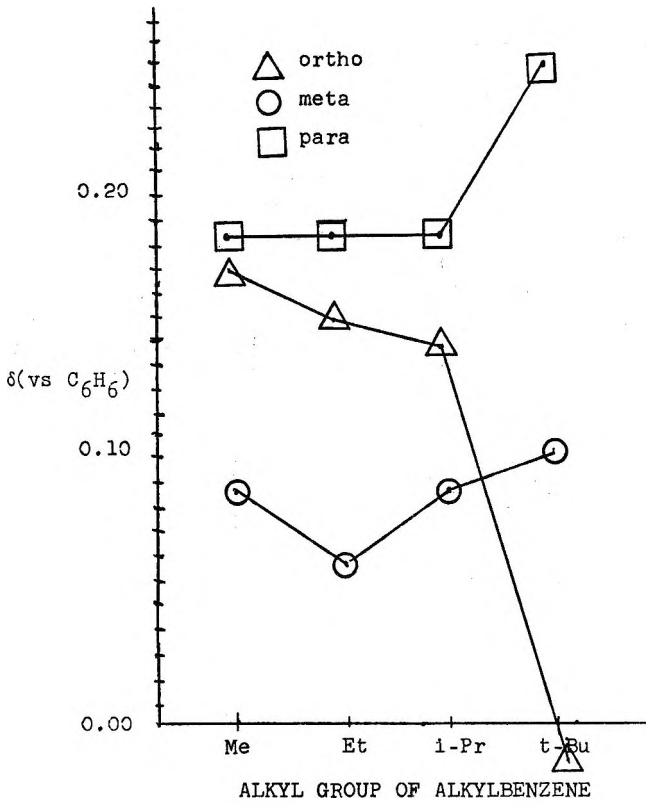


Figure 3.—Chemical shifts of ring protons of alkylbenzenes.

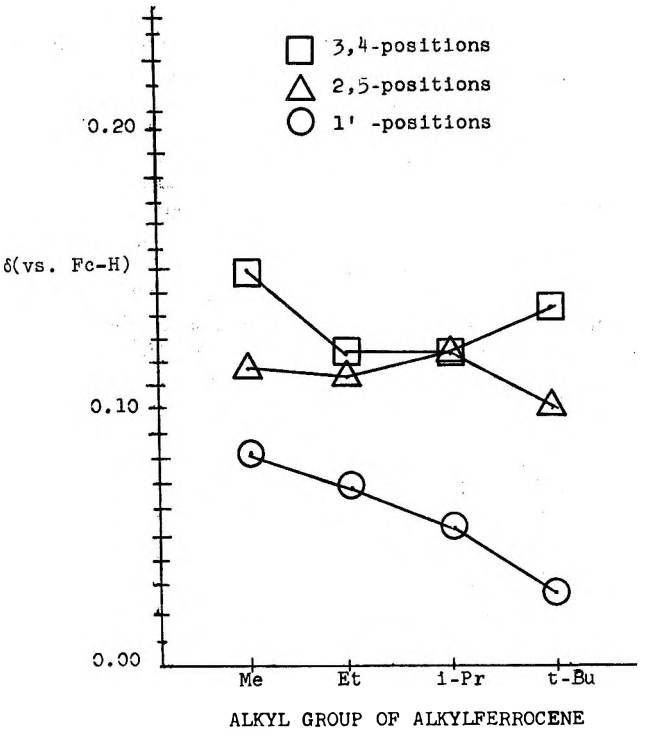


Figure 4.—Chemical shifts of homoannular ring protons of alkylferrocenes.

protons and the 3,4-position ferrocene protons, particularly with regard to the anomalous upfield trend for the respective *tert*-butyl compounds. This observation in turn reinforces our arguments of the position of chloromercuration of *tert*-butylferrocene and hence also the position of deuteration. A lesser correlation is noted between the ortho benzene protons and the 2,5 protons of the alkylferrocenes.

Although too few substituents were studied to obtain a meaningful correlation of chemical shift data with substituent constants, a positive correlation did exist for the 3,4-position data with σ_{para} and Lupton–Swain σ_R[11] constants. A similar correlation could not be obtained for the 2,5 and 1′ positions, however. The lack of correlation for the 2,5-position protons was due principally to an abnormal shift for these protons in *tert*-butylferrocene. A similar shift for the ortho protons in *tert*-butylbenzene has been attributed to a van der Waals interaction with the substituent.[10] The downfield trend for the 1′-position protons through the series suggests that such an interaction may also be involved for these protons.

In conclusion, the assignment of the resonances in this series of alkylferrocenes should be of great aid in the future analysis of alkylferrocene spectra. An evaluation of the relative importance of resonance (hyperconjugation) and induction to the electronic effects of the alkyl substituents and a better understanding of the transmission of resonance effects in the ground state of alkylferrocenes has also been provided.

Experimental Section

General.—The 220-MHz spectra were obtained at an ambient temperature of 20° on a Varian HR 220 spectrometer located at the University of Illinois. All samples were 3% (molar) in carbon tetrachloride with tetramethylsilane as an internal standard. Mass spectra were obtained on a CEC 21-109 spectrometer at an inlet temperature of 200°. Gas chromatography was carried out on a Varian Aerograph 90-p gas chromatograph on a 6% Apiezon L on Chromosorb W column. The undeuterated alkylferrocenes except for isopropylferrocene were prepared by published procedures.[12,13] Methylferrocene was prepared by the Na/NH_3 reduction of dimethylaminomethylferrocene methiodide.[14] The *n*-butyllithium used in the following reactions was 1.6 *M* in hexane and was provided by Foote Mineral Co.

Preparation of Isopropylferrocene.—α-Methylvinylferrocene[15] (1.08 g, 4.8 mmol) was placed in a hydrogenation flask along with 10 ml of ethanol, 3 ml of benzene, and 0.03 g of Pd/C catalyst. Hydrogenation was carried out at an operating pressure of 52 psi for 2.0 hr. The resulting mixture was filtered, diluted with 200 ml of water, and extracted repeatedly with ether. The ether extracts were combined, dried over anhydrous $MgSO_4$, and stripped under vacuum. The remaining oil was chromatographed on 100 g of neutral alumina I; elution with petroleum ether (bp 40–60°) afforded 1.04 g (95%) of a red oil. An ir of this product was identical with that of isopropylferrocene as described in the literature.[16]

Preparation of 2-Deuteriomethylferrocene.—Dimethylaminomethylferrocene (10 g, 41.2 mmol) was dissolved in about 125 ml of anhydrous ether in a 250-ml flask equipped with a nitrogen inlet tube. *n*-Butyllithium (40 ml, 60 mmol) was added and the resulting solution was stirred for 1.5 hr, after which time excess deuterium oxide was added.[7] After sitting for 2 hr at room temperature, the reaction mixture was filtered and the filtrate was stripped of solvent. The resulting oil was dissolved in ether and treated with excess methyl iodide. A copious precipitate of the methiodide was collected. This methiodide (1.68 g, 4.25 mmol), sodium amalgam (23.94 g, 10%), water (117 ml), and benzene (75 ml) were combined and allowed to set for several hours. The benzene layer was separated and stripped and the resulting oil was chromatographed on alumina I. Elution with petroleum ether yielded 2-deuteriomethylferrocene (0.32 g, 37%) which

(11) C. G. Swain and E. C. Lupton, *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

(12) P. Pauson and W. Watts, *J. Chem. Soc.*, 3886 (1962).

(13) Prepared by Dr. T. R. Engelmann according to the procedure of W. P. Fitzgerald, Jr., *Diss. Abstr.*, **24**, 2687 (1964).

(14) W. E. Jones and D. W. Slocum *J. Organometal. Chem.*, **15**, 262 (1968).

(15) T. Leigh, *J. Chem. Soc.*, 3294 (1964).

(16) A. N. Nesmeyanov and L. A. Kazitsyna, *Dokl. Akad. Nauk SSSR*, **125**, 1040 (1959).

was identified by its pmr spectrum. The product's vpc retention time was equal to that of an authentic sample of methylferrocene. Pmr analysis indicated that approximately 0.6 atom of deuterium had been incorporated into the molecule. Mass spectral analysis of the *m/e* 200 and 201 peaks corrected for natural isotopic abundance indicated the incorporation of 0.55 atom of deuterium.

Preparation of 2,5-Dideuterioethylferrocene.—*N*,*N*-Dimethylaminoethylferrocene (2.57 g, 10 mmol) along with 25 ml of anhydrous ether were placed in a flame-dried, round-bottom flask equipped with a magnetic stirrer, gas inlet, and reflux condenser. *n*-Butyllithium (10 ml, 15 mmol) was added under an argon atmosphere and the solution was stirred at room temperature for 2 hr,[8] after which time the reaction mixture was hydrolyzed with 1 ml of deuterium oxide. The resulting mixture was stirred for 30 min, diluted with ether, and dried over anhydrous $MgSO_4$. The dried ethereal solution was stripped of its solvent, yielding a red oil. The lithiation and deuteration of this oil was repeated twice, yielding 2,5-dideuteriodimethylaminoethylferrocene (2.40 g, 95%). Pmr analysis of the resulting amine indicated that *ca.* 1.8–2.0 atoms of deuterium were incorporated into the molecule.

The above deuterated amine (2.40 g, 9.4 mmol) was treated with excess methyl iodide (2.48 g, 20 mmol) at room temperature. Upon cooling, precipitation of the ammonium salt occurred. Subsequent isolation and air drying afforded 1.85 g (50%) of the methiodide. In a 250-ml flask sodium (2 g, 87 mmol) was dissolved in about 150 ml of ammonia and the blue solution obtained was poured over the methiodide (1.8 g, 4.5 mmol) contained in another 250-ml flask. After about 45 sec ammonium chloride was added followed by water. The reaction mixture was extracted with ether. Evaporation of the ether left a crude oil which was chromatographed on activated alumina. The first band was eluted with petroleum ether and yielded 2,5-dideuterioethylferrocene (0.50 g, 5%), identified by its pmr spectrum and by comparison of its retention time at 187° with that of an authentic sample of ethylferrocene.[12] A second band was eluted with petroleum ether–benzene, and was identified by its ir and pmr spectra as 2,5-dideuteriovinylferrocene (0.223 g, 22%), mp 51–52.5° (lit.[3] mp 51–52°). The pmr spectrum was identical in appearance with that reported by Rausch and Siegel,[3] although chemical shifts varied slightly.

Chloromercuration of *tert*-Butylferrocene.—*tert*-Butylferrocene (1.8 g, 7.4 mmol) was dissolved in ether in a 250-ml flask, to which was added an ether–hexane solution of mercuric acetate (2.5 g, 9.7 mmol). After about 16 hr lithium chloride (0.5 g, 12 mmol) was added in ether solution. The heterogeneous mixture was stripped and chromatographed on alumina III with benzene–ether. A small band of *tert*-butylferrocene was eluted first followed by a larger band which yielded 3,1′-di(chloromercuri)-*tert*-butylferrocene (0.30 g, 8.5%), a brown sold which melted at 163–166°. A portion of this material (0.184 g, 0.26 mmol) was added to about 30 ml of ether in a 100-ml flask. To this heterogeneous mixture was added about 3 ml of *n*-butyllithium solution upon which the solid material dissolved immediately. After the resulting solution was allowed to sit for 1 hr, excess deuterium oxide was added and the resultant mixture was extracted twice with ether. The crude ether extracts were stripped of solvent and purified by vapor phase chromatography, yielding 3,1′-dideuterio-*tert*-butylferrocene (retention time equal to that of an authentic sample of *tert*-butylferrocene[13]). The 60-MHz pmr spectrum of this compound was consistent with the incorporation of approximately 1.6 atoms of deuterium. The 100-MHz and 220-MHz spectra indicated that approximately 1.1 of these deuterium atoms were in the unsubstituted ring, and 0.6 of these were in the 3,4 positions, with essentially no deuterium incorporation in the 2,5 position. Mass spectral analysis of the *m/e* 242, 243, and 244 peaks corrected for natural isotopic abundance indicated that 70% of the molecules contained two atoms of deuterium, that 13% of the molecules contained one deuterium, and that 17% of the molecules contained no deuterium.

Registry No.—2-Deuteriomethylferrocene, 36862-98-3; 3,1′-dideuterio-*tert*-butylferrocene, 36862-99-4.

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The Conformational Analysis of 1-Butene

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The temperature dependences of two nmr spectral parameters have been utilized in the conformational analysis of *1,1,4,4,4-d*$_5$-1-butene (1). The three-bond vinyl–allylic coupling constant and the chemical shift of the methylene protons were observed to have a small but real temperature dependence which was correlated with the cis–skew conformational equilibrium of 1. A qualitative estimate of the enthalpy difference between the two conformers was made on the basis of the coupling constant data. It was concluded that the cis conformer is more stable than the skew one by 100 ± 50 cal/mol with $\Delta S = 1.376$ eu.

A wide variety of open-chain organic compounds containing a single bond between tetrahedral and trigonal carbon atoms have been shown to exist as a mixture of rotational conformers.[1b] The majority of these compounds contain one or more heteroatoms and the effect of unsaturation on the conformational equilibrium is not clear. In the case of propene, microwave spectroscopy has confirmed that the most stable conformation is that in which a methyl carbon–hydrogen bond is eclipsed with the carbon–carbon double bond.[2]

Various spectroscopic methods (infrared,[3] Raman,[3,4] nuclear magnetic resonance,[5] and microwave[6]) have been applied to establish the conformational preference of the ethyl group in 1-butene (1). The nmr work of Bothner-By[5a,b] and coworkers suggested that two conformers, the cis (**1a**) and skew (**1b**) forms, were present in about equal proportions. Kondo,[6] *et al.*, confirmed the existence of **1a** and **1b** from a detailed microwave study of 1-butene and estimated **1b** to be more stable than **1a** by 150 ± 150 cal/mol. Empirical and theoretical estimates of the enthalpy difference for eq 1 are −400 and −690 cal/mol, respectively.[5c,7]

(1) (a) Correspondence concerning this article should be addressed to E. W. G., Center for Applied Research in Environmental Sciences, P.O. Box P, St. Michaels, Md. 21663. (b) G. J. Karabatsos and D. J. Fenoglio, *Top. Stereochem.*, **5**, 167 (1970).

(2) D. R. Herschbach and L. C. Krisher, *J. Chem. Phys.*, **28**, 728 (1958).

(3) N. Sheppard, *ibid.*, **17**, 74 (1949).

(4) L. Kahovek and K. W. F. Kohlransch, *Z. Physik. Chem.*, **B46**, 165 (1940).

(5) (a) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **83**, 231 (1961); (b) A. A. Bothner-By, C. Naar-Colin, and H. Gunther, *ibid.*, **84**, 2748 (1962); (c) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3923 (1968).

(6) S. Kondo, E. Hirota, and Y. Morino, *J. Mol. Spectrosc.*, **28**, 471 (1968).

(7) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski,, *J. Amer. Chem. Soc.*, **90**, 5773 (1968).

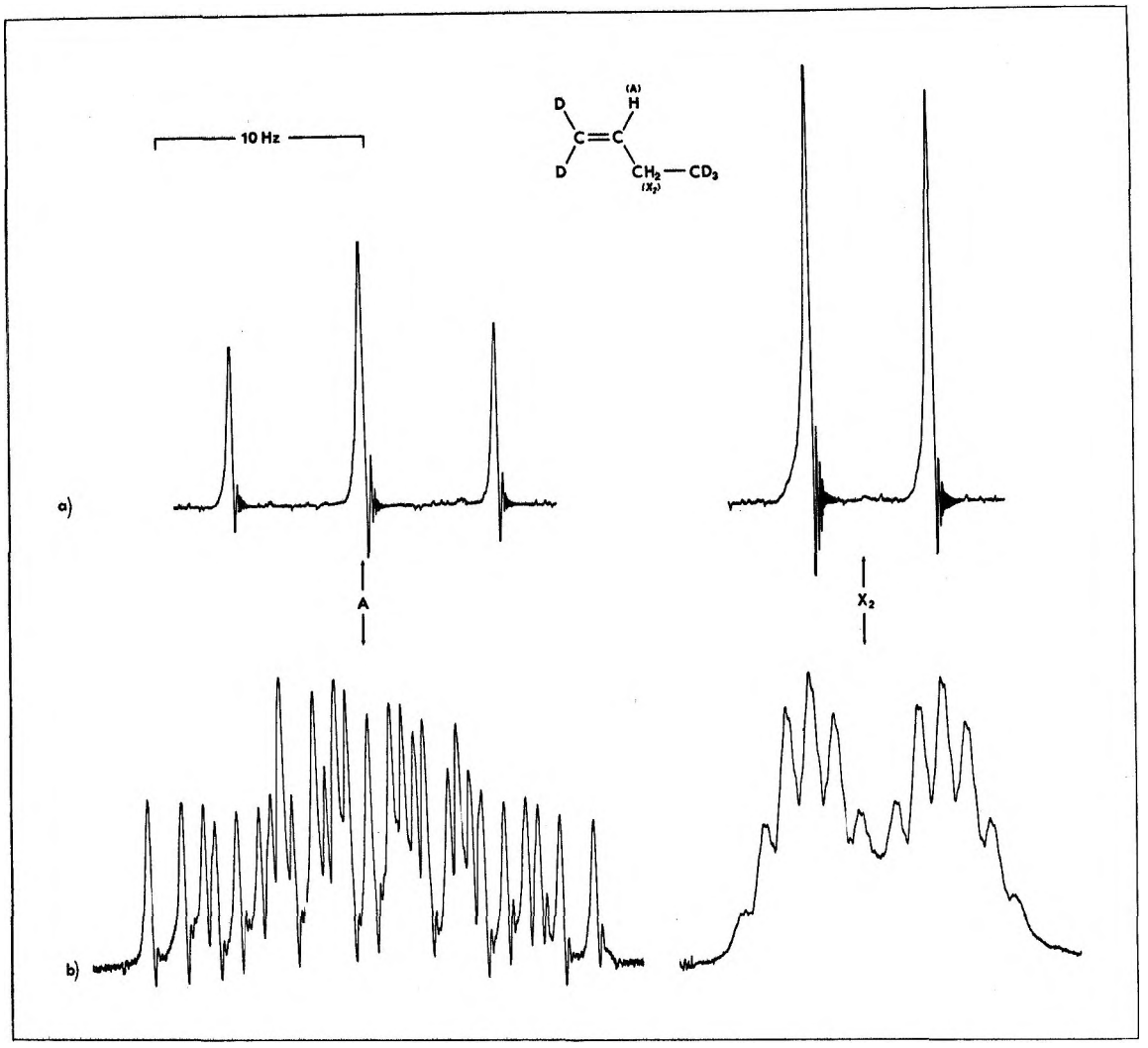
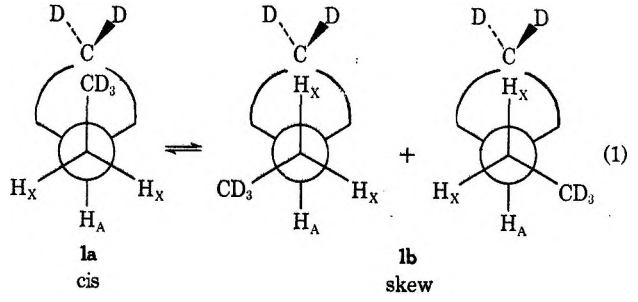


Figure 1.—The (a) deuterium-decoupled and (b) normal nmr spectra of neat 1 recorded at 45°. The vinyl, A, and allylic, X_2, portions in b were recorded at relative spectrum amplitudes of 1.0 and 0.5, respectively.



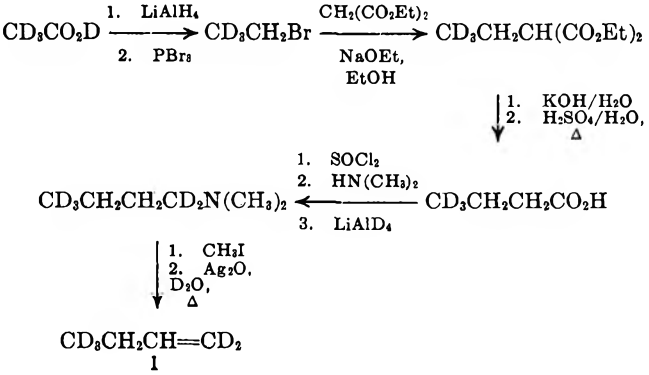
The present work describes an attempt to obtain another experimental value of the enthalpy difference between **1a** and **1b** utilizing the temperature dependences of nmr spectral parameters.

Results and Discussion

1,1,1,4,4-d$_5$-1-Butene (**1**), prepared according to Scheme I, was used in all variable-temperature nmr experiments. Figure 1 shows typical deuterium-decoupled and normal spectra of neat **1**.

The temperature dependences of the spin–spin coupling constant, $J°$, and the chemical shift, $\nu_x°$, of the methylene protons are compiled in Table I. Instrumental difficulties[8] precluded obtaining sufficiently precise measurements of $\nu_A°$. Both parameters exhibit a small (0.14 Hz for $J°$ and 0.22 Hz for $\nu_x°$) but real decrease in magnitude upon decreasing the temperature from 64 to −78°.

SCHEME I



(8) Phase lock instability at the audiofrequencies necessary to calibrate the spectra precluded obtaining sufficiently precise measurements of the chemical shift of the olefinic proton and reduced the number of potentially observable temperature-dependent parameters from three (ν_A, ν_X, and J_{AX}) to two (ν_A and J_{AX}).

TABLE I

OBSERVED TEMPERATURE DEPENDENCES OF $J°$ AND $\nu_x°$ IN NEAT 1[a]

Temp,[b] °C	$J°$	$\nu_x°$
64	6.257 (0.027)[c]	117.023 (0.032)[c]
61	6.254 (0.016)	117.010 (0.051)
55	6.254 (0.015)	117.029 (0.036)
46	6.263 (0.036)	117.030 (0.045)
39	6.241 (0.018)	117.029 (0.037)
38	6.252 (0.029)	117.061 (0.047)
26	6.249 (0.021)	117.013 (0.042)
21	6.233 (0.023)	117.054 (0.030)
19	6.230 (0.030)	117.035 (0.036)
16	6.226 (0.021)	117.046 (0.035)
12	6.229 (0.022)	117.040 (0.042)
0	6.222 (0.030)	117.037 (0.040)
−1	6.222 (0.027)	117.030 (0.040)
−10	6.220 (0.010)	116.995 (0.043)
−20	6.204 (0.042)	117.005 (0.045)
−29	6.203 (0.036)	116.983 (0.035)
−38	6.180 (0.011)	116.959 (0.023)
−45	6.177 (0.022)	116.981 (0.029)
−52	6.153 (0.023)	116.939 (0.029)
−59	6.145 (0.029)	116.935 (0.028)
−61	6.144 (0.026)	116.910 (0.018)
−68	6.139 (0.023)	116.879 (0.028)
−78	6.112 (0.029)	116.839 (0.030)

[a] $J°$ is given in hertz and $\nu_x°$ is given in hertz downfield from hexamethyldisilane (HMDS). [b] Accurate to ±1°. [c] Parenthetical values denote standard deviations.

These data subsequently were used in an attempt to obtain a qualitative estimate of ΔH for eq 1 by solving eq 2 for P_{aj}, P_{bj}, and ΔH using an iterative least-squares approach that has been described in detail elsewhere.[9,10a] In eq 2, P_{aj} and P_{bj} are the jth of l

$$\ln\left(\frac{P_{aj} - P°_{ij}}{P°_{ij} - P_{bj}}\right) = \frac{-\Delta H}{RT_{ij}} + \frac{\Delta S}{R} \qquad (2)$$

intensive parameters of conformers **1a** and **1b**, respectively, and $P°_{ij}$ is the jth of l observed parameters at the ith of k temperatures, T_{ij}.

Whereas there are several criteria for the applicability of eq 2 to equilibrium systems,[10a,b,11] the most critical criterion for conformational equilibria is that P_{aj} and P_{bj} be temperature independent. It is understood that P_{aj} and P_{bj}, in principle, may exhibit temperature dependences that arise from temperature dependences of vibrational state populations.[11a,b] Examples, possibly, of such temperature dependences have been noted for heteroatom-substituted hydrocarbons,[11c,12] but not for simple hydrocarbons. The proton–proton couplings in cyclohexane[13a] and in cyclohexene[13b] have been found to be temperature independent within experimental uncertainty over temperature changes of 141 and 102°, respectively.

Because of this impending uncertainty of the applicability of eq 2 to problems concerning conformational equilibria, we have set for ourselves an operational standard for applicability. This standard is that, if solutions of eq 2 using chemical shift and coupling constant temperature dependences separately provide comparable solution values of ΔH at common set values of ΔS, then P_{aj} and P_{bj} may be taken as being temperature independent and the temperature dependence of $P°_{ij}$ is considered to be dominated by the changes in conformer populations with temperature. The basis for this standard for applicability of eq 2 presumes that the contribution to the temperature dependences of $P°_{ij}$ that arise from effects of vibrational state population changes will be different for nuclear spin couplings than for nuclear resonance frequencies and will weight the solutions of eq 2 for ΔH, P_{aj}, and P_{bj} differently.

This operational standard for the applicability of eq 2 has been met for 11 saturated and unsaturated hydrocarbons[9,10a,13b,14] and we have yet to encounter or learn of a hydrocarbon for which this standard is not realized.

As $|P_{aj} - P_{bj}| \to 0$ or as $\Delta H \to \infty$ or $\Delta H \to 0$, unique solutions of eq 2 for all of the unknowns become increasingly problematical.[10a] This is understandable, because, at the indicated limits, $P°_{ij}$ will be temperature independent. Extensive calculations have shown that unique solutions of eq 2 for all unknowns and for ΔH (between 200 and 2000 cal/mol), P_{aj}, and P_{bj} (ΔS held constant) may be expected only when the standard deviations, σ, in $P°_{ij}$ are $<0.4|P_{aj} - P_{bj}|$ (10^{-3}) and $<2|P_{aj} - P_{bj}|$ (10^{-3}), respectively.[9a] The average standard deviations in $J°$ and $\nu_x°$ are 0.025 and 0.036, respectively. Unique solutions of eq 2 for ΔH, P_{aj}, and P_{bj} would require that $|J_a - J_b|$ and $|\nu_{x,a} - \nu_{x,b}|$ be of the magnitudes 13 and 18 Hz, respectively. As it is unlikely (see later) that $|J_a - J_b| \simeq 13$ Hz, we were disappointed but not surprised that the iterative least-squares processing of $J°$ and $\nu_x°$ separately and collectively did not lead to a unique (convergent) solution of eq 2.[10a]

Results from the solution of eq 2 for P_{aj} and P_{bj} holding ΔH constant at values between 50 and 250 cal/mol and ΔS constant at 1.376 eu, and using the temperature dependences of $\nu_x°$ and $J°$ separately, are collected in Table II. The statistical fit of the data (see RMS in Table II) is seen to be identical for all values of ΔH between 50 and 250 cal/mol. Clearly, a unique solution of eq 2 does not exist. Figure 2 also graphically illustrates this point. There, it is seen that the calculated temperature dependence of $J°$ (solid line) is identical for ΔH = 100, 150, and 200 cal/mol.

If we make the reasonable assumption, based on our previous experiences[9,10a,13b,14] (see earlier discussion), that the temperature dependence of $J°$ in **1** is dominated by conformer population changes, the sign of

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(14) B. L. Hawkins, Ph.D. Thesis, University of Minnesota, 1969; H. W. Tan, Ph.D. Thesis, University of Minnesota, 1971; unpublished results of P. B. Woller and R. L. Lipnick.

TABLE II
SOLUTION RESULTS OF EQUATION 2 USING THE TEMPERATURE DEPENDENCES OF $J°$ AND $\nu_x°$ AT FIXED ΔH AND ΔS[a]

ΔH[b] (fixed)	RMS[c]	J_a[d]	J_b[d]	$\nu_{x,a}$[d]	$\nu_{x,b}$[d]
50	0.0068	−1.28 ± 0.18	10.33 ± 0.10		
100	0.0068	2.69 ± 0.08	8.34 ± 0.05		
150	0.0068	3.99 ± 0.05	7.68 ± 0.03		
200	0.0068	4.64 ± 0.04	7.36 ± 0.03		
250	0.0068	5.02 ± 0.03	7.17 ± 0.02		
50	0.0250			108.03 ± 0.64	121.93 ± 0.35
150	0.0249			114.34 ± 0.19	118.76 ± 0.13
250	0.0249			115.57 ± 0.10	118.15 ± 0.08

[a] ΔS fixed at 1.376 eu. [b] In cal/mol. [c] Standard deviation (in hertz) of the observed and calculated parameters $P_{i,j}°$ and $P_{i,j}^{calcd}$, respectively. [d] In hertz. Subscripts a and b denote nmr property parameters calculated for the cis and skew conformers, respectively.

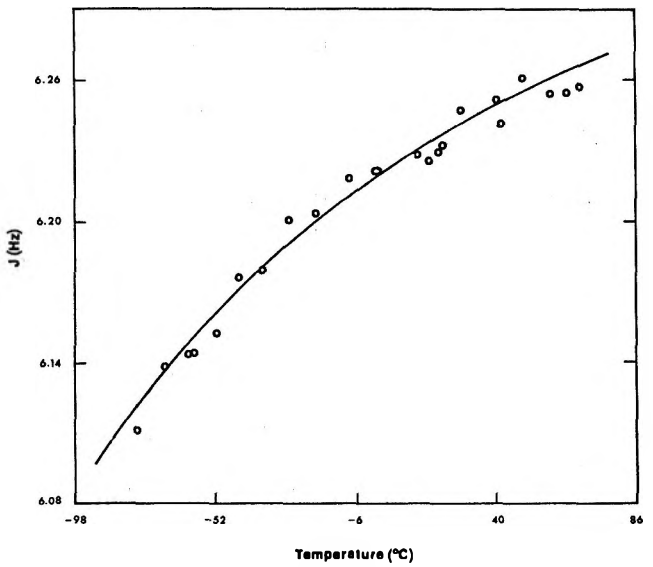

Figure 2.—Observed temperature dependence of $J°$ in neat 1. The solid line through the experimental points is the calculated temperature dependence of $J°$ using the solution parameters J_a and J_b corresponding to ΔH = 100, 150, and 200 cal/mol and ΔS = 1.376 eu.

and an estimate of the magnitude of ΔH may be made. As $J°$ is observed to increase with increasing temperature, the most stable conformer in eq 1 must have the smaller magnitude of J. As J_a in **1a** will be smaller than J_b in **1b**, **1a** is established as being more stable than **1b**, and ΔH for eq 1 is positive.

A qualitative estimate of the magnitude of the coupling constant expected between the vinyl and allylic protons in the cis conformer is calculated from semiempirical relationships[15] to be 3.6 Hz. By setting upper and lower limits of 4.0 and 0.0 Hz, respectively, on the allowed values of J_a, and from the data in Table II, the enthalpy change for eq 1 can be estimated to be 100 ± 50 cal/mol.

The positive value of ΔH for eq 1 is at variance with the microwave study by Kondo,[6] *et al.*, which proposes that the methyl–vinyl hydrogen interactions in **1a** led to **1b** being the most stable conformer, but by only 150 ± 150 cal/mol. A similar result is predicted by Johnson and Malhotra's[16] concept of $A^{(1,3)}$ strain.

From the results reported herein and those reported by Kondo,[6] *et al.*, it can be concluded with some confidence that there is little enthalpy difference between the cis and skew conformers of 1-butene.

(15) E. W. Garbisch, Jr., *J. Amer. Chem. Soc.*, **86**, 5561 (1964).
(16) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

Experimental Section

Diethyl *3,3,3-d*$_3$-Propane-1,1-dicarboxylate.—This compound was prepared from diethyl malonate (83.0 g, 0.52 mol) and 1-bromo-*2,2,2-d*$_3$-ethane[17] (55.3 g, 0.49 mol) in the presence of sodium ethoxide.[18] Distillation of the crude product gave 83.0 g of material, bp 176–179° (8–9 mm). The nmr spectrum of the distillate indicated it to be a mixture of diethyl malonate (8–10%) and the desired deuterium-labeled alkylation product (90–92%). The material was used without further purification.

***4,4,4-d*$_3$-Butyric Acid.**—An 83-g sample of the mixture of diesters obtained above was hydrolyzed and decarboxylated in the usual manner.[19] After the decarboxylation was complete, 100 ml of aqueous liquid was distilled, saturated with sodium chloride, and extracted with 50 ml of ether. A 100-ml portion of water was returned to the distillation flask and a second 100 ml of distillate was collected and extracted with ether. This procedure was repeated until about 1.5 l. of liquid had been distilled. The extracts were combined and the ether was removed by distillation. The crude product was dried by the addition of 100 ml of benzene and distilling the mixture. After 80 ml of distillate had been collected the residual liquid was fractionated at atmospheric pressure to afford 30.0 g (0.33 mol) of *4,4,4-d*$_3$-butyric acid, bp 163°.

***N,N*-Dimethyl-*4,4,4-d*$_3$-butyramide.**—A 30-g (0.33 mol) sample of *4,4,4-d*$_3$-butyric acid was treated with thionyl chloride (50.0 g, 0.42 mol) according to a general procedure.[20] The crude acid chloride, 40.0 g, which was obtained upon distillation (bp 91–102°) of the reaction mixture at atmosphere pressure, was diluted with 200 ml of anhydrous benzene and slowly added to a stirred solution of 45 g (1.0 mol) of anhydrous dimethylamine in 200 ml of dry benzene which was cooled in an ice bath. The crude amide obtained after work-up[21] was fractionated under reduced pressure, giving a 90% yield of *N,N*-dimethyl-*4,4,4-d*$_3$-butyramide, bp 97–98° (35 mm) [lit.[22] bp 70° (10 mm)], based on the starting carboxylic acid. The nmr spectrum (CCl_4) of the pure product exhibits the following characteristics: τ 8.47 (broad t, $J \cong 7.0$ Hz, 2 H), 7.79 (t, $J \cong 7.0$ Hz, 2 H), 7.15 (s, 3 H), and 7.02 (s, 3 H).

***N,N*-Dimethyl-*1,1,4,4-d*$_5$-*n*-butylamine.**—Lithium aluminum deuteride (6.3 g, 0.15 mol) reduction of the above amide (17.7 g, 0.15 mol) in refluxing ether according to a general method[23] gave 9.54 g (60%) of *N,N*-dimethyl-*1,1,4,4,4,4-d*$_5$-*n*-butylamine, bp 92–93° (lit.[24] bp 94°). No attempt was made to isolate the small amount of amine which codistilled with ether during work-up. Analysis of the ether distillate by glpc indicated that the loss was not substantial (<5%).

***1,1,4,4,4,4-d*$_5$-*n*-Butyltrimethylammonium Iodide.**—To a solution of 5.30 g (0.05 mol) of the deuterium-labeled tertiary amine in 10 ml of absolute methanol was added dropwise 10.65 g (0.075

(17) Lithium aluminum hydride reduction of acetic acid-d_4 in ether afforded *2,2,2-d*$_3$-ethanol (50% yield), which was converted to the corresponding alkyl bromide in 66% yield by treatment with phosphorus tribromide at −10°. See V. J. Shiner, *J. Amer. Chem. Soc.* **75**, 2925 (1953).
(18) C. S. Marvel, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 495.
(19) E. B. Vliet, C. S. Marvel, and C. M. Hsuch, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 416.
(20) B. Helferich and W. Schaeffer, "Organic Syntheses," Collect. Vol. I, Wiley New York, N. Y., 1941 p 147.
(21) A. C. Cope and E. Ciganek, *Org. Syn.*, **39**, 19 (1959).
(22) P. G. Gassman and B. L. Fox, *J. Org. Chem.*, **31**, 982 (1966).
(23) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshauss, *J. Amer. Chem. Soc.*, **55**, 4571 (1933).

mol) of methyl iodide at such a rate that gentle refluxing was observed. A small amount of the quaternary salt separated during the addition and the remainder was precipitated upon dilution with 50 ml of ethyl acetate and cooling. After being collected and dried at room temperature, the product, mp 229–230° (lit.[24] mp 231–232°), amounted to 11.75 g (94%).

1,1,4,4,4-d$_5$-1-**Butene** (1).—A solution of 3.72 g (0.015 mol) of the deuterium-labeled quaternary ammonium iodide in 35 ml of deuterium oxide and 5 ml of methanol-*O-d* was stirred for 1 hr with freshly precipitated silver oxide. The mixture was rapidly filtered through Celite and lyophilized. The solid material was dissolved in 25 ml of deuterium oxide and the lyophilization procedure was repeated. The viscous, colorless residue was dissolved in 40 ml of deuterium oxide and pyrolyzed according to a known procedure.[24] The olefin was condensed in a trap immersed in liquid nitrogen during the pyrolysis and later allowed to distil into a constricted 5-mm nmr tube containing hexamethyldisilane (HMDS) and immersed in a Dry Ice–acetone slush. The nmr tube was subsequently degassed and sealed at atmospheric pressure at −68°. From a typical run it was possible to obtain two samples of 1 suitable for analysis by nmr spectroscopy.

The isotopic purity of 1 prepared in this manner was 97% in the methyl group and 93% at C-1 as determined by nmr. When the pyrolysis was conducted in water *ca.* 15% of the terminal olefinic deuteriums were exchanged.

The silver oxide used in the above synthesis was prepared by treatment of a hot (85°) solution of 5.1 g (0.03 mol) of silver nitrate in 51 ml of water with an equally warm solution of 1.2 g of sodium hydroxide in 12 ml of water. The precipitated material was washed by decantation with five 20-ml portions of hot deuterium oxide.

Nmr Spectral Determinations.—All spectra were recorded on a Varian A-60 spectrometer equipped with an NMR Specialities HD-60A heteronuclear spin decoupler, a V-6058A homonuclear decoupler, and a V-6040 temperature controller. Conditions of deuterium decoupling were maintained on phase lock mode of the homonuclear decoupler for all spectral determinations. Spectra were calibrated by interpolation between audio-modulation sidebands of internal hexamethyldisilane (HMDS) produced using a Hewlett-Packard Model 3300A function generator monitored by a Hewlett-Packard Model 3734A frequency counter.

The probe temperatures were measured before and after each experiment by means of a copper–constantan thermocouple inserted into an empty stationary nmr tube positioned in the probe. The temperatures generally agreed within 0.5°. The average of the two temperatures was used as the temperature of the experiment and is believed to be accurate to ±1°. For each experiment, the probe and sample were allowed to thermally equilibrate 4–5 hr before commencing spectral determinations.

Spectra were determined using neat samples containing *ca.* 15% v/v) HMDS as internal standard and prepared as described above. In general, 24 HMDS side-band calibrated spectra were recorded for the allylic protons at each temperature by alternately sweeping up-field and downfield. A FORTRAN IV computer program was written and used to facilitate data refinement. The program calculated the frequency of each observed transition of each spectrum from the center at half-height using the frequencies of the sidebands and the corresponding calibration factor. The calculated frequencies for a given transition were averaged over all spectra and those frequencies whose deviations were greater than or equal to twice the standard deviation were discarded. The calculation was repeated for each transition in the spectrum until all deviations from the average were less than twice the corresponding standard deviations. This procedure led to an average of 18 spectra at each temperature and afforded standard deviations of the transition frequencies of less than 0.06 Hz with the majority in the range 0.02–0.04 Hz.

The deuterium-decoupled nmr spectrum of neat 1 consists of a triplet and a doublet for the vinyl (A) and allylic (X_2) protons, respectively. The frequency difference between transitions composing the doublet was taken as J_{AX} and the chemical shift, ν_x, of the allylic protons was taken as the mean frequency of the doublet transitions. All transitions at each temperature had widths at half-height comparable to that of HMDS (0.3–0.6 Hz).

Phase lock instability at the audiofrequencies necessary to calibrate spectra between 340 and 380 Hz by interpolation resulted in intolerably large (0.08–0.12 Hz) standard deviations in the transition frequencies of the triplet. In normal mode of operation, field fluctuations precluded obtaining optimum deuterium decoupling. Other spectrum calibrated techniques[9] led to an improvement in precision, but not to the degree that the standard deviations in ν_A were less than the change of ν_A over the temperature range adopted. Consequently, ν_A could not be used in the conformational analysis of 1.

Registry No.—1, 36789-12-5; diethyl-*3,3,3-d*$_3$-propane-1,1-dicarboxylate, 36789-13-6; *4,4,4-d*$_3$-butyric acid, 36789-14-7; *N,N*-dimethyl-*4,4,4-d*$_3$-butyramide, 36789-15-8.

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(24) P. A. S. Smith and S. Frank, *J. Amer. Chem. Soc.*, **74**, 509 (1952).

Conformational Inversion of 9,10-Dihydro-9,10-*o*-xylyleneanthracenes[1a]

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2,7-Dimethyl-9,10-dihydro-9,10-*o*-xylyleneanthracene (2), synthesized from the reaction of 2,7-dimethylanthracene with *o*-xylylene, was used for a variable-temperature nmr study of the conformational inversion proposed earlier for the parent hydrocarbon (1). The signal for the six methyl hydrogens of 2 remained a sharp singlet in a variety of solvents down to −120°, the lowest attainable temperature. The Diels–Alder adduct (8) from 2,7-dimethylanthracene and benzocyclobutadiene, prepared as a model of 2 "locked" in its preferred conformation, showed two sharp singlets separated by 13.5 Hz for the two methyl groups. Use of this value as a minimum $\Delta\nu_{max}$ for 2 and −120° as a maximum temperature of coalescence of the methyl signals in 2 leads to a ΔG_{max}^* of 7.7 kcal/mol for conformational inversion in 2. This value is compared with values reported for related systems.

Several years ago, Sisido and coworkers[2–4] reported the preparation of 9,10-dihydro-9,10-*o*-xylyleneanthracene (1) from the reaction of anthracene with *o*-xylylene. They noted that molecular models of the symmetrical conformer **1b** can only be constructed with substantial expansion of the tetrahedral angles about the methylene carbon atoms whereas conformers **1a** and **1a′**, although being fully eclipsed, are devoid of angle distortion. This, along with the observation that in the room temperature nmr spectrum of **1**

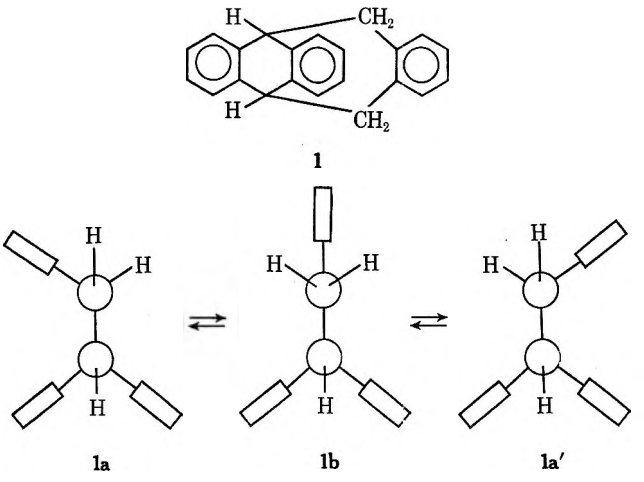
(1) (a) Support in part by NASA Grant No. Ns(T)-21 is gratefully acknowledged. (b) Abstracted from the Ph.D. Thesis of D. M. Wieland, West Virginia University, 1970; NASA Trainee, 1965–1968.

(2) K. Sisido, Y. Udo, and H. Nozaki, *J. Org. Chem.*, **26**, 584 (1961).

(3) K. Sisido, R. Noyori, and H. Nozaki, *J. Amer. Chem. Soc.*, **84**, 3562 (1962).

(4) K. Sisido, R. Noyori, N. Kozaki, and H. Nozaki, *Tetrahedron*, **19**, 1185 (1963).

the methine hydrogens appeared as a simple triplet from coupling with two adjacent and equivalent methylene hydrogens, led them to conclude that **1** is not frozen as **1a** or **1a'** but is rapidly interconverting between these two conformers *via* **1b**. They further speculated that conformer **1a** (or **1a'**) may be as much as 10 kcal/mol more stable than **1b**.[3]



1

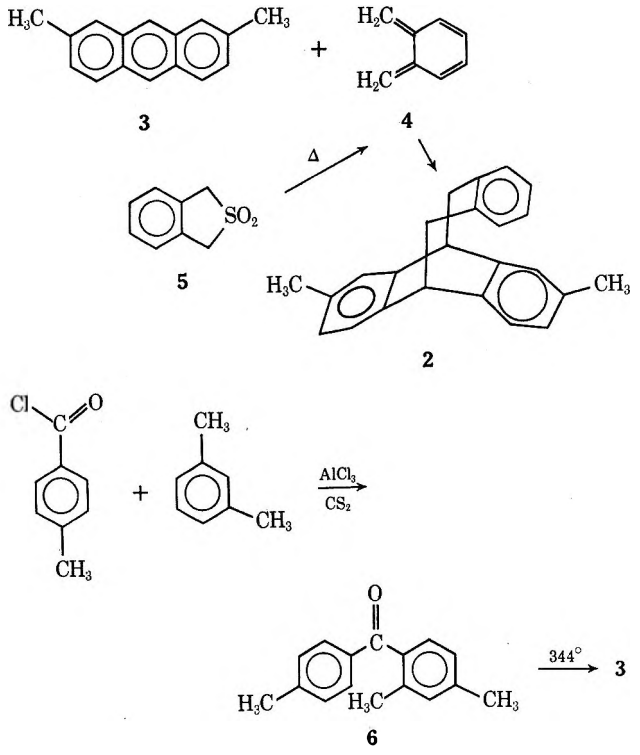
1a **1b** **1a'**

We felt that, if this is indeed an accurate description of the conformational dynamics of this molecule, then the rate of such an inversion might be amenable to a variable-temperature nmr study. However, the anticipated complexity of the nmr pattern for the methylene and methine hydrogens in **1** at low temperatures prompted us to consider the use of the 2,7-dimethyl derivative (**2**) as a model for **1**. In the 2 and 7 positions the methyl groups should be remote enough not to interact sterically with the *o*-xylylene moiety and yet close enough to lie within the shielding region of its benzene ring. A Dreiding model of **2** shows the closest approach of the *o*-xylylene group to the methyl substituent to be about 5 Å, or 1.3 Å greater than the sum of the van der Waals radii of the benzene ring (1.70 Å) and the methyl group (2.0 Å).[5]

Use of the Johnson–Bovey[6] tables of isoshielding values for the benzene ring suggests that when "flipping" in **2** is sufficiently slow (below the coalescence temperature), the two methyl groups should have resonances separated by approximately 15.6 Hz, a chemical shift difference large enough to permit facile analysis at low temperatures. Assuredly this value may be subject to some error, not the least of which could be introduced by a perturbation of the shielding effect of the *o*-xylyl ring by virtue of its face-to-face encounter with the anthranyl ring. The crux of concern is whether this encounter would cause a sizable reduction of the shielding effect, consequently resulting in a diminution in the chemical shift difference between the two methyl groups. It has been found, however, that compounds with a similar, but somewhat closer, positioning of benzene rings (*viz.*, 1,8-diphenylnaphthalene,[7] 1,2-diphenylcyclopropane,[8] and janusene[9]) exhibit a strong mutual shielding of their aromatic protons.

Results and Discussion

The synthesis of **2** was in direct analogy with that of the parent compound (**1**)[2] as shown by the following sequence.



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

The work of Morgan and Coulson[10] provided an unambiguous synthesis of **3** *via* the ketone **6** which was itself synthesized from the Friedel–Crafts reaction of *m*-xylene with *p*-toluoyl chloride. When subjected to the conditions of the Elbs reaction,[11] **6** provided **3** in modest yield.

The room temperature nmr spectrum of **2** in CS_2 is consistent with the proposed structure. The six methyl hydrogens appear as a single sharp peak at δ 2.18, consistent with the idea of rapid conformational interconversion. The methylene protons show a sharp doublet (J = 7.0 Hz) centered at δ 3.08 and further downfield near δ 4.0 are the two methine hydrogens appearing as two triplets (J = 7.0 Hz) separated by 2.2 Hz. The two pair of methylene hydrogens, although not chemically equivalent, are seemingly too far removed from the source of asymmetry to suffer an observable chemical shift difference. Correct integral ratios were obtained for all peaks including the aromatic multiplet centered at δ 6.8. The ultraviolet spectrum of **2** correlates well with that reported for **1**,[4] a small bathochromic shift (4–5 nm) being noted for **2**.

No real change in the room temperature nmr spectrum of **2** was noted down to −65° in $CDCl_3$, to −90° in CS_2, and to −50° in chlorobenzene (chosen because of the ability of aromatic solvents to accentuate some-

(5) L. D. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1963, p 214.
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(7) H. O. House, R. W. Magin, and H. W. Thompson, *J. Org. Chem.*, **28**, 2403 (1963).
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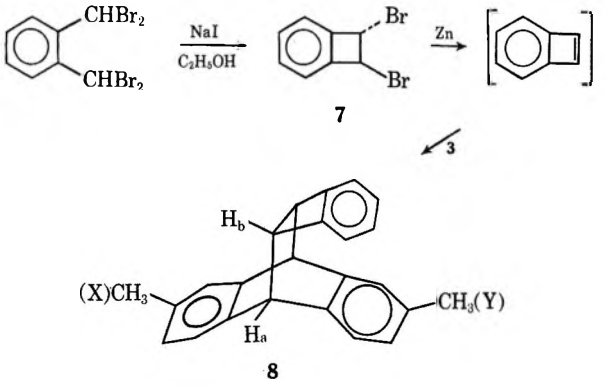
(9) S. J. Cristol and D. C. Lewis, *J. Amer. Chem. Soc.*, **89**, 1476 (1967).
(10) G. T. Morgan and E. A. Coulson, *J. Chem. Soc.*, 2203 (1929).
(11) L. F. Fieser, *Org. React.*, **1**, 129 (1942).

times a chemical shift difference[12]). Attainment of lower temperatures was thwarted by either the freezing of the solvent or by insufficient solubility of the compound. The halocarbon $CHFCl_2$ was found to lend sufficient solubility to **2** for spectra down to $-120°$. However, even at $-120°$, **2** still displayed a single, sharp methyl hydrogen peak (no real broadening when compared to the change in half-height width of TMS over the same temperature interval). Resolution of the methine peaks was insufficient at temperatures below $-90°$ to observe any change, and the methylene resonance remained a poorly resolved doublet down to $-120°$. Solubility and technical difficulties prevented the attainment of spectra in $CHFCl_2$ at temperatures below $-120°$.

These results provoked efforts to show irrevocably that the two methyl groups in **2** will have an observable chemical shift difference if the conformational inversion can be sufficiently retarded. Ideally what is needed is a means of "locking" **2** into its supposed preferred conformation to prevent conformational exchange and, in doing so, not introduce any factor that would modify the hopefully already inherent chemical shift difference of the two methyl substituents. The model compound which approximates this ideal is **8**, conveniently synthesized by Diels–Alder addition of benzocyclobutadiene to 2,7-dimethylanthracene (**3**) as shown in the following scheme.



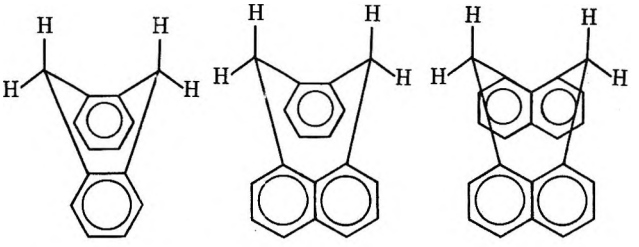
Dreiding models show the methyl group (Y) in **8** to be 0.4 Å further from the center of *o*-xylyl benzene ring than the respective methyl group in **2**. The calculated chemical shift difference for the two methyl groups in **8** (using the Johnson–Bovey tables) is 13.5 Hz. The observed nmr spectrum of **8** in $CDCl_3$ displays a sharply defined aromatic multiplet centered at δ 6.90, two narrow multiplets of equal intensity at δ 4.45 and 3.70 for the H_a and H_b methine protons, respectively, and, of utmost concern, two sharp methyl peaks of equal intensity at δ 2.24 and 2.10. It would be reasonable to assume that the methyl group (Y) is the peak at higher field (δ 2.10). The chemical shift difference between the two methyl peaks in $CHFCl_2$ is 13.4 Hz, and spectra in this solvent taken at temperatures down to $-120°$ showed this chemical shift difference to be essentially independent of temperature.

Whether 13.4 Hz represents a valid figure for the expected maximum separation ($\Delta\nu_{max}$) of the methyl groups in **2** depends of course on the validity of assuming **8** as the model for the slow exchange or preferred conformation of **2**. The nmr spectrum of equimolar amounts of **2** and **8** in $CHFCl_2$ shows the lone methyl peak of **2** almost exactly midway between the two methyl peaks of **8**. This observation indicates that introduction of the methylene cross link has not, to any appreciable extent, unsymmetrically altered the magnetic environments of the two methyl groups—an observation not wholly unexpected in view of the small anisotropic effect of the C–C single bond in cyclobutane.[13]

The remarkably close agreement between the calculated (13.5 Hz) and the observed (13.4 Hz) values for **8** might encourage one to predict the actual experimental value for **2** to be near the calculated figure of 15.6 Hz. However, the safest prediction is that the experimental $\Delta\nu_{max}$ for **2** will have a minimum value of 13.4 Hz. Inspection of eq 1[14] reveals that, as $\Delta\nu_{max}$ increases, the value for ΔG^* decreases. By using 13.4 Hz as a reasonable minimum value for $\Delta\nu_{max}$ and $-120°$ as the maximum temperature of coalescence (T_c) a ΔG_{max}^* value of 7.7 kcal/mol is obtained for the free energy of activation associated with the conformational inversion in **2**. Since the methyl substituents are not expected to raise the ground-state energy of **2** relative to **1**, this maximum of 7.7 kcal/mol is also applicable to the parent compound **1**.

$$\Delta G^* = 4.57T_c[9.97 + \log (T_c/\Delta\nu_{max})] \quad (1)$$

It is interesting to compare the ΔG_{max}^* value for "flipping" in **1** and **2** with the values obtained for ring inversion in related systems. Lansbury,[15] in a recent review article, gives perspective to the present case by comparing conformational inversion in 9,10-dihydroanthracene (**9**), 7,10-dihydropleiadene (**10**), and 1,8-(1′,8′-naphthyldimethyl)naphthalene (**11**). The



9 $\Delta G^* = <5$ kcal/mol

10 13.5 kcal/mol

11 <23 kcal/mol

ΔG^* values for inversions in these compounds are given below the structures.

An examination of molecular models suggests that **1** has much in common with **10**. In each molecule the *o*-xylene moiety bridges a distance of ~2.8 Å, and both molecules are folded to the same extent (~109°). Yet the ΔG^* value for **10** is a minimum of 5.8 kcal/mol higher than that of **1**. The reason for this ΔG^* variance is no doubt manifold, but an important contributing factor could be the difference in the pathways for relief of angle strain in the respective transition states of the two compounds. The bond angle strain about the methylene carbon atoms

(12) (a) D. L. Harris and K. M. Wellman, *Tetrahedron Lett.*, 5225 (1968); (b) D. J. Bertelli and J. T. Gerig, *ibid.*, 2481 (1967).

(13) J. J. Burke and P. C. Lauterbur, *J. Amer. Chem. Soc.*, **86**, 1870 (1964).

(14) J. E. Anderson and J. M. Lehn, *Tetrahedron*, **24**, 123 (1968).

(15) P. T. Lansbury, *Accounts Chem. Res.*, **2**, 210 (1969).

in the transition state of **1** (or **2**) is readily eased by a downward flexing of the central boat of the anthranyl moiety. Such relief should not be possible in **10** because of the planar and rigid aromatic rings to which the *o*-xylylene group is directly attached.

Generalizations on **9**, **10**, and **11**[15] were made possible because the hinge carbons similarly connect aromatic rings. The inability to extend these generalizations to **1** demonstrates that not only the degree of folding of the molecule but also the nature and flexibility of the substituent to which the *o*-xylyl group is bound are important factors affecting the ΔG^* for conformational exchange in *o*-xylyl systems.

Experimental Section

General.—All nmr spectra were obtained by Mr. Robert Smith and D. M. W. on a Varian Model HA-60-EL spectrometer equipped with a V-4340 variable-temperature probe. Signal positions are reported in parts per million with respect to tetramethylsilane (δ = 0.0) used as an internal standard. Samples were run as 10% w/v solutions or as saturated solutions if not soluble to the extent of 10%. All variable-temperature samples were run in Wilmad 507-PP Imperial tubes sealed with Teflon caps, except for samples run in $CHFCl_2$ in which case the sample tubes were precision sealed. Sample temperature was measured with a Leeds & Northrup Model 8686 precision potentiometer and a calibrated copper–constantan thermocouple mounted in a dummy sample tube containing acetone or carbon disulfide. Cooling was achieved by controlled vaporization of liquid N_2 in a 25-l. dewar flask connected *via* a vacuum-jacketed tube to a dewar insert in the probe. Temperature readings were reproducible to within ±0.50° down to −60° and to within ±1.0° on down to −120°.

Microanalytical work was performed by Galbraith Laboratories, Inc., Knoxville, Tenn. All melting points were taken on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were obtained on a Bausch and Lomb Spectronic 505 spectrophotometer. In some of the synthesis reported here no attempt was made to optimize yields since only small quantities of pure compounds were needed for subsequent spectral studies.

2,4,4′-Trimethylbenzophenone (6) was prepared according to the procedure of Morgan and Coulson.[10] Equimolar amounts (0.33 mol) of *p*-toluoyl chloride (50.0 g) and *m*-xylene (34.4 g), mixed in carbon disulfide and combined with 50.0 g of aluminum chloride, afforded 54 g (74%) of the clear, oily ketone, bp 69–71° (4.0 mm) [lit.[10] bp 69° (4.0 mm)].

2,7-Dimethylanthracene (3) was formed in low yield when the 54 g of ketone from the preceding procedure was boiled (344°) beneath an air reflux for 6 hr and then cooled. The crude dimethylanthracene which separated upon cooling was removed by filtration. Recrystallization from acetic acid followed by a second recrystallization from toluene produced 2.25 g of yellow-green fluorescent plates, mp 240–241° (lit.[10] mp 241°). The nmr spectrum was in agreement with the proposed structure.

Anal. Calcd for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 93.10; H, 6.80.

1,3-Dihydroisothianaphthene 2,2-Dioxide (5).—The method of Cava and Deana[16] was used with minor modification. Equal volumes (55 ml) of acetic acid and acetic anhydride were mixed in a flask with 53 ml of 30% hydrogen peroxide. The addition of 13 g of 1,3-dihydroisothianaphthalene[16] was made over a 3-hr period while the reaction mixture was being stirred and cooled. The mixture was then stirred at room temperature for 120 hr. Addition of 50 ml of cold water and filtration of the precipitated sulfone gave 14.5 g (90%) of white needles, mp 147–148°. Recrystallization from methylene chloride–petroleum ether yielded white needles, mp 147–148° [lit.[16] mp 150–152°].

2,7-Dimethyl-9,10-dihydro-9,10-*o*-xylyleneanthracene (2).—A finely ground mixture of **5** (1.0 g, 0.006 mol) and **3** (1.27 g, 0.006 mol) was heated at 245–265° for 15 min in a Wood's Metal bath. After an additional 15 min at 295–305°, the mixture was cooled and dissolved in warm petroleum ether (bp 65°). Elution with petroleum ether–benzene on a column of neutral alumina afforded 0.43 g (25%) of white, fluffy needles, mp 187–189°. Recrystallization from ethanol followed by a second recrystallization from petroleum ether gave white needles: mp 190.5–191°; nmr (CS_2) δ 2.18 (s, 6, methyl), 3.08 (d, 4, J = 7.0 Hz, methylene), 4.01 (t, 1, J = 7.0 Hz, methine), 4.07 (t, 1, J = 7.0 Hz, methine), 6.18 (m, 10, aromatic); uv (95% ethanol) λ_{max}, nm (log ϵ), 263 (3.47), 269 (3.64), 275 (3.62), 278 (3.55).

Anal. Calcd for $C_{24}H_{22}$: C, 92.90; H, 7.10. Found: C, 92.82; H, 7.25.

***trans*-1,2-Dibromobenzocyclobutane** (7).—The procedure of Cava and Napier[17] was adopted using 50 g of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene (Aldrich Chemical Co.), 75 g of sodium iodide, and 275 ml of absolute ethanol. This mixture was heated under reflux with stirring for 46 hr. Some ethanol (125 ml) was then removed by distillation. Water (100 ml) was added, and more ethanol (100 ml) was removed. Sulfur dioxide was bubbled through the reaction mixture to reduce the iodine which had been liberated during the reaction. After 30 min of vigorous stirring at 0°, the aqueous layer was decanted from the gray precipitate. The precipitate was collected by filtration, washed with cold water, and then dissolved in Skellysolve C and dried over magnesium sulfate. The solution was concentrated to 40 ml and passed through a column of neutral alumina with Skellysolve C as eluent. The first fraction (130 ml) produced 20 ml of a pink oil which, upon distillation, bp 80–86° (0.2 mm) [lit.[17] bp 95–100° (0.6 mm)], double recrystallization from petroleum ether (bp 65°) and a third from methanol gave 4.17 g of white crystals, mp 42–43°. This material was used without further purification for the subsequent reaction.

Diels–Alder Adduct of 2,7-Dimethylanthracene and Benzocyclobutadiene (8).—To a near boiling solution of 1.43 g (0.007 mol) of **3** and 30 ml of dimethylformamide containing 1.50 g of suspended zinc dust (preactivated with 5% hydrochloric acid) was added dropwise 2.62 g (0.010 mol) of **7** in 10 ml of dimethylformamide. The reaction mixture was heated under reflux with stirring for 1.5 hr and cooled; then 100 ml of *m*-xylene and 1.5 g of maleic anhydride were added to the solution. After 5 hr under reflux, the solvent was evaporated and the solid residue triturated with warm, concentrated aqueous sodium hydroxide to dissolve the maleic anhydride adduct. The base-insoluble solid was dissolved in benzene and passed through a short column of neutral alumina to yield a yellow solid. This solid was sublimed (100°, 0.2 mm) and recrystallized from methanol to give 40 mg of white needles: mp 155–156°; nmr ($CDCl_3$) δ 6.90 (m, 10, aromatic), 4.45 (m, 2, anthranyl methine), 3.70 (m, 2, cyclobutyl methine), 2.24 (s, 3, methyl), 2.10 (s, 3, methyl).

Anal. Calcd for $C_{24}H_{20}$: C, 93.51; H, 6.49. Found: C, 93.28; H, 6.58.

Registry No.—**2**, 36803-32-4; **3**, 782-23-0; **7**, 14420-75-8; **8**, 36803-34-6.

(16) M. P. Cava and A. A. Deana, *J. Amer. Chem. Soc.*, **81**, 4266 (1959).

(17) M. P. Cava and D. R. Napier, *ibid.*, **79**, 1701 (1957).

The Synthesis of Ketones from Dihydro-1,3-oxazines *via* Stepwise Alkyl or Aryl Introduction

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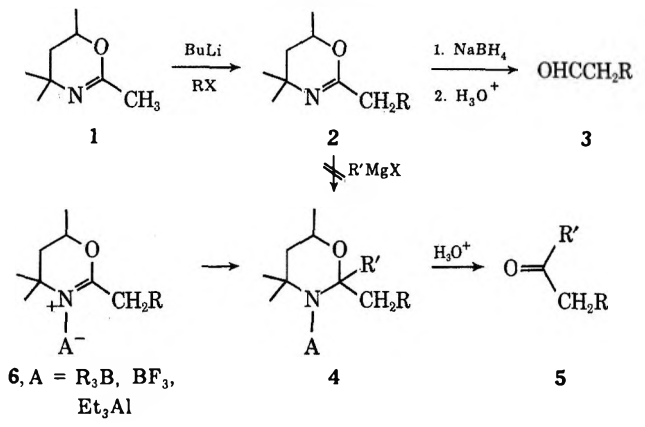
Although the dihydro-1,3-oxazine system is inert to Grignard reagents, the *in situ* formation of their corresponding *N*-methyl quaternary salts allows introduction of alkyl or aryl groups. Hydrolysis of the Grignard addition products leads to a variety of ketonic products. The scope and limitations of this process are described.

The synthetic utility of dihydro-1,3-oxazines as precursors to homologated acetaldehyde derivatives has been described in detail[3] (Scheme I, 1 → 2 → 3). The

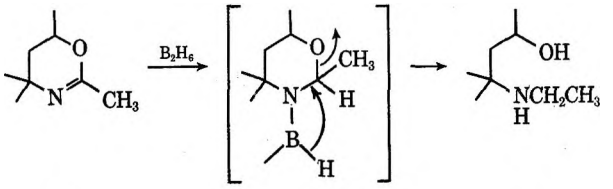
SCHEME I



ease of introduction of a variety of substituents in **1** by virtue of its lithio salt suggested that an equally versatile ketone synthesis was possible provided that a nucleophilic carbon species could be induced to add to the C=N moiety. This would afford the 2,2-disubstituted oxazine **4** which, after hydrolysis, would produce the ketone derivatives **5**. All attempts to add Grignard reagents to **2** were without success, resulting in complete recovery of starting material. This property of dihydro-1,3-oxazines has been capitalized upon by demonstrating that the ring system is an excellent protecting group against the Grignard reagent.[3-5] The inertness of the C=N link in **2** is undoubtedly due to the delocalization present in the OC=N group, rendering it poorly electrophilic.

It soon became apparent that some type of complex was required (*e.g.*, **6**) in order to increase the electrophilic nature of carbon 2 in the oxazine ring. Since it is well known that iminium bonds (>C=N<$^+$) are highly reactive toward nucleophiles (RMgX, $^-$OR, etc.), an effort in this direction was undertaken.

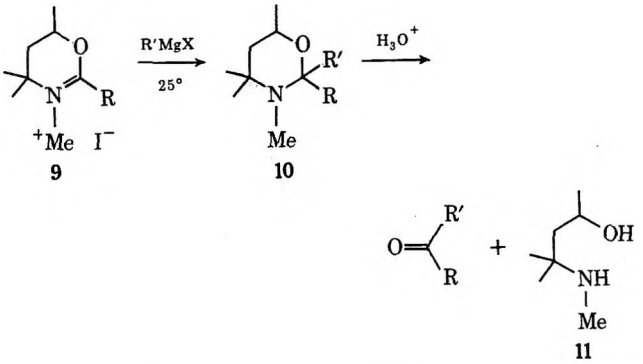
Treatment of **1** with 1 equiv of boron trifluoride etherate gave a solid complex **6** (A = BF_3) which failed to yield any appreciable quantity of **4** (R′ = Ph; R = H) when added to phenylmagnesium bromide in ether or tetrahydrofuran. A variety of experiments involving trioctylborane, triethylaluminum, and triphenylborane as complexing agents likewise produced unsatisfactory results. Although small yields of the desired products were obtained in most of these experiments, the complexity of handling and preparing these reagents detracted from the potential of this ketone synthesis and further study was terminated. Only the reaction of **1** with diborane, which was also evaluated as a complexing agent, is worthy of note. When equimolar amounts of **1** and diborane were allowed to react for 30 min in tetrahydrofuran, a good yield of the amino alcohol **7** was isolated. Thus the oxazine is reduced, initially to the tetrahydro derivative **8** and



1 **8** **7**

then on to the open-chain amino alcohol. This result is reminiscent of the susceptibility of dihydro-1,3-oxazine to reductively cleave to amino alcohols with other reducing agents.[3]

The failure of the above complexing agents to enhance the reactivity of the C=N link in dihydro-1,3-oxazines prompted an investigation on the behavior of the *N*-methyl quaternary salts **9** toward Grignard addition.[6] The oxazines **1** and **2** all formed stable *N*-methyl quaternary iodides in good yield merely by stirring in excess methyl iodide at room temperature or at the boiling point of methyl iodide. The portionwise addition of the solid methiodides to a solution of Grignard reagent (2–2.5 equiv) and stirring at room temperature



9 **10** **11**

produced variable yields of the adduct **10** which upon treatment with aqueous oxalic acid led to the ketone (Table I). The amino alcohol **11** could be isolated in

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(2) Medical Research Council of Canada Postdoctoral Fellow, 1968–1970.

(3) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. Portnoy, *J. Org. Chem.*, in press.

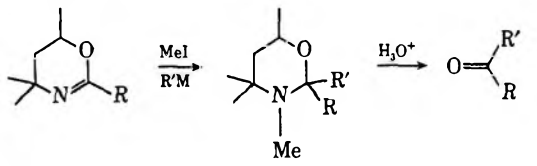
(4) A. I. Meyers, I. R. Politzer, B. K. Bandlish, and G. R. Malone, *J. Amer. Chem. Soc.*, **91**, 5887 (1969).

(5) A. I. Meyers and D. L. Temple, *ibid.*, **92**, 6644, 6646 (1970).

(6) A preliminary report has appeared: A. I. Meyers and E. M. Smith, *ibid.*, **92**, 1084 (1970).

TABLE I

FORMATION OF KETONES FROM 2-SUBSTITUTED 4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3-OXAZINES AND ORGANOMETALLICS



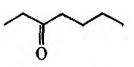
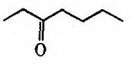
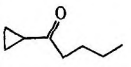
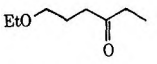
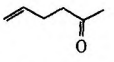
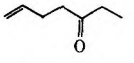
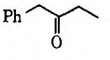
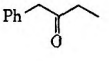
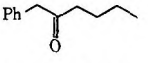
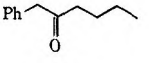
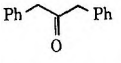
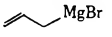
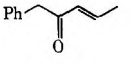
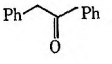
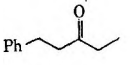
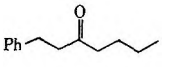
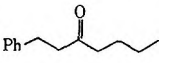
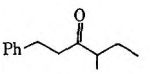
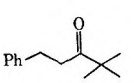
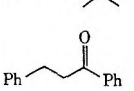
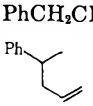
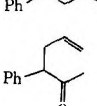
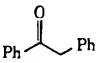
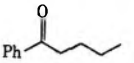
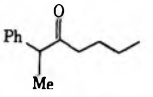
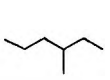
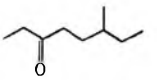
Entry	R	R'M	Ketone	Registry no.	Yield, %	Derivative mp,[a] °C
1	Me	*n*-BuMgBr		106-35-4	22	121–123 Sm[e]
2	Et	*n*-BuMgBr			58	97–98 Sm[f]
3		MeMgBr		765-43-5	30[d]	145–148 Dn[f]
4		*n*-BuMgBr		14113-86-1	35[d]	110–111 Dn[g]
5	$EtO(CH_2)_3$	EtMgBr		36808-92-1	53	88–90 Sm[h]
6		MeMgBr		109-49-9	70	98–100 Sm[f]
7		EtMgBr		2565-39-1	63	83–84[f]
8	$PhCH_2$	EtMgBr		1007-32-5	55	119–120 Dn[f,i]
9	Et	$PhCH_2MgBr$			20	
10	$PhCH_2$	MeMgI		103-79-7	58	148–150 Dn[e,i]
11	$PhCH_2$	*n*-BuMgBr		25870-62-6	52	113–114 Sm[j]
12	$PhCH_2$	*n*-BuLi			35	
13	$PhCH_2$	$PhCH_2MgBr$		102-04-5	25	108–110 Dn[f]
14	$PhCH_2$			36808-95-4	40	*b, o*
15	$PhCH_2$	PhLi		451-40-1	23	146–148 Sm[f]
16	$PhCH_2CH_2$	EtMgBr		20795-51-1	85	108–115 Sm[f]
17	$PhCH_2CH_2$[c]	*n*-BuMgBr		19969-04-1	70	118–120 Dn[k]
18	$PhCH_2CH_2$[c]	*n*-BuLi			50	
19	$PhCH_2CH_2$	*sec*-BuMgBr		36808-96-5	46	*b*
20	$PhCH_2CH_2$	*t*-BuLi		5195-24-4	28	175–176 Dn[l]
21	$PhCH_2CH_2$	PhLi		1083-30-3	75	140–142 Sm[m]
22		MeMgBr		26965-15-1	57	121–123 Dn[n]

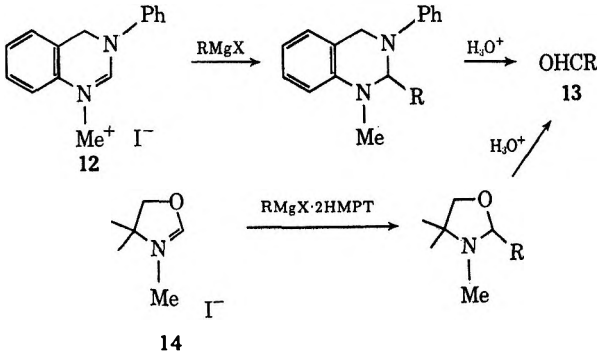
TABLE I (*Continued*)

Entry	R	R'M	Ketone	Registry no.	Yield, %	Derivative mp,[a] C[a]
23	Ph	EtMgBr		93-55-0	70	191–192 Dn[e]
24	Ph	MeMgBr		98-86-2	55	252–254 Dn[e]
25	Ph	$PhCH_2MgBr$		451-40-1	12	144–146 Sm[f]
26	Ph[c]	*n*-BuLi		1009-14-9	53	164–166 Sm[e]
27		*n*-BuMgBr		7661-44-1	54	*b*
28		EtMgBr		36808-98-7	74	90–95° (30 mm)[b]

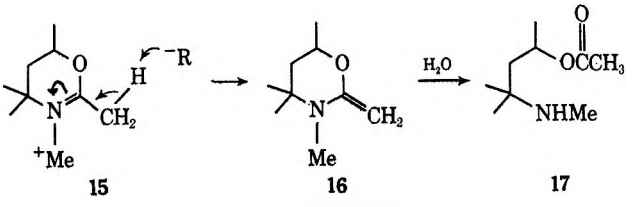
[a] Sm = semicarbazone, Dn = 2,4-dinitrophenylhydrazone. [b] Compound gave correct mass and combustion analysis. [c] Methiodide and methanesulfonate salts gave comparable yield results. [d] Azeotropes with ether thus making isolation difficult; *cf. Org. Syn.*, **31**, 74 (1951). [e] A. I. Vogel, "Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1957. [f] I. Heilbron, "Dictionary of Organic Compounds," Oxford Press, New York, N. Y., 1956. [g] M. Julia, S. Julia, and T. S. Yu, *Bull. Soc. Chim. Fr.*, 1849 (1961). [h] H. Normant, *C. R. Acad. Sci.*, **232**, 1942 (1951). [i] Infrared spectrum identical with that of an authentic sample (Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia, Pa.). [j] H. H. Schluback and A. Braun, *Justus Liebigs Ann. Chem.*, **627**, 28 (1959). [k] I. N. Nazarov and L. I. Shmonina, *Zh. Obshch. Khim.*, **20**, 1114 (1950). [l] E. Berliner and F. Berliner, *J. Amer. Chem. Soc.*, **72**, 222 (1950). [m] N. Maxim, *C. R. Acad. Sci.*, **182**, 1393 (1926). [n] M. Mousseron, R. Jacquier, and H. Christol, *Bull. Soc. Chim. Fr.*, 346 (1957). [o] Ir (neat) 1660–1695 (C=O), 1626 cm^{-1} (C=C); nmr (CCl_4) 7.15 (s, 5), 6.66 (q, 1, J = 17 Hz), 6.00 (d, 1, J = 1 Hz), 3.65 (s, 2), 1.76 ppm (d, 3).

comparable yields to the ketone by neutralization and extraction of the oxalic acid solution.

It was subsequently found that the *N*-methyl salts **9** need not be prepared in a separate operation, but may be obtained, ready for use, by formation in the same reaction vessel in which the Grignard addition is carried out (Experimental Section). Thus, the aim of the study was achieved not by a Lewis acid complex, but by a simple derivative, the *N*-methyl quaternary salt. A report by Fales[7] for converting Grignard reagents to their formyl derivatives **13** *via* *N*-methylquinazolinium salts (**12**), and the report[8] of Grignard addition to *N*-methyloxazolinium salts **14** and ultimately to aldehydes, demonstrate the enhanced electrophilicity of C=N in related systems.



An examination of Table I reveals that the yields of ketone from various 2-substituted dihydro-1,3-oxazines (*via* the *N*-methyl salts) range from poor (12–20%) to good (50–85%). These results are a function of either the nature of the 2 substituent on the oxazine or the organometallic employed. When the 2 substituent is methyl (**15**), the Grignard reagent is sufficiently basic to remove the α proton as well as addition to the $C{=}N^+$-Me linkage. Proof of proton abstraction was obtained by isolation of the ketene *N*,*O*-acetal **16** using various bases. The synthetic utility of **16** is the subject of another investigation.[9] The first entry in Table I, showing a poor yield of the methyl ketone, is a reflection of the competing proton-abstraction process. The major product obtained was the amino ester **17**, which is



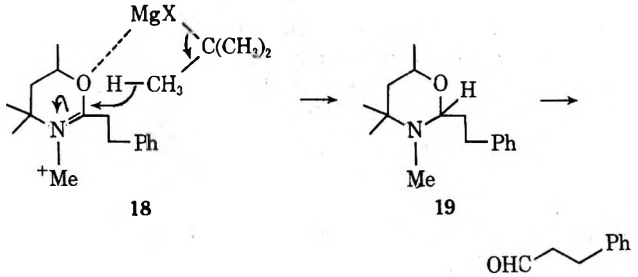
formed by reaction of the ketene *N*,*O*-acetal with water during the aqueous work-up. The second entry in Table I involves addition of a typical Grignard to the 2-ethyloxazine. The yield of ethyl ketone (58%) is considered close to optimum for this sequence, but more important is the fact that the acidity of the α proton in this oxazine is sufficiently reduced so as not to interfere with Grignard addition to the iminium linkage.

It was both fortunate and surprising to learn that the 2-benzyl substituent (entry 8) did not exhibit its usual acidity when the ethyl Grignard reagent was introduced. The 55% yield of benzyl ketone indicates that the Grignard's poor basicity decreases proton abstraction, thus allowing nucleophilic addition to proceed efficiently. When this reaction was repeated using *n*-butyllithium (entry 12) in place of the Grignard (entry 11) the yield of ketone was lower, reflecting the greater base strength of the lithium reagent. Of fur-

(7) H. M. Fales, *J. Amer. Chem. Soc.*,., **77**, 5118 (1955).
(8) A. I. Meyers and E. W. Collington, *ibid.*, **92**, 6676 (1970).
(9) A. I. Meyers and N. Nazerenko, *ibid.*, **94**, 3243 (1972).

ther interest is the reaction of the 2-phenethyloxazine (entry 17, 18) with butyl Grignard and lithium reagents. The removal of the activating phenyl group to a β position in the oxazine now allowed a 70% yield of the phenethyl ketone from the Grignard and 50% from the lithium reagent. Since the oxazine may be elaborated in high yield to a variety of 2 substituents (Scheme 1), the choice of oxazine and Grignard reagent for a desired ketone may be made to provide optimum results. This is seen from entries 8 and 9 in Table I. The use of ethylmagnesium bromide on the readily available 2-benzyloxazine[3] is favored over the addition of benzyl Grignard to the ethyloxazine. Coupling products (bibenzyl) were the reason for almost consistently low yields whenever the benzyl Grignard reagent was utilized (*cf.* entries 13 and 25). Furthermore, since the 2-methyloxazinium salt **15** failed to give good yields of Grignard addition products, the synthesis of methyl ketones could be made quite efficient by utilizing methyl Grignard reagents in place of 2-methyloxazinium salts. This is seen from entries 6, 10, 22, and 24 to lead to good yields of methyl ketones. The absence of phenyl Grignard reagents from Table I of ketones is due to their failure to add in a number of attempted experiments. However, this limitation may also be overcome by using the 2-phenyloxazinium methiodides and the appropriate organometallic (entries 23–26). The reason for the failure of phenyl Grignard reagents can only be ascribed to its bulk and hence its reluctance to add to the C=N$^+$–Me moiety. This is further avoided by use of the phenyllithium reagent, which added normally (entries 15 and 21).

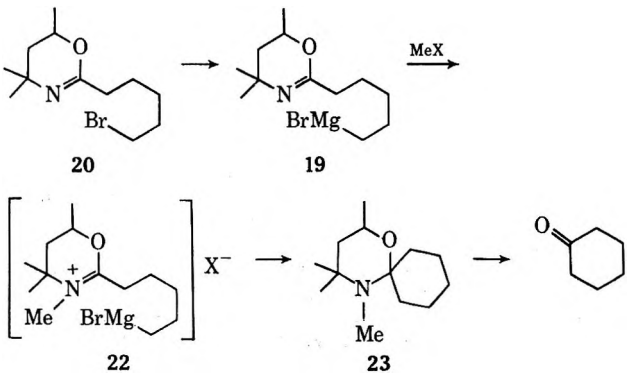
The use of organolithium reagents on the *N*-methyl quaternary salts must also be judiciously chosen, as seen by entries 12, 15, 18, 20, 21, and 26. The strongly basic nature of organolithium reagents precludes the presence of activated α protons in the oxazinium salts. However, in the case of the 2-phenethyloxazinium salts (entries 18–21), the expected reaction took place using *n*-butyl-, *sec*-butyl-, and *tert*-butyllithium reagents. As mentioned earlier, the yields were higher when the corresponding Grignard reagents were utilized owing to the weaker basic nature which minimized proton abstraction. In that instance, when *tert*-butylmagnesium chloride was utilized, no addition occurred owing to the competing reduction which is so typical of hindered Grignard reagents.[10] Thus, addition of *tert*-butylmagnesium chloride to the 2-phenethyloxazinium iodide (**18**) gave the tetrahydrooxazine **19**



which upon hydrolysis afforded 3-phenylpropionaldehyde.

In some instances, depending upon the complexity of the 2 substituent, the methiodide salts were not crystalline, but viscous oils. This could involve a cumbersome purification prior to Grignard addition and it would be desirable to avoid this problem. In this regard, the methanesulfonate or fluoroborate salts were found to be satisfactory crystalline products.[11]

Studies to extend this ketone synthesis to cyclic ketones utilizing the principle already discussed met only with disappointments. Although the 5-bromopentyloxazine **20** and its corresponding Grignard reagent **21** have been previously prepared and utilized,[3] all efforts to form the quaternary salt **22** (X = I, SO_4Me, BF_4), which would be expected to rapidly cyclize to the ketone precursor **23**, failed. The study was discontinued at this point.



Experimental Section

Infrared spectra were taken on a Perkin-Elmer 257 grating spectrophotometer, and nmr spectra were taken on a Varian T-60 instrument using tetramethylsilane as the internal standard. Melting points are uncorrected. Microanalyses were performed by Midwest Microlabs, Indianapolis, Ind. Mass spectra were taken on a AEI MS-9 instrument. The organolithium reagents were obtained from Lithium Corp., Bessemer City, N. C., and utilized as received.

Dihydro-1,3-oxazines 1 and 2 (R = Ph) were purchased from Columbia Organic Chemicals, Columbia, S. C., whereas the other oxazines in Table I were prepared by procedures already described.[3]

2-Phenyloxazine (entry 23, Table I) was prepared in 63% yield from benzonitrile and 2-methyl-2,4-pentanediol.[12]

2-Phenethyloxazine (entry 16, Table I) was prepared in 93% yield from the lithio salt of 1 and benzyl chloride, bp 151–153° (12 mm).

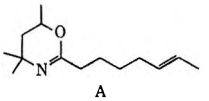
2-(3-Butenyl)oxazine (entry 6, Table I) was prepared in 91% yield from the lithio salt of 1 and allyl chloride, bp 90–93° (20 mm).

2-(3-Ethoxypropyl)oxazine (entry 5, Table I) was prepared in 89% yield from the lithio salt of 1 and 2-bromoethyl ether or ethylene oxide followed by addition of ethyl iodide, bp 100–102° (1.8 mm).

2-(1-Phenylethyl)oxazine (entry 27, Table I) was prepared in 99% yield from the lithio salt of 2 (R = Ph) and methyl iodide, bp 85–88° (0.2 mm).

(10) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954.

(11) Although all the compounds in Table I gave crystalline methiodide salts, we have encountered during the course of another study the oxazine A, which gave an oily methiodide. However, addition of the oxazine to a



A

suspension of $Me_3O^+BF_4^-$ in dichloromethane resulted in formation of the soluble *N*-methyl fluoroborate salt. Filtration of any excess $Me_3O^+BF_4^-$, followed by concentration of the dichloromethane solution, gave crystalline oxazinium fluoroborate which was sufficiently pure for Grignard addition.

(12) E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).

2-(1-Phenyl-3-butenyl)oxazine (entry 22, Table I) was prepared in 97% yield from the lithio salt of **2** (R = Ph) and allyl chloride, bp 104–106° (0.25 mm).

2-(3-Methyl-*n*-amyl)oxazine [R = $CH_2CH_2CH(CH_3)CH_2CH_3$] was prepared by addition of 1-iodo-2-methylbutane[13] to the lithio salt of 1 in 87% yield, bp 80–84° (0.3 mm).

Preparation of 2-Substituted 4,4,6-Trimethyl-5,6-dihydro-1,3-oxazine Methiodides (9). Method A.—A solution of the oxazine (20–60 mmol) in 5 equiv of methyl iodide was heated to reflux for 2 hr. Tetrahydrofuran (30–50 ml) was added and the suspension was stirred for 3–18 hr at room temperature after which the quaternary salt was removed by filtration, washed with ether, and dried *in vacuo*. No further purification was performed (Table II)

TABLE II

2-SUBSTITUTED OXAZINE METHIODIDES (9)

Registry no.	R	Method	Yield, %	Mp, °C	ν(C=N⁺-Me), cm⁻¹
36808-99-8	Et	A	74	175–180	1605
36809-00-4	Ph	A	33	143–144	1620
		B	83		
36809-01-5	$PhCH_2$	B	99[a]	135–138	1609
36809-02-6	CH_2=$CH(CH_2)_2$	A	70	165–167	1612
36809-03-7	$PhCH_2CH_2$	B	98	195–196	1612
36809-04-8	Cyclopropyl	A	90	184–185	1603

[a] Unstable in air and was stored under nitrogen.

and the methiodides (Table I) were used directly for the synthesis of ketones.

Method B.—The mixture of oxazine and methyl iodide was stirred at room temperature overnight (12–15 hr) followed by addition of anhydrous ether to precipitate the methiodides. Filtration, washing, and drying were performed as above.

Synthesis of Ketones from Previously Isolated *N*-Methyloxazinium Iodides. General Procedure.—A 100-ml three-necked round-bottomed flask equipped with a magnetic stirring bar, a three-way stopcock with a gas bubbler, a rubber septum, and a flask containing the oxazine methiodide salt attached by Gooch tubing was flushed with nitrogen. The Grignard reagent (2.5 equiv) was injected into the 100-ml flask. The oxazine methiodide salt (0.01 mol) was added in small portions to the Grignard reagent over 5 min. Gas evolution and heat were observed during this addition. The resulting pale yellow to orange-brown solution was stirred at room temperature for 48 hr, and then decomposed with 30 ml of ice water. The aqueous solution was extracted with five 40-ml portions of ether. These ether extracts were dried (K_2CO_3) and evaporated under vacuum on a rotary evaporator. A yellow to orange oil (crude tetrahydro-1,3-oxazine, **10**) was obtained.

Cleavage of Crude Tetrahydro-1,3-oxazine (10). A. *Via* Steam Distillation.—In a 250-ml flask equipped with a steam distillation head and steam inlet, the crude tetrahydro-1,3-oxazine was added to a solution of 5 g (0.04 mol) of hydrated oxalic acid in 100 ml of water. The steam distillation was continued until the distillate was free of organic material (*ca.* 400–700 ml). The distillate was extracted with three 40-ml portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate or potassium carbonate and evaporation of the ether under vacuum on a rotary evaporator gave the ketone, yield 45–60%.

B. *Via* Ether Extraction.—The tetrahydro-1,3-oxazine was placed in a flask together with 5 g of hydrated oxalic acid and 40 ml of water, and the mixture was heated under reflux for 1 hour. The aqueous solution was cooled and extracted with four 40-ml portions of ether. The ether extracts were washed with two 25-ml portions of 5.0% sodium bicarbonate. The dried (K_2CO_3) ether solution was evaporated *in vacuo* to yield the ketone.

Synthesis of Ketones by *in Situ* Preparation of Methiodide Salts of Dihydro-1,3-oxazines. General Procedure.—A three-necked reaction flask fitted with a magnetic stirring bar, a three-way stopcock containing an oil bubbler, and a rubber septum was flushed with nitrogen and thereafter maintained under a static pressure (0.1 atm) of nitrogen. The appropriate 2-substituted dihydro-1,3-oxazine was introduced (10 mmol) into the flask *via* syringe followed by a similar introduction of methyl iodide (5 ml). The solution was allowed to stir overnight and the suspension was treated with anhydrous ether, introduced and removed carefully *via* syringe. The salt was dried for 30–60 min *in vacuo* in the reaction flask by applying vacuum to the three-way stopcock. The Grignard (or lithium) reagent was added through the septum, using a syringe, and the suspension was stirred at room temperature for 4–18 hr. The syrupy mixture, which may in some instances contain a suspension of magnesium or lithium salts, was decomposed with 50 ml of ice water and the aqueous mixture was extracted with 5 × 40 ml of ether or ether–pentane (1:1). Drying (K_2CO_3) and concentration gave the 2,2-dialkyltetrahydro-1,3-oxazine (**10**). Hydrolysis to the ketone was performed using either the steam distillation technique or extraction directly from oxalic acid solution as described above.

Acknowledgment.—Financial assistance for this study was provided by the National Institutes of Health and the Petroleum Research Fund, administered by the American Chemical Society. The authors are also thankful to the Lithium Corporation for generous supplies of organolithium reagents.

(13) H. Schechter and H. Stone, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 323.

Synthesis of 10,11-Dihydro-5,10-ethano-5*H*-dibenzo[*a*,*d*]cycloheptenes with Various Side Chains at Position 12

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Novel 5,10-ethano- and methano-bridged compounds **3**, **5**, and **10** were synthesized from known **1** and **7**. Difficulties inherent in further work with these and similar bridged ketols were circumvented by developing a new, independent, and unambiguous synthetic approach to 5,10-ethano-bridged 12-oxo compound **22** *via* Dieckmann closure of diester **18** to enolic keto ester **19**, hydrolysis, and decarboxylation. In order to reach **17**, the precursor of **18**, from either **12** or **15**, alkylation of malonic ester with 5-chloro-10-bromodibenzo[*a*,*d*]cycloheptene giving **13** and selective triethyl phosphonoacetate reaction of **15** and hydrolysis giving **16** were invoked, followed by further reactions through **14** and **16**, respectively, involving selective hydrolyses taking advantage of the relatively inert character of the 10-carboxamide group and the 10,11 double bond. Hydrogenation of the latter function in hot HOAc (Pd) is possible, given an inert group at position 10. A number of typical reactions of **19** and bridged ketone **22** are described, including hydride reduction of **19** to **20** and conversion of **22** to oximes **21**, to aldehyde **23** by $(CH_3)_2S(O)CH_2$, and to unsaturated nitrile **24a** and ester **24b** by Wadsworth–Emmons reactions. The latter, *via* intermediates **25** and methoxime **21b**, were converted by standard methods to a series of homologous, 12-ω-aminoalkyl compounds **26**.

A preceding paper[1] described a novel synthesis of 10-cyano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one and from it a number of 5,10-bridged heterocyclic compounds. An objective similar to that in the earlier work was to synthesize 5,10-*carbon* bridged 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenes bearing functional groups suitable for further conversion to other moieties. As will be evident in this report, such a goal was reached by the use of classical synthetic methods.

Alkylations of the versatile intermediate **1**, *e.g.*, to **4** (Scheme I), were explored earlier,[1] and we now report on its Michael additions. With acrylonitrile and methyl acrylate in the presence of Triton B, **2a** and **2b**, respectively, were obtained from **1**. With a stronger base ($KOCMe_3$) the sterically favored closure to ethano-bridged ketols, **3a** and **3b**, respectively, occurred, **3a** predictably being formed more readily than **3b**. The change ketone → **3** was easily detected by disappearance of the intense uv 270-nm absorption. In the presence of NaH, ester **2b** similarly gave acid ketol **3c**. The related closure of **4** to a 5,10-methano-bridged ketol **5** was found to be less facile than **2** → **3**, as one might expect on steric grounds and from the greater efficiency of ethano as compared to methano bridging found by Nenitzescu, *et al.*, in exploring a different type of bridge closure ($\Delta^{10,11}$-π participation in solvolysis of 5-ω-hydroxyalkyl) in the same system.[2]

A related approach also explored was reaction of epoxy ketone **7** with nucleophiles. Earlier, **7** had been found to yield cyanoenone **15** with cyanide.[1] Reactions of **7**[3] with sodio ethylmalonate and ethyl cyanoacetate[4] now gave lactone ester **8a** and lactone nitrile **9**, respectively. With its highly reactive NCCHC=O system, compound **9** proved to be very sensitive to solvolysis, and with mere traces of base in methanol compound **10** was obtained. Ester **8a** was not so readily alcoholyzed, thus did not behave similarly and could be selectively hydrolyzed to **8b**. Reduction of **8a** with $NaBH_4$ and acidification of the resulting aqueous solution gave a crystalline substance, mp 224°, believed at first to be an acid, but lacking (ir, uv) a carbonyl group and on analysis proving to be a cyclic ether diol; thus reduction of the 1,3-dicarbonyl moiety to 1,3-diol had occurred. The compound contained both primary and secondary OH groups, and on acetylation formed a *mono-O*-acetyl derivative still containing a secondary OH attached to carbon 11 (nmr); this evidence eliminated other tentative structures and led to assignment of structures **11a** and **11b** to the ether diol and its monoacetyl derivative, respectively. Tosylation of **11a** led to formation of a reopened tetraol monotosylate.

Ketols **3**, **5**, and **10** were not useful for further work. Hydrolytic conditions tended to bring about the reverse of ketol closure, the same difficulty as has been encountered in similarly constituted, 9,10-ethano-bridged dihydroanthracenes.[5] Acid hydrolysis, for example, gave **6** from either **4** or **5**. The 10-carbonitrile group, attached to a quaternary C atom in **3** and **5**, is relatively resistant to useful attack, except by hydrogen. Hydrogenolysis of ketol OH might be applied, were it not for the presence of this equally reducible CN group. Our limited efforts with **3** and **5**, *e.g.*, preparation of **3d**, were terminated when there appeared reports on synthesis of less polyfunctional, methano-bridged compounds similar to **5** by somewhat different approaches.[6,7] Still another synthesis of a 12-carboalkoxy-5,10-methano-bridged compound lacking other, complicating functional groups had been described earlier.[8]

Bridged ketols having been found wanting as intermediates, we decided that, aside from photochemical rearrangements,[8,9] a stable ethano bridge with a useful functional group could be established by reaction between suitable substituents on positions 5 and 10 if

(1) G. N. Walker, D. Alkalay, A. R. Engle, and R. J. Kempton, *J. Org. Chem.*, **364**, 66 (1971), with many references to prior art.

(2) E. Cioränescu, M. Banciu, R. Jelescu, M. Rentzea, M. Elian, and C. D. Nenitzescu, *Rev. Roum. Chim.*, **14**, 911 (1969).

(3) F. Hoffmann La Roche, *Chem. Abstr.*, **65**, 15297 (1966); J. Rigaudy and L. Nedelec, *Bull. Soc. Chim. Fr.*, 400 (1960).

(4) See A. C. Cope, H. L. Holmes, and H. O. House, *Org. React.*, **9**, 107 (1957).

(5) J. S. Meek, P. A. Monroe, and C. J. Bouboulis, *J. Org. Chem.*, **28**, 2572 (1963); see also T. W. Campbell, V. E. McCoy, J. C. Kauer, and V. S. Foldi, *ibid.*, **26**, 1422 (1961), and references cited therein.

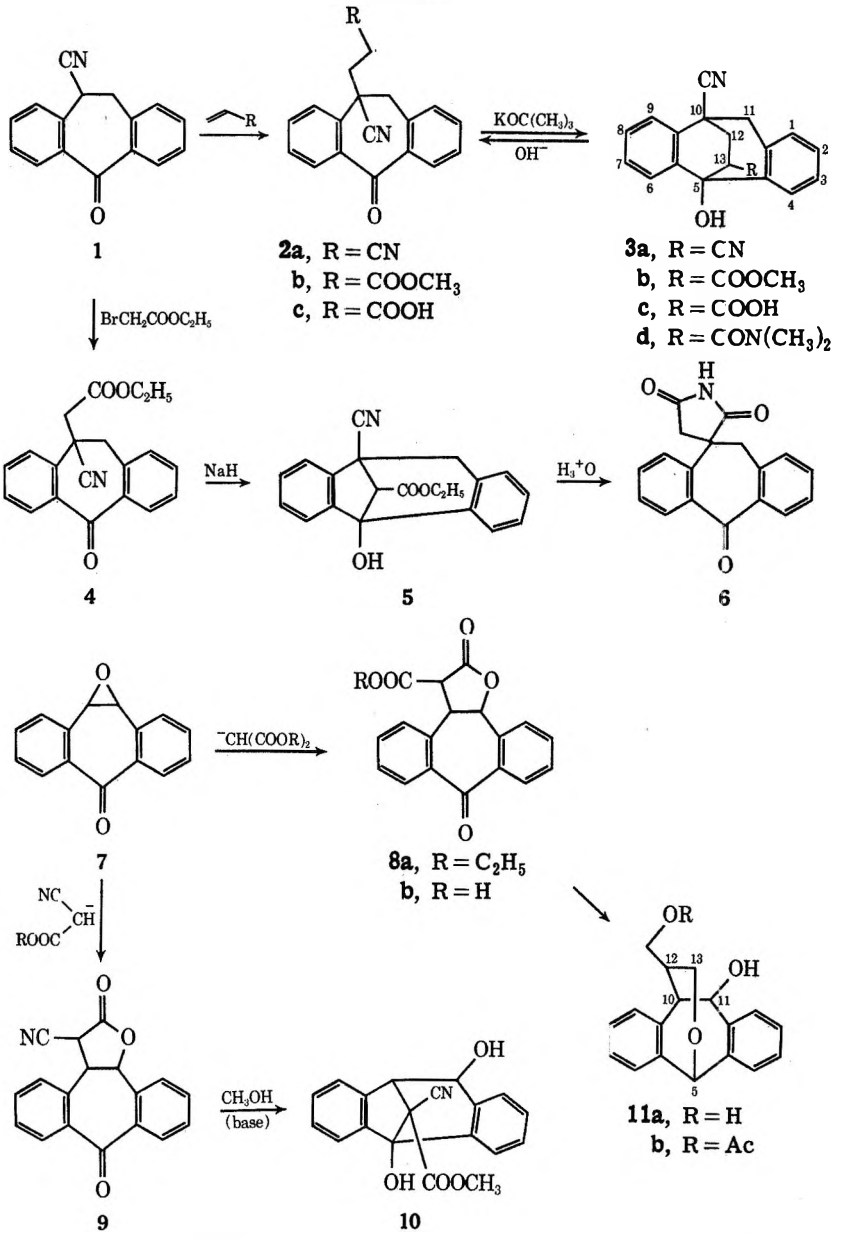
(6) W. Lettré, W. Winter, and K. Stach, German Patent 1,568,092 (1970); *Chem. Abstr.*, **74**, 141405 (1971). W. Winter, M. Thiel, K. Stach, K. Hardebeck, and E. Roesch, German Patent 1,953,334 (1971); *Chem. Abstr.*, **75**, 20048 (1971).

(7) M. E. Christy, *Chem. Abstr.*, **72**, 121245 (1970).

(8) S. J. Cristol and B. J. Jarvis, *J. Amer. Chem. Soc.*, **88**, 3095 (1966).

(9) S. J. Cristol, *et al.*, *ibid.*, **87**, 4007 (1965); **90**, 5564 (1968); **91**, 214 (1969); *J. Org. Chem.*, **34**, 2363 (1969).

SCHEME I



those carbon atoms were saturated. The logical choice was Dieckmann closure (Scheme II), preferably in that diester with the carboalkoxy group attached at position 10 rather than 5, to avoid the foreseeable complications in a diphenylacetic acid analog. Available precursors were **12** and **15**.[1,10,11] Whereas **15** is now known to undergo conjugate addition of anions (and $NaBH_4$ reduction) at the unsaturated nitrile moiety, ketone **12** had been converted to the carbinol[10] and thence to the corresponding 10-bromo-5-chloro compound.[10] Using the latter, rather than attempting direct reaction of the 5-hydroxy compound with malonic acid,[12] we prepared **13** by alkylation of malonic ester, using NaH in DMF. From **13**, two alternate routes as shown were found, both rather tedious, converging on the easily purified acid amide **17**, and actually depending for their success on the relatively inert character of Br[13] or CN group in the dibenzotropone system. The more practical, albeit longer, of these two routes is that proceeding *via* **14**: the vinyl bromide withstands well the operations of hydrolysis, decarboxylation, and reesterification, whereas side reactions, perhaps bridging, conjugate addition of carbanion to $\Delta^{10,11}$ (to be explored further) may occur in **13** → **17**. A third, probably superior approach to **17** was *via* highly selective Wadsworth–Emmons–Arbuzov reaction of triethyl phosphonoacetate with the keto[14] group of **15**. Alkaline hydrolysis of the ester group in the resulting nitrile is accompanied (as in **14** → **17**) by conversion of nitrile to corresponding carboxamide, giving **16**. Completely selective, Pd-catalyzed hydrogenation of the exocyclic double bond in **16** (a mixture of isomers) can be carried out, giving **17**,

(10) J. Gootjes, A. B. H. Funcke, and W. T. Nauta, *Arzneim. Forsch.*, **19**, 1936 (1969); J. Gootjes, A. B. H. Funcke, and H. Timmerman, *ibid.*, **22**, 632 (1972).

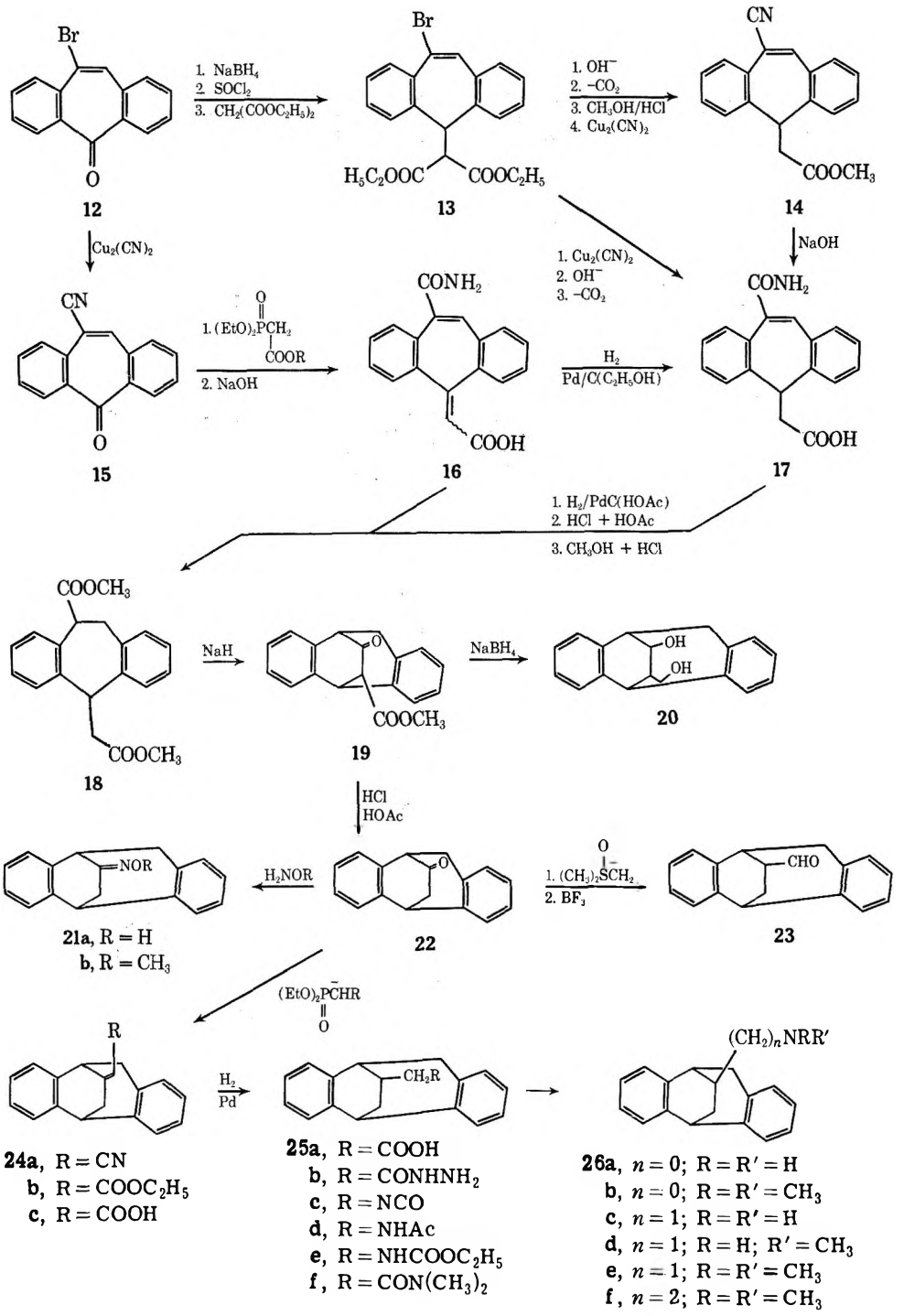
(11) T. A. Dobson and M. A. Davis, *Can. J. Chem.*, **49**, 1027 (1971).

(12) C. Vander Stelt, A. Haasjes, H. M. Tersteege, and W. T. Nauta, *Recl. Trav. Chim. Pays-Bas*, **84**, 1466 (1965).

(13) See F. Hoffmann La Roche, Netherlands Patent Application 6,600,200 (1966); *Chem. Abstr.*, **64**, 5023, 5024 (1966).

(14) See L. H. Werner, S. Ricca, A. Rossi, and G. deStevens, *J. Med. Chem.*, **10**, 575 (1967); E. D. Bergmann and A. Solomonovici, *Synthesis*, 183 (1970).

SCHEME II



a single isomer, identical with that from the longer routes.

Further Pd-catalyzed hydrogenation of the relatively resistant 10,11 double bond in **17** was then done quantitatively in warm HOAc medium.[1] For this operation it is necessary to have the inert $CONH_2$ group (or, less readily achieved, a carboxyl group) in place of the reducible CN group at position 10. The straightforward, three-step sequence from **17** to **18** was carried out with no serious attempt to isolate crystalline intermediates, since each undoubtedly is a mixture of cis and trans isomer. We anticipated that equilibria (thermodynamic control) involving proton 10 in the presence of sufficiently strong base might serve to isomerize **18** favorably. Whether this actually occurred or **18** was predominantly the cis isomer cannot be stated precisely and soon became an academic question, for in fact Dieckmann closure of crude **18** in the presence of NaH in DMF gave crystalline, 30% enolic (nmr), bridged keto ester **19** in 70% yield.

Like other 1,3-dicarbonyl compounds, **19** was reduced by $NaBH_4$ to a diol, **20**. Hydrolysis and decarboxylation of **19** under alkaline conditions gave a *ca.* 50% yield of bridged ketone **22**, whereas refluxing HCl and HOAc gave **22** in 82% yield. Our multistep route to **22** is not the first synthesis of a compound of this type, but has the virtue of being unambiguous, whereas all previous work[2,9,12] has given 5,10-ethano-10,11-dihydrodibenzo[*a*,*d*]cycloheptenes as by-products or components of mixtures. In addition, the 12-oxo group

in **22** affords the handle required for equally unambiguous preparation of pharmacologically potentially interesting compounds, to which we proceeded forthwith.

Ketone **22**, having been well characterized as oxime (**21a**) and 2,4-dinitrophenylhydrazone, and by reduction with $NaBH_4$ to corresponding 12-ol, was found to behave typically, if somewhat sluggishly, in reactions with a number of other reagents. Mannich reactions were very poor, and **22** was acylated at position 13 with HCOOEt and ethyl oxalate to give somewhat low yields of typical enols. Our primary objective was to introduce an array of homologous, basic side chains (**26**, n = 0–3) to permit at least preliminary assay of the drug potential of the ring system.

Reduction of methoxime **21b** with $LiAlH_4$, superior to that of **21a**, gave **26a**, which was in turn Eschweiler–Clarke methylated to give **26b**. Reaction of ketone **22** with $(EtO)_2(P{=}O)CH_2COOEt$ (NaH in glyme)[15] gave a high yield of **24b**, as nearly all one isomer, evidently the one depicted, which is least eclipsed in models and presumably is analogous to the predominant isomer of nitrile **24a** from reaction of **22** with $(EtO)_2P(O)CH_2CN$ which showed (nmr) a downfield shift of the proton 10 signal owing to deshielding by the CN group. Reaction of **22** with dimethylsulfoxonium methylide[16] to give an epoxide, converted by BF_3 to aldehyde **23**, was less practical, and Wittig ($Ph_3P{=}CHR$) reactions of **22** did not work at all. It was decided to proceed from **24b,c**, particularly since hydrolysis and hydrogenation (10% Pd/C) led to **25a** in high yield. By $LiAlH_4$ reduction of amides (**25f**), easily prepared *via* acid chloride from **25a**, good yields (n = 2) of amines, *e.g.*, **26f**, were secured. Nitrous acid converted the acid hydrazide **25b** smoothly to the corresponding azide, which in turn Curtius rearranged easily (reflux in benzene) to isocyanate **25c**, not characterized other than by its typical ir 4.40-μ absorption but converted with Ac_2O to **25d** (in turn hydrolyzed to **26c**) and with EtOH to urethane **25e**.[17] The latter on $LiAlH_4$ reduction gave a very good yield of **26d**, in turn methylated with CH_3I to provide **26e**. Finally, **22** on reaction with $ClMg(CH_2)_3N(CH_3)_2$ in THF gave a mixture of two isomeric, basic, tertiary carbinols (n = 3; R, R^1 = CH_3), which did not dehydrate smoothly, completing the present array of substances.

Experimental Section

Melting points were obtained using a Thomas-Hoover (silicone oil bath) apparatus; infrared spectra (Nujol mulls unless otherwise noted) were taken with a Perkin-Elmer double-beam instrument; ultraviolet spectra (methanol solutions unless otherwise noted) were measured with a Beckman recording spectrophotometer; and nmr spectra were recorded using a Varian A-60 apparatus with TMS internal standard.

10-(β-Cyanoethyl)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one-10-carbonitrile (2a).—A solution of 3.4 g of keto nitrile 1[1] in 20 ml of THF containing 0.7 ml of 40% methanolic benzyltrimethylammonium methoxide was treated with 1.2 ml of acrylonitrile at 25°. The temperature rose spontaneously to 40° and the purple color originally present faded and disappeared. After standing for 0.5 hr the solution was treated with a few milliliters of glacial HOAc and poured over ice water. An ether extract of the material was washed (H_2O), dried ($MgSO_4$), and evaporated. A small amount of **3a** was present, and crystallized first; it was removed with the aid of ether. The residual oil (3 g) then crystallized, and on trituration with methanol afforded colorless crystals: mp 95–105°, raised on recrystallization from methanol and drying *in vacuo* to 105–107°; ir 4.43–4.46 and 6.06 μ; uv 269 nm (ϵ 11,760).

Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.70; H, 4.66; N, 9.74.

5-Hydroxy-5,10-ethano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-10,13-dicarbonitrile (3a).—A solution of 1 g of **2a** and 0.5 g of $KOC(CH_3)_3$ in 15 ml of *tert*-butyl alcohol was heated on a steam cone for 25 min. An insoluble salt separated from the orange-brown solution. Treatment of the cooled suspension with 2 ml of glacial HOAc, then water, converted the precipitate to a crystalline product, which was collected, washed with water, dried, and recrystallized from methanol to give a quantitative yield of colorless crystals: mp 293–295°; ir 2.92 and 4.43–4.46 μ; uv 260 nm (ϵ 440).

Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.90; H, 4.69; N, 9.69.

Compound **3a** was also prepared directly from **1**, again in virtually quantitative yield, as follows. Keto nitrile 1 (4 g) in 25 ml each of THF and *t*-BuOH was treated with 0.68 ml of 40% Triton B methoxide and cyanoethylated by adding 2 ml of acrylonitrile. Then 2.1 g of K *tert*-butoxide was added, the solution was boiled for 40 min, and the product was isolated as in the preceding experiment, giving 4 g of crude solid, mp *ca.* 265–280°, recrystallization of which from methanol afforded 3.5 g of **3a**, mp 287–290°. Further purification gave material identical with the preceding sample.

Compound **3a** resisted 4-hr reflux with concentrated HCl and glacial HOAc solution, overnight treatment with excess PCl_5 in CH_2Cl_2 solution, and 9-hr reflux with saturated methanolic HCl. Treatment with aqueous bases gave poorly characterized material, uv λ_{max} ~270 nm (ϵ ca. 10,000).

Compounds 2b and 3b were both obtained in appreciable amount in the following experiment. 1 (5 g) in 30 ml of THF with 0.7 ml of 40% Triton B methoxide (methanol solution) was treated with 3.2 ml of methyl acrylate, which caused a temperature rise from 23° to 43° and disappearance of the intense purple color. After 0.8 hr the reddish solution was rewarmed to 40° briefly, then chilled, neutralized with HOAc, and treated with cold water, and the oily products were extracted with ether. The washed ($NaHCO_3$ solution) and dried ($MgSO_4$) ether solution on evaporation gave 4.9 g of yellow oil; in the presence of ether this gave 0.6 g of **3b**, mp 215–222°. A pure sample, recrystallized from EtOAc, had mp 230–232°; ir 2.94, 4.46, and 5.85 μ; uv 262 nm (ϵ 410); nmr ($CDCl_3$) δ 7.0–8.1 (m, 8, aromatic H), 4.83 (s, 1, D_2O exchanges, OH), 3.6 (s, 3, ester CH_3), 3.36–3.60 (m, 3, bridge methine and 11-methylene protons) and 2.78 (d, 2, J = 7.6 Hz, bridge CH_2).

Anal. Calcd for $C_{20}H_{14}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.35; H, 5.43; N, 4.45.

The material remaining from isolation of **3b** consisted of crude **2b** (4.3 g) as an oil, ir 4.45, 5.77, and 6.07 μ, uv 268 nm (ϵ 18,490). On further treatment with K *tert*-butoxide in *tert*-butyl alcohol this material afforded additional **3b** admixed with corresponding acid **3c**.

Compound **2b** was reduced with $NaBH_4$ to a corresponding cyanoester carbinol [not crystalline, ir 2.94, 4.47, and 5.80 μ; uv 262 nm (ϵ 550)] which reacted readily with $SOCl_2$. Attempts to bring about internal displacement of Cl in the resulting 5-chloro cyano ester with agents such as NaH and K *tert*-butoxide were not successful.

10-Cyano-5-hydroxy-5,10-ethano-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene-13-carboxylic Acid (3c).—A stirred solution of 3.5 g of **2b** in 45 ml of DMF was treated with 0.55 g of 56% NaH (oil) without cooling, and following a moderately exothermic reaction the solution was warmed on a steam cone gently (*ca.* 70°) for periods of 10 min each at 2-hr intervals over the course of 6 hr. The cooled solution was treated with ice and water. Acidification (HCl) of the ether-washed, alkaline solution gave several crops of crystals totalling 2.3 g, mp 195–205°. Recrystallization from ether gave a pure sample of the acid mp 208–210°; ir 2.89 4.44, and 5.88 μ; uv lacking conjugated C=O band; the sample tenaciously held solvents.

Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 73.94; H, 4.75; N, 4.03.

Esterification of a sample of the acid with saturated methanolic HCl (3 hr reflux) gave **3b**: mp 229–230° (from EtOAc); mixture

(15) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

(16) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1353 (1965).

(17) See P. A. S. Smith, *Org. React.*, **3**, 337 (1946).

melting point with **3b** from preceding experiment, 229–230° (undepressed); ir identical.

The corresponding *N,N*-dimethylamide (**3d**) was obtained by treating 1 g of **3c** with 50 ml of $SOCl_2$ (reflux 5 min) and the acid chloride, after removal of excess reagent, with excess dimethylamine. After evaporation, treatment with water, isolation of neutral product, and recrystallization from ether there were obtained crystals: mp 224–226°; ir 3.12, 4.50, and 6.15 μ.

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 75.58; H, 5.92; N, 8.37.

Ethyl 10-Cyano-5-hydroxy-10,11-dihydro-5,10-methano-5*H*-dibenzo[*a,d*]cycloheptene-12-carboxylate (5).—Preparation of keto cyano ester **4** (mp 101–103°) was described previously.[1] When the alkylation of **1** (15 g) with ethyl bromoacetate was carried out in the presence of excess NaH (DMF) and the solution was allowed to stand for 5 hr before work-up, or when **4** was treated with NaH as described in the preceding experiment, there was obtained a mixture of **4** and **5** from which **5** (5.2 g, mp 163–165°) separated readily on fractional crystallization with methanol. Recrystallization from the same solvent gave colorless crystals: mp 166–168°; ir 2.86, 4.45, and 5.83 μ; uv benzenoid; nmr ($CDCl_3$) δ 6.8–7.8 (m, 8, aromatic H), 4.14 (q, 2, J = 7 Hz, methylene of ester), 3.87 (s, 1, D_2O exchange, OH), 3.78 (s, 1, bridge methine), 3.44 (q, 2, J = 17.5 Hz, 11-methylene), and 1.06 (t, 3, ester CH_3).

Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.5; H, 5.43; N, 4.42.

Attempted selective hydrolyses (and other reactions) of **5** were not successful. However, hydrolysis (concentrated HCl, glacial HOAc, 3 hr reflux) of **4** or **5** gave keto imide **6**, crystallizing directly from the hydrolysis solution on addition of water as colorless crystals (from EtOAc): mp 246–248°; ir 5.64, 5.90, and 6.07 μ; uv 208 and 269 nm (ε 24,060 and 12,640, respectively); nmr (DMSO) δ 11.4 (s, 1, D_2O exchange, NH), 7.2–8.1 (m, 8, aromatic H), 3.48 (q, 2, J = 15 Hz, 11-methylene), and 2.80 (q, 2, $J \cong 15$ Hz, methylene of imide).

Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.21; H, 4.50; N, 4.81. Found: C, 74.37; H, 4.18; N, 4.74.

Keto Lactone Ester 8a.—To a solution of 2.5 g of sodium in 250 ml of absolute ethanol was added 20 ml of ethyl malonate, then 10.9 g of epoxy ketone **7**.[1,3] The solution on reflux (2.5 hr) first turned deep red and within 1 hr became a thick suspension of sodio salt. The cooled mixture was filtered; the salt was washed with two small portions of ethanol, dissolved in 250 ml of water at 70°, and acidified strongly with hydrochloric acid. After standing for 1–2 hr, the resulting suspension of crystals was filtered, and the crude product was washed with water, dried, and triturated with methanol: yield 11.2 g of colorless crystals; mp 163–165°, raised on recrystallization from methanol to mp 168–170°; ir 5.63, 5.79, and 6.12 μ; uv 269 nm (ε 14,510); nmr ($CDCl_3$) δ 7.1–8.3 (m, 8, aromatic H), 5.63 (d, 1, J = 10 Hz, 11-methine adjacent to oxy), 4.1–4.75 (m, 3, methylene of ester and methine), and 1.34 (t, 3, methyl of ester). After D_2O exchange of the enolic proton, δ 4.45 (d, 1, J = 10 Hz, 10-methine) was seen.

Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80. Found: C, 71.60; H, 4.89.

Hydrolysis of **8a** with either concentrated HCl and glacial HOAc (2 hr reflux) or 10% KOH (3 hr reflux, followed by acidification) gave samples (ir identical) of the corresponding keto lactone acid **8b**, as solvated crystals: melting point varying from 171–173° dec (from ether) to 199–201° (from methanol); soluble in $NaHCO_3$ solution and recovered subsequently by acidification; ir 3.10 (broad, OH), 5.60, 5.76, and 6.13 μ; uv 269 nm (ε 15,920); nmr (DMSO) 7.2–8.2 (m, 8, ArH), 5.88 (d, 1, J = 10 Hz, 11-methine), and 4.43–4.48 (m, 2, remaining CH) resolved by D_2O exchange to δ 4.45 (d, 1, J = 10 Hz, 10-methine proton). The carboxyl H was buried in the base line.

Anal. Calcd for $C_{18}H_{12}O_5 \cdot {}^1/_2H_2O$: C, 68.14; H, 4.13. Found: C, 68.42; H, 3.93.

Keto Nitrile Lactone 9.—Ethyl cyanoacetate (3 ml) was added to a solution of 0.5 g of sodium in 50 ml of absolute ethanol, followed by 1.5 g of epoxy ketone **7**, and the solution was refluxed for 2 hr. The very deep red solution, on chilling or evaporation, deposited a thick precipitate of sodium salt, which was collected, washed with ether–ethanol, and treated with 10% HCl. The crystals were collected, washed (H_2O), dried (1.1 g yield), and triturated and recrystallized with methanol to give material: mp 247–250° dec; ir 4.42, 5.61, and 6.08 μ; uv 269 nm (ε 12,680).

Anal. Calcd for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.52; H, 3.61; N, 4.85.

On warming, solutions of **9** (especially in alcohols) gradually lost the uv 269-nm absorbance. A satisfactory nmr spectrum was not obtained.

Compound 10.—Methanol solutions of **9** on reflux gradually became mixtures of **9** and **10**, as was evident from uv spectra, and the change was hastened by presence of a very small amount of $NaOCH_3$. The product, easily separated from any remaining **9** by use of methanol, was recystallized from ether: mp 186–188° dec; ir 2.84, 2.89, 4.47 (weak), and 5.79 μ; uv lacking conjugated C=O band. The compound did not give a satisfactory nmr spectrum.

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.25; H, 4.47; N, 4.35.

Bridged Dihydroxy Ether 11a.—Treatment of a suspension of 6 g of **8a** in methanol (100 ml) with sodium borohydride (*ca.* 10 g) in portions gave a solution, which was heated for 0.5 hr on a steam cone, and the residue was cooled and treated with water. The resulting colorless solution was acidified with HCl. Colorless crystals which emerged were collected, washed with water, and dried, mp 217–221° (yield 3.5 g). The compound was insoluble in aqueous alkali. Recrystallization from methanol afforded a pure sample: mp 223–225°; ir 3.00 and 3.08 μ; uv showing no conjugated C=O peak; nmr (DMSO) δ 7.0–7.7 (m, 8, ArH), 5.48 (s, 1, proton 5), 5.22 (d, 1, J = 5 Hz, D_2O exchange, 11-OH), 4.93 (m, 1, proton 11; D_2O exchange giving d, 1, J = 3 Hz), 4.5 (t, 1, J = 5 Hz, D_2O exchange, primary OH), 3.65–3.20 (m, 5, both CH_2 and proton 10), and 1.9 (m, 1, not D_2O exchange, proton 12).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.80; H, 6.47.

Monoacetate 11b was obtained when 0.7 g of **9** was heated with 40 ml of acetic anhydride at 100° for 3.5 hr. Evaporation of the excess reagent and recrystallization of the residue from ethyl acetate–ether gave crystals: mp 180–181.5°; ir 3.00 and 5.75 μ; nmr ($CDCl_3$) δ 7.1–7.7 (m, 8, ArH), 5.46 (s, 1, proton 5), 4.86 (m, 1, proton 11; shifting to δ 6.39, d, 1, J = 4 Hz, on reaction of OH with $Cl_3CCONCO$), 3.6–4.1 (m, 4, methines 10 and 12, and methylene adjacent to OR), 3.41 (m, 1, D_2O exchange, OH), 2.12 (m, 2, methylene 13), and 2.02 (s, 3, CH_3 of acetyl).

Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 73.87; H, 6.29.

Tosylation of **11a** by the standard procedure gave crystals, from ethyl acetate, mp 172–173° dec, ir 3.05 μ. The nmr spectrum and analysis indicate that the compound was a monotosylate of a tetracarbinol.

Anal. Calcd for $C_{25}H_{26}O_6S$: C, 66.05; H, 5.77. Found: C, 65.83; H, 5.64.

***trans*-10,11-Dibromo-10,11-dihydro-5*H*-dibenzo[*a,d*]-cycloheptene-5-one.**—This intermediate (for dehydrobromination to **12**) was prepared in two ways. (A) A solution of 103 g of 5*H*-dibenzo[*a,d*]cycloheptene-5-one in 1 l. of CCl_4 was treated with 84 g of bromine and allowed to stand for 3 days. The product was collected, 174 g (95%) of crystals, mp 212–214° dec (lit.[18] mp 211°). (B) A solution of 104 g of 10,11-dihydro-5*H*-dibenzo-[*a,d*]cycloheptene-5-one in 700 ml of CCl_4 was treated with 93 g of *N*-bromosuccinimide and 0.5 g of dibenzoyl peroxide, and refluxed gently for *ca.* 1 hr or until all NBS was converted to floating succinimide. After filtration the solution was charged with 93 g of additional NBS and 0.5 g of benzoyl peroxide, and warmed again until reflux occurred spontaneously. When the reaction subsided, the crystalline mixture was collected (188 g), washed with 500 ml of 5% NaOH solution to remove succinimide and with water, and dried, to give a total of 146 g (80%) of crystals, mp 208–210°.

10-Bromo-5*H*-dibenzo[*a,d*]cycloheptene-5-one (12).—Dehydrobromination of 50 g of 10,11-dibromo-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-one by refluxing with a solution of 17 g of 85% KOH in 900 ml of methanol for 2 hr gave a quantitative yield of crystals, mp 116–118° (lit.[13,18] mp 116°).

10-Bromo-5*H*-dibenzo[*a,d*]cycloheptene-5-ol.—After 48 g of **12** in 300 ml of methanol was treated with 4.5 g of $NaBH_4$, 80 ml of water was added, the methanol was evaporated, and the solidified oil was collected, washed with dilute HCl and water, and dried, yield 40.5 g, mp 123–126° (lit.[10] mp 121–123°); recrystallization from cyclohexane gave colorless crystals, mp 122–124°, uv 210 nm (ε 39,010) and 283 (13,670).

(18) W. Treibs and H. J. Klinkhammer, *Ber.*, **84**, 671 (1951); W. Tochtermann, K. Oppenländer, and U. Walter, *ibid.*, **97**, 1318 (1964).

10-Bromo-5-chloro-5*H*-dibenzo[*a*,*d*]cycloheptene.—By the action of 25 ml of $SOCl_2$ on a chloroform solution of 42 g of carbinol from the preceding experiment, after 1 hr at room temperature and evaporation and recrystallization from benzene and ether, the chloro compound, reported as not crystalline,[10] was obtained as crystals, mp 127–129°, uv 213 nm (ε 31,630) and 284 (13,540).

Anal. Calcd for $C_{15}H_{10}BrCl$: C, 58.95; H, 3.30. Found: C, 58.92; H, 3.72.

Diethyl 5-(10-Bromo-5*H*-dibenzo[*a*,*d*]cycloheptenyl)malonate (13).—Sodium hydride (15 g of 56%, in oil, washed with ligroin) was suspended in DMF (20 ml), diethyl malonate (25.6 g) was added gradually with cooling (40° or less), and an ether–DMF solution of the chlorobromo compound from the preceding experiment was added in one portion. The exothermic reaction was allowed to proceed and boil off the ether. After 0.5 hr, cold water was added and an ether extract of the product was washed twice with water, dried ($MgSO_4$), and evaporated, giving 65 g of crude **13**. On long standing the oil crystallized. A sample, recrystallized from ethanol, had mp 84–86°; ir 5.74 and 5.80 μ (sharp doublet); uv 211 nm (ε 32,340) and 291 (13,640); nmr ($CDCl_3$) δ 7.71 (s, 1, proton 11), 8.1–7.2 (m, 8, ArH), 4.88 (d, 1, J = 11.5 Hz, proton 5), 4.27 (d, 1, J = 11.5 Hz, malonic CH), 3.90 (2 overlapping q, 4, J = 7 Hz, ester CH_2 groups), and 0.96 (2 overlapping t, 6, J = 7 Hz, ester CH_3 groups).

Anal. Calcd for $C_{22}H_{21}BrO_4$: C, 61.55; H, 4.93. Found: C, 61.71; H, 5.14.

Hydrolysis (150 ml of 10% NaOH and 300 ml of ethanol, 3 hr reflux) of 58 g of crude bromo diester **13** gave the corresponding diacid, 35 g of crystals from ether–ligroin: mp 207–208° dec; ir 5.80–5.85 μ; uv 210 nm (ε 32,050) and 290 (12,840); Beilstein test positive; nmr (DMSO) δ 7.78 (s, 1, proton 11), 8.0–7.2 (m, 8, ArH), 4.83 (d, 1, J = 12 Hz, proton 5), and 3.98 (d, 1, J = 12 Hz, malonic CH); COOH δ *ca.* 12 (very broad, 2, D_2O exchange).

Anal. Calcd for $C_{18}H_{13}BrO_4$: C, 57.93; H, 3.51. Found: C, 58.17; H, 3.79.

A neutral by-product isolated in this hydrolysis (9.4 g) proved to be 10-bromodibenzo[*a*,*d*]cyclohepten-5-ol, mp 123–125°, identical with the authentic sample.

5-(10-Bromodibenzo[*a*,*d*]cycloheptenyl)acetic Acid.—The 10-bromo diacid (19.5 g) was heated at 230° (oil bath) for 10 min until evolution of CO_2 ceased. Trituration of the cooled, dark melt with ether gave 16 g (94%) of gray crystals, mp 228–231°. A colorless sample after recrystallization from ethanol had mp 230–232°; ir 5.89 μ; uv 210 nm (ε 35,160) and 286 (14,220) with inflection at 236 nm; nmr (DMSO) δ 7.82 (s, 1, proton 11), 8.0–7.1 (m, 8, ArH), 4.64 (t, 1, J = 8 Hz, proton 5), and 2.68 (d, 2, J = 8 Hz, CH_2); COOH δ *ca.* 12 (very broad, 1, D_2O exchange)

Anal. Calcd for $C_{17}H_{13}BrO_2$: C, 62.02; H, 3.98. Found: C, 62.31; H, 4.19.

The corresponding methyl ester was prepared by refluxing the bromo acid with 30 parts of saturated, methanolic HCl for 3 hr and isolated as usual: 91% yield of neutral oil, ir 5.80 μ, uv 210 nm (ε 32,530) and 288 (13,200), strong Beilstein test.

Ester Nitrile 14.—To a solution of 41 g (0.12 mol) of crude bromo ester from the preceding experiment in 200 ml of DMF (reagent grade) was added 22.4 g (0.125 mole) of cuprous cyanide, and the mixture was stirred and refluxed for 2.5 hr. Water and an excess of NH_4OH were added to the cooled solution, and the product was extracted with chloroform. The organic solution was diluted with ether, washed with dilute HCl and water, dried ($MgSO_4$), and evaporated to give 38.5 g of crude, red oil. The material did not crystallize; a rewashed (ether solution), dried sample of the oil still contained some DMF; ir 4.52 and 5.78 μ; uv 231 nm (ε 19,960) and 304 (15,700).

Acid Amide 17.—Crude **14** (90 g) was refluxed with 400 ml of 10% NaOH and 500 ml of ethanol for 4 hr; the solution was evaporated to remove most of the ethanol and refluxed for 4 hr longer. The diluted, hot solution was treated with Norit, washed with chloroform, cooled, and acidified with HCl, and the tan precipitate was collected, washed with water, and dried. The crude acid when triturated with ethanol gave 31 g of slightly discolored crystals, mp 226–236°, suitable for further work. Recrystallization from ethanol or aqueous HOAc gave a sample as colorless crystals: mp 241–244°; ir 2.92, 3.02, 3.10, 5.90, and 6.05 μ; uv 210 nm (ε 30,580) and 290 (13,220); nmr (DMSO) δ 7.77 (s, 1, proton 11), 7.9–7.1 (m, 10, 2 slowly D_2O exchange, ArH and $CONH_2$), 4.61 (t, 1, J = 7.5 Hz, proton 5), and 2.66 (d, 2, J = 7.5 Hz, CH_2); COOH δ far downfield (1, D_2O exchange).

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 74.01; H, 4.94; N, 4.72.

Diethyl 5-(10-Cyano-5*H*-dibenzo[*a*,*d*]cycloheptenyl)malonate.—Reaction of 63 g of **13** with $Cu_2(CN)_2$ in DMF (3 hr reflux) as described for **14** afforded, after a similar work-up, 51 g of viscous oil. A filtered, ether solution of the crude material on slow evaporation gave a sample of the diester nitrile as colorless crystals: mp 143–145° (from ether); ir 4.51 and 5.74–5.79 μ; uv 210 nm (ε 32,100), 231 (19,500), and 306 (16,160); nmr ($CDCl_3$) δ 7.80 (s, 1, proton 11), 8.0–7.2 (m, 8, ArH), 4.93 (d, 1, J = 11.5 Hz, proton 5), 3.99 (d, 1, J = 11.5 Hz, malonic CH), 3.89 (2 overlapping q, 4, J = 7 Hz, ester CH_2), and 0.97 (2 overlapping t, 6, J = 7 Hz, ester CH_3).

Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.94; H, 5.84; N, 3.94.

Hydrolysis of 50 g of the crude diester nitrile by 2.5-hr reflux with 200 ml of 10% NaOH solution and 200 ml of ethanol gave, on acidification of the diluted, ether-washed, and Norit-treated solution, 22 g of crude solids, from which, on trituration with ether–ethyl acetate, there was obtained 6 g of the corresponding amide malonic acid: mp 164–167° dec after recrystallization from ether–acetone or water; ir broad, bonded OH, 5.86 and 6.08 μ; uv 294 nm (ε 13,420) and inflection at 212 (35,000); nmr (DMSO) δ 7.56 (s, 1, proton 11), 7.7–7.1 (m, 10, 2 D_2O exchange, ArH and $CONH_2$), 4.80 (d, 2, J = 11.5 Hz, proton 5), and 3.93 (d, 1, J = 11.5 Hz, malonic CH); COOH δ *ca.* 12 (very broad, 1, D_2O exchange).

Anal. Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.52; H, 4.53; N, 3.73.

Decarboxylation of 5.6 g of the diacid amide at 230°, trituration of the cooled melt with ether–acetone, and recrystallization from ethanol gave 3 g of **17**, mp 242–245°, spectra identical with those of the first sample, mixture melting point undepressed.

Acid Amide 16. A. Arbuzov Reaction.—A suspension of 0.8 g of 56% NaH in 30 ml of dimethoxyethane (dried over CaH_2) was stirred and cooled while 4.5 g of triethyl phosphonoacetate (5 min) was added, and stirring was continued at room temperature until a clear solution was obtained (10 min). A solution of 3.4 g of cyano enone **15**[10] in 20 ml of dimethoxyethane was added. The solution was warmed gently (50°) for 4.5 hr and allowed to stand at room temperature for 3 days. After addition of ice water (300 ml) the material was extracted with ether, and the ether solution was washed thrice with water, dried ($MgSO_4$), and evaporated to give *ca.* 5 g of cyano ester as an oil: ir 4.49, 5.82, and 6.13 μ; uv 233 nm (ε 27,000) and 298 (12,500) with inflection at 268 nm.

B. Hydrolysis.—Crude A in 30 ml of ethanol and 10 ml of water with 4 g of NaOH was refluxed for 3.5 hr; slight NH_3 evolution occurred, and the red solution became light orange. Acidification of the diluted solution gave crude **16**, which was collected, washed with water, and triturated with methanol; 2.5 g of crystals, mp *ca.* 250–262°, a mixture of isomers. Recrystallization gave a pure sample of the higher melting compound: mp 286–290°; ir 3.05, 3.16, and 5.95–6.03 μ (doublet); uv 229 nm (ε 30,650) and inflection at 273 (14,300); nmr (DMSO) δ 8.0–7.2 (m, 11, 2 slowly D_2O exchange, ArH, $CONH_2$, and proton 11), and 5.92 (s, 1, =CH–); COOH δ far downfield (very broad, 1, D_2O exchange).

Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.21; H, 4.50; N, 4.81. Found: C, 74.16; H, 4.42; N, 4.80.

Hydrogenation of 2 g of **16** in warm (60°) ethanol (60 ml) and ethyl acetate (200 ml) in the presence of 1.5 g of 10% Pd/C for 2 hr, filtration, and evaporation of the solvents gave acid amide **17** as crystals from ethanol: mp 243–246°; ir 2.94, 3.05, 3.13, 5.91 and 6.07 μ; uv 210 nm (ε 33,010) and 289 (12,570); identical by spectra and mixture melting point with the first sample of **17**.

Methyl 5-(10-Carbomethoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenyl)acetate (18). A. Hydrogenation of 30 g of **17** in 500 ml of glacial acetic acid in the presence of *ca.* 12 g of 10% Pd/C at 50-lb pressure and 80° for 20 hr resulted in uptake of 95% of the calculated amount of H_2. Filtration and evaporation afforded 31 g of pale yellow glass. A sample, reprecipitated from alkaline solution, extracted with ether, and dried *in vacuo*, was colorless and did not crystallize: ir NH_2 bands, 5.86, and 6.01 μ; uv benzenoid.

B. Hydrolysis of 30 g of crude acid amide from A by 5-hr reflux with 300 ml of glacial HOAc and 200 ml of concentrated HCl, evaporation of excess reagents, and treatment with water gave a tan precipitate of mixed isomers of diacid which was col-

lected, washed with water and dried: yield 26 g, mp 200–205°. The isomers could not be separated efficiently by fractional crystallization from various solvents. A sample, reprecipitated from NaOH solution by dilute HCl, ether extracted, ether triturated, and dried *in vacuo* had mp 237–241° and may have been one of the isomers in reasonably pure form: ir broad, bonded OH and 5.89 μ (intense, sharp); uv 262 nm (ε 1070), 270 (1010), and 280–290 (640).

C. Esterification of 26 g of crude diacid isomer mixture from B by 6-hr reflux with 500 ml of methanolic HCl, removal of excess reagent *in vacuo*, and addition of water gave oil which was extracted with ether. The ether solution was washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated to give 28 g of **18** as an oil, sufficiently pure for further use, ir 5.77 μ, uv 262 nm (ε 720) and 265 (790).

Methyl 10,11-Dihydro-12-oxo-5*H*-5,10-ethanodibenzo[*a*,*d*]-cycloheptene-13-carboxylate (19).—Dieckmann closure of 10 g of crude **18** in 15 ml of DMF was carried out by adding 2.4 g of 56% NaH in 10 ml of DMF during 2 hr, keeping the temperature at 20–30° by means of external cooling. The dark brown solution was poured into 400 ml of water and the oily solution was treated with 9 ml of 18% HCl. The colorless, crude product usually could be filtered; if too sticky it was extracted with ether. An ether solution of the water-washed, dried ($MgSO_4$) material was filtered and evaporated, giving 8.4 g of viscous, pale yellow oil. Crystallization occurred in methanol, giving 6.4 g (71%) of colorless crystals: mp 116–118°, raised to 119–121° on recrystallization from methanol; ir 5.75, 5.86, 6.06, and 6.19 μ; $FeCl_3$ test deep purple; uv 260–264 nm (ε 3390) and 267 (3470) with inflection at 275 (3110); nmr ($CDCl_3$) δ 11.6 (0.3 H, readily D_2O exchange).

Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.72; H, 5.76.

Compound **19** was *partly* soluble in 5% NaOH solution. Use of K *tert*-butoxide in the Dieckmann closure also gave **19** but in lower yield.

The closure of **18** with NaH was carried out with amounts *ca.* four times those described above by the same procedure, with essentially the same results. Although total, crude **19** (90% yield could be carried through hydrolysis, decarboxylation, with fairly good results (*e.g.*, 65 g of crude **19** gave 34 g of **22** as described under **22**), it was found best to isolate **19** in crystalline form by means of methanol before proceeding further.

The corresponding 2,4-dinitrophenylhydrazone could be recrystallized from aqueous methanol as orange, ill-defined crystals, mp 131–135°, ir 5.78, 6.19, and 6.28 μ.

Anal. Calcd for $C_{25}H_{20}N_4O_6$: C, 63.55; H, 4.27; N, 11.86. Found: C, 63.85; H. 4.26; N, 11.67.

Diol 20.—From $NaBH_4$ reduction of a sample of **19** (in methanol) there were obtained colorless crystals, from ether, mp 174–175°, ir 3.04 μ (very strong).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.29; H, 6.84.

5,10-Ethano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-12-one (22).—A solution of 19 g of **19**, in 150 ml each of concentrated HCl and glacial HOAc was refluxed for 2 hr. Most of the reagent was removed *in vacuo*, the residue was treated with water, the product was extracted with ether, and the washed (2% NaOH, H_2O) and dried ($MgSO_4$) ether solution was evaporated. The ketone crystallized nicely in ether or ethanol: 12.5 g (82%) of colorless crystals: mp 144–147°, raised to 148–149° on recrystallization from ether; ir 5.84 μ; uv benzenoid, with moderate end absorption; nmr ($CDCl_3$) δ 7.5–6.9 (m, 8, ArH), 4.06 (q, 1, J = 3.0, J' = 4.4 Hz, proton 5 coupled to nonequivalent protons 13), 3.78 (t, 1, J = 4 Hz, J' = 4 Hz, proton 10 coupled to 11), 3.30 (q, 2, J_{ax} = 4 Hz, J_{gem} = 7.0 Hz, protons 11), apd 2.88 (m, 2, $J \simeq 3$ Hz, $J' \simeq 4.4$ Hz, protons 13).

Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.27; H, 6.14.

The corresponding 2,4-dinitrophenylhydrazone was prepared as usual (aqueous ethanolic H_2SO_4) and recrystallized from ethanol as yellow crystals, mp 193–195°, ir 6.18, 6.25 μ.

Anal. Calcd for $C_{23}H_{18}N_4O_4$: C, 66.66; H, 4.38; N, 13.52. Found: C, 66.67; H, 4.59; N, 13.29.

Formylation of 1 g of **22** with HCOOEt (5 ml) in the presence of dry $NaOCH_3$ (from 0.13 g of Na) in dry ether (250 ml) gave a *ca.* 50% yield of the enolic, corresponding 13-hydroxymethylene compound as slightly pink crystals from ether: mp 141–143°; ir 6.01 and 6.28 μ; 268 nm (ε 7820) and 275 (7800); $FeCl_3$ positive; nmr not first-order resolvable.

Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.37; H, 5.20.

Similar $NaOCH_3$-mediated reaction with ethyl oxalate gave the enolic 13-$COCOOCH_3$ derivative as crystals from ethanol: mp 169.5–171°; ir 5.79, 6.12, and 6.26 μ; uv 304 nm (ε 7270) and inflection at 276 (5980).

Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 75.16; H, 5.34.

5,10-Ethano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-12-ol.—From treatment of 0.5 g of **22** with 0.8 g of $NaBH_4$ in methanol, evaporation, and addition of water, there was obtained a colorless solid, mp 146–151°, recrystallizing from cyclohexane to give colorless crystals: mp 151–155°; ir 3.07 μ; uv 266 nm (ε 1080), 270 (980), and 274 (1130); nmr ($CDCl_3$) too complex to discern J values.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.33; H, 6.87.

Aldehyde 23.—A suspension of 0.45 g of NaH (56%) and 3.3 g of trimethyl sulfoxonium iodide[16] in 50 ml of DMSO was warmed very gently and stirred until nearly all the material dissolved (15 min), ketone **22** (1.0 g) in 10 ml of DMSO was added, and the solution was stirred at 35° for 1.3 hr and allowed to stand overnight. After addition of 500 ml of cold water and extraction of the material with ether, the washed and dried ($MgSO_4$) ether solution was evaporated, and the residual yellow oil (1.1 g) was placed in 25 ml dry ether, the solution was chilled, and 0.7 ml of 47% BF_3 etherate was added. After standing for 0.8 hr at room temperature, the decanted ether solution was washed with dilute $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated to give *ca.* 1.0 g of crude **23** as a colorless, viscous oil, ir 5.80 μ.

The 2,4-dinitrophenylhydrazone recrystallized from ethanol–ethyl acetate as yellow, fluffy needles, mp 238–240° dec.

Anal. Calcd for $C_{24}H_{20}N_4O_4$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.32; H, 4.89; N, 13.15.

Oxime 21a.—Ketone **22** was refluxed for 2 hr with aqueous, ethanolic, NaOH-neutralized $H_2NOH \cdot HCl$ solution, and the crystals appearing on dilution were collected, washed and recrystallized from benzene, mp 146–149°, ir 3.09 and 6.00 μ.

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.93; H, 6.12; N, 5.32.

Methoxime 21b.—Ketone **22** (5 g) and 8.4 g of *O*-methylhydroxylamine HCl in 200 ml of methanol were treated with 5.4 g of $NaOCH_3$ in 50 ml of methanol, and the solution was refluxed for 4 hr. Evaporation and addition of water gave crystals which, after being collected, washed (H_2O), and dried, weighed 5.6 g, mp 151–156°, evidently a mixture of syn and anti forms; ethanol recrystallization gave colorless crystals, mp 156–161°, ir 6.09 μ.

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.36; H, 6.36; N, 5.50.

Amine 26a.—Crude methoxime (5.6 g) together with 4.1 g of $LiAlH_4$ in 200 ml of dry THF (the reaction did not proceed in Et_2O) was refluxed and stirred for 6 hr, the cooled suspension was treated with 25 ml water (stirring) and after 1 hr filtered, the THF was removed *in vacuo*, and an ether solution of the crude base was dried (K_2CO_3) and evaporated, giving 5 g of acid-soluble, pale yellow oil. The amine was converted to the corresponding hydrochloride with ethereal HCl, *ca.* 5 g of crystals, mp 132–136°. Trituration with ethyl acetate gave the predominant and least soluble isomer, 3.3 g of colorless crystals, mp 149–151°, nmr very complex.

Anal. Calcd for $C_{17}H_{17}N \cdot HCl$: C, 75.12; H, 6.67; N, 5.15. Found: C, 75.03; H, 6.43; N, 4.97.

From the EtOAc filtrate, on evaporation there remained 1.7 g of glassy material, crystallizing in ether, and which, on recrystallization from acetone–ether or ethanol–ether, gave what appeared to be a pure sample of the lesser isomer, mp 262–264°.

Amine 26b.—Primary amine **26a**, regenerated from 3.2 g of the principal isomer hydrochloride of the preceding experiment, was heated on a steam cone with 25 ml of anhydrous HCOOH and 5 ml of 36% formalin for 6 hr; effervescence ceased after 2 hr. A water solution of the residue remaining after evaporation of the reagents *in vacuo* was washed with ether and made basic by addition of 10% NaOH. The base was extracted with ether, the water-washed, dried (K_2CO_3) solution was evaporated, and the crude base (2.3 g, oil) was converted to the corresponding hydrochloride. A water solution of the ether-titurated salt was treated with NaOH to regenerate a better sample of the base, which was isolated by extraction with ether as before and for

characterization converted to the picrate; yellow crystals from ethanol, mp 247–249°.

Anal. Calcd for $C_{25}H_{24}N_4O_7$: C, 60.97; H, 4.91; N, 11.38. Found: C, 60.73; H, 4.97; N, 11.70.

Nitrile 24a.—Diethyl phosphonoacetonitrile (1.1 g) was added in portions to a stirred suspension of 0.3 g of 56% NaH in 20 ml of THF, followed 10 min later by 1.2 g of **22** in 25 ml of THF. Gentle reflux for 1 hr deposited a viscous, orange syrup (water-soluble, in work-up). The cooled, supernatant THF solution was treated with water, the oil was extracted with ether, and the water-washed, dried ($MgSO_4$) ether solution was evaporated, yielding 1.3 g of turbid, colorless oil, soon crystallizing on standing, apparently a mixture of isomers (mp *ca.* 160–175°). Recrystallization from ether afforded colorless crystals: mp 189–191°; ir 4.51 and 6.17 μ; nmr ($CDCl_3$) δ 7.4–7.0 (m, 8, ArH), 5.20 (t, 1, $J \cong 2$ Hz, vinyl H long-range coupled to protons 13), 4.43 (t, 1, $J \cong J' \cong 4$ Hz, proton 10 coupled to 11), 3.93 (q, 1, $J = 2.5$, 4.5 Hz, proton 5 coupled to 13), 3.30 (q appearing to be t, 2, $J_{ax} = 4$, $J_{gem} \simeq 4.5$ Hz, protons 11), and 3.0 (m, 2, somewhat simplified by irradiating vinyl proton, protons 13).

Anal. Calcd for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.79; H, 5.96; N, 5.26.

Ester 24b.—Sodium hydride (3.5 g of 56% in oil) was washed with ligroin and suspended in 70 ml of dimethoxyethane, and the suspension was stirred while 22 g of triethyl phosphonoacetate was added gradually with cooling to prevent the temperature from exceeding 25–30°; stirring was continued until a clear solution was obtained,[15] ketone **22** (13.0 g) was added, and the solution was warmed to 70° (air condenser) for 5 hr; after standing overnight it was warmed again to 70° for 1.5 hr. Work-up as in the preceding experiment after adding 1 l. of water gave *ca.* 20 g of oil which crystallized on standing (or seeding with samples from preliminary runs). Trituration with ether–ligroin gave several crops of colorless crystals totalling 9 g, mp 83–87°. Recrystallization from ether gave a pure sample: mp 86.5–88.5°; ir 5.88 and 6.10 μ (intense); uv 266 nm (ϵ 1660) with inflection at 219 (32,850); nmr ($CDCl_3$) of this and all succeeding compounds, in agreement with structure but not first-order interpretable.

Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.68; H, 6.62. Found: C, 83.10; H, 6.57.

Acid 24c.—The entire, crude product from the preceding experiment was hydrolyzed with 100 ml of concentrated HCl and 190 ml of glacial HOAc (3.5-hr reflux). The solution was distilled *in vacuo* to smaller volume, water was added, and the crystals were collected, washed with water, and air dried: 14.8 g of crude solid, mp *ca.* 180–245°. Trituration with ether removed oily material effectively, giving 10.1 g of colorless crystals, mp 240–254°; a second ether trituration raised the melting point to 267–272°, and recrystallization from ethyl acetate gave a pure sample of the single isomer, mp 273–274°, ir 5.95 (very intense) and 6.11 μ (intense).

Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.65; H, 5.86.

Acid 25a.—A solution of 6.5 g of Et_2O-triturated **24c** in 150 ml of ethanol and 100 ml of ethyl acetate containing 2 g of 10% Pd/C was shaken under 45 lb of H_2 at 50° for 5 hr. The filtered solution was evaporated to give 6.5 g of crystals, mp 172–180°. Recrystallization from ether gave a sample, mp 184–186°, ir 5.88 μ.

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 82.28; H, 6.31.

Similar reduction of ester **24b** gave an oil, ir 5.80 μ, and no C=C absorption.

The corresponding *N*,*N*-dimethylamide **25f** was prepared by sequential treatment of the acid with $SOCl_2$ (20 min reflux) and reaction with Me_2NH in benzene. Evaporation of washed (H_2O) and dried ($MgSO_4$) ether–benzene solution gave crystals, mp 134–136° (from ether), ir 6.12 μ.

Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.54; H, 7.77; N, 4.58.

Amine 26f.—Lithium aluminum hydride (1.4 g) reduction of 2.3 g of amide **25f** in 25 ml of THF and 125 ml of ether (6 hr reflux), hydrolysis (7 ml of water), filtration, and evaporation of the dried (K_2CO_3) solution gave 2.2 g of the amine as an oil. It was converted to the hydrochloride (2.5 g): mp 286–287° dec after recrystallization from methanol–ether; ir 3.88 and 4.04 μ.

Anal. Calcd for $C_{21}H_{25}N \cdot HCl$: C, 76.92; H, 7.99; N, 4.27. Found: C, 76.71; H, 7.63; N, 4.42.

Acid hydrazide 25b was prepared either by refluxing crude ester from hydrogenation of **24b** with hydrazine or by adding a benzene solution of acid chloride (from **25b**) to excess hydrazine, with stirring: colorless crystals (from ether–benzene); mp 180–182°; ir 3.00 and 6.06–6.14 μ (doublet).

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 77.81; H, 6.97; N, 9.60.

Isocyanate 25c. A. Azide.—A solution of 4.5 g of hydrazide **25b** in 45 ml of glacial HOAc and 25 ml of 18% aqueous HCl was chilled in ice, stirred, and treated slowly with an excess (starch-I^- test) of concentrated aqueous $NaNO_2$ solution. The oily azide separated immediately. After 10 min, ice water was added, the oil was extracted with ether (500 ml), and the ether solution was washed with two portions of ice water, iced $NaHCO_3$ solution, and two more portions of water, and dried ($MgSO_4$), and filtered.

B. Curtius Rearrangement.—The ether solution from A was diluted with 200 mg of dry benzene, evaporated to a volume of *ca.* 150 ml, heated gradually, and when N_2 evolution appeared to be practically complete the solution was refluxed for 0.5 hr. Evaporation then gave 4.5 g of pale yellow glass, ir 4.37–4.42 μ (intense). The material was used in subsequent operations without undue delay.

Urethane 25e.—Ethanol (150 ml) was added to crude **25c** or its benzene solution (50–100 ml) and the solution was refluxed for 1 hr. Evaporation then gave 4.5 g of pale yellow, viscous oil, ir 3.05 and 5.90–6.05 μ, also used soon in subsequent reactions.

Acetamide 25d.—In a separate experiment, crude, dry azide solution (from 1 g of **25b**) was treated with 2 ml of glacial HOAc and 15 ml of acetic anhydride, the ether was distilled, and the remaining solution was heated on the steam cone for 1 hr (N_2 evolution for 10 min) and then evaporated. The yellow residue crystallized rapidly in ether, giving 0.75 g of colorless crystals, mp 160–162° (from ether), ir 2.99 and 6.08 μ.

Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.76; H, 7.47; N, 4.86.

Amine 26c.—Prolonged (8 hr) reflux of 0.5 g of **25d** in 45 ml of concentrated HCl and 20 ml of glacial HOAc, evaporation *in vacuo*, and alkalinization of an ether-washed, aqueous solution of the residue gave colorless crystals, purified with some difficulty by recrystallization from ether–ligroin, mp 115–117°, ir 3.15 μ (weak, intermolecular bonding).

Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62; mol wt, 249.34. Found: C, 86.59; H, 7.33; N, 5.67; M^+, 249.

Acetylation (Ac_2O) gave again **25d**.

Amine 26d.—A solution of 4.6 g of crude **25e** in 10 ml of THF was added to 1.9 g of $LiAlH_4$ in 200 ml of ether, and the suspension was stirred and refluxed for 4.5 hr. After treatment of the cooled suspension with water (5 ml), filtration of the dried (K_2CO_3) solution and evaporation gave *ca.* 3.8 g of crude amine, pale orange oil (ir NH band) which was converted to 3.1 g of hydrochloride, mp 237–247°, purified by recrystallization from ethanol–ether, mp 252–256°, ir 3.65 and 4.11 μ.

Anal. Calcd for $C_{19}H_{21}N \cdot HCl$: C, 76.10; H, 7.40; N, 4.67. Found: C, 76.48; H, 7.21; N, 4.49.

Amine 26e.—Amine **26d** (1.5 g, regenerated from hydrochloride), in 50 ml of dry ether was treated with 4 ml of iodomethane. On standing, a precipitate of hydroiodide gradually accumulated, and after 5 hr was collected and recrystallized from ethanol–ether, colorless crystals, mp 272–276° dec.

Anal. Calcd for $C_{20}H_{23}N \cdot HI$: C, 59.26; H, 5.97; N, 3.46. Found: C, 59.47; H, 6.04; N, 3.63.

The amine, generated by treatment of the hydriodide with 5% NaOH solution and the aid of methanol, extracted with ether, and isolated by evaporation of the water-washed, dried (K_2CO_3) ether solution was an oil, lacking NH ir absorption. It was converted in turn to the hydrochloride, recrystallized from ethanol–ether, mp 249–252°, ir 3.70 and 4.10 μ.

Anal. Calcd for $C_{20}H_{23}N \cdot HCl$: C, 76.53; H, 7.71; N, 4.46. Found: C, 76.61; H, 7.82; N, 4.43.

Registry No.—**2a**, 36736-52-4; **3a**, 36736-53-5; **3b**, 36826-34-3; **3c**, 36736-54-6; **3d**, 36736-55-7; **5**, 36736-56-8; **6**, 36826-36-4; **8a**, 36736-57-9; **8b**, 36736-58-0; **9**, 36736-59-1; **10**, 36736-60-4; **11a**, 36736-61-5; **11a** tosylate, 37767-81-0; **11b**, 36736-63-7; **13**, 36736-64-8; **13** diacid, 36736-65-9; **16**, 36736-66-0; **17**,

36736-67-1; **18**, 36736-68-2; **19**, 36736-69-3; **19** DNP, 36736-70-6; **20**, 36736-71-7; **21a**, 36736-72-8; *syn*-**21b**, 36744-46-4; *anti*-**21b**, 36744-47-5; **22**, 36736-73-9; **22** DNP, 36736-74-0; **22** (13-hydroxymethylene derivative), 36736-75-1; **22** (13-$COCOOCH_3$ derivative), 36736-76-2; **23** DNP, 36736-77-3; **24a**, 36736-78-4; **24b**, 36736-79-5; **24c**, 36736-80-6; **25a**, 36736-81-9; **25b**, 36736-82-0; **25d**, 36736-83-1; **25f**, 36736-84-2; **26a** HCl, 36736-85-3; **26b** picrate, 36736-86-4; **26c**, 36736-87-5; **26d** HCl, 36736-88-6; **26e** HI, 36736-89-7; **26e** HCl, 36736-90-0; **26f** HCl, 36736-91-1; 10-bromo-5-chloro-5*H*-dibenzo[*a*,*d*]cycloheptene, 36736-92-2; 5-(10-bromodibenzo[*a*,*d*]cycloheptenyl)acetic acid, 36736-93-3; diethyl 5-(10-cyano-5*H*-dibenzo[*a*,*d*]cycloheptenyl)malonate, 36736-94-4; 5-(10-carboxamide-5*H*-dibenzo[*a*,*d*]cycloheptenyl)malonic acid, 36736-95-5; 5,10-ethano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-12-ol, 36736-96-6.

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Hybridization in Fused Strained Rings by the Maximum Overlap Method. II. Benzocyclobutene and Benzocyclopropene[1a]

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The hybridization in benzocyclobutene and benzocyclopropene is considered using the method of maximum overlap. The results show considerable variations of s–p content of hybrids describing the molecular skeleton. In benzocyclopropene the hybrids of the carbon atom at the fusion site are $sp^{1.99}$, $sp^{3.20}$, and $sp^{1.34}$, the first two describing the propene ring, the latter being directed outward. In benzocyclobutene the corresponding hybrids show lesser deviations from sp^2 forms. For the C_3 ring the directions of the calculated hybrids deviate from bond directions by the expected values 20–25°, giving the so-called bent bonds. For C_6 rings the deviation angles are close to zero, which gives rise to asymmetrically half-bent bonds where benzene joins the small rings. The calculated hybrids are used for a prediction of spin–spin coupling constants $J_{C^{13}-H}$ which are discussed and compared with the experimentally available data.

The hybridization model has been found very useful for discussion of such molecular properties as bond angles, bond lengths, bond energies, spin–spin coupling constants, proton acidities, etc.[2] Approximate hybridization parameters may be found by transforming available semiempirical molecular orbitals to localized orbitals. An alternative procedure arises from use of localized models, one or which is the method of maximum overlap.[3] This method utilizes the assumption that a large bond overlap results in a stronger bond. Although this approach is based on intuitive concepts and cannot be derived rigorously from the first principles, it is expected to yield useful results in systems with covalent bonding.[4] Moreover an application to a large number of structurally related molecules, like for example hydrocarbons, may be expected to give a good description of many molecular properties.

In this paper we consider an application of the maximum overlap method to two highly strained fused-ring hydrocarbons, benzocyclobutene and benzocyclopropene. This work is a continuation of the study of fused-ring systems initiated by the work on biphenylene and benzo[1,2:4,5]dicyclobutene.[5] These molecules are characterized by unusual constraints and are of considerable interest as their aromatic ring will produce changes in bond lengths, and as a consequence unusual spectral and chemical properties are expected.[6] The simple description in terms of sp^2 and sp^3 hybrids is clearly not adequate for such molecules. More general hybrids of the form sp^n, where n is not restricted to integers 2 and 3, lead to a problem of establishing the hybrid exponent n. The situation is complicated by the presence of opposing tendencies of individual hybrids to increase or decreasd their s content and to reorient as to balance the total bond overlap. The molecular structure of benzocyclobutene and benzocyclopropene introduces bond angles of 150 and 180° which indicate that the hybrids must have unusual s–p content.

The maximum overlap method has been described in the literature.[2-4] Briefly, we search for optimal exponents n of all individual sp^n hybrids of a given molecule which would make a sum of suitably weighted bond overlaps maximum. The weighting factors are introduced to account for the fact that the bond overlap–bond energy ratio is different for CH and CC bonds. These factors take care of a "scaling" of the problem

(1) (a) Part I: *J. Amer. Chem. Soc.*, **93**, 64 (1971). (b) During the academic year 1972–1973 address correspondence to Department of Chemistry, Harvard University, Cambridge, Mass. 02138.

(2) M. Randić and Z. B. Maksić, *Chem. Rev.*, **72**, 43 (1972).

(3) (a) M. Randić and Z. Maksić, *Theor. Chim. Acta*, **3**, 59 (1965); (b) L. Klasinc, Z. Maksić, and M. Randić, *J. Chem. Soc. A*, 755 (1966).

(4) R. J. Bartlett and Y. Öhrn, *Theor. Chim. Acta*, **21**, 215 (1971).

(5) M. Randić and Z. B. Maksić, *J. Amer. Chem. Soc.*, **93**, 64 (1971), part I in this series.

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so that it corresponds as close as possible to an energy minimization principle. Recently Bartlett and Öhrn[4] have shown that for predominantly covalent systems the minimum energy and the maximum overlap matrices approximately commute. This implies that it is possible to obtain approximate wave functions solely from a diagonalization of the overlap matrix. The weighting procedure introduced in the maximum overlap method only improves the approximate commutation of the overlap and the energy matrices. Indirectly this is supported by the similarities between the maximum overlap hybrids and those calculated by more ambitious methods.[7] The exponent n of hybrids centered on the same carbon atom are subject to the orthogonality conditions

$$1 + (n_{ij}n_{ik})^{1/2} \cos \theta_{jk} = \begin{matrix} 0 \text{ for } j \neq k \\ 1 \text{ for } j = k \end{matrix} \quad (1)$$

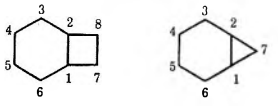
where θ_{ik} is the angle between the directions of hybrids ϕ_{ij} and ϕ_{ik}. The exponent n and the coefficients of s and p orbital in a hybrid are simply related: $n = (b/a)^2$ (a is the coefficient of s, and b of p orbital). The best hybrid parameters are found by a systematic variations of all independent parameters.

Results

Benzocyclobutene.—The molecule is assumed planar,[8] and the standardized bond lengths for hydrocarbons suggested by Dewar and Schmeising[9] have been adopted. The aromatic CC bond is taken to be 1.40 Å. The molecular geometry and numbering of atoms is shown in Chart I. Clementi double ζ-type orbitals are adopted

CHART I

SCHEMATIC DIAGRAMS AND NUMBERING OF ATOMS FOR BENZOCYCLOBUTENE AND BENZOCYCLOPROPENE



in the calculations.[10] The basic overlap integrals are available for atomic separations of interest.[11]

Benzocyclobutene has four nonequivalent carbon atoms leading to eight independent hybrids. Once these eight hybrids are selected the s–p composition of the remaining hybrids is determined by the orthogonality relationships in eq 1. We selected the hybrids ϕ_{12}, ϕ_{16}, ϕ_{61}, ϕ_{65}, ϕ_{56}, ϕ_{54}, ϕ_{71}, and ϕ_{78} as the set to be optimized. To reduce the calculations we also assumed the deviation angles, d, at benzene carbons C_5 and C_6 to be equal at each atom separately: $d_{54} = d_{56}$ and $d_{65} = d_{61}$. Since these atoms constitute a strain-free part of the benzene ring, the deviation angles are expected to be close to zero, and the assumption is hardly a restriction. The deviation angles d_{12}, d_{16}, and d_{17} at carbon C_1 may differ considerably and have to be determined separately (subject only to the constraint that all bonds lay in a plane). Since hybrids ϕ_{12} and ϕ_{16} are varied in the optimization procedure a choice of the pair of exponents n_{12} and n_{16} determines all interhybrid angles at C_1 (eq 1). Thus the only remaining parameter is the angle of rotation of the three hybrids relative to the molecular skeleton. When the angle of rotation is found, the deviation angles follow from geometrical considerations. The calculation is then repeated for another set of n_{12} and n_{16}, until the weighted sum of bond overlaps is maximum. The best hybrids, the corresponding bond overlaps and deviation angles are listed in Table I.

TABLE I

CALCULATED MAXIMUM OVERLAP HYBRIDS, BOND OVERLAPS, INTERHYBRID ANGLES, AND ANGLES OF HYBRID DEVIATIONS FROM THE INTERNUCLEAR LINE

Hybrids	Bond overlaps	Interhybrid angles, deg	Deviation angles, deg
	Benzocyclobutene		
$\phi_{12} = sp^{2.160}$	$S_{12} = 0.7216$	$\theta_1^{26} = 120.6$	$d_{12} = -9.3$
$\phi_{17} = sp^{2.088}$	$S_{17} = 0.6616$	$\theta_1^{67} = 121.3$	$d_{17} = 16.1$
$\phi_{71} = sp^{3.326}$		$\theta_7^{18} = 107.6$	$d_{71} = 11.6$
$\phi_{16} = sp^{1.780}$	$S_{16} = 0.7332$		$d_{16} = 9.9$
$\phi_{61} = sp^{2.170}$		$\theta_6^{15} = 121.0$	$d_{61} = 0.5$
$\phi_{65} = sp^{1.734}$	$S_{56} = 0.7309$		$d_{65} = 0.5$
$\phi_{56} = sp^{1.928}$		$\theta_5^{46} = 121.3$	$d_{56} = 0.7$
$\phi_{78} = sp^{3.304}$	$S_{78} = 0.6407$		$d_{78} = 8.6$
$\phi_{5H} = sp^{2.164}$	$S_{5H} = 0.7406$		
$\phi_{6H} = sp^{2.137}$	$S_{6H} = 0.7412$		
$\phi_{7H} = sp^{2.728}$	$S_{7H} = 0.7233$		
	Benzocyclopropene		
$\phi_{12} = sp^{3.203}$	$S_{12} = 0.6662$	$\theta_1^{26} = 118.9$	$d_{12} = -15.8$
$\phi_{16} = sp^{1.336}$	$S_{16} = 0.7461$	$\theta_1^{67} = 127.8$	$d_{16} = 14.7$
$\phi_{61} = sp^{1.890}$			$d_{61} = 1.1$
$\phi_{17} = sp^{1.994}$	$S_{17} = 0.6152$		$d_{17} = 35.0$
$\phi_{71} = sp^{3.858}$		$\theta_7^{12} = 105.0$	$d_{71} = 25.0$
$\phi_{56} = sp^{1.928}$	$S_{56} = 0.7417$		$d_{56} = 0.6$
$\phi_{65} = sp^{1.812}$		$\theta_6^{15} = 122.7$	$d_{65} = 1.1$
$\phi_{54} = sp^{1.920}$	$S_{45} = 0.7390$	$\theta_5^{46} = 121.3$	$d_{54} = 0.6$
$\phi_{5H} = sp^{2.164}$	$S_{5H} = 0.7406$		
$\phi_{6H} = sp^{2.352}$	$S_{6H} = 0.7369$		
$\phi_{7H} = sp^{2.399}$	$S_{7H} = 0.7295$		

Of particular interest are the hybrids at carbon C_1, which describe the most strained molecular fragment. We obtained $\phi_{12} = sp^{2.16}$, $\phi_{17} = sp^{2.09}$, and $\phi_{16} = sp^{1.78}$ while $sp^{1.93}$ is a typical form for CC hybrids in the strain-free part of benzene. Thus the hybrids associated with the cyclobutene ring have increased their p content, while the hybrid directed outward consequently increased its s content, in agreement with findings for other four-membered rings.[12] The deviation angles at C_5 and C_6 are practically zero (justifying the assumption that the deviation angles at each atom are equal). The deviation angles at C_1 and C_7 are appreciable, about 10° and more. Hybrids describing the bond C_1–C_6 have a considerably different deviation angle:

(7) Z. B. Maksić and M. Randić, *J. Amer. Chem. Soc.*, submitted for publication.

(8) G. Fraenkel, Y. Asaki, M. J. Mitchell, and M. P. Cava [*Tetrahedron*, **20**, 1179 (1964)] discuss the possibility of nonplanar cyclobutene ring of benzocyclobutene. From the experimental geminal J_{HH} spin–spin coupling constants using the Karplus equation they deduce for the dihedral angle between adjacent CH bonds of the four-membered ring the value 40°. The puckering, though significant, is not expected to produce dramatic changes in hybrids. The amount of the change can be, for example, estimated by comparing hybrids in some polyacetylenes for which results have been given for planar and puckered conformation: M. Randić and A. Rubčić, *J. Mol. Struct.*, **14**, 193 (1972).

(9) M. J. S. Dewar and H. N. Schmeising, *Tetrahedron*, **5**, 166 (1959); **11**, 96 (1960).

(10) E. Clementi, *IBM J. Res. Develop.*, **9**, 2 (1965).

(11) L. Klasinc, D. Schulte-Frohlinde, and M. Randić, *Croat. Chem. Acta.*, **39**, 125 (1967).

(12) M. Randić, "Tables of Hybrids Calculated by the Maximum Overlap Method," under preparation. Results for some 30 small-ring hydrocarbons are available on request.

d_{16} close to 10° while d_{61} approaches zero (about 0.5°). Because at one end of the bond there is an appreciable deviation while at the other end the deviation is negligible, the corresponding bond is characteristically asymmetrical and has been referred to as a half-bent bond type.[5]

The bond overlaps found indicate some deviations from the assumed standard bond lengths if bond overlap–bond length correlation is used for theoretical predictions of CC bond lengths.[13,14] The bond overlap S_{78} was found very small, and this points to an increase of the bond length C_7–C_8. This is in agreement with the experimental result in related biphenylene[15] and benzo[1,2:4,5]dicyclobutene.[16] Other bond overlaps show smaller variations in their magnitudes. However, the bond overlap S_{12} is not particularly large, and C_1–C_2 is not predicted as particularly short as the experimental results for biphenylene indicate.[15] It is difficult to explain the discrepancy. The shortening of the C_1–C_2 bond length cannot be due to σ-electron contributions and probably not due to perturbed π electrons either. If future experimental work suggests this to be a typical situation for the bond of fusion when highly strained and relatively strain-free rings are fused, a theoretical explanation will probably require models which go beyond the maximum overlap and the Hückel method.

The perturbation of the σ skeleton of benzene ring will produce changes in the π-electron system, and we can no longer expect the two Kekulé-type valence structures of benzocyclobutene to be equivalent (Chart II). It is difficult, however, to guess which of the two

CHART II

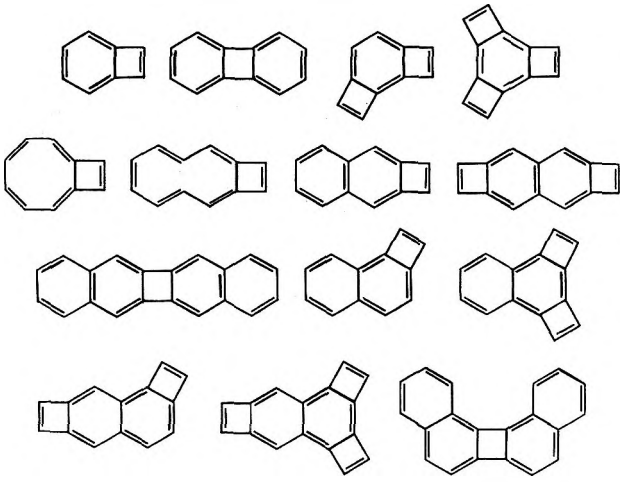
KEKULÉ VALENCE BOND STRUCTURES OF BENZOCYCLOBUTENE

A B

structures is more important. It seems plausible to assume that the four-membered ring which is more strained will dictate the issue. A comparison of the hybrid compositions, bond overlaps, and deviation angles of 1,2-dimethylenecyclobutane and cyclobutene indicates that the exo CC double bonds are relatively strong (bond overlap is 0.7737) while the endocyclic CC double bond is relatively weak (bond overlap is 0.7581).[12] This is because in the former case the tendency of C=C double bonds to increase their s content is supported by the tendency of hybrids involved in small rings to increase their p character, while in the latter case the two contributions are opposing one another. This indicates that structure A will energetically be favored and will have a larger weight. This then agrees with the bond lengths alternation in the strain-free part of the benzene rings of biphenylene (C_1–C_6 = 1.37 Å and C_5–C_6 = 1.42 Å), but is not consistent with the reported unusually short C_1–C_2 bond length.[17] More elaborate SCF–MO calculations, which might clarify the partial inconsistencies between the experimental and theoretical results, are not available. However, the above discussion about the relative weights of the two Kekulé-type structures for benzocyclobutene has some indirect support from calculated Kekulé indices for series of related conjugated polycyclic hydrocarbons.[18] Kekulé indices are defined for individual valence structures and can be calculated from given molecular orbital wave functions. They are defined as projections of selected MO wave functions on various Kekulé structures, and the valence bond structures can be ordered according to the magnitude of this index. The structure with the largest index corresponds to the Kekulé-type structure with the greatest number of formal benzene Kekulé formulas, *i.e.*, to a structure which the empirical Fries rule[19] predicts as the most stable. The Kekulé index is thus indicative of the relative importance of various valence bond structures. Chart III listed Kekulé structures

CHART III

VALENCE BOND STRUCTURES WITH THE HIGHEST KEKULÉ INDEX FOR SEVERAL CONJUGATED HYDROCARBONS CONTAINING THE C_4 RING



corresponding to the largest value of the Kekulé index for some conjugated systems having the cyclobutadiene ring. In all cases the structures with exocyclic C=C double bonds have been found to have the largest stability. Since we do not expect qualitative change in the relative magnitudes of bond overlaps and the forms of hybrids between benzocyclobutene and benzocyclobutadiene,[20] we may conclude that the information in Chart III indicates rather conclusively that the Kekulé structure A of benzocyclobutene is expected to be more important.

Benzocyclopropene.—The standard bond lengths were used.[9] The numbering of atoms is shown in Chart I. The maximum overlap hybrids, bond overlaps, and interhybrid and deviation angles are listed in Table I. The hybridization at carbon C_1 is of a par-

(13) Z. B. Maksić and M. Randić, *J. Amer. Chem. Soc.*, **92**, 424 (1970).

(14) M. Randić, Z. B. Maksić, and M. Eckert-Maksić, *J. Amer. Chem. Soc.*, submitted for publication.

(15) J. K. Fawcett and J. Trotter, *Acta Crystallogr.*, **20**, 87 (1966).

(16) J. L. Lawrence and S. G. G. MacDonald, *Acta Crystallogr., Sect. B*, **25**, 978 (1969).

(17) In three-membered rings CC bonds are even more strained. However the bond lengths are not lengthened and sometimes are even shorter than normal CC single bond. So behavior of CC bonds in C_4 rings are not quite unusual.

(18) A. Graovac, I. Gutman, M. Randić, and N. Trinajstić, submitted for publication.

(19) K. Fries, *Justus Liebigs Ann. Chem.*, **454**, 121 (1927).

(20) Lj. Vujisić, unpublished results, Ph.D. Thesis, University of Zagreb, Zagreb, 1971.

ticular interest because of unusual bond angles for three coplanar bonds: 60, 120, and 180°. To accommodate these angles by three hybrids in a plane is not that simple. As can be seen from Table I, the three hybrids have the following s–p composition: $sp^{1.34}$, $sp^{1.99}$, and $sp^{3.20}$. To indicate the origin of these rather unusual results we will examine the interhybrid angles more closely. If we assume all three hybrids to be sp^2, *i.e.*, interhybrid angles of 120°, we can orient them relatively toward the molecular skeleton so that all deviation angles are 30°. The resulting bending of bonds is too large. It can be reduced by decreasing the angle between ϕ_{12} and ϕ_{17}, while at the same time the interhybrid angle between ϕ_{16} and ϕ_{17} is increased. The interorbital angles between the above hybrids are given by

$$\cos \theta_1^{27} = -(a_{12}/b_{12})(a_{17}/b_{17}) \quad (2)$$

$$\cos \theta_1^{67} = -(a_{16}/b_{16})(a_{17}/b_{17}) \quad (3)$$

A way to meet the above requirements is to decrease the ratio (a_{12}/b_{12}) and increase (a_{16}/b_{16}), while keeping (a_{17}/b_{17}) constant. The orthogonality condition $a_{12}^2 + a_{16}^2 + a_{17}^2 = 1$ still has to be fulfilled. For example, we may consider the following set of nonequivalent trigonal hybrids

$$\phi_{12} = (4/15)^{1/2}s + (11/15)^{1/2}p = sp^{2.75} \quad (4)$$

$$\phi_{16} = (2/5)^{1/2}s + (3/5)^{1/2}p = sp^{1.50} \quad (5)$$

$$\phi_{17} = (1/3)^{1/2}s + (2/3)^{1/2}p = sp^2 \quad (6)$$

The interhybrid angles are then already changed by about 5° in desirable direction: θ_1^{27} is 115.25° and θ_1^{67} becomes 125.25°. These particular hybrids are better adapted to the special local environment of the carbon atom C_1 than ordinary sp^2 hybrids. If hybrids ϕ_{16} and ϕ_{17} increase their s content and tend to be colinear as much as possible, this would leave ϕ_{12} with very little or no s content, which would result in a very small value of the bond overlap S_{12}. A compromise has to be found. By further reducing the s content in ϕ_{12} and increasing it in ϕ_{16} and allowing ϕ_{17} to vary, we finally arrive at the results given in Table I.

The hybrids describing the benzene ring are not so drastically altered from the idealized sp^2 hybridization types usually assumed for carbons in aromatic molecules. Similarly the hybrids at carbon C_7 have their usual s–p composition characteristic for highly strained three-membered rings. Again, as in biphenylene and benzo[1,2:4,5]dicyclobutene there are half-bent bonds, which it seems are characteristic for molecules having fused rings of which one is highly strained while another is essentially nonstrained.[5]

Correlation with Experimental $J_{C^{13}-H}$ Spin–Spin Coupling Constants

The hybrid s character and the bond overlaps calculated by the maximum overlap method have been found to correlate well with various experimental quantities.[2] In particular $J_{C^{13}-H}$ spin–spin coupling constants, according to the currently accepted views, provide a direct measure of the s character of CH hybrids involved in the formation of C–H bonds. In Table II we compare the experimental and the calculated $J_{C^{13}-H}$ spin–spin constants of benzocyclobutene and benzocyclopropene. For benzocyclobutene the agreement is very good, while in the case of methylene $J_{C^{13}-H}$ of benzocyclopropene the calculated spin–spin constant is too small. The discrepancy, however, is also present in other three-membered rings. For example, in cyclopropane $J_{C^{13}-H}$ is calculated to be 143.0 cps, the experimental value being 161 cps. This difference, about 20 cps, seems to be rather characteristic for calculations on highly strained three-membered rings.[21] The empirical relationship of Muller and Pritchard,[22] $J_{C^{13}-H} = 500a^2$, has been used for deducing the s content of hybrids. If applied on three-membered rings it indicates that hybrids have somewhat higher s content than calculated by the maximum overlap method (and other semiempirical methods). The CH hybrids of three-membered rings should according to an empirical estimate in some cases have s per cent approximately equal to, or even somewhat higher than, the aromatic C–H bonds. In the case of cyclopropane the Muller and Pritchard relationship yields $sp^{2.10}$ methylene hybrids and in benzocyclopropene even $sp^{1.80}$. Characteristic higher infrared frequencies for C–H stretching vibrations of three-membered rings[23] (about 3100 cm^{-1}) indicate, compared with parafinic C–H stretching frequencies (between 2850 to 2950 cm^{-1}), that the empirical estimate is consistent with the data from the vibrational spectroscopy.

TABLE II

A COMPARISON BETWEEN THE EXPERIMENTAL AND CALCULATED $J_{C^{13}-H}$ SPIN–SPIN COUPLING CONSTANTS FOR BENZOCYCLOBUTENE AND BENZOCYCLOPROPENE

	Muller and Pritchard	Modified expression	Experiment
	Benzocyclobutene		
H_6	157.8		158.7 ± 0.8[a]
H_5	159.9		
H_7	133.3	136.9	138.0[b]
	Benzocyclopropene		
H_7	147.1	152.2	178 ± 2[c]

[a] J. W. Emsley, J. Feeny, and L. H. Sutcliffe, "High Resolution N.M.R. Spectroscopy," Vol. 2, Pergamon Press, Oxford, 1966, p 1023; the value shown is for benzene. [b] G. Fraenkel, J. Asaki, M. J. Mitchell, and M. P. Cava, *Tetrahedron*, **20**, 1179 (1964). [c] E. Vogel, W. Grimme, and S. Korte, *Tetrahedron Lett.*, **No. 41**, 3625 (1965).

A more general linear relationship between $J_{C^{13}-H}$ and a^2, which includes the variations of CC bond overlaps,[21] gives somewhat better agreement with the experimental J values than the Muller and Pritchard formula for a number of molecules including benzocyclobutene and benzocyclopropene. In benzocyclobutene the modified J value is within the limits of ±1.0 cps, which is less than a typical experimental error in several reported J values. In benzocyclopropene the J value is increased by 5 cps, which is a significant improvement, though not at all sufficient to eliminate the disagreement between experiment and theory. Calculations on several other three-membered rings indicate that 5 cps is a typical increase for methylene $J_{C^{13}-H}$, while for olefinic CH (in cyclopropene

(21) Z. B. Maksić, M. Eckert-Maksić, and M. Randić, *Theor. Chim. Acta*, **22**, 70 (1970); Z. B. Maksić, *Int. J. Quantum Chem.*, **5**, 301 (1971); M. Randić, Z. Meić, and A. Rubčić, *Tetrahedron*, **28**, 565 (1972).

(22) N. Muller and D. E. Pritchard, *J. Chem. Phys.*, **31**, 768, 1471 (1959).

(23) E. R. Lippincott, *J. Amer. Chem. Soc.*, **73**, 2001 (1951).

rings) the increase is approaching 20 cps.[24] It is evident that the application of more general linear relationship better accounts for the experimental data. But is is not quite clear to what extent the reported improvement is due to the adoption of a linear relationship between J and a^2 (instead of the simple proportionality $J = 500a^2$) or to what extent it arises from inclusion of variations of bond overlaps.

(24) M. Randić, A. Rubčić, and L. Klasinc, *Tetrahedron*, **27**, 5771 (1971).

Registry No.—Benzocyclobutene, 4026-23-7; benzocyclopropene, 4646-69-9.

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Transmission of Substituent Effects in Heterocyclic Systems. The Rates of Solvolysis of Some Substituted 1-(2-Benzofuryl)ethanol Derivatives[1]

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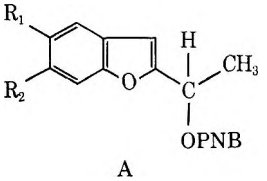
The rates of solvolysis for a series of 5-substituted and 6-substituted 1-(2-benzofuryl)ethanol derivatives (A) have been determined. Though there is excellent correlation of the rates for the 6-substituted compounds with σ_p^+, σ_m^+ fails to give a correspondingly good correlation for the 5-substituted series. Deviations show a clear regularity, with rates for compounds bearing electron donating substituents being too high. A modification of the Dewar–Grisdale equation which uses CNDO/2 molecular orbital parameters to calculate the change in regional charge at the point of attachment of the substituent gives a high quality correlation for both series. These results show that substituents in the 5 position exert their influence more by way of resonance interaction than σ_m^+ would predict.

A number of studies from these laboratories have examined the influence of substituents on reactivity in heterocyclic systems. Information has been presented for furans[3,4] and thiophenes,[5,6] with primary attention being given to solvolysis reactions of the 1-heteroarylethyl derivatives in 80% ethanol. In those studies it was observed that Brown's σ^+ substituent constants[7] were not uniformly successful in predicting relative reactivity in all structural situations. Useful correlations with σ_p^+ were obtained for "conjugating" positions; but σ_m^+ did not generally work well for "nonconjugating" positions.

We have extended these studies to the benzofuran system. A number of substituted 1-(2-benzofuryl)ethanol derivatives (**1**–**9**) have been prepared, and their rates of solvolysis in 80% ethanol have been measured. Table I presents relative rates at 75°. Consideration of these data in two subsets reveals the following. When the 6-substituted series (compounds **1**, **2**, **4**, **6**, **8**; subset A) is considered separately, σ_p^+ gives an excellent correlation (correlation coefficient 0.998) with ρ −3.61. However, the data for the 5-substituted series (compounds **1**, **3**, **5**, **7**, **9**; subset B) show only a fair correlation with σ_m^+. Furthermore, there is a definite trend to the deviations of the 5-substituted series from the least squares line which is defined by the 6-substituted series. Those substituents (methoxy, methyl, and chloro) which effectively donate electrons *via* resonance are clearly above the correlation line. We are therefore led to the conclusion that the 5 position in benzofuran differs from a meta position in benzene in that the sensitivity of the solvolysis reaction toward resonance-donating capability is greater.



A

1, $R_1 = R_2 = H$
2, $R_1 = H$; $R_2 = OCH_3$
3, $R_1 = OCH_3$; $R_2 = H$
4, $R_1 = H$; $R_2 = CH_3$
5, $R_1 = CH_3$; $R_2 = H$
6, $R_1 = H$; $R_2 = Cl$
7, $R_1 = Cl$; $R_2 = H$
8, $R_1 = H_2$; $R_2 = NO_2$
9, $R_1 = NO_2$; $R_2 = H$

TABLE I

RATES OF SOLVOLYSIS OF SUBSTITUTED 1-(2-BENZOFURYL)ETHYL *p*-NITROBENZOATES IN 80% ETHANOL AT 75°

Substituent (compound solvolyzed)	k, sec^{-1}	log k/k_0
H (1)	2.45×10^{-5}	0.00
6-OCH_3 (2)	7.67×10^{-3} [a]	2.50
5-OCH_3 (3)	8.23×10^{-6}	0.53
6-CH_3 (4)	2.87×10^{-4}	1.07
5-CH_3 (5)	6.80×10^{-5}	0.44
6-Cl (6)	6.30×10^{-6}	−0.59
5-Cl (7)	1.50×10^{-6}	−1.21
6-NO_2 (8)	1.87×10^{-8} [b]	−3.12
5-NO_2 (9)	5.12×10^{-8} [b]	−2.68

[a] Extrapolated from rates at lower temperatures. [b] Computed from the rate for the phenylphosphinate, using $k_{pp}/k_{OPNB} = 1.97 \times 10^3$.

The rate data given in Table I have also been fitted to the field and resonance substituent parameters (F and

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) National Institutes of Health Predoctoral Fellow, 1968–1970, GM 41,852.

(3) D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).

(4) D. S. Noyce and H. J. Pavez, *ibid.*, **37**, 2620, 2623 (1972).

(5) D. S. Noyce, C. A. Lipinski, and G. M. Loudon, *ibid.*, **35**, 1718 (1970).

(6) D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *ibid.*, **37**, 2615 (1972).

(7) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

ℜ) introduced by Swain and Lupton.[8] For the rates in subset A regression eq 1 results.

$$-\log k = 2.029\mathcal{F} + 6.433\mathcal{R} + 4.596 \quad (1)$$

Following Swain and Lupton,[8] this defines the percentage resonance component (% ℜ) as 66.5 ± 2.9. Inasmuch as Swain determines that σ_p^+ has 66 + 5% ℜ, this explains the excellent correlation observed.

When the rate data for subset B are fitted, regression eq 2 results.

$$-\log k = 2.089\mathcal{F} + 2.665\mathcal{R} + 4.723 \quad (2)$$

From eq 2, it follows that % ℜ is 44.35 ± 3.5. The larger resonance component is to be contrasted with that calculated by Swain and Lupton for σ_m^+, 33% ℜ. This quantifies the foregoing discussion on the nature of the deviations for subset B.

The Swain and Lupton treatment is excellent for analysis of information in this fashion; it suffers from a lack of providing a suitable basis for predictions.

We have investigated molecular orbital methods for providing a basis for prediction of reactivity in heterocyclic systems, and have had good success using CNDO/2 methods and a modification of the Dewar–Grisdale equation.[9] Alternative formulations using INDO methods have shown equal success.[10]

We have presented an outline of our procedure[6,11] previously, and there is no need to repeat it here. It is useful, however, to emphasize that we calculate the change in regional charge[12] at any position within the heterocyclic nucleus, Δq, which results from the transformation of the methylarene to the arylmethylene cation. For all heterocyclic systems we use the parameters of Pople, Santry, and Segal,[13] as fixed; we use experimental geometries where available, or those determined by reasonable analogy. The Δq's thus determined are incorporated in the modified Dewar–Grisdale equation (eq 3), where the F_X^+ and M_X^+ values

$$(\sigma_{ij})_X^+ = F_X^+/r_{ij} + \Delta q_{ij} M_X^+ \quad (3)$$

for each substituent are uniquely determined by the application of eq 3 to benzene and σ^+ constants.[4] For the benzofuran system $r_{6,2} = 3.27$, $\Delta q_{6,2} = 0.1377$, $r_{5,2} = 3.29$, $\Delta q_{5,2} = 0.0473$. From typical substituent constants[14] for the 5- and 6-substituted 2-benzofuryl system, it is easily predicted by regression analysis that 6-substituted 1-(2-benzofuryl)ethyl derivatives should show 66% ℜ and 5-substituted 1-(2-benzofuryl)ethyl derivatives should show 47% ℜ resonance component. Thus this method gives a good prediction of the observed results.

An important additional plus feature of this predicting framework is that using the substituent constants which are calculated by eq 3, plot of the observed rate data against σ_{ij}^+ gives a single correlation line for both subsets of data, A and B, with a ρ of −5.8, which is very similar to the ρ values for the solvolysis of 1-phenylethyl derivatives at 75°.[11b,15,16] Thus this method allows the prediction of rates of solvolysis for a very wide range of heterocyclic systems, given only the CNDO/2 calculations on the system, and a measured rate for the parent 1-(heteroaryl)ethyl derivative.

Experimental Section[17]

1-(2-Benzofuryl)ethyl *p*-Nitrobenzoate (1).—2-Acetylbenzofuran[18] was reduced with sodium borohydride in methanol to 1-(2-benzofuryl)ethanol.[19] This alcohol was converted to the *p*-nitrobenzoate using *p*-nitrobenzoyl chloride in pyridine. Crystallization from absolute ethanol afforded pure 1 as fine yellow needles: mp 112–113°; nmr (CCl_4) δ 1.82 (d, 3, J = 7 Hz, CH_3), 6.33 (q, 1, J = 7 Hz, $CHCH_3$), 6.76 (s, 1, HC_3), 7.08–7.62 (m, 4, phenyl protons), and 8.17 (s, 4, OPNB).

Anal. Calcd for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.52; H, 4.26; N, 4.74.

1-(6-Methoxy-2-benzofuryl)ethyl *p*-Nitrobenzoate (2).—From 2,4-dihydroxybenzaldehyde and methyl sulfate was prepared 4-methoxysalicylaldehyde, mp 40.5–41.5 (lit.[20] mp 41°), which was converted to 6-methoxy-2-acetylbenzofuran, mp 101–102° (lit.[21] mp 97–99°), in 71% yield. Reduction with sodium borohydride in methanol afforded 93% of 1-(6-methoxy-2-benzofuryl)ethanol as an oil: nmr (CCl_4) δ 1.48 (d, 3, J = 7 Hz, $CHCH_3$), 3.10 (s, 1 OH), 3.96 (s, 3, OCH_3), 4.82 (q, 1, J = 7 Hz, $CHCH_3$), 6.35 (s, 1, HC_3), 6.97 [AB q, ν_4 = 7.22 and ν_5 = 6.72, 2, J_{4-5} = 8.6 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is meta split, J_{5-7} = 2 Hz)], and 6.82 ppm (m, 1, HC_7). Treatment with *p*-nitrobenzoyl chloride in pyridine afforded 1-(6-methoxy-2-benzofuryl)ethyl *p*-nitrobenzoate (2) as cottonlike crystals from hexane: mp 106–107°; nmr (CCl_4) δ 1.78 (d, 3, J = 7 Hz, $CHCH_3$), 6.62 (s, 1, HC_3), 7.02 [AB q, ν_4 = 7.30 and ν_5 = 6.74, 2, J_{4-5} = 8 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is meta split, J_{5-7} = 2 Hz)], 6.90 (d, 1, J_{3-7} = 2 Hz, HC_7), and 8.16 ppm (s, 4, OPNB).

Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.28; H, 4.32; N, 4.01.

5-Methoxy-2-acetylbenzofuran.—5-Methoxysalicylaldehyde[22] (25 g, 0.164 mol), anhydrous potassium carbonate (22.8 g, 0.164 mol), and acetone (300 ml) were heated to reflux and chloroacetone (14 ml, 0.176 mol) was added over a 1-hr period. After another 1 hr of reflux, the reaction mixture was filtered and passed through a short column of alumina (Woelm, activity grade I), and the eluate was concentrated under reduced pressure, giving a yellow-red oil which soon solidified. Ethanol was added, and from the resulting solution 15.4 g (49%) of 5-methoxy-2-acetylbenzofuran crystallized as very small white plates: mp 85–85.5°; 100-MHz nmr (CCl_4) δ 2.48 (s, 3, $COCH_3$), 3.78 (s, 3, OCH_3), 7.17 [AB q, ν_6 6.99 and ν_7 7.35, 2, J_{6-7} = 10 Hz, HC_6 (the upfield half of the AB quartet is meta split, J_{4-6} = 2.5 Hz, and the downfield half is also split, J_{3-7} = 1 Hz)], 6.97 (d, 1, J_{4-5} = 2.5 Hz, HC_4), and 7.27 (d, 1, J_{3-7} = 1 Hz, HC_3).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.53; H, 5.50.

1-(5-Methoxy-2-benzofuryl)ethanol.—5-Methoxy-2-acetylbenzofuran (5 g, 0.0263 mol) and methanol 150 ml) were cooled to 0° in an ice bath. Sodium borohydride (0.5 g, 0.0180 mol) was added in small portions over a 1-hr period. After stirring at room temperature for 20 min the methanol was removed under reduced pressure, water was added, and the product was extracted into ether. The ether was dried ($MgSO_4$) and removed under reduced pressure to give 4.75 g (94%) of 1-(5-methoxy-2-benzofuryl)ethanol as a white solid: nmr (CCl_4) δ 1.52 (d, 1,

(8) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

(9) M. J. S. Dewar and P. J. Grisdale, *ibid.*, **84**, 3539 (1962).

(10) R. W. Nichols, Ph.D. Dissertation, University of California, Berkeley, 1970.

(11) (a) D. S. Noyce and R. W. Nichols, *Tetrahedron Lett.*, 3889 (1972); (b) D. A. Forsyth and D. S. Noyce, *ibid.*, 3893 (1972).

(12) Regional charge: the sum of the charges on the carbon atom and any hydrogen atoms attached to it. A. Streitwieser, Jr., and R. J. Jesaitis in "Sigma Molecular Orbital Theory," O. Sinanoglu and K. B. Wiberg, Ed., Yale University Press, New Haven, Conn., 1970, p 197.

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(14) For calculation purposes we have used the set, $-OCH_3$, $-CH_3$, $-C_2H_5$, −Cl, −Br, −H, −COOEt, −CN, $-CF_3$, $-NO_2$.

(15) V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Amer. Chem. Soc.*, **90**, 418 (1970).

(16) D. S. Noyce and B. Bartmen, unpublished results.

(17) Melting points and boiling points are uncorrected. Analyses are by the Chemical Analytical Services Laboratory, College of Chemistry, University of California, Berkeley, Calif.

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(19) R. L. Shriner and J. Anderson, *J. Amer. Chem. Soc.*, **61**, 2705 (1939).

(20) S. Kawai, T. Nakamura, and M. Yoshida, *Ber.*, **73**, 581 (1940).

(21) W. Gruber and K. Horvath, *Monatsh. Chem.*, **81**, 828 (1950).

(22) We are indebted to the Upjohn Co. for a generous sample of 5-methoxysalicylaldehyde.

J = 6 Hz, $CHCH_3$), 2.60 (b, 1, OH), 3.73 (s, 1, OCH_3), 4.82 (q, 1, J = 6 Hz, $CHCH_3$), 6.35 (s, 1, HC_3), 7.00 [AB q, ν_6 6.76 and ν_7 7.24, 2, HC_6 and HC_7 (the upfield half of the AB quartet is *meta*-split, J_{4-6} = 2 Hz)], and 6.78 ppm (s apparent, 1, HC_4). A sample recrystallized from petroleum ether (bp 30–60°)–ether had mp 62–63°.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.53; H, 6.39.

1-(5-Methoxy-2-benzofuryl)ethyl *p*-Nitrobenzoate (3).—1-(5-Methoxy-2-benzofuryl)ethanol was treated with *p*-nitrobenzoyl chloride in pyridine to give 1-(5-methoxy-2-benzofuryl)-ethyl *p*-nitrobenzoate as small, white crystals from hexane: mp 107–108°; nmr (CCl_4) δ 1.80 (d, 3, J = 6.5 Hz, $CHCH_3$), 3.77 (s, 3, OCH_3), 6.27 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.63 (s, 1, HC_3), 7.05 [AB q, ν_6 6.81 and ν_7 7.29, 2, J_{6-7} = 9 Hz, HC_6 and HC_7 (the upfield half of the AB quartet is meta split, J_{4-6} = 2 Hz)], 6.89 (s apparent, 1, HC_4), and 8.13 ppm (s, 4, OPNB).

Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.47; H, 4.50; N, 3.93.

A mixture melting point determination of this compound with its 6-methoxy isomer (mp 106–107°) melted at 89–101°.

6-Methyl-2-acetylbenzofuran.—4-Methylsalicylaldehyde was prepared by the Duff[23] reaction, incorporating the refinements of Liggett and Diehl.[24]

4-Methylsalicylaldehyde (10 g, 0.074 mol), anhydrous potassium carbonate (10.0 g, 0.072 mol), and acetone (220 ml) were heated to reflux and chloroacetone (5.9 ml, 0.074 mol) was added over 30 min. Stirring and heating were continued for 1.25 hr. The orange reaction mixture was gravity filtered and passed through a short column of alumina (Woelm, activity grade I). The residue obtained by removal of the acetone under reduced pressure was recrystallized from ethanol to give 7.24 g (56%) of 6-methyl-2-acetylbenzofuran as yellow plates. Treatment with Norit and recrystallization from ethanol gave white plates (6.06 g, 47%): mp 76–79°; nmr (CCl_4) δ 2.47 (s, 6, $COCH_3$ and CH_3), 7.22 [AB q, ν_4 7.43 and ν_5 7.01, 2, $J_{4,5}$ = 8 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is noticeably broadened)], and 7.25 ppm (m, 2, HC_3 and HC_7).

Sublimation at 68° (0.1 mm) raised the melting point to 79–80°.

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.91; H, 5.82.

1-(6-Methyl-2-benzofuryl)ethyl *p*-Nitrobenzoate (4).—6-Methyl-2-acetylbenzofuran was reduced with sodium borohydride in methanol to give 1-(6-methyl-2-benzofuryl)ethanol: mp 40–41° from ether–petroleum ether; nmr (CCl_4) δ 1.50 (d, 3, J = 7 Hz, $CHCH_3$), 2.40 (s, 3, CH_3), 3.13 (b, 1, OH), 4.82 (q, 1, J = 7 Hz, $CHCH_3$), 6.34 (s, 1, HC_3), 7.05 [AB q, ν_4 7.21 and ν_5 6.89, 2, J_{4-5} = 8 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is noticeably broadened)], and 7.07 (b, 1, HC_7).

1-(6-Methyl-2-benzofuryl)ethanol in dry pyridine was treated with *p*-nitrobenzoyl chloride to give flocculent, white crystals of 1-(6-methyl-2-benzofuryl)ethyl *p*-nitrobenzoate: mp 81–82° from hexane; nmr (CCl_4) δ 1.79 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.42 (s, 3, CH_3), 6.27 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.65 (s, 1, HC_3), 7.12 [AB q, ν_4 7.31 and ν_5 6.93, 2, J_{4-5} = 8 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is broadened)], 7.16 (b, 1, HC_7), and 8.17 ppm (s, 4, OPNB).

Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.45; H, 4.65; N, 4.31. Found: C, 66.58; H, 4.81; N, 4.54.

5-Methyl-2-acetylbenzofuran.—5-Methylsalicylaldehyde [5.45 g, 0.04 mol, mp 48–56° (lit.[24] mp 55.8°), Aldrich Chemical Co.], anhydrous potassium carbonate (5.55 g, 0.04 mol), and acetone (100 ml) were refluxed and a solution of chloroacetone (3.90 g, 0.042 mol) in acetone (20 ml) was added over a period of 30 min. After 3 hr of refluxing the reaction mixture was filtered and passed through a short column of alumina (Woelm, activity grade I). Removal of the acetone left an oil which solidified on standing. Recrystallization from 80% aqueous ethanol gave 2.30 g (33%) of 5-methyl-2-acetylbenzofuran as plates with a greenish coloration that intensified on standing: mp 78–80°. Sublimation at 70° (0.1 mm) removed all color but did not change the melting point. The sublimed ketone was recrystallized from petroleum ether–ether, giving white platelets: mp 80–81°; nmr (CCl_4) δ 2.43 (s, 3, CH_3), 2.50 (s, 3, CH_3), and 7.07–7.50 (m, 4, aromatic protons).

(23) J. C. Duff, *J. Chem. Soc.*, 547 (1941).

(24) L. M. Liggett and H. Diehl, *Proc. Iowa Acad. Sci.*, **52**, 191 (1945).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.87; H, 5.73.

1-(5-Methyl-2-benzofuryl)ethyl *p*-Nitrobenzoate (5).—5-Methyl-2-acetylbenzofuran was reduced with sodium borohydride in methanol to give 1-(5-methyl-2-benzofuryl)ethanol (97%) as an oil: nmr (CCl_4) δ 1.47 (d, 3, J = 7 Hz, $CHCH_3$), 2.37 (s, 3, CH_3), 3.50 (b, 1, OH), 4.78 (q, 1, J = 7 Hz, $CHCH_3$), 6.30 (s, 1, HC_3), 7.02 [AB q, ν_7 7.16 and ν_6 6.88, 2, J_{6-7} = 8 Hz, HC_6 and HC_7 (the upfield half of the AB quartet is broadened)], and 7.08 (b, 1, HC_4).

The alcohol was converted to the *p*-nitrobenzoate without further purification. 1-(5-Methyl-2-benzofuryl)ethyl *p*-nitrobenzoate crystallized from hexane as white, flocculent crystals: mp 74–75°; nmr (CCl_4) δ 1.80 (d, 3, J = 7 Hz, $CHCH_3$, 2.41 (s, 3, CH_3), 6.28 (q, 1, J = 7 Hz, $CHCH_3$), 6.68 (s, 1, HC_3), 7.16 [AB q, ν_6 7.03 and ν_7 7.29, 3, J_{6-7} = 8 Hz, HC_6 and HC_7 [the upfield half of the AB quartet is broadened)], 7.25 (b, 1, HC_4), and 8.18 (s, 4, OPNB).

Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.45; H, 4.65; N, 4.31. Found: C, 66.49; H, 4.62; N, 4.46.

6-Chloro-2-acetylbenzofuran.—2-Methyl-5-chlorophenol[25] was converted to the acetate and brominated to give 5-chloro-2-dibromomethylphenyl acetate, mp 78–79°, in 87% yield following the procedure of Segesser and Calvin.[26] The benzal bromide was hydrolyzed to 4-chlorosalicylaldehyde, 88% yield, mp 47.5–48.5° (lit.[27] mp 47.0–47.8°).

4-Chlorosalicylaldehyde (10 g, 0.064 mol), anhydrous potassium carbonate (8.85 g, 0.064 mol), and acetone (250 ml) were heated to reflux and chloroacetone (5.1 ml, 0.064 mol) was added over a 1-hr period. Stirring and refluxing were continued for 3 hr. The deep red reaction mixture was filtered of salts and passed through a short column of alumina. The acetone was removed under reduced pressure to give a yellow solid that was recrystallized from ethanol to give 8.49 g (68%) of 6-chloro-2-acetylbenzofuran: mp 119–121° [sublimation (95%, 0.1 mm) raised the melting point to 120–121°, as did crystallization from petroleum ether–ether]; nmr (CCl_4) δ 2.50 (s, 3, $COCH_3$), 7.11 and 7.28 (m, 2, HC_5 and HC_3 or HC_7), and 7.62 and 7.48 (s, 2, HC_4 and HC_7 or HC_3).

Anal. Calcd for $C_{10}H_7ClO_2$: C, 61.71; H, 3.63; Cl, 18.22. Found: C, 61.86; H, 3.66; Cl, 18.38.

1-(6-Chloro-2-benzofuryl)ethyl *p*-Nitrobenzoate (6).—6-Chloro-2-acetylbenzofuran was reduced with sodium borohydride in methanol to give 93% of 1-(6-chloro-2-benzofuryl)ethanol as a white solid. Recrystallization from petroleum ether–ether gave a white powder: mp 53–55°; nmr (CCl_4) δ 1.52 (d, 3, J = 6.5 Hz, $CHCH_3$), 3.03 (b, 1, OH), 4.83 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.39 (s, 1, HC_3), 7.16 [AB q, ν_4 7.25 and ν_5 7.07, 2, J_{4-5} = 8.5 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is meta split, J_{5-7} = 2 Hz)], and 7.30 (m, 1, HC_7).

Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 60.95; H, 4.63; Cl, 18.10.

The *p*-nitrobenzoate was prepared in the usual manner: mp 97–98° (needles from ethanol); nmr (CCl_4) δ 1.80 (d, 3, J = 6.5 Hz, $CHCH_3$), 6.27 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.70 (s, 1, HC_3), 7.29 [AB q, ν_4 7.41 and ν_5 7.17, 2, J = 8.5 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is meta split, J_{5-7} = 2 Hz)], 7.47 (m, 1, HC_7), and 8.19 (s, 4, OPNB).

Anal. Calcd for $C_{17}H_{12}ClNO_5$: C, 59.05; H, 3.50; Cl, 10.26; N, 4.05. Found: C, 59.24; H, 3.63; Cl, 10.30; N, 4.28.

1-(5-Chloro-2-benzofuryl)ethyl *p*-Nitrobenzoate (7).—5-Chloro-2-acetylbenzofuran, mp 99°,[28,29] was reduced with sodium borohydride in methanol to give 1-(5-chloro-2-benzofuryl)ethanol: mp 69.0–69.5° from ether–petroleum ether; nmr (CCl_4 δ 1.48 (d, 3, J = 6.5 Hz, $CHCH_3$), 3.83 (s, 1, OH), 4.83 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.32 (s, 1, HC_3), 7.10 [m, 2, HC_6 and HC_7 (AB quartet near the limit of equivalence)], and 7.27 (m, 1, HC_4).

Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 60.97; H, 4.69; Cl, 18.05.

(25) J. Cason, R. E. Harmon, P. T. Adams, and S. Goodwin, *J. Org. Chem.*, **16**, 328 (1951).

(26) J. R. Segesser and M. Calvin, *J. Amer. Chem. Soc.*, **64**, 825 (1942).

(27) C. Postmus, Jr., I. A. Kaye, C. A. Craig, and R. S. Matthews, *J. Org. Chem.*, **29**, 2693 (1964).

(28) R. Stoermer, *Justus Liebigs Ann. Chem.*, **312**, 333 (1900).

(29) M. Bisagni, M. P. Buu-Hoi, and R. Royer, *J. Chem. Soc.*, 3688 (1955).

The *p*-nitrobenzoate was prepared in the usual fashion. 1-(5-Chloro-2-benzofuryl)ethyl *p*-nitrobenzoate had mp 106.5–107.5°; nmr (CCl_4) δ 1.82 (d, 3, J = 6.5 Hz, $CHCH_3$), 6.28 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.68 (s, 1, HC_3), 7.28 [m, 2, HC_6 and HC_7 (AB quartet near the limit of equivalence)], 7.47 (m, 1, HC_4), and 8.18 (s, 4, OPNB).

Anal. Calcd for $C_{17}H_{12}ClNO_5$: C, 59.05; H, 3.50; Cl, 10.26; N, 4.05. Found: C, 58.97; H, 3.53; Cl, 10.42; N, 3.98.

1-(5-Chloro-2-benzofuryl)ethyl Phenylphosphinate.—The method of Virgilio and Noyce[30] was used. 1-(5-Chloro-2-benzofuryl)ethanol (2.0 g, 0.0102 mol), dicyclohexylcarbodiimide (2.10 g, 0.0102 mol), and phenylphosphinic acid (1.45 g, 0.0102 mol, Victor Chemical Works) were refluxed for 1 hr in dry benzene (100 ml). After the solution had stood for 2 hr at room temperature, it was cooled to the freezing point of benzene, and the dicyclohexylurea was filtered off on a Büchner funnel. The benzene was removed under reduced pressure and the residual oil was taken up in a small amount of ether, which caused precipitation of more dicyclohexylurea. The mixture was filtered, the ether was removed under reduced pressure, and the residual oil was placed under vacuum (0.1 mm) overnight. The yield of crude 1-(5-chloro-2-benzofuryl)ethyl phenylphosphinate was 3.21 g (98.5%). The nmr spectrum (CCl_4) showed the methine resonances of the ester at δ 5.87–5.43. A trace absorption (*ca.* 5% as large) possibly due to the methine resonances of the starting material was present at *ca.* 4.85. The resonance of HC_3 occurred at 6.50; the corresponding resonance of the starting alcohol at 6.32 was not present. The infrared spectrum (liquid film) showed the characteristic P–O–C band[31] at 1050 (s), the P=O band at 1220 (b), and the invariant *P*-phenyl band at 1440 cm^{-1} (s).

This compound was solvolyzed without further purification.

6-Nitro-2-acetylbenzofuran.—4-Nitrosalicylaldehyde was prepared by the method of Segesser and Calvin.[26]

4-Nitrosalicylaldehyde (1.70 g, 0.0102 mol), chloroacetone (0.95 g, 0.0103 mol), anhydrous potassium carbonate (1.41 g, 0.0102 mol), and methyl ethyl ketone (15 ml) were refluxed for 45 min (it was found necessary to substitute MEK for acetone in order to obtain a higher reflux temperature). The solvent was removed under reduced pressure, water was added to the dark residue, and the product was extracted into chloroform. The chloroform was dried ($CaCl_2$) and evaporated, leaving a brown solid that was sublimed at 120° (0.05 mm) to give 1.07 g of yellow crystals: mp 146–147°; nmr (CF_3CO_2H) δ 2.83 (s, 3, $COCH_3$), 7.85 (s, 1, HC_3), 8.13 [AB q, ν_4 7.96 and ν_5 8.30, 2, J_{4-5} = 8.6 Hz, HC_4 and HC_5 (the downfield half of the AB quartet is meta split, J_{5-7} = 2 Hz)], and 8.53 (m, 1, HC_7).

Anal. Calcd for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.85. Found: C, 58.34; H, 3.62; N, 6.63.

1-(6-Nitro-2-benzofuryl)ethanol.—6-Nitro-2-acetylbenzofuran suspended in methanol was reduced with sodium borohydride added in three portions, the ketone dissolving as the reduction progressed. Work-up in the usual fashion gave 92% of 1-(6-nitro-2-benzofuryl)ethanol as a pale yellow solid. A small sample was purified by chromatography on silica gel. Elution with 10% ether–hexane gave material with the following characteristics: mp 74–75°; nmr (CCl_4) δ 1.62 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.50 (b, 1, OH), 4.98 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.67 (s, 1, HC_3), 7.82 (AB q, ν_4 7.65 and ν_5 8.09, 2, J_{4-5} = 8.4 Hz (the downfield half of the AB quartet is meta split, J_{5-7} = 2 Hz)], HC_4 and HC_5), and 8.27 (m, 1, HC_7).

Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.02; H, 4.51; N, 6.77.

1-(6-Nitro-2-benzofuryl)ethyl Phenylphosphinate.—This ester was prepared by the method of Virgilio and Noyce.[30] 1-(5-Nitro-2-benzofuryl)ethanol (0.8 g, 0.0039 mol), dicyclohexylcarbodiimide (0.88 g, 0.0043 mol), and phenylphosphinic acid (0.55 g, 0.0039 mol, Victor Chemical Works) were refluxed in dry benzene (50 ml) for 1 hr. The solution was cooled in an ice bath and the dicyclohexylurea was filtered off on a Büchner funnel. Removal of the benzene under reduced pressure left a yellow oil in which some solid material was suspended. The oil was thinned with carbon tetrachloride and filtered to remove the solid material. Solvents were removed on a vacuum line (0.05 mm) overnight. The nmr spectrum (CCl_4) of the oil showed the methine resonance of the ester at δ 5.57–5.97 and the HC_3 resonance at 6.73. The corresponding methine resonance of the starting material at 4.98 was absent. The infrared spectrum (liquid film) showed bands at 1515 (s, NO_2), 1340 (s, NO_2), 1225 (s, P=O stretch), and 1060 cm^{-1} (s, P–O–C stretch). The crude 1-(5-nitro-2-benzofuryl)ethyl phenylphosphinate was solvolyzed without further purification.

5-Nitro-2-acetylbenzofuran.—5-Nitrosalicylaldehyde (5 g, 0.03 mol, Eastman Organic Chemicals), chloroacetone (3.3 g, 0.036 mol), anhydrous potassium carbonate (5.4 g, 0.039 mol), and methyl ethyl ketone (50 ml) were refluxed on a steam bath for 7 hr. The solvent was removed under reduced pressure, water was added to the dark residue, and the mixture was extracted with ether. Large amounts of insoluble material made extraction difficult. The mixture was extracted with chloroform, and the organic layer was combined with the ether extract, dried ($MgSO_4$), and evaporated to give a brown powder that was sublimed at 115° (0.05 mm) to give 1.70 g (28%) of yellow crystals: mp 175–177°; nmr (CF_3CO_2H) δ 2.83 (s, 3, $COCH_3$), 8.17 [AB q, ν_7 7.80 and ν_6 8.54, 2, J_{6-7} = 8.6 Hz (the downfield half of the AB quartet is meta-split, J_{4-6} = 2 Hz), HC_6 and HC_7], 7.98 (s, 1, HC_3), and 8.85 (d, 1, J_{4-6} = 2 Hz, HC_4).

Anal. Calcd for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.85. Found: C, 58.68; H, 3.59; N, 7.04.

1-(5-Nitro-2-benzofuryl)ethanol.—5-Nitro-2-acetylbenzofuran (1 g, 0.0049 mol) and methanol (25 ml) were equilibrated in an ice bath. Sodium borohydride (0.10 g, 0.0028 mol) was added in portions to the stirring slurry. After 10 min the ketone had dissolved. The hydride was added over 20 min, after which the ice bath was removed. When the solution had warmed to room temperature the solvent was removed under reduced pressure, water was added, and the product was extracted into ether. Drying ($MgSO_4$) and evaporation of the ether under reduced pressure left 0.97 g (96%) of a pale yellow solid. Recrystallization from methanol–water gave fine white needles of 1-(5-nitro-2-benzofuryl)ethanol, recrystallized from petroleum ether–ether: mp 73–76°; nmr ($CDCl_3$) δ 1.62 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.30 (s, 1, OH), 4.98 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.67 (s, 1, HC_3) [AB q, ν_4 7.47 and ν_5 8.13, 2, J_{6-7} = 9.2 Hz (the downfield half of the AB quartet is meta split, J_{4-6} = 2 Hz), HC_6 and HC_7], and 8.37 (d, 1, J_{4-7} = 2 Hz, HC_4).

Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.17; H, 4.61; N, 6.88.

1-(5-Nitro-2-benzofuryl)ethyl phenylphosphinate was prepared as described above for the 6-nitro isomer. The crude product was solvolyzed without further purification.

Kinetic Methods.—Three different methods were used, as appropriate for the temperature and reactivity being investigated. Method 1 is the usual aliquot method, with aliquots being withdrawn by syringe from a serum capped flask at appropriate time intervals. The samples were titrated for amount of developed acid with standardized KOH in ethanol. For more sluggish situations, method 2, involving sealed ampoules, was used. A few of the more rapid reaction rates were measured by maintenance of static pH (method 3), using a Radiometer automatic titrator, consisting of a TTT 1c automatic titrator, an ABU 1c autoburette, a TTT 3c titrator assembly, and SBR 2c recorder.

First-order rate constants were calculated by LSKIN 1,[32] a least squares program for computing the zero and infinity values of the reaction variable as well as the rate constant.

Generally, between 12 and 16 points were taken when methods 1 or 2 were used. The points were taken at intervals of *ca.* 5% reaction. Solvolyses were followed for at least 3 half lives. Each run was performed in duplicate, the agreement being within 3%. With 1-(5-nitro-2-benzofuryl)ethyl phenylphosphinate the quality of the titration curves was poor. In this case the rate constants differed by 7%.

(30) D. S. Noyce and J. Virgilio, *J. Org. Chem.*, **37**, 1052 (1972).

(31) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951). These authors found that P–O–C bands for a wide range of phosphorus esters were within 15 cm^{-1} of 1045 cm^{-1}. Bands in this area were absent in the case of phosphorus acids. With ethyl phenylphosphinate, a close analog, the P–O–C band came at 1052 cm^{-1}. When a phenyl group was substituted on a phosphorus atom, a band very near 1440 cm^{-1} occurred. The P=O band varied widely, being ill defined with acids, and being at 1236 cm^{-1} in ethyl phenylphosphinate.

(32) D. F. DeTar and C. E. DeTar in "Computer Programs for Chemistry," Vol. I, D. F. DeTar, Ed., W. A. Benjamin, New York, N. Y., 1968, Chapter 6.

TABLE II

RATE CONSTANTS FOR THE SOLVOLYSES OF SUBSTITUTED 1-(2-BENZOFURYL)ETHYL *p*-NITROBENZOATES

Substituent (compound)	Solvent	Temp, °C	Method[a]	k, sec^{-1}
Parent (1)	80% EtOH	75	2	$2.48 \pm 0.03 \times 10^{-5}$
Parent	80% EtOH	75	2	$2.43 \pm 0.02 \times 10^{-5}$
Parent	80% EtOH	100	2	$2.53 \pm 0.05 \times 10^{-4}$
Parent	80% EtOH	100	2	$2.55 \pm 0.07 \times 10^{-4}$
6-Methoxy (2)	80% EtOH	45	1	$4.53 \pm 0.10 \times 10^{-4}$
6-Methoxy	80% EtOH	45	3	$4.60 \pm 0.03 \times 10^{-4}$
6-Methoxy	80% EtOH	60	3	$1.87 \pm 0.02 \times 10^{-3}$
6-Methoxy	80% EtOH	60	3	$1.92 \pm 0.02 \times 10^{-3}$
6-Methoxy	80% EtOH	60	3	$1.92 \pm 0.02 \times 10^{-3}$
6-Methoxy	80% EtOH	25	1	$4.42 \pm 0.08 \times 10^{-5}$
6-Methoxy	80% EtOH	25	1	$4.58 \pm 0.07 \times 10^{-5}$
6-Methyl (4)	80% EtOH	75	1	$2.85 \pm 0.07 \times 10^{-4}$
6-Methyl	80% EtOH	75	1	$2.90 \pm 0.07 \times 10^{-4}$
6-Methyl	80% EtOH	60	1	$6.22 \pm 0.07 \times 10^{-5}$
6-Methyl	80% EtOH	60	1	$6.00 \pm 0.13 \times 10^{-5}$
6-Methyl	80% EtOH	45	1	$1.10 \pm 0.02 \times 10^{-5}$
6-Methyl	80% EtOH	45	1	$1.10 \pm 0.02 \times 10^{-5}$
6-Methyl	70% EtOH	60	1	$1.38 \pm 0.02 \times 10^{-4}$
6-Methyl	90% EtOH	60	1	$1.80 \pm 0.05 \times 10^{-5}$
5-Methyl (5)	80% EtOH	75	1	$6.72 \pm 0.05 \times 10^{-5}$
5-Methyl	80% EtOH	75	1	$6.88 \pm 0.03 \times 10^{-5}$
5-Methoxy (3)	80% EtOH	75	1	$8.25 \pm 0.08 \times 10^{-5}$
5-Methoxy	80% EtOH	75	1	$8.22 \pm 0.05 \times 10^{-5}$
5-Chloro (7)	80% EtOH	75	2	$1.50 \pm 0.03 \times 10^{-6}$
5-Chloro	80% EtOH	75	2	$1.49 \pm 0.02 \times 10^{-6}$
5-Chloro	80% EtOH	110	2	$4.45 \pm 0.05 \times 10^{-5}$
5-Chloro	80% EtOH	110	2	$4.50 \pm 0.05 \times 10^{-5}$
6-Chloro (6)	80% EtOH	110	2	$6.30 \pm 0.13 \times 10^{-6}$

[a] See description of kinetic methods.

Tables II and III give additional rate constants which were determined during the course of this work, which are supplementary to those recorded in Table I. Table IV gives some activation parameters, calculated from the relevant data by ACTENG.[33]

TABLE III

RATE CONSTANTS FOR THE SOLVOLYSIS OF 1-(X-2-BENZOFURYL)ETHYL PHENYLPHOSPHINATES IN 80% ETHANOL AT 75°

X	Method	k, sec^{-1}
5-Chloro	1	$2.90 \pm 0.08 \times 10^{-3}$
5-Chloro	1	$3.00 \pm 0.07 \times 10^{-3}$
5-Nitro	1	$9.62 \pm 0.30 \times 10^{-6}$
5-Nitro	1	$1.03 \pm 0.02 \times 10^{-4}$
6-Nitro	1	$3.68 \pm 0.12 \times 10^{-5}$

TABLE IV

CALCULATED RATE CONSTANTS AND ACTIVATION PARAMETERS FOR SUBSTITUTED 1-(X-2-BENZOFURYL)ETHYL *p*-NITROBENZOATES AT 25°

X (compound)	k, sec^{-1}	$\Delta H^{\pm}$, kcal	$\Delta S^{\pm}$, eu
6-Hydrogen (1)	7.08×10^{-1}	23.5 ± 0.2	-12.3 ± 0.6
6-Methoxy (2)	4.60×10^{-1}	20.5 ± 0.1	-9.6 ± 0.3
6-Methyl (4)	8.68×10^{-1}	23.4 ± 0.2	-7.9 ± 0.4
5-Chloro (7)	2.92×10^{-1}	25.2 ± 0.1	-13.2 ± 0.4

Registry No.—**1**, 36744-26-0; **2**, 36744-27-1; **3**, 36744-28-2; **4**, 36826-27-4; **5**, 36744-29-3; **6**, 36744-30-6; **7**, 36744-31-7; **8**, 36744-32-8; **9**, 36744-33-9; 1-(6-methoxy-2-benzofuryl)ethanol, 36744-34-0; 5-methoxy-2-acetylbenzofuran, 21587-39-3; 1-(5-methoxy-2-benzofuryl)ethanol, 36744-36-2; 6-methyl-2-acetylbenzofuran, 16564-18-4; 1-(6-methyl-2-benzofuryl)ethanol, 36744-38-4; 5-methyl-2-acetylbenzofuran, 17133-94-7; 1-(5-methyl-2-benzofuryl)ethanol, 36744-40-8; 6-chloro-2-acetylbenzofuran, 36744-41-9; 1-(6-chloro-2-benzofuryl)ethanol, 36739-78-3; 1-(5-chloro-2-benzofuryl)ethanol, 36739-79-4; 1-(5-chloro-2-benzofuryl)ethyl phenylphosphinate, 36739-80-7; 6-nitro-2-acetylbenzofuran, 36739-81-8; 1-(6-nitro-2-benzofuryl)ethanol, 36739-82-9; 1-(6-nitro-2-benzofuryl)-ethyl phenylphosphinate, 36739-83-0; 5-nitro-2-acetylbenzofuran, 23136-39-2; 1-(5-nitro-2-benzofuryl)ethanol, 36739-84-1; 1-(5-nitro-2-benzofuryl)ethyl phenylphosphinate, 36739-85-2.

(33) "Computer Programs for Chemistry," Vol. III, D. F. DeTar, Ed., W. A. Benjamin, New York, N. Y., 1969, Chapter 2.

Transmission of Substituent Effects in Heterocyclic Systems. The Solvolysis of Some Substituted 1-(3-Benzofuryl)ethanol Derivatives[1]

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Two pairs of substituted 1-(3-benzofuryl)ethyl *p*-nitrobenzoates have been prepared and their rates of solvolysis have been measured. Substituents in either the 5-position or the 6-position exert nearly identical influences on the solvolysis rates. These results are in accord with a model using CNDO/2 calculations for predicting relative rates of solvolysis of heteroarylmethyl derivatives.

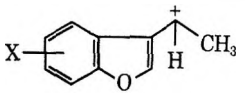
Recent studies from these laboratories have reported the behavior of substituted 1-(2-furyl)ethyl *p*-nitrobenzoates[3,4] and of analogous 3-furyl systems[5] in solvolytic reactions. Similar results have been reported for a set of thiophene derivatives.[6]

The results reported therein show that the use of Brown's[7] σ_p^+ and σ_m^+ substituent constants provides only a limited basis for correlation of the observed reactivities in the furan and thiphene series. We achieved much better success with a modification of the Dewar–Grisdale equation,[8] used to calculate effective substituent constants and expected relative reactivity. In eq 1, Δq_{ij} is obtained from CNDO/2 calculations on

$$(\sigma_{ij}^+)_X = F_X^+/r_{ij} + \Delta q_{ij} M_X^+ \quad (1)$$

both the methylarene and the arylmethylene cation; it is the difference in regional charge,[9] at the position to which the substituent X is attached, generated upon conversion to the cationic intermediate. F_X^+ and M_X^+ are uniquely determined constants for each substituent, obtained from σ_p^+ and σ_m^+ in conjunction with $1/r_{ij}$ and Δq_{ij} values appropriate for the toluene–benzyl cation pair. Equation 1 is also useful as a predictive tool.

In the present study we wish to examine the results obtained with a modest group of substituted benzofurans generating cation **1** with substituents in the



1

benzene ring, and a side chain as the point of solvolytic reactivity attached at the 3 position. In this structural situation it is to be noted that ordinary valence bond resonance representation does not permit any direct conjugation between the side chain and the substituent X. On this basis the effects of substituents might be expected to be relatively modest, an expectation which is borne out by the facts. One might also expect that the effect of substituents might show a preponderance of inductive influences, an expectation that is not borne out by the facts.

As applied to benzofurans, eq 1 generates eq 2 for 6-substituted 3-benzofuryl systems and eq 3 for 5-substituted 3-benzofuryl systems.

$$(\sigma_{\epsilon,3}^+)_X = F_X^+/3.045 + 0.0666 M_X^+ \quad (2)$$

$$(\sigma_{5,3}^+)_X = F_X^+/2.782 - 0.069 M_X^+ \quad (3)$$

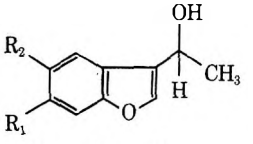
Inserting the values for the F_X^+ and M_X^+ constants for appropriate substituents leads to the predicted substituent constants given in Table I. The close similarity of the constant for a particular substituent at either the 5 position or the 6 position is to be noted.

TABLE I

PREDICTED SUBSTITUENT CONSTANTS FOR USE IN SOLVOLYSIS REACTIONS FOR BENZOFURYL DERIVATIVES

System	Substituent constants, σ_{ij}^+		
	CH_3O	CH_3	Cl
6-X-3-Benzufuryl	−0.187	−0.102	0.168
5-X-3-Benzofuryl	−0.177	−0.104	0.191

The *p*-nitrobenzoates of 1-(3-benzofuryl)ethanol (**2**), 1-(6-chloro-3-benzofuryl)ethanol (**3**), 1-(5-chloro-3-benzofuryl)ethanol (**4**), 1-(5-methoxy-3-benzofuryl)ethanol (**5**), and 1-(6-methoxy-3-benzofuryl)ethanol (**6**) were



2, $R_1 = R_2 = H$
3, $R_1 = Cl$; $R_2 = H$
4, $R_1 = H$; $R_2 = Cl$
5, $R_1 = H$; $R_2 = OCH_3$
6, $R_1 = OCH_3$; $R_2 = H$

prepared and solvolyzed. The relevant rate data are given in Table II.

Both chloro compounds, **3** and **4**, solvolyze about five times more slowly than the parent system (**2**). They solvolyze at very nearly identical rates, indicating a remarkably similar balance of electronic effects at the two positions, 5 and 6. Similarly both methoxy compounds **5** and **6** have very closely similar rates; more importantly, however, **5** and **6** solvolyze faster than **2**, indicating that appreciable electronic deficiency is transmitted to both the 5 and 6 position in the carbonium ion intermediate (**1**). This indicates the importance of the M_X^+ term in eq 2 and 3.

Using the substituent constants given in Table II, ρ was calculated to be −3.8 rather than −5.8 observed for the substituted 2-benzofuryl systems.[10] This no

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) National Institutes of Health Predoctoral Fellow, 1968–1970 (GM 41,892).

(3) D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).

(4) D. S. Noyce and H. J. Pavez, *ibid.*, **37**, 2620 (1972).

(5) D. S. Noyce and H. J. Pavez, *ibid.*, **37**, 2623 (1972).

(6) D. S. Noyce, R. W. Nichols, and C. A. Lipinski, *ibid.*, **37**, 2615 (1972).

(7) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(8) M. J. S. Dewar and P. J. Grisdale, *ibid.*, **84**, 3548 (1962).

(9) Regional charge: The sum of the charges on a carbon atom and any hydrogen atoms bonded to it. A. Streitwieser, Jr., and R. G. Jesaitis in "Sigma Molecular Orbital Theory," O. Sinanoglu and K. B. Wiberg, Ed., Yale University Press, New Haven, Conn., 1970, p 197.

(10) D. S. Noyce and R. W. Nichols, *J. Org. Chem.*, **37**, 4306 (1972).

TABLE II

RATE CONSTANTS FOR THE SOLVOLYSIS OF SUBSTITUTED 1-(3-BENZOFURYL)ETHYL *p*-NITROBENZOATES IN 80% ETHANOL

Compd	Temp, °C	k, sec^{-1}
2-OPNB (H)	75.00	$2.07 \pm 0.07 \times 10^{-5}$
		$2.10 \pm 0.05 \times 10^{-5}$
		$2.05 \pm 0.02 \times 10^{-5}$
	100.00	$2.30 \pm 0.05 \times 10^{-4}$
		$2.37 \pm 0.05 \times 10^{-4}$
3-OPNB (6-Cl)	75.00	$3.55 \pm 0.17 \times 10^{-6}$
		$3.47 \pm 0.08 \times 10^{-6}$
4-OPNB (5-Cl)	75.00	$3.62 \pm 0.17 \times 10^{-6}$
		$3.68 \pm 0.07 \times 10^{-6}$
5-OPNB (5-OCH_3)	75.00	$4.00 \pm 0.03 \times 10^{-5}$
		$3.95 \pm 0.02 \times 10^{-5}$
6-OPNB (6-OCH_3)	75.00	$4.38 \pm 0.05 \times 10^{-5}$
		$4.40 \pm 0.08 \times 10^{-5}$

doubt arises from the interaction of the side chain (position 3) with the peri hydrogen at carbon 4. This influence is difficult to place on a firm quantitative basis, though there are a number of indications that such an effect is operative.

Comparison of α-naphthyl and β-naphthyl systems shows a regular decrease in the relative reactivity of the α-naphthyl moiety as the steric demands of the side chain are increased (Table III), indicative of decreased effectiveness of the resoance interaction.

TABLE III

COMPARATIVE REACTIVITY OF α-NAPHTHYL AND β-NAPHTHYL SYSTEMS IN SOLVOLYSIS

System	Solvent	k_α/k_β[a]	Ref
$ArCH_2Cl$	HCOOH	15.7	*b*
$ArCH_2OTos$	AcOH	7.40	*c*
$ArCH(CH_3)Cl$	80% Acetone	2.56	*d*
$ArCH(C_6H_5)Cl$	90% Acetone	1.36	*e*
$ArC(CH_3)_2Cl$	90% Acetone	1.02	*d*
$ArC(C_6H_5)_2Cl$	Et_2O–EtOH	0.71	*f*

[a] $k_{\alpha\text{-naphthyl}}/k_{\beta\text{-naphthyl}}$. [b] M. J. S. Dewar and R. J. Sampson, *J. Chem. Soc.*, 2789 (1956). [c] A. Streitwieser, Jr., H. A. Hammond, R. H. Jagow, R. M. Williams, R. G. Jesaitis, C. J. Chang, and R. Wolf, *J. Amer. Chem. Soc.*, 92, 5141 (1970). [d] Y. Okamoto and H. C. Brown, *ibid.*, 79, 1903 (1957). [e] L. Verbit and E. Berliner, *ibid.*, 86, 3307 (1964). [f] A. C. Nixon and G. E. K. Branch, *ibid.*, 58, 492 (1936).

In another study Brown and Inukai[11] have shown that an ortho methyl group depresses the response of cumyl chlorides to substituents in the para position. 4-Phenyl-2-methylcumyl chloride is only five times more reactive than 2-methylcumyl chloride, whereas *p*-phenylcumyl chloride is six times more reactive than cumyl chloride. 4-Methoxy-2-methylcumyl chloride is only 1100 times more reactive than *o*-methylcumyl chloride, whereas *p*-methoxycumyl chloride is 3360 times more reactive than cumyl chloride. The value of ρ calculated from the limited data on ortho methyl cumyl chlorides is -4.0 at 0° rather than the standard ρ of -4.54 (at 25°) or -4.9 (at 0°).

In summary, solvolyses of substituted 3-benzofurylmethyl systems have been satisfactorily correlated in a straightforward fashion which is useful for further prediction of reactivities.

(11) H. C. Brown and T. Inukai, *J. Amer. Chem. Soc.*, **83**, 4825 (1961).

Experimental Section[12]

1-(3-Benzofuryl)ethanol (2).—3-Bromobenzofuran was prepared from benzofuran by the method of Stoermer and Kahlert.[13] Conversion to 3-lithiobenzofuran by halogen metal interchange was followed by addition of acetaldehyde. The reaction mixture was worked up in the usual fashion and chromatographed on silica gel. Elution with hexane gave some benzofuran. With 3:1 hexane–ether, 1-(3-benzofuryl)ethanol was eluted: nmr (CCl_4) δ 1.43 (d, 3, J = 7 Hz, CH_3), 3.38 (b, 1, OH), 4.83 (q, 1, CHOH), 7.28 (s, 1, HC_2), and 6.97–7.57 (m, 4, H aromatic).

1-(3-Benzofuryl)ethyl *p*-Nitrobenzoate.—The alcohol **2** was converted in the usual fashion to the *p*-nitrobenzoate: mp 109–110° (from hexane); nmr (CCl_4) δ 1.85 (d, 3, J = 6.5 Hz, CH_3); 6.73 (q, 1, J = 6.5 Hz, –CHOPNB), 7.01–7.67 (m, 5, benzofuryl protons), and 8.17 (s, 4, OPNB).

Anal. Calcd for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.31; H, 4.10; N, 4.64.

3-Bromo-6-chlorobenzofuran.—4-Chlorosalicylaldehyde[10] was converted to 6-chlorobenzofuran-2-carboxylic acid following the procedure of Andrisano and Duro[14] in 79% yield, mp 244–246° (lit.[14] mp 224–225°). The acid was decarboxylated with copper powder in boiling quinoline to give 6-chlorobenzofuran.

To 6-chlorobenzofuran (5 g) in carbon tetrachloride (10 ml) bromine (5.6 g) in carbon disulfide (10 ml) was added in small portions, while the temperature of the reaction flask was maintained at -5 to -20°. The reaction mixture was kept at -20° overnight. The solvent and remaining bromine were removed under reduced pressure, leaving a white solid which was recrystallized from chloroform (20 ml) at -20°. This gave 5.33 g of product, and a second crop of 3.14 g was collected from the concentrated mother liquor, total yield 8.47 g (83%) of 6-chloro-2,3-dibromo-2,3-dihydrobenzofuran: mp 63–65°; nmr (CCl_4) δ 5.63 (s, 1, HC_3), 6.83 (s, 1, HC_2), 7.23 [AB q, ν_4 7.36 and ν_5 7.10, 2, J_{4-5} = 8.6 Hz, HC_4 and HC_5 (superimposed on the upfield half of the AB quartet is a meta splitting, J_{5-7} = 1.7 Hz)], and 7.03 (m, 1, HC_7).

6-Chloro-2,3-dibromo-2,3-dihydrobenzofuran (7.15 g) was added all at once to a solution of potassium hydroxide (2.5 g) in absolute ethanol (35 ml) at 0°. The reaction was stirred for 4 hr at 0° and neutralized with glacial acetic acid, and most of the ethanol was removed under reduced pressure. After the addition of water to the residue, ether extraction, drying ($MgSO_4$), and evaporation of the ether under reduced pressure, 5.20 g (98%) of 3-bromo-6-chlorobenzofuran was obtained: mp 36–37°; nmr (CCl_4) δ 7.28 [AB q, ν_4 7.32 and ν_5 7.24, 2, J_{4-5} = 8.6 Hz, HC_4 and HC_5 (superimposed on the upfield half of the AB quartet is a meta splitting, J_{5-7} = 1.4 Hz)], 7.41 (m, 1, HC_7), and 7.52 (s, 1, HC_2).

Anal. Calcd for C_8H_4BrClO: C, 41.51; H, 1.74; Br, 34.52; Cl, 15.32. Found: C, 41.52; H, 1.75; Br, 34.48; Cl, 15.32.

1-(6-Chloro-3-benzofuryl)ethanol (3).—A solution of 15.2% *n*-butyllithium in hexane (13.0 ml, 0.0212 mol, Foote Mineral Co.) was added from a Dry Ice jacketed addition funnel to a solution of 6-chloro-3-bromobenzofuran (4.0 g, 0.0173 mol) in dry ether (50 ml) maintained at Dry Ice–acetone temperature. The flame-dried apparatus was kept under a nitrogen atmosphere. The addition was completed in 20 min, and the reaction was stirred for 20 min longer. Then acetaldehyde (2.9 ml, 0.052 mol) was rapidly injected into the reaction mixture. The reaction mixture was worked up in the usual fashion. The nmr spectrum of the isolated material indicated that a mixture of products had been formed. Chromatography on silica gel, using hexane–ether eluents, gave 6-chlorobenzofuran (0.73 g, 28%), identified by and pure by the standards of nmr, and 0.23 g (9%) of 2-hydroxy-4-chlorophenylacetylene: nmr (CCl_4) δ 3.37 (s, 1, –C≡CH), 5.73 (b, 1, OH), 6.93 (d, 1, J_{3-5} = 2.0 Hz, HC_3), and 7.01 ppm [AB q, ν_5 6.80 and ν_6 7.22, 2, J_{5-6} = 8.0 Hz, HC_5 and HC_6 (superimposed on the upfield half of the AB quartet is a meta splitting, J_{3-5} = 2.0 Hz)]. The resonance for the acetylenic proton at δ 3.37 is identical with the published[15]

(12) Melting points and boiling points are uncorrected. Analyses are by the Chemical Analytical Services Laboratory, College of Chemisty, University of California, Berkeley, Calif.

(13) R. Stoermer and B. Kahlert, *Ber.*, **35**, 1633 (1902).

(14) R. Andrisano and F. Duro, *Gazz. Chim. Ital.*, **85**, 381 (1955).

(15) C. C. Cook and J. S. Danyluk, *Tetrahedron*, **19**, 177 (1963).

value.[16] With 4:1 hexane–ether, 0.31 g (9%) of 1-(6-chloro-3-benzofuryl)ethanol was collected: nmr (CCl_4) δ 1.52 (d, 3, J = 6.6 Hz, CH_3), 3.15 (b, 1, OH), 4.86 (q, 1, J = 6.6 Hz, CHOH), 7.25 [AB q, ν_4 7.08 and ν_5 7.42, 2, J_{4-5} = 8.0 Hz, HC_4 and HC_5 (superimposed on the upfield half of the AB quartet is a meta splitting, J_{5-7} = 2 Hz)], and 7.34 ppm (b, 2, HC_2 and HC_7).

Minimizing the time lapse between addition of *n*-butyllithium and acetaldehyde gave a substantially improved yield (>50%) of 1-(6-chloro-3-benzofuryl)ethanol (**3**), still contaminated with some 6-chlorobenzofuran.

1-(6-Chloro-3-benzofuryl)ethyl *p*-Nitrobenzoate.—The alcohol **3** was converted to the *p*-nitrobenzoate in the usual way, and recrystallized from absolute ethanol: mp 108.5–109.5°; nmr (CCl_4) δ 1.82 (d, 3, J = 6 Hz, CH_3), 6.37 (q, 1, J = 6 Hz, –CHOPNB), 7.37 [AB q, ν_4 7.55 and ν_5 7.19, 2, $J_{4,5}$ = 8 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is meta split, J_{5-7} = 2 Hz)], 7.47 (m, 1, HC_7), 7.67 (s, 1, HC_2), and 8.15 (s, 4, OPNB).

Anal. Calcd for $C_{17}H_{12}ClNO_5$: C, 59.05; H, 3.50; Cl, 10.26; N, 4.05. Found: C, 58.86; H, 3.36; Cl, 10.23; N, 4.08.

3-Bromo-5-Chlorobenzofuran.—5-Chlorosalicylaldehyde[10] was converted to diethyl 5-chloro-3-hydroxy-2,3-dihydrobenzofuran-2,2-dicarboxylate, mp 93–94°, by the procedure of Andrisano and Duro.[14] Saponification and concurrent decarboxylative dehydration afforded 5-chlorobenzofuran-2-carboxylic acid, mp 264–265° (lit.[14] mp 266–267°). Decarboxylation with copper powder in quinoline afforded 5-chlorobenzofuran.

To a cooled solution of 5-chlorobenzofuran (5.5 g) in carbon disulfide, bromine (6.0 g) in carbon tetrachloride was added as rapidly as decolorization occurred. After 4 hr of additional stirring at −10°, the solvent and remaining bromine were removed under reduced pressure, leaving a white solid which was recrystallized from chloroform at 0° to give 9.6 g (85%) of 5-chloro-2,3-dibromo-2,3-dihydrobenzofuran as heavy, white crystals: nmr (CCl_4) δ 5.60 (s, 1, HC_3), 6.80 (s, 1, HC_2), 7.09 [AB q, ν_6 7.25 and ν_7 6.93, 2, $J_{6,7}$ = 8.0 Hz, HC_6 and HC_7 (the downfield half of the AB quartet is meta split, J_{4-6} = 2.0 Hz)], and 7.43 (d, 1, J_{4-6} = 2 Hz, HC_4).

5-Chloro-2,3-dibromo-2,3-dihydrobenzofuran (7.84 g) was added to a solution of potassium hydroxide (2.9 g) in 95% ethanol (20 ml) at 0°. The reaction was stirred for 5 hr at 0°, and neutralized with acetic acid; water was added, and the mixture was extracted with ether. The extract was dried ($MgSO_4$) and concentrated under reduced pressure to give 5.70 g (98%) of 3-bromo-5-chlorobenzofuran as a white powder: mp 75–76.5°; nmr (CCl_4) δ 7.30 (m, 2, HC_6 and HC_7), 7.47 (m, 1, HC_4), and 7.60 (s, 1, HC_2).

Anal. Calcd for C_8H_4BrClO: C, 41.51; H, 1.74; Br, 34.52; Cl, 15.32. Found: C, 41.36; H, 1.85; Ar, 34.38; Cl, 15.28.

1-(5-Chloro-3-benzofuryl)ethanol (4).—A solution of *n*-butyllithium in hexane (8.0 ml, 0.0127 mol, Foote Mineral Co.) was added from a Dry Ice jacketed addition funnel to a solution of 5-chloro-3-bromobenzofuran (2.5 g) in dry ether (60 ml), the flame-dried reaction flask being cooled by a Dry Ice–acetone bath and kept under positive nitrogen pressure. The addition was completed in 3 min and the reaction mixture was stirred 7 min longer, at which time acetaldehyde (2.5 ml, 0.038 mol) was rapidly injected, causing the cloudy, light green reaction mixture to clarify. The reaction mixture was worked up in the usual fashion. Low-temperature crystallization from ether–petroleum ether (bp 30–60°) afforded 1.25 g (59%) of 1-(5-chloro-3-benzofuryl)ethanol (**4**) as fine, white needles: mp 84–85°; nmr (CCl_4) δ 1.54 (d, 3, J = 6 Hz, CH_3), 2.50 (s, 1, OH), 4.96 (q, 1, J = 6 Hz, CHOH), 7.27 [AB q, ν_6 7.21 and ν_7 7.33, 2, J_{6-7} = 9 Hz, H-C_6 and H-C_7 (the upfield half of the AB quartet is meta split, J_{4-6} = 2 Hz)], 7.47 (s, 1, HC_2), and 7.60 ppm (m, 1, HC_4).

Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 60.89; H, 4.45; Cl, 18.18.

1-(5-Chloro-3-benzofuryl)ethyl *p*-nitrobenzoate was prepared in the usual fashion: mp 118–119°; nmr (CCl_4) δ 1.84 (d, 3, J = 7 Hz, CH_3), 6.37 (q, 1, J = 7 Hz, $CHCH_3$), 7.33 (AB q, ν_6 7.25 and ν_7 7.41, 2, J_{6-7} = 8.5 Hz, HC_6 and HC_7), 7.62 (m, 1, HC_4), 7.68 (s, 1, HC_2), and 8.19 (s, 4, OPNB).

Anal. Calcd for $C_{17}H_{12}ClNO_5$: C, 59.05; H, 3.50; Cl, 10.26; N, 4.05. Found: C, 59.29; H, 3.71; Cl, 10.14; N, 4.20.

4-Bromo-5-methoxybenzofuran.—5-Methoxybenzofuran was prepared by the method of Andrisano, Duro, and Pappalardo.[17,18]

A solution of bromine (6.15 g) in carbon disulfide (10 g) was added to 5-methoxybenzofuran (5.65 g, 0.038 mol) in carbon disulfide (10 g) as fast as it could be decolorized, the addition taking 30 min. Throughout the addition, the reaction flask was maintained at −20 to −25°. After an additional 30 min the solvent was removed under reduced pressure. Crystallization from hexane gave 5.5 g (64%) of 4-bromo-5-methoxybenzofuran, mp 81–88°. A small quantity was recrystallized from hexane to give a pure sample: mp 88.0–89.5°; 100-MHz nmr (CCl_4) δ 3.87 (s, 3, OCH_3), 6.72 (dd, J_{2-3} = 2.2 and J_{3-7} = 1 Hz, HC_3), 7.06 [AB q, ν_6 6.84 and ν_7 7.28, J_{6-7} = 8.7 Hz (the downfield half of the AB quartet is split by a long-range coupling, J_{3-7} = 1 Hz)], and 7.57 (d, J_{2-3} = 2.2 Hz, HC_2).

Anal. Calcd for $C_9H_7BrO_2$: C, 47.60; H, 3.11; Br, 35.20. Found: C, 47.79; H, 3.34; Br, 35.38.

2,3,4-Tribromo-5-methoxy-2,3-dihydrobenzofuran.—Bromide (3.8 g) in carbon disulfide (10 ml) was added to a solution of 4-bromo-5-methoxybenzofuran (5.32 g) in carbon disulfide and carbon tetrachloride (10 ml), and the mixture was allowed to stand for 5 days. The solvents were removed under reduced pressure, and the residue was crystallized at low temperature from hexane–ether; 7.1 g (78%) of 2,3,4-tribromo-5-methoxy-2,3-dihydrobenzofuran was obtained as yellow crystals: mp 81–83°; nmr (CCl_4) δ 3.82 (s, 3, OCH_3), 5.56 (s, 1, HC_3), and 6.79 ppm [s, 3, HC_2, HC_6, and HC_7 (HC_6 and HC_7 actually form an AB quartet, but do so near the limit of equivalence of the two protons involved; very small resonances are symmetrically disposed about the central 6.79 peak at a distance of 8 Hz. The appearance of HC_2 at 5.29 is coincidental, but normal for dibromodihydrobenzofurans)].

Anal. Calcd for $C_9H_7Br_3O_2$: Br, 61.97. Found: Br, 60.40. This analysis establishes the presence of three bromine atoms in the molecule. The compound was used without further purification.

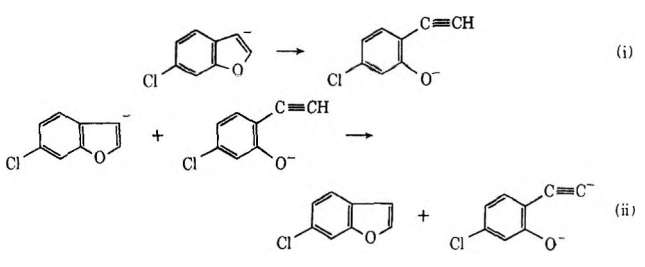
3,4-Dibromo-5-methoxybenzofuran.—2,3,4-Tribromo-5-methoxy-2,3-dihydrobenzofuran (5.8 g) was added to a cold (0°) solution of potassium hydroxide (1.1 g) in nitrogen-flushed ethanol (40 ml). After 5 hr of stirring at 0° (with precipitation of potassium bromide) the reaction mixture was left standing at −15° overnight. Water was added, and the mixture was extracted with ether. The ether was removed from the washed (water) and dried ($MgSO_4$) extract to give 4.45 g (97%) of 3,4-dibromo-5-methoxybenzofuran, mp 80–85°. A sample recrystallized from petroleum ether–ether gave needles: mp 84–85°; 100-MHz nmr (CCl_4) δ 3.87 (s, 3, OCH_3), 7.09 (AB q, ν_6 6.88 and ν_7 7.30, 2, J_{6-7} = 9 Hz, HC_6 and HC_7), and 7.59 (s, HC_2).

Anal. Calcd for $C_9H_6Br_2O_2$: Br, 52.25. Found: Br, 51.96.

1-(4-Bromo-5-methoxy-3-benzofuryl)ethanol.—A preliminary experiment with a small sample of 3,4-dibromo-5-methoxybenzofuran showed that halogen–metal interchange occurred most facilely at the 3 position, as evidenced by the recovery of 4-bromo-5-methoxybenzofuran upon addition of water.

Thus, to 3.72 g of 3,4-dibromo-5-methoxybenzofuran in 125 ml of dry ether at −78° was added 1 equiv of *n*-butyllithium in

(16) These side products may have arisen from the successive side reactions i and ii.



The intramolecular cleavage reaction i is reminiscent of the isolation of *o*-hydroxyphenylacetylene [H. Gilman and D. S. Melstrom, *J. Amer. Chem. Soc.*, **70**, 1655 (1948)] from the products of the reaction of *n*-butyllithium with 3-bromobenzofuran in ether, followed by carbonation. In an analogous experiment in this work, benzofuran was a minor side product, but acetylenic product was not noted. The apparent acceleration of the intramolecular cleavage by a 6-chloro substituent is consistent with the greater acidity of *m*-chlorophenol relative to that of phenol.

(17) R. Andrisano, F. Duro, and G. Pappalardo, *Boll. Sci. Fac. Chim. Ind. Bologna*, **14**, 96 (1956); *Chem. Zentr.*, 667 (1958).

(18) We wish to express our appreciation to the Upjohn Co. for the gift of a generous quantity of 5-methoxysalicylaldehyde.

hexane (Foote Mineral Co.). The addition was completed in 7 min, and the reaction was stirred 7 min longer. Then acetaldehyde (2.5 ml, 0.044 mol) was rapidly injected, causing the white precipitate to dissolve. After 5 min the contents of the reaction flask were mixed with salted water (100 ml) and extracted with three 75-ml portions of ether. The extract was dried ($MgSO_4$) and concentrated; chromatography on silica gel using hexane as eluent gave small amounts of starting material and of 4-bromo-5-methoxybenzofuran. Elution with 85:15 hexane–ether gave an isolated yield of 1.61 g (49%) of 1-(4-bromo-5-methoxy-3-benzofuryl)ethanol as colorless needles: mp 87–88° (from petroleum ether–ether); nmr (CCl_4) δ 1.60 (d, 3, J = 7 Hz, $CHCH_3$), 2.07 (b, 1, OH), 3.92 (s, 3, OCH_3), 5.51 (q, 1, J = 7 Hz, $CHCH_3$), 7.10 (AB q, ν_6 6.93 and ν_7 7.27, 2, J_{6-7} = 9 Hz, HC_6 and HC_7), and 7.63 (s, 1, HC_2).

Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09; Br, 29.47. Found: C, 48.81; H, 4.22; Br, 29.28.

1-(5-Methoxy-3-benzofuryl)ethanol (5).—A solution of 15.2% *n*-butyllithium in hexane (10.1 ml) was added from a Dry Ice jacketed addition funnel to a solution of 1-(4-bromo-5-methoxy-3-benzofuryl)ethanol (1.44 g) in dry ether (100 ml). The dried reaction flask was maintained under a nitrogen atmosphere. During the 5-min addition period the reaction was stirred in a Dry Ice–acetone bath. After 2 hr of stirring at −78° the reaction mixture was quenched with water (10 ml) and methanol (1 ml). After the usual work-up the nmr indicated complete conversion to 1-(5-methoxy-3-benzofuryl)ethanol (**5**): nmr (CCl_4) δ 1.48 (d, 3, J = 7 Hz, $CHCH_3$), 3.17 (b, 1, OH), 3.75 (s, 3, OCH_3), 5.88 (q, 1, J = 7 Hz, $CHCH_3$), 7.00 [AB q, ν_6 6.76 and ν_7 7.24, 2, J_{6-7} = 9 Hz, HC_6 and HC_7 (the upfield half of the AB quartet is meta split, J_{4-6} = 2 Hz)], 7.00 (d, 1, J_{4-6} = 2 Hz, HC_4), and 7.33 (s, 1, HC_2).

The alcohol was converted to the *p*-nitrobenzoate without further purification.

1-(5-Methoxy-3-benzofuryl)ethyl *p*-Nitrobenzoate.—Impure 1-(5-methoxy-3-benzofuryl)ethanol [1.14 g (total possible 1-(5-methoxy-3-benzofuryl)ethanol is 1.02 g, 0.0053 mol)] prepared from 1-(5-methoxy-4-bromo-3-benzofuryl)ethanol (1.44 g, 0.0053 mol) was dissolved in dry pyridine (7 ml), and *p*-nitrobenzoyl chloride (1.15 g) was added. After stirring overnight, most of the pyridine was removed under reduced pressure and the residual solid material was triturated with boiling hexane. From the cooled, filtered hexane solution 1.30 g (78%) of 1-(5-methoxy-3-benzofuryl)ethyl *p*-nitrobenzoate crystallized: mp 126–127°; nmr (CCl_4) δ 1.82 (d, 3, J = 6.5 Hz, $CHCH_3$), 3.74 (s, 3, OCH_3), 6.37 (q, 1, J = 6.5 Hz, $CHCH_3$), 7.05 [AB q, ν_6 6.81 and ν_7 7.29, 2, J_{6-7} = 9 Hz, HC_6 and HC_7 (the upfield half of the AB quartet is meta split, J_{4-5} = 3 Hz)], 7.01 (d, 1, J_{4-5} = 3 Hz, HC_4), 7.59 (s, 1, HC_2), and 8.15 (s, 4, $-C_6H_4-$).

Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.11. Found: C, 63.35; H, 4.43; N, 4.36.

Ethyl 6-Methoxy-2-carboxybenzofuran-3-carboxylate.—The procedure of Koelsch and Whitney[19] was used. Ethyl *m*-methoxyphenoxyacetate[20] was condensed with diethyl oxalate using commercial sodium ethoxide in ether. The resulting diethyl α-keto-α'-*m*-methoxyphenoxysuccinate (100 g) was cyclized directly using a mixture of acetic acid (200 ml), sulfuric acid (200 ml), and acetic anhydride (10 ml). After the solution had stood overnight, it was heated on the steam bath for 20 min. The reaction mixture was poured over crushed ice, and the resulting precipitate was removed by filtration and was then recrystallized from ethanol. In this fashion there was obtained 33.3 g (39%) of impure ethyl 6-methoxy-2-carboxybenzofuran-3-carboxylate, contaminated with the 4 isomer. Fractional crystallization from ethanol (three stages) gave pure ethyl 6-methoxy-2-carboxybenzofuran-3-carboxylate as brittle, pale yellow needles: mp 164–165°; yield 24%; 100-MHz nmr (CF_3COOH) δ 1.64 (t, 3, J = 7 Hz, OCH_2CH_3), 3.98 (s, 3, OCH_3), 4.74 (q, 2, OCH_2CH_3), 7.20 (dd, 1, J_{4-5} = 9 Hz and J_{5-7} = 2.4 Hz, HC_4).

Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.11; H, 4.64.

From the mother liquors, **ethyl 4-methoxy-2-carboxybenzofuran-3-carboxylate** was isolated as long, fine, wooly, colorless needles: mp 153.5–154.5°; yield 1.5 g (2%); 100-MHz nmr (CF_3COOH) δ 1.57 (t, 3, J = 7 Hz, OCH_2CH_3), 4.01 (s, 3, OCH_3), 4.68, (q, 2, OCH_2CH_3), 7.10–7.26 (m, 2, ArH), and 8.20–8.34 (m, 1, ArH).

Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.22; H, 4.49.

6-Methoxybenzofuran-3-carboxylic Acid.—A mixture of ethyl 6-methoxy-2-carboxybenzofuran-3-carboxylate, copper powder, and quinoline was heated to 225–230°. After 20 min, evolution of carbon dioxide had virtually ceased. Work-up in the usual fashion gave 12.3 g (76%) of crude **ethyl 6-methoxybenzofuran-3-carboxylate**. A small sample was crystallized from ethanol for purposes of characterization: mp 55–56°; nmr (CCl_4) δ 1.39 (t, 3, J = 7 Hz, OCH_2CH_3), 7.34 [AB q, ν_4 7.81 and ν_5 6.87, 2, J_{4-5} = 9.5 Hz, HC_4 and HC_5 (the upfield half of the AB quartet is meta split, J_{5-7} = 2 Hz)], 6.93 (m, 1, HC_7) and 8.03 (s, 1, HC_2).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.70; H, 5.54.

The remainder of the ester was saponified by potassium hydroxide in aqueous ethanol. Work-up in the usual fashion gave **6-methoxybenzofuran-3-carboxylic acid** (99%) as a white powder: mp 179–180° (from chloroform–methanol); nmr ($CDCl_3$) δ 3.85 (s, 3, OCH_3), 6.98–7.22 (m, 2, HC_5 and HC_7), 7.88 (d, 1, J = 8 Hz, HC_4), and 8.28 (s, 1, HC_2).

Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.19. Found: C, 62.38; H, 4.08.

6-Methoxy-3-acetylbenzofuran.—To a cooled solution of 6-methoxybenzofuran-3-carboxylic acid (4.0 g) in dry ether (400 ml), methyllithium in ether (50 ml, 0.075 mol, Foote Mineral Co.) was added over a period of 30 min. After 3 hr more methyllithium solution (25 ml) was added, and the reaction mixture was stirred overnight at room temperature. Methanol (30 ml) was rapidly injected[21] into the cooled, rapidly stirring reaction mixture, and the solution was neutralized with acetic acid. The reaction mixture was washed with two 200-ml portions of water, a 125-ml portion of saturated sodium bicarbonate, and with water again. The ether solution was dried ($MgSO_4$) and the ether was removed to give 3.09 g of crude 6-methoxy-3-acetylbenzofuran as a pale brown solid. The nmr spectrum indicated only a very small gem-dimethyl resonance from the corresponding tertiary alcohol. Recrystallization from petroleum ether gave 2.64 g (67%) of product, mp 68–73°.

A sample was recrystallized from petroleum ether–ether and then sublimed (0.1 mm, bath temperature 65°) for purposes of characterization: mp 72.5–73.0°; nmr (CCl_4) δ 2.39 (s, 3, $COCH_3$), 3.76 (s, 3, OCH_3), 6.72–6.95 (m, 2, HC_5, HC_7), 7.94 (d, 1, J_{4-5} = 9 Hz, HC_4), and 7.97 (s, 1, HC_2).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.41; H, 5.51.

1-(6-Methoxy-3-benzofuryl)ethanol (6).—6-Methoxy-3-acetylbenzofuran (1.2 g) in methanol (35 ml) was reduced with sodium borohydride. The reaction mixture was worked up in the usual fashion to give 1.20 g (99%) of 1-(6-methoxy-3-benzofuryl)-ethanol (**6**) as an oil: nmr (CCl_4) δ 1.43 (t, 3, J = 7 Hz, $CHCH_3$), 3.20 (b, 1, OH), 3.71 (s, 3, OCH_3), 4.82 (q, 1, J = 7 Hz, $CHCH_3$), 6.65 (dd, 1, J_{4-5} = 8.5 and J_{5-7} = 2 Hz, HC_5), 6.80 (d, 1, J_{5-7} = 2 Hz, HC_7), 7.21 (s, 1, HC_2), and 7.32 (d, 1, J_{4-5} = 8.5 Hz, HC_4).

1-(6-Methoxy-3-benzofuryl)ethyl *p*-nitrobenzoate was prepared directly from crude **6** in the usual fashion. Purification was achieved by crystallization from hexane–ether: mp 106.5–108.0°; nmr (CCl_4–$CDCl_3$) δ 1.82 (t, 3, J = 6.5 Hz, $CHCH_3$), 3.80 (s, 3, OCH_3), 6.40 (q, 1, J = 6.5 Hz, $CHCH_3$), 6.83 (dd, 1, J_{4-5} = 8.5 and J_{5-7} = 2 Hz, HC_5), 6.98 (d, 1, J_{5-7} = 2 Hz, HC_7), 7.50 (d, 1, J_{4-5} = 8.5 Hz, HC_4), 7.57 (s, 1, HC_2), and 8.17 (s, 4, $-C_6H_4-$).

Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.26; H, 4.25; N, 4.21.

Kinetic Procedures.—Kinetic methods have been described previously.[10]

Registry No.—**2**, 36739-86-3; 2-OPNB, 36739-87-4; **3**, 36739-88-5; **3**-OPNB, 36739-89-6; **4**, 36739-90-9; **4**-OPNB, 36739-91-0; **5**, 19303-55-0; **5**-OPNB, 36739-93-2; **6**, 36739-94-3; **6**-OPNB, 36739-95-4; 6-chloro-

(19) C. F. Koelsch and A. G. Whitney, *J. Amer. Chem. Soc.*, **63**, 1762 (1941).

(20) J. Myska, V. Ettel, and M. Bowar, *Collect. Czech. Chem. Commun.*, **26**, 904 (1961).

(21) Following the suggestion of Dr. M. J. Jorgenson; *cf. Org. React.*, **18**, 321 (1970).

2,3-dibromo-2,3-dihydrobenzofuran, 36739-96-5; 3-bromo-6-chlorobenzofuran, 36739-97-6; 2-hydroxy-4-chlorophenylacetylene, 36739-98-7; 5-chloro-2,3-dibromo-2,3-dihydrobenzofuran, 36826-29-6; 3-bromo-5-chlorobenzofuran, 36739-99-8; 4-bromo-5-methoxybenzofuran, 36826-30-9; 2,3,4-tribromo-5-methoxy-2,3-dihydrobenzofuran, 36740-00-8; 3,4-dibromo-5-methoxybenzofuran, 36826-31-0; 1,(4-bromo-5-methoxy-3-benzofuryl)ethanol, 36740-01-9; ethyl 6-methoxy-2-carboxybenzofuran-3-carboxylate, 28238-33-7; ethyl 4-methoxy-2-carboxybenzofuran-3-carboxylate, 36748-73-9; ethyl 6-methoxybenzofuran-3-carboxylate, 36748-74-0; 6-methoxybenzofuran-3-carboxylic acid, 29822-97-7; 6-methoxy-3-acetylbenzofuran, 36748-76-2.

Confirmation of Concurrent General Acid, General Base Catalysis in the Lactonization of 2-(Hydroxymethyl)benzoic Acid

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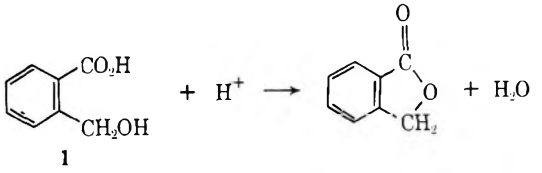
An earlier report that lactonization of 2-(hydroxymethyl)benzoic acid in water is general acid and general base catalyzed (by formic acid and formate ion, respectively) is confirmed, and for the first time substantiating experimental details are presented.

Although *intra*molecular general base catalysis of the reactions of carboxylic acids and esters is fairly common,[1] *inter*molecular general acid catalysis has been observed in only a few cases.[1]

In 1969, Milstien and Cohen[2a] reported in a preliminary communication that the lactonizations of 2-(hydroxymethyl)benzoic acid (1) and some phenolic



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acids in water are subject to concurrent general acid and general base catalysis by formate, acetate, and several other buffers. A subsequent full paper[2b] reported details of their study in respect to the phenolic acids, but details concerning lactonization of 1 have not appeared. Inasmuch as catalysis of the lactonization of 1 was of special interest to us, we undertook a reexamination of the rates of lactonization of 1 in formic acid–formate ion buffers at 60°. Our results confirm the report[2a] that the reaction is catalyzed by both the acidic and basic constituents of the buffer.

Results and Discussion

The rates of lactonization of 1 in formic acid buffers were studied under pseudo-first-order conditions identical with those used by Milstien and Cohen,[2a] that is, 60.0° and an ionic strength, μ, of 0.30. Although previous studies[3,4] were available on the hydrogen ion catalyzed lactonization at 60° under slightly different conditions, we also determined this rate constant at 60.0° and μ 0.30 using two different hydrochloric acid concentrations. Also, the apparent ionization constants (K_a's) of 1 and of formic acid were measured under the reaction conditions.

A composite rate law[1] was found for the lactonization in formic acid buffers, as set forth in eq 1, where

$$k_\psi = \alpha(k_0 + k_{H^+}[H^+] + k_{HA}[HA] + k_{A^-}[A^-]) \quad (1)$$

k_ψ is the pseudo-first-order rate coefficient, α is the fraction of substrate undissociated at a particular pH, k_0 and k_{H^+} are the water and hydrogen ion catalyzed components of the rate, and k_{HA} and k_{A^-} are the rate constants for catalysis by the buffer acid and its conjugate base, respectively.

Since the buffer components are present in large excess over the substrate, α can be calculated for each buffer without knowledge of the actual pH, provided that the relative pK_a's of the buffer acid and the substrate are known under the reaction conditions. The determination of these ionization constants is described in the Experimental Section; the observed values are pK_a = 3.66, formic acid, and pK_a = 3.79, 1. These values compare with pK_a = 3.77 at 30° and μ 0.3 for formic acid, reported by Milstien and Cohen,[2b] and pK_a = 3.84 at room temperature and μ <0.01, reported[4] for 1. From these experimental pK_a's, α was evaluated for each buffer and used to calculate the corrected pseudo-first-order rate coefficients, $k_\psi' = k_\psi/\alpha$.

In order to simplify determination of the several rate constants, two sets of buffer experiments were performed. The first set consisted of eight kinetic runs at a constant buffer ratio of [HA]/[A$^-$] = 1 but with variation of the total buffer concentration. Under these conditions eq 1 simplifies to eq 2, where

$$k_\psi' = k_0 + k_{H^+}K_{HA} + (k_{HA} + k_{A^-})[HA] \quad (2)$$

K_{HA} is the ionization constant of formic acid. A plot of k_ψ' *vs.* [HA] for these runs (Table I, runs 1–8) is shown in Figure 1; the slope is (k_{HA} + k_{A^-}) and the intercept (k_0 + $k_{H^+}K_{HA}$).

In the second set of experiments the concentration of formate ion was held constant at 0.30 *M* while five different formic acid concentrations were employed (runs 8, 12–15). For these conditions eq 3 applies.

$$k_\psi' = k_0 + k_{A^-}[A^-] + (k_{H^+}K_{HA}/[A^-] + k_{HA})[HA] \quad (3)$$

The anticipated linear plot of k_ψ' *vs.* [HA] was obtained; it is not shown. Since the intercept is k_0 + 0.30 k_{A^-},

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(2) (a) S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **91**, 4585 (1969); (b) *ibid.*, **92**, 4377 (1970).
(3) J. Tirouflet, *Bull. Soc. Chim. Fr.*, 799 (1954).
(4) J. F. Bunnett and C. F. Hauser, *J. Amer. Chem. Soc.*, **87**, 2214 (1965).

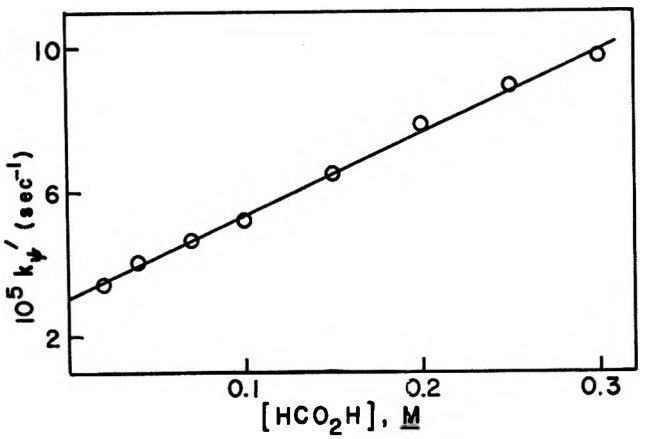

Figure 1.—Plot of pseudo-first-order rate coefficients *vs.* formic acid concentration, $[HCO_2H]/[HCO_2^-] = 1$.

TABLE I
PSEUDO-FIRST-ORDER RATE COEFFICIENTS FOR THE LACTONIZATION OF 2-(HYDROXYMETHYL)BENZOIC ACID IN WATER AT 60.0° [a]

Run	[HCO$_2$H], *M*	[HCO$_2$Na], *M*	$10^5 k_\psi$, sec^{-1}	$10^5 k_\psi'$,[b] sec^{-1}
1	0.020	0.020	1.98	3.45
2	0.040	0.040	2.32	4.04
3	0.070	0.070	2.69	4.68
4	0.100	0.100	2.99	5.21
5	0.150	0.150	3.74	6.51
6	0.200	0.200	4.50	7.84
7	0.250	0.250	5.15	8.96
8	0.300	0.300	5.60	9.75
9	0.020	0.020	1.94	3.38
10[c]	0.020	0.020	1.98	3.45
11[d]	0.020	0.020	1.92	3.34
12	0.100	0.300	2.28	7.35
13	0.150	0.300	3.45	8.56
14	0.600	0.300	11.0	15.1
15	0.900	0.300	15.7	18.5
16	0.001[e]		6.61	7.69
17	0.002[e]		13.9	15.0

[a] μ 0.30 with added NaCl; substrate concentration 5.0×10^{-4} *M*. [b] $k_\psi' = k_\psi/\alpha$; see text. [c] Added salt was $NaNO_3$. [d] Added salt was $NaClO_4$. [e] Acid was HCl.

k_{HA} and k_{A^-} can now be evaluated, provided that k_0 can be determined.

The value of k_0 was evaluated from the intercept of Figure 1, by subtracting from it $k_{H^+}K_{HA}$ (*cf.* eq 2), experimentally determined values of k_{H^+} and K_{HA} being used. The rate constant for hydrogen ion catalyzed lactonization, k_{H^+}, was determined by measuring the pseudo-first-order coefficients at 60° and μ 0.30 at two HCl concentrations, 1.0×10^{-3} and 2.0×10^{-3} *M* (runs 16 and 17). Under these conditions the rate law is $k_\psi = \alpha(k_0 + k_{H^+}[H^+])$. Also, α equals $[H^+]/([H^+] + K_a)$, where K_a is the ionization constant of the substrate. Assuming that $[H^+] = [HCl]_{st}$, we calculated k_{H^+} as 7.3×10^{-2} M^{-1} sec^{-1}. This value is in good agreement with 7.2×10^{-2} M^{-1} sec^{-1} found by Tirouflet[3] for the reaction in water and 6.9×10^{-2} M^{-1} sec^{-1} reported by Bunnett and Hauser[4] for lactonization in 9% (v/v) ethanol–water.

An alternative method[4] of reckoning k_{H^+}, which allows for the small increase in $[H^+]$ due to ionization of the substrate, gave the same value as the above method. Multiplication of k_{H^+} by 2.2×10^{-4} *M*, the ionization constant of formic acid, gives $k_{H^+}K_{HA} = 1.6 \times 10^{-5}$ sec^{-1}. Subtraction from the intercept of Figure 1 gives $k_0 = 1.45 \times 10^{-5}$ sec^{-1}.

Subtraction of this k_0 from the intercept of a plot of k_ψ' *vs.* [HA], based on the data of runs 8 and 12–15 of Table I (*cf.* eq 3), provided an evaluation of k_{A^-} as 1.54×10^{-4} M^{-1} sec^{-1} for formate ion catalysis. Furthermore, subtraction of this value from the slope of Figure 1 (*cf.* eq 2) afforded $k_{HA} = 7.6 \times 10^{-5}$ M^{-1} sec^{-1} for formic acid catalysis of the lactonization reaction.

These results compare with the corresponding values reported by Milstien and Cohen,[2a] namely, 1.54×10^{-4} M^{-1} sec^{-1} for k_{A^-} and 3.45×10^{-5} M^{-1} sec^{-1} for k_{HA}. The agreement between the values of k_{A^-} is perhaps fortuitous and, in view of the numerous arithmetic operations required to obtain the rate coefficients, the discrepancy between the values of k_{HA} is not disturbing. On the contrary, it serves to emphasize the difficulties involved in obtaining precise data in systems such as this one, in which sizable corrections for equilibria are involved. The problem is particularly acute at temperatures very different from ambient.

Although our results appeared to confirm the earlier work, there remained the (unlikely) possibility that the variation in rate in runs 1–8 was due to a specific salt effect arising from the replacement of chloride ion by formate ion. Salomaa, Kankaanperä, and Lahti[5] observed specific salt effects in the hydrolysis of acetals and ortho esters when buffer experiments of this type were carried out in mixed aqueous solvents, and Bunton and coworkers[6] found similar effects in other types of reactions. To test this possibility, three runs (runs 9–11, Table I) were carried out simultaneously at the lowest buffer concentration employed, with formic acid and formate ion both 0.02 *M*, with three different added electrolytes used to bring the ionic strength to 0.30. The eleetrolytes chosen, NaCl, $NaNO_3$, and $NaClO_4$, were those shown by Salomaa and coworkers[5] to give very different slopes in their buffer experiments and widely divergent rate coefficients at low buffer concentration. Our results provide no indication of such a specific salt effect in this system and assure that the variation in rate with buffer concentration is in fact due to buffer catalysis. Table II summarizes the kinetic data.

TABLE II
SUMMARY OF KINETIC DATA

k_0, sec^{-1}	k_{H^+}, M^{-1} sec^{-1}	k_{HA},[a] M^{-1} sec^{-1}	k_{A^-},[b] M^{-1} sec^{-1}
1.45×10^{-5}	7.3×10^{-2}	7.6×10^{-5}	1.54×10^{-5}

[a] HA = formic acid. [b] A^- = formate ion.

Experimental Section

Material.—Phthalide, mp 72–74° (lit.[7] mp 72–73°), was an old sample prepared by Dr. C. F. Hauser.[4] Formic acid, sodium hydroxide, sodium chloride, sodium nitrate, and sodium perchlorate were analytical reagent grade materials and were used without further purification. Ordinary distilled water was distilled from potassium permanganate solution before use.

(5) P. Salomaa, A. Kankaanperä, and M. Lahti, *J. Amer. Chem. Soc.*, **93**, 2084 (1971).

(6) C. A. Bunton, T. W. Del Pesco, A. M. Dunlop, and K.-U. Yang, *J. Org. Chem.*, **36**, 887 (1971).

(7) J. H. Gardner and C. A. Naylor, Jr., "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 526.

pK_a Determinations.—The apparent pK_a's of formic acid and 2-(hydroxymethyl)benzoic acid were measured at 60 ± 1° and 0.3 *M* sodium chloride using a Model E 300B Metrohm pH meter, equipped with scale expander and temperature calibration. The electrode used was the Metrohm EA-120X combination electrode and the meter was calibrated at 60° using commercial standard buffers.

Standard (0.01 *M*) solutions of the sodium salts of the acids were prepared [the sodium salt of 2-(hydroxymethyl)benzoic acid was prepared by heating phthalide with a slight excess of sodium hydroxide[4]], made up to μ 0.30 with sodium chloride, and titrated with standard 0.1 *N* HCl solution (Titrisol). The pH's of the solutions were measured after every 5% neutralization from 10 to 90% neutralization, and the pK_a for each point was calculated using the equation

$$pK_a = pH + \log\{([HA]_{st} - [H^+])/([A^-]_{st} + [H^+])\}$$

where pH is the value read from the pH meter and $[H^+]$ is calculated therefrom. Values of pK_a in the region of 30–70% neutralization agreed very well and were averaged to determine the final pK_a value. Owing to instrument drift and instability at the temperature used, the absolute values of the pK_a's are probably less reliable than the relative values, which were determined consecutively as rapidly as possible. The effect of a small error in the absolute value of the pK_a of I on the value of k_{H^+} is not appreciable.

The pK_a value of 1 was 3.79 ± 0.01, while that of formic acid was 3.66 ± 0.01.

Kinetic Procedures.—The rates of lactonization of 1 were determined under pseudo-first-order conditions by measuring absorbance due to the hydroxy acid reactant and the lactone product of aliquots of the reaction solution kept in sealed ampoules immersed in an oil bath at 60.00 ± 0.05°. The absorbances at 254 and 276 nm, respectively, were calculated from transmittance values measured on a Hitachi Perkin-Elmer Model 139 spectrophotometer.

A standard solution of the sodium salt of 1 (5×10^{-3} *M*) was prepared by saponification of the phthalide. In a typical experiment, 10 ml of the standard was combined with appropriate amounts of standard formic acid, sodium hydroxide, and sodium chloride solutions and diluted to the mark in a 100-ml volumetric flask. Aliquots (10 ml) of this solution were then transferred to 10-ml glass ampoules (Kimble Neutraglas), and the ampoules were sealed and immersed in the constant-temperature bath. At appropriate intervals samples were removed from the bath and quenched in ice; the sample was then transferred to a quartz cuvette and the transmittance was recorded. Six to eight points were obtained over a period of *ca.* 2 half-lives; infinity values were recorded at 10 or more half-lives.

The observed pseudo-first-order rate coefficients (k_ψ) were reckoned by a least-squares plot of log $(A_\infty - A)$ *vs.* time on an Olivetti-Underwood Programma 101 programmable calculator. Correlation coefficients (r) were 0.999 or better and were typically 0.9999. Agreement between the two rate constants as determined by reactant decrease and product increase was excellent, although the latter generally gave better r values. The k_ψ values reported in Table I are those of product increase. The slopes and intercepts of Figure 1 and of the plot of k_ψ' *vs.* [HA] according to eq 3 (plot 2) were also evaluated by least-squares analysis and the results are summarized in Table III.

TABLE III
EVALUATION OF KINETIC PARAMETERS

Plot	Runs	Slope, M^{-1} sec^{-1}	Intercept, sec^{-1}	r
1	1–8	2.30×10^{-4}	3.05×10^{-5}	0.998
2	8, 12–15	1.42×10^{-4}	6.06×10^{-5}	0.995

Registry No.—1, 612-20-4.

Acknowledgments.—This research was supported in part by the National Science Foundation. N. Tomoto expresses his thanks for a fellowship from the Japanese Ministry of Education.

Solution Photochemistry. X. A Study of the Effects of Double-Bond Geometry and of Increasing Double-Bond Separation on the Photochemical Reactions of Acyclic Nonconjugated Dienes[1,2]

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The triplet-sensitized photochemical reactions of the geometric isomers of the homologous dienes **2a–c**, **3a–c**, **5a–c**, and **6a–c** have been investigated. In the case of the 1,5 dienes **2a–c**, irradiation using acetone as the triplet energy sensitizer leads to cis,trans isomerization and, at a similar rate, to internal "crossed" [2 + 2] cycloaddition to give adducts **7** and **8** in a ratio of 65:35. Similar excitation of the 1,6 dienes **3a–c** causes concurrent geometric isomerism and "straight" [2 + 2] cyclization yielding adducts **9** and **10** (ratio of 3:1). Based on the stereochemistries of the adducts and on the triplet nature of these processes, these cyclizations are interpreted as occurring *via* two-step mechanisms involving the intermediacy of 1,4 diradicals. The specificity observed in the direction of initial bond formation (straight *vs.* crossed) is discussed in terms of excited states **15** and **16** which bond in accordance with strain and entropy effects. Final 1,4-diradical closure is shown to be kinetically controlled and possible explanations for the product ratios are advanced. Triplet excitation of the 1,8 and 1,9 dienes **5a–c** and **6a–c** leads only to geometric isomerism. Since previous work showed that the corresponding 1,7 dienes in this series undergo straight cyclization, the limit of double-bond separation for cyclization has been reached. Direct irradiation studies on trans,trans dienes **2a** and **3a** reveal that α,β to β,γ double-bond migration is an important process; geometric isomerism and internal cyclization are also observed in these cases.

The photochemistry of acyclic nonconjugated dienes has been a subject of continuing interest.[4] Apart from 1,4 dienes, which commonly undergo the di-π-methane rearrangement,[5] the major pathways by which these molecules react upon absorption of a photon of light are cis,trans isomerization and intramolecular [2 + 2] cycloaddition.[6] This latter process can lead to two

(1) Solution Photochemistry. IX: J. R. Scheffer and R. A. Wostradowski, *Tetrahedron Lett.*, 677 (1972).

(2) Portions of this work have appeared as preliminary communications: J. R. Scheffer and R. A. Wostradowski, *Chem. Commun.*, 144 (1971); J. R. Scheffer, R. A. Wostradowski, and K. C. Dooley, *ibid.*, 1217 (1971).

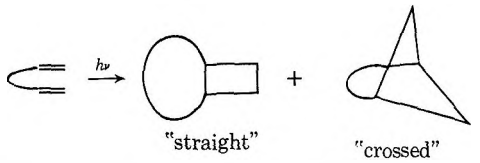
(3) National Research Council Predoctoral Fellow, 1968–1971.

(4) W. L. Dilling, *Chem. Rev.*, **66**, 373 (1966). For two key references not included in this review, see R. Srinivasan and K. H. Carlough, *J. Amer. Chem. Soc.*, **89**, 4932 (1967); R. S. H. Liu and G. S. Hammond, *ibid.*, **89**, 4936 (1967).

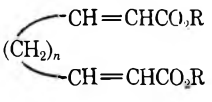
(5) H. E. Zimmerman and P. S. Mariano, *ibid.*, **91**, 1718 (1969).

(6) In addition, substituted 1,5 dienes are occasionally observed to undergo 1,3-allyl shifts from their singlet excited states. For examples, see R. C. Cookson and J. E. Kemp, *Chem. Commun.*, 385 (1971), and references therein.

basic classes of photoproducts, namely, those formed as a result of "straight" cycloaddition and those derived from "crossed" cyclization.



We have been engaged in a systematic study of this class of reactions to identify those structural features in the starting dienes that are important in determining which mode of cycloaddition will predominate under a standard set of photolysis conditions. For our initial efforts in this area we have chosen to investigate the photochemistry of the homologous series **1** in which n, the number of methylene groups separating the two double bonds, has been varied from 2 to 6.

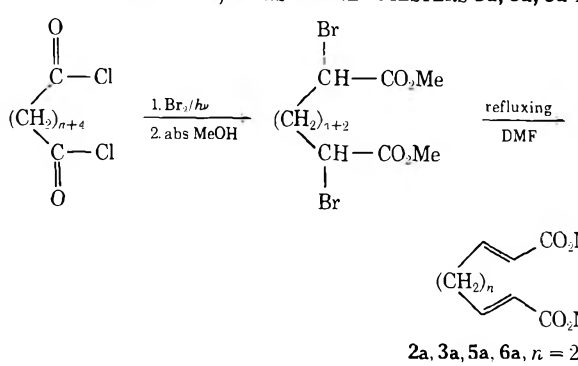


1, $n = 2, 3, 4, 5, 6$

In addition to allowing a study of the effect of double-bond separation on cycloaddition, the system **1** has the added advantages of (a) the existence of cis,cis, cis,-trans, and trans,trans geometric isomers thereby permitting a study of the effect of double-bond geometry on the cyclizations, (b) identical double-bond substituents in every case, a factor which eliminates possible ambiguities which might arise from differing intermediate biradical stabilization energies, (c) a readily accessible uv absorption region for direct irradiations and a triplet energy which is sufficiently low to permit the use of common triplet energy sensitizers, and (d) ease of synthesis and product characterization. This paper reports on the photochemistry of the diene diesters **2**, **3**, **5**, and **6** (n = 2, 3, 5, and 6, respectively); the n = 4 case has been the subject of a previous report.[7]

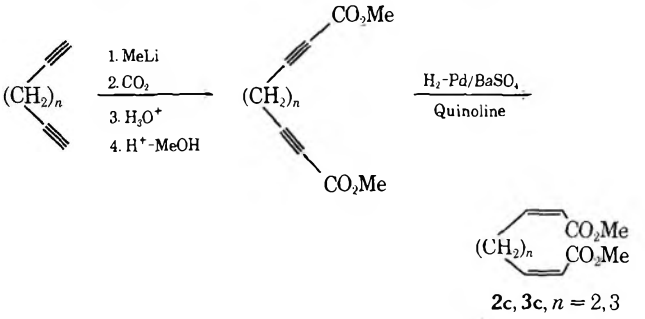
Synthesis of Starting Materials and General Procedures.—The trans,trans diene–diesters **2a**, **3a**, **5a**, and **6a** were synthesized by the general procedures of Luttringhaus and Merz[8] and Anderson, Baizer, and Petrovitch[9] as shown in Scheme I. This procedure also gave small amounts (<20%) of the corresponding cis,trans isomers **2b**, **3b**, **5b**, and **6b** which could be isolated using preparative vapor phase chromatography. They could also be obtained by the triplet-sensitized photoisomerization (see later) of the corresponding trans,trans isomers followed by preparative vpc. This photoequilibration method, while useful for the preparation of the cis,trans isomers, gave smaller amounts of the cis,cis species. The cis,cis compounds **5c** and **6c** (n = 5 and 6) *could* be isolated in useful amounts through vpc, but, in the cases of the cis,cis isomers **2c** and **3c**, it was necessary, owing to overlapping vpc peaks, to resort to an independent stereoselective synthesis. This was accomplished as shown in Scheme II.

SCHEME I
SYNTHESES OF TRANS,TRANS DIENE–DIESTERS **2a**, **3a**, **5a** AND **6a**



2a, **3a**, **5a**, **6a**, $n = 2, 3, 5, 6$

SCHEME II
SYNTHESIS OF CIS,CIS DIENE–DIESTERS **2c** AND **3c**



2c, **3c**, $n = 2, 3$

All new compounds described gave satisfactory elemental analyses and exhibited spectral characteristics completely in accord with their proposed structures.

The general procedures followed in the photolysis of the diene diester systems **2**, **3**, **5**, and **6** were the following. Direct irradiations were conducted in methanol or hexane at a concentration of 0.1–0.2% using a 450-W Hanovia lamp and a Vycor filter (transmitting λ >220 nm). Sensitized photolyses were performed in the same concentration range in acetone as the solvent and triplet-energy sensitizer using the same lamp equipped with a Corex filter (transmitting λ >260 nm); >98% of the light was absorbed by the acetone under these conditions. For each of the diene systems **2**, **3**, **5**, and **6**, all three geometric isomers were irradiated. Each photolysis was monitored at suitable intervals by quantitative vpc and plots of the various photoproduct percentages as a function of time constructed.

Results

Photolyses in Acetone. Irradiation of 2a–2c.—The results of the photolysis of dimethyl *trans,trans*-octa-2,6-diene-1,8-dioate (**2a**) in acetone are shown in Scheme III. Thus, as indicated by vpc, the reaction was one of the disappearance of **2a**, the formation and decay of the cis,trans and cis,cis isomers **2b** and **2c**, and, at a similar rate, the buildup of the internally cyclized products **7** and **8**. After 16–20 hr, depending on the starting diene, none of the diene–diesters **2a–c** remained, and the photostable cycloadducts **7** and **8** were present in the ratio 65:35 **7**:**8** in ~65% yield. A typical plot of the photoisomer percentages as a function of time is shown in Figure 1A.

Photolysis of the cis,trans and cis,cis dienes **2b** and **2c** gave results essentially identical with the results described above. Both **2b** and **2c** gave **7**:**8** ratios of 65:35. The photoproduct time dependence plots for

(7) J. R. Scheffer and B. A. Boire, *J. Amer Chem. Soc.*, **93**, 5490 (1971).
(8) A. Luttringhaus and H. Merz, *Arch. Pharm.*, **293**, 881 (1960).
(9) J. D. Anderson, M. M. Baizer, and J. P. Petrovich, *J. Org. Chem.*, **31**, 3890 (1966).

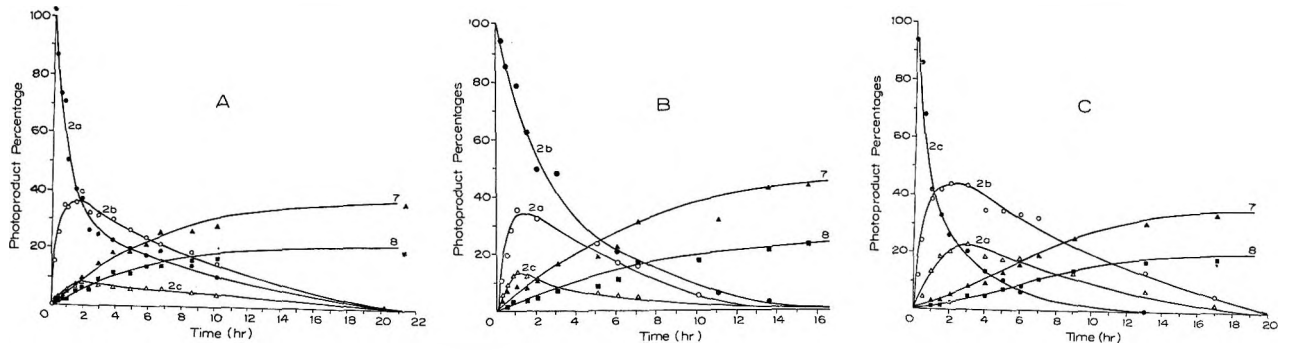


Figure 1.—Photoproduct percentages *vs.* time plots for the photolysis of (A) trans, trans diene–diester **2a**, (B) cis,trans diene–diester **2b**, and (C) cis,cis diene–diester **2c**.

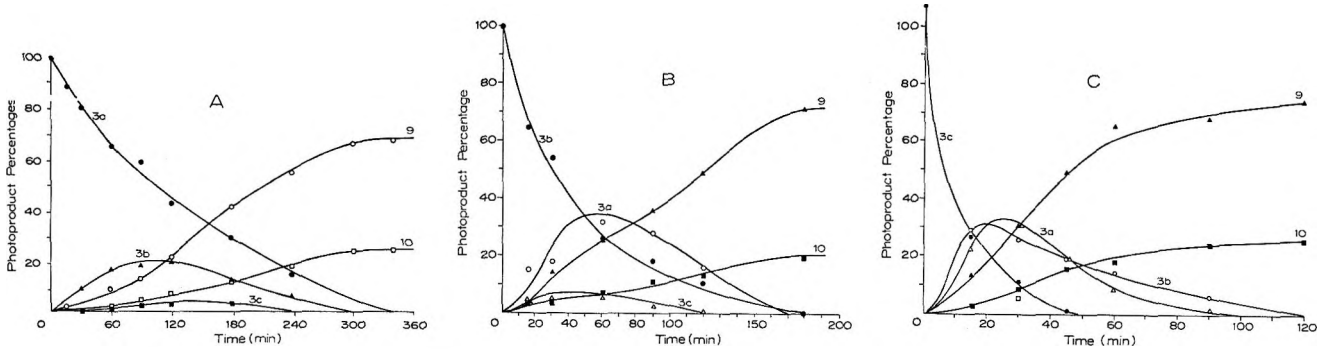
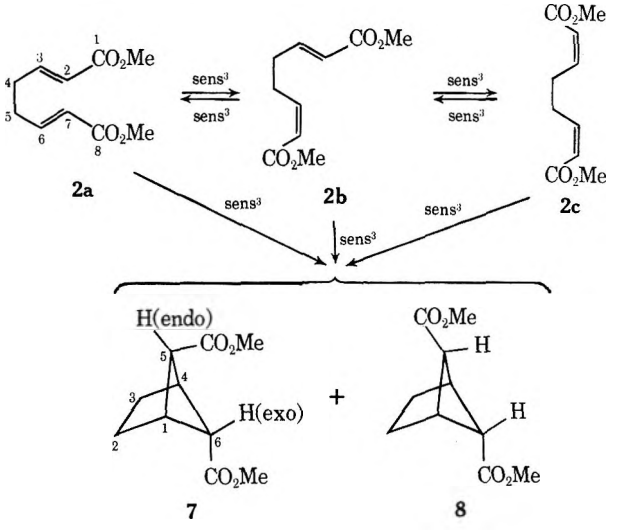


Figure 2.—Photoproduct percentages *vs.* time plots for the photolysis of (A) trans,trans diene–diester **3a**, (B) cis,trans diene–diester **3b**, and (C) cis,cis diene–diester **3c**.

SCHEME III
ACETONE-SENSITIZED PHOTOLYSIS OF DIENE–DIESTERS **2a–2c**



the irradiations of **2b** and **2c** are shown in Figures. 1B and 1C, respectively.

Photoisomers **7** and **8** were easily separable by vpc. Each was shown to be isomeric with starting material by elemental analysis and mass spectrometry. A strong indication that photoproducts **7** and **8** were the result of "crossed" [2 + 2] cycloaddition came from the observation that their melting points (65–66 and 83–85°, respectively) differed from the melting points of the three known[10] stereoisomeric dimethyl bicyclo-[2.2.0]hexane-2,3-dicarboxylates. The final structure assignments for **7** and **8** were made on the basis of their 100-MHz nmr spectra; neither showed signals attributable to vinyl hydrogens. For **7**, the nmr (CCl_4) showed τ 8.27 (m, 4, C_2 and C_3 CH_2), 7.96 (s, 1, C_5 *endo*-CH), 7.02 (d, 2, J = 3 Hz, C_1 and C_4 CH), 6.75 (m, 1, C_6 *exo*-CH deshielded by C_5 *exo*-CO_2Me), 6.40 (s, 3, C_6 *endo*-CO_2Me), and 6.32 (s, 3, C_5 *exo*-CO_2Me). Photoisomer **8** exhibited the following nmr in CCl_4: τ 8.32 (s, 4, C_2 and C_3 CH_2), 7.76 (t, 2, J = 2.5 Hz, C_5 and C_6 *exo*-CH), 7.11 (t, 2, J = 2.5 Hz, C_1 and C_4 CH), and 6.42 (s, 6, *endo*-CO_2Me). Structure **8** for the symmetrical (C_{2v}) cycloadduct is preferred to the alternative symmetrical structure in which the ester groups are both exo since (a) the experimental coupling $J_{1,6}$ = $J_{4,6}$ = $J_{1,5}$ = $J_{4,5}$ = 2.5 Hz in **8** is typical of exo proton–bridgehead coupling in bicyclo[2.1.1]hexane systems;[11] endo proton–bridgehead proton coupling in bicyclo-[2.1.1]hexane systems is zero[11] as typified in adduct **7** ($J_{1,5}$ = $J_{4,5}$ = 0 Hz, causing the C_5 endo proton to appear as a singlet), and (b) the equivalent C_5 and C_6 protons of the symmetrical photoproduct are likely to be exo since they appear at lower field (τ 7.76) than would be expected if they were endo. For example, the endo proton in **7** appears at τ 7.96.

Attempted epimerization of either **7** or **8** under a variety of conditions was unsuccessful. Similar behavior has been observed for the methyl bicyclo[2.1.1]-hexane-5-carboxylate system.[12]

Photolysis of 3a–3c in Acetone.—The three geometric isomers of dimethyl nona-2,7-diene-1,9-dioate (**3a–3c**) were irradiated in acetone as previously decsribed. In each case the reaction was one of simultaneous cis,trans isomerization and intramolecular [2 + 2] cyclization. Eventually (2–6 hr depending on the geometry of the starting diene; see Figure 2), the acyclic dienes were

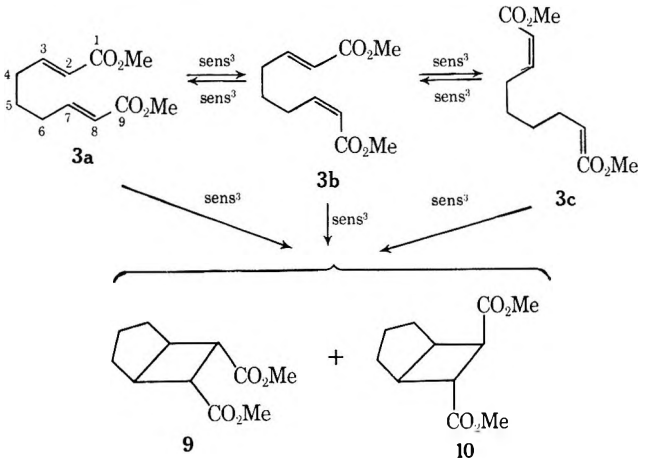
(10) L. A. Paquette and J. A. Schwartz, *J. Amer. Chem. Soc.*, **92**, 3215 (1970).

(11) (a) J. Meinwald and A. Lewis, *ibid.*, **83**, 2769 (1961); (b) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *ibid.*, **84**, 1594 (1962).

(12) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *ibid.*, **83**, 3993 (1961).

totally consumed. In each photolysis the final product mixture consisted of the two internally cyclized adducts **9** and **10** in a ratio of 3:1 in an overall yield of ~90%. These results are shown schematically in Scheme IV and quantitatively in Figure 2.

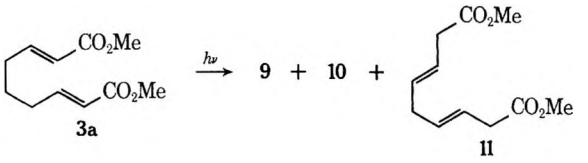
SCHEME IV
ACETONE-SENSITIZED PHOTOLYSIS OF DIENE–DIESTERS **3a–3c**



Photoproducts **9** and **10** were separated by means of preparative glc and identified by hydrolysis to the known[13] dicarboxylic acids as well as by direct comparison with authentic samples independently prepared by the photochemical addition of dimethyl maleate to cyclopentene.[13]

Photolysis of 5a–c and 6a–c in Acetone.—The trans,-trans, cis,trans, and cis,cis 1,8 diene–diesters **5a**, **5b**, and **5c**, respectively, failed to undergo cyclization upon irradiation in acetone. Not surprisingly, similar behavior was observed for the corresponding 1,9 diene–diesters **6a**, **6b**, and **6c**. In all six cases, the sole reaction observed was cis,trans isomerization resulting in each instance in a photostationary trans,trans:cis,trans:cis,-cis ratio of 1.5:2.5:1. Interestingly, this ratio differs from the ratio found for the corresponding 1,7 diene–diesters.[7] In this case, photolysis in acetone resulted in a trans,trans:cis,trans:cis,cis ratio of 3.8:3.5:1 which was formed prior to (and maintained during) straight [2 + 2] cycloaddition. As can be seen from inspection of Figures 1 and 2, a constant ratio of geometric isomers is not formed in the acetone-sensitized photolysis of the 1,5- and 1,6-diene–diester systems **2** and **3**. Finally, these results indicate that the limit of double-bond separation which will lead to internal cyclization has been reached at $n = 4$, at least for the homologous series **1**.

Direct Photolyses.—Photolysis of either dimethyl *trans,trans*-octa-2,6-diene-1,8-dioate (**2a**) or dimethyl *trans,trans*-nona-2,7-diene-1,9-dioate (**3a**) in methanol or petroleum ether led to geometrical isomerism, to internal cyclization, and to a process not observed in the sensitized irradiations, namely α,β to β,γ double-bond migration. For example, the photolysis mixture from the direct irradiation of **3a** in methanol consisted of ~60% adducts **9** and **10** (ratio of 3:1) and 40% dimethyl *trans,trans*-nona-3,6-diene-1,9-dioate (**11**), the double deconjugation product. Photolysis of **3a** in



hexane led to similar results. In this case the photoisomer mixture consisted of compounds **9**, **10**, and **11** in the ratio of 2:1:3.2. The structure of **11** was proved by spectral data, in particular by nmr using the shift reagent Eu(DPM)$_3$ (see Experimental Section). The preference, in the case of **3a**, for formation of trans-disubstituted β,γ double bonds has been observed in one other similar instance and an explanation advanced.[7] The photochemical conversion of α,β-unsaturated esters possessing γ hydrogen atoms to their β,γ congeners is a well-documented process.[14]

Direct irradiation of dimethyl *trans,trans*-octa-2,6-diene-1,8-dioate (**2a**) in methanol led to a mixture of at least six new transient or photostable products. Four of these were identified as the geometric isomers **2b** and **2c** (transient) and the cycloadducts **7** and **8** (photostable). These latter were formed in ~20% yield in the ratio 73:27, a ratio similar to that observed in the sensitized photolyses of **2a–c**. Examination of the spectra of the remaining two photoproducts (separated by glc) revealed that they were most likely geometric isomers of the 1,3 dienes resulting from double deconjugation.

The use of piperylene as a triplet-energy quencher in the direct irradiation of trans,trans 1,6 diene **3a** in hexane led, in addition to cis,trans isomerization and α,β to β,γ double-bond deconjugation, to a final 2:1 **9**:**10** ratio. This is identical with the ratio obtained in hexane in the absence of piperylene and close to the 3:1 ratio observed in acetone and methanol. It thus appears that internal cyclization can occur in the case of diene–diester **3a** from both the singlet and triplet manifolds depending on the reaction conditions and that the ratio of the cycloaddition products, but not their stereochemistry or the direction (*i.e.*, straight or crossed) of bonding, may differ slightly in each case. Finally, it should be pointed out that unsaturated ester deconjugation is characteristically a singlet-state reaction.[7,14,15]

Discussion

The acetone-sensitized internal cyclizations described in this paper undoubtedly occur in a stepwise fashion involving the formation of one or more reactive intermediates most easily pictured as being 1,4 diradical like in nature. This conclusion is based on two observations: (1) the exclusively triplet nature of the cycloadditions, and (2) the product stereochemistries. In regard to this latter point, if the cyclizations were completely concerted one would expect,[16] for example, that photolysis of the trans,trans 1,5 diene **2a** would lead to the exo,exo cycloadduct **14**. The fact that this product was *not* observed even though cyclization and geometric isomerism are taking place concurrently

(13) P. de Mayo, S. T. Reid, and R. W. Yip, *Can. J. Chem.*, **42**, 2828 (1964).

(14) (a) J. A. Barltrop and J. Wills, *Tetrahedron Lett.*, 4987 (1968); (b) M. J. Jorgenson and L. Gundel, *ibid.*, 4991 (1968).

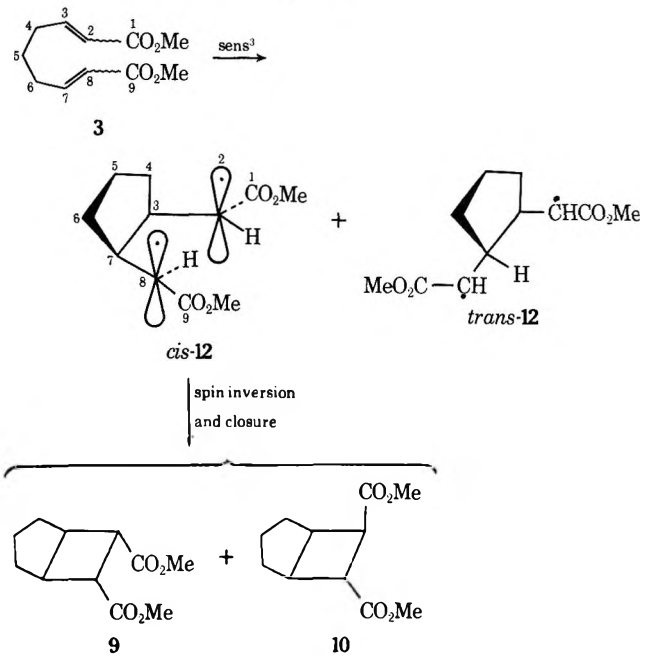
(15) See, however, P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967).

(16) G. M. Whitesides, G. L. Goe, and A. C. Cope, *J. Amer. Chem. Soc.*, **91**, 2608 (1969).

(*cf.* Figure 1A) rules out complete concertedness. Similar arguments and conclusions can be made for the other cyclizations described in this work. In fact, nonconcertedness appears to be a general feature of internal [2 + 2] cycloadditions.[4,7]

Leaving aside for the moment the question of the *direction* of cyclization (*i.e.*, straight *vs.* crossed), it is next pertinent to address ourselves to the question of what factors govern the closure stereochemistries of the intermediate 1,4 diradicals involved. In the 1,6-diene case, if we make the reasonable assumption that initial 3,7-bond formation is favored over initial 2,8-bond formation,[17] two 1,4-diradical intermediates may be produced, *i.e.*, *cis*-**12** and *trans*-**12**. While the intermediate *trans*-**12** does not lead to any new photoproducts detectable by glc, the intermediate *cis*-**12** can give three stereoisomeric cis-fused bicyclo[3.2.0]heptanedicarboxylates, only two of which, **9** and **10**, are observed in a ratio of 3:1 (Scheme V). These products must be

SCHEME V



the result of kinetic control in the closure of singlet *cis*-**12** since they are formed in amounts which are in inverse order to their relative thermodynamic stabilities. Thus sealed-tube thermolysis (250°, 24 hr) of either **9** or **10** leads to an equilibrium **9**:**10** ratio of ~1:7 with no other isomeric products being formed. The source of this kinetic control is likely the avoidance of syn nonbonded C_1–C_4 and C_6–C_9 interactions in the transition state for closure of *cis*-**12**. No interactions of this type are involved in the formation of the major photoproduct **9**, one is necessary for the closure to give minor isomer **10**, and two interactions would be present in the closure leading to the third possible (but not observed) cis,syn,cis adduct. The difference in thermodynamic stability between **9** and **10** is thus seen to arise from the presence in **9** (less stable) or absence in **10** (more stable) of vicinal cis ester group interactions. The cis,syn,cis adduct, combining both unfavorable steric effects, was not observed in the equilibration studies.

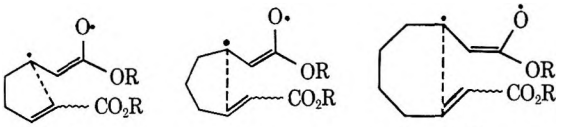
(17) K. Fukui, *Accounts Chem. Res.*, **4**, 57 (1971).

These arguments are supported by the observation[13] that **10**, not **9**, is the major cycloaddition product formed in the dimethyl maleate–cyclopentene photolysis. In this case, the bond joining the ester substituents is present *prior* to closure of the probable diradical intermediate, and the stereochemistry of the closure is governed by the avoidance of vicinal syn ester group interactions thus leading to **10** in preference to **9**.

Unlike the 1,6-diene case described above, initial 2,6- (or 3,7-) bond formation in the 1,5-diene series **2** can lead to isomeric 1,4-diradical intermediates (*cis*- or *trans*-**13**, Scheme VI) *both* of which can close to give stable adducts.

While there is no experimental evidence available on the relative thermodynamic stabilities of adducts **7** and **8** owing to their extreme reluctance to epimerize, there is no reason to expect that the closure step will be reversible, and we are likely dealing with kinetic control of closure in this case as well. Molecular models reveal no marked steric effects which would favor formation of **7** over **8** as is observed experimentally (ratio of 65:35). It may be that this ratio is partially governed by statistical factors, photoproduct **7** being capable of being formed from both diradical intermediates while **8** can be formed from only one. In any case, the failure to observe adduct **14** is not surprising since models reveal that its formation would involve severe nonbonded ester group interactions.

Straight *vs.* Crossed Bonding.—The remarkably general finding that both cyclic and acyclic 1,5 dienes undergo preferential "crossed" photochemical cyclization while 1,6 dienes cycloadd in a predominantly "straight" manner has been noted previously.[4,7] The results described in this paper are seen to be no exception. However, it still remains to explain these results in a satisfactory manner. A rationalization which has ground-state analogy involves the reasonable assumption that initial bond formation originates from triplet excited states (intramolecular exciplexes?) which can be represented in valence bond terms as **15**, **16**, and **17**

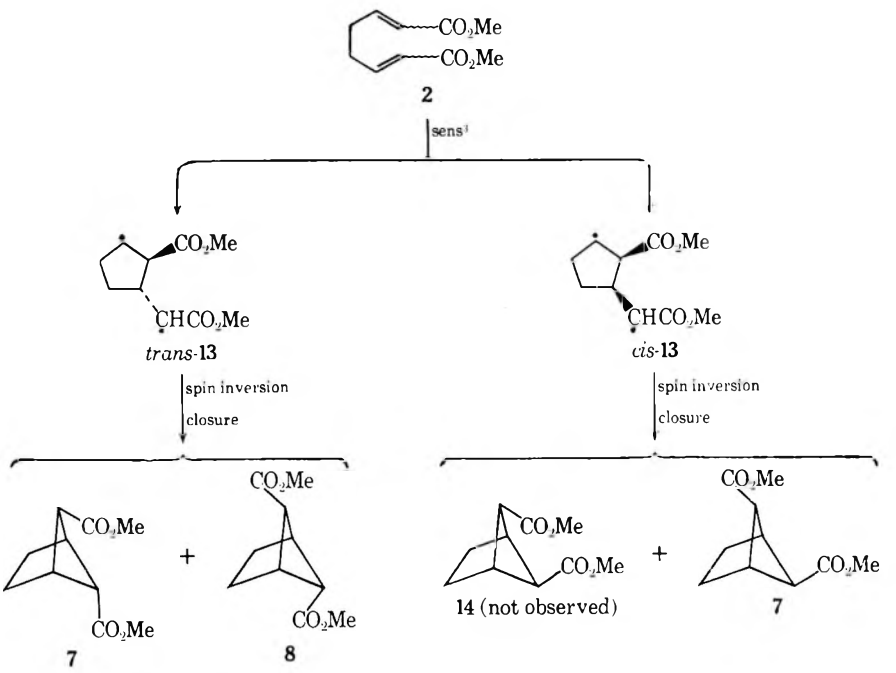


(n = 2, 3, and 4, respectively).[18] The direction of initial bond formation then becomes a question of which end of the ground-state double bond the radical center on the β carbon atom prefers to bond to in each case.[19] The experimentally observed directions are shown by the dotted lines in structures **15**–**17**. Thus five-membered formation is preferred to both four-membered- and six-membered-ring formation (*cf.* **15** and **16**), and six-membered-ring formation predominates over seven (*cf.* **17**).[7] This is exactly the pattern which has been found for the ground-state cyclizations of the 1-penten-5-yl, 1-hexen-6-yl, and 1-hepten-7-yl

(18) These excited states are presumably n → π^* in nature and are represented as having diradical character in analogy to α,β-unsaturated ketone n → π^* triplets. See H. E. Zimmerman, R. W. Binkley, J. J. McCullough, and G. A. Zimmerman, *J. Amer. Chem. Soc.*, **89**, 6589 (1967).

(19) Initial bonding from the β carbon of an excited α,β-unsaturated carbonyl compound to a ground-state olefin has recently been demonstrated. See W. L. Dilling, T. E. Tabor, F. P. Boer, and P. P. North, *ibid.*, **92**, 1399 (1970).

SCHEME VI



free radicals, respectively.[20] These cyclizations have been interpreted in terms of strain and entropy effects, and, while readily understandable in the 1-penten-5-yl and 1-hepten-7-yl cases, these effects do not clearly predict the preferential formation of the cyclopentylmethyl radical in the closure of the 1-hexen-6-yl radical. To the best of our knowledge, this dilemma has not yet been resolved.

Finally, the possibility that the direction of initial bond formation in the photochemical cyclizations of nonconjugated dienes may be the result of orbital symmetry effects should not be overlooked. A rationalization in these terms of the exclusive straight photocyclization observed in the case of the 1,7-diene system **1** ($n = 4$) has been presented[7] and may be applied without modification to the cyclization of the 1,6-diene system **3**. The situation with regard to the 1,5-diene–diester system **2** is more complex, and a discussion of these complexities will be deferred until our photoelectron spectroscopic studies on these and related systems are complete.

Experimental Section[21]

Synthesis of Trans,trans Diene–Diesters 2a, 3a, 5a, and 6a.—These materials were prepared by bromination of the di(acid chlorides) of the appropriate α,ω-dicarboxylic acids (Eastman) followed by treatment with methanol[8] and dehydrobromination in refluxing dimethylformamide.[9] The following procedure for the preparation of dimethyl *trans,trans*-octa-2,6-diene-1,8-dioate (**2a**) is typical.

A mixture of suberic acid (technical grade, 25 g, 0.14 mol) and thionyl chloride (43 g, 0.33 mol) in a flame-dried 1-l. round-bottom flask equipped with a thermometer, condenser, and dropping funnel was heated at 70–85° for 1.5 hr. Heating was discontinued and bromine (52 g, 0.33 mol) was added dropwise to the now clear yellow solution while irradiating the entire apparatus with a 275-W sun lamp. After addition was complete (45 min), the dark red reaction mixture was heated at 85° for 6 hr and cooled in an ice bath, and 40 ml of absolute methanol was carefully added followed by 50 ml of saturated sodium bicarbonate solution. After stirring overnight, the reaction mixture was extracted with 2 × 50 ml of chloroform. The combined chloroform extracts were washed with water (2 × 50 ml), saturated sodium bicarbonate (2 × 50 ml), saturated sodium chloride (2 × 50 ml), and saturated sodium thiosulfate (2 × 50 ml) and dried ($MgSO_4$). Removal of chloroform *in vacuo* gave 51 g of pale yellow oil which was shown to be dimethyl 2,7-dibromosuberate from the following spectral data: ir (neat) 5.75 (C=O) μ; nmr (CCl_4) τ 5.84 (t, 2, J = 7 Hz, $CHBrCO_2Me$), 6.25 (s, 6, CO_2Me), 8.0 (m, 4, CH_2CHBr), 8.5 (m, 4). This material was refluxed in dimethylformamide (100 ml) for 4 hr. The dark reaction mixture was cooled, diluted with 100 ml of water, and extracted with 2 × 75 ml of ether. The combined ether extracts were washed as above and dried over $MgSO_4$. Removal of ether *in vacuo* gave 25 g (90%) of pale yellow oil. Vapor phase chromatographic analysis of this material (5 ft × 0.25 in. stainlesss steel column packed with 20% DEGS on 60–80 Chromosorb W) at 160° and a flow rate of 120 ml/min showed that this mixture was composed of trans,trans diene–diester **2a** (retention time 14 min) and cis,trans isomer **2b** (retention time 8 min) in a ratio of 5:1. Distillation yielded pure **2a**, a colorless liquid, bp 115–120° (0.01 mm), which exhibited the following spectral data:[23] uv max (MeOH) 228 nm; ir (neat) 5.79 (C=O), 6.03, 10.2 μ; nmr (CCl_4) τ 3.10 (d of t, 2, $J_{2,3} = J_{6,7} = 15.5$, $J_{3,4} = J_{5,6} = 7$ Hz, *trans*-CH=CHCO$_2$Me), 4.20 (d, 2, $J_{2,3} = J_{6,7} = 15.5$ Hz, *trans*-CH=CHCO$_2$Me), 6.30 (s, 6, CO_2Me), 7.60 (m, 4, methylenes).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.61; H, 7.07. Found: C, 60.60; H, 6.91.

Trans,trans diene–diesters **3a**,**5a**, and **6a**, all colorless liquids were prepared in an analogous manner and were characterized on the basis of the following information.

(20) M. Julia, *Pure Appl. Chem.*, **16**, 167 (1967), and references cited therein.

(21) Ir spectra were obtained, unless otherwise stated, on neat liquid samples between sodium chloride plates with a Perkin-Elmer 137 spectrophotometer. Nmr spectra were determined in carbon tetrachloride solution with either a Varian T-60, HA-100, or XL-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained on a direct-inlet AEI MS-9 instrument at 70 eV, and uv spectra were recorded on a Unicam SP-820 spectrophotometer. Melting points were taken on either a Thomas-Hoover capillary apparatus or a Fisher-Johns hot stage apparatus and are uncorrected. Elemental analyses were performed by the departmental microanalyst, Mr. P. Borda. Vpc was carried out on a Varian-Aerograph 90-P3 instrument using helium as the carrier gas. The most useful columns for separating the compounds described in this work were found to be those packed with DEGS on Chromosorb W. All solvents were distilled, the methanol being distilled from a sclution of sodium methoxide and dimethyl phthalate,[22] and the tetrahydrofuran being distilled from sodium–potassium alloy. All photolysis solutions were degassed prior to irradiation with Canadian Liquid Air argon containing <5 ppm of oxygen.

(22) E. L. Smith, *J. Chem. Soc.*, 1288 (1927).

(23) This compound has been very briefly described in ref 10.

Dimethyl *trans,trans*-nona-2,7-diene-1,9-dioate (**3a**): uv max (MeOH) 215 nm; ir (neat) 5.79 (C=O), 6.02, 10.1 μ; nmr (CCl_4) τ 3.15 (d of t, 2, $J_{2,3} = J_{7,8} = 16$, $J_{3,4} = J_{6,7} = 7$ Hz, *trans*-CH=CHCO$_2$Me), 4.30 (d, 2, $J_{2,3} = J_{7,8} = 16$ Hz, *trans*-CH=CHCO$_2$Me), 6.35 (s, 6, CO$_2$Me), 7.77 (m, 4, allylic CH$_2$), 8.30 (m, 2).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 62.15; H, 7.75.

Dimethyl *trans,trans*-undeca-2,9-diene-1,11-dioate (**5a**): ir (neat) 5.80 (C=O), 6.01, 10.2 μ; nmr (CCl_4) τ 3.13 (d of t, 2, $J_{2,3} = J_{9,10} = 16$, $J_{3,4} = J_{8,9} = 6.5$ Hz, *trans*-CH=CHCO$_2$Me), 4.25 (d, 2, $J_{2,3} = J_{9,10} = 16$ Hz, *trans*-CH=CHCO$_2$Me), 6.32 (s, 6, CO$_2$Me), 7.83 (m, 4, allylic CH$_2$), 8.58 (m, 6).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 65.00; H, 8.33. Found: C, 64.72; H, 8.27.

Dimethyl *trans,trans*-dodeca-2,10-diene-1,12-dioate (**6a**): ir (neat) 5.80 (C=O), 6.04, 10.2 μ; nmr (CCl_4) τ 3.15 (d of t, 2, $J_{2,3} = J_{10,11} = 16$, $J_{3,4} = J_{9,10} = 6.5$ Hz, *trans*-CH=CHCO$_2$Me), 4.30 (d, 2, $J_{2,3} = J_{10,11} = 16$ Hz, *trans*-CH=CHCO$_2$Me), 6.35 (s, 6, CO$_2$Me), 7.85 (m, 4, allylic CH$_2$), 8.58 (m, 8).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.14; H, 8.66. Found: C, 65.89; H, 8.84.

Preparation of Cis,trans Diene–Diesters 2b, 3b, 5b, and 6b.—These compounds were obtained by preparative vpc of the crude reaction mixtures from dehydrohalogenation of the corresponding α-bromo esters and by preparative vpc of the mixtures obtained from brief triplet-sensitized (acetone) irradiation of the corresponding trans,trans compounds. All were colorless liquids; they were characterized on the basis of the following data.

Dimethyl *cis,trans*-octa-2,6-diene-1,8-dioate (**2b**):[23] uv max (MeOH) 233 nm; ir (neat) 5.79 (C=O), 6.03, 10.1, 12.2 μ; nmr (CCl_4) τ 3.10 (d of t, 1, $J_{2,3} = 15.5$, $J_{3,4} = 7$ Hz, *trans*-CH=CHCO$_2$Me), 3.81 (d of t, 1, $J_{6,7} = 11.2$, $J_{5,6} = 7$ Hz, *cis*-CH=CHCO$_2$Me), 4.19 (d, 1, $J_{2,3} = 15.5$ Hz, *trans*-CH=CHCO$_2$Me), 4.23 (d, 1, $J_{6,7} = 11.2$ Hz, *cis*-CH=CHCO$_2$Me), 6.32 (s, 6, CO$_2$Me), 7.20 (m, 2, cis allylic CH$_2$), 7.60 (m, 2, trans allylic CH$_2$).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.61; H, 7.07. Found: C, 60.60; H, 6.69.

Dimethyl *cis,trans*-nona-2,7-diene-1,9-dioate (**3b**): uv max (MeOH) 216 nm; ir (neat) 5.79 (C=O), 6.02, 10.2, 11.8 μ; nmr (CCl_4) τ 3.15 (d of t, 1, $J_{2,3} = 16$, $J_{3,4} = 7$ Hz, *trans*-CH=CHCO$_2$Me), 3.88 (d of t, 1, $J_{7,8} = 12$, $J_{6,7} = 7$ Hz, *cis*-CH=CHCO$_2$Me), 4.26 (d, 1, $J_{2,3} = 16$ Hz, *trans*-CH=CHCO$_2$Me), 4.30 (d, 1, $J_{7,8} = 12$ Hz, *cis*-CH=CHCO$_2$Me), 6.37 (s, 6, CO$_2$Me), 7.32 (m, 2, cis allylic CH$_2$), 7.75 (m, 2, trans allylic CH$_2$), 8.34 (m, 2).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 62.10; H, 7.70.

Dimethyl *cis,trans*-undeca-2,9-diene-1,11-dioate (**5b**): ir (neat) 5.80 (C=O), 6.03, 10.2, 12.2 μ; nmr (CCl_4) τ 3.13 (d of t, 1, $J_{2,3} = 16$, $J_{3,4} = 6.5$ Hz, *trans*-CH=CHCO$_2$Me), 3.83 (d of t, 1, $J_{9,10} = 11.5$, $J_{8,9} = 6.5$ Hz, *cis*-CH=CHCO$_2$Me), 4.28 (d, 1, $J_{2,3} = 16$ Hz, *trans*-CH=CHCO$_2$Me), 4.30 (d, 1, $J_{9,10} = 11.5$ Hz, *cis*-CH=CHCO$_2$Me), 6.35 (s, 6, CO$_2$Me), 7.37 (m, 2, cis allylic CH$_2$), 7.86 (m, 2, trans allylic CH$_2$), 8.58 (m, 6).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 65.00; H, 8.33. Found: C, 64.79; H, 8.34.

Dimethyl *cis,trans*-dodeca-2,10-diene-1,12-dioate (**6b**): ir (neat) 5.80 (C=O), 6.06, 10.2, 12.2 μ; nmr (CCl_4) τ 3.15 (d of t, 1, $J_{2,3} = 16$, $J_{3,4} = 6.5$ Hz, *trans*-CH=CHCO$_2$Me), 3.90 (d of t, 1, $J_{10,11} = 11.5$, $J_{9,10} = 6.5$ Hz, *cis*-CH=CHCO$_2$Me), 4.28 (d, 1, $J_{2,3} = 16$ Hz, *trans*-CH=CHCO$_2$Me), 4.32 (d, 1, $J_{10,11} = 11.5$ Hz, *cis*-CH=CHCO$_2$Me), 6.37 (s, 6, CO$_2$Me), 7.36 (m, 2, cis allylic CH$_2$), 7.79 (m, 2, trans allylic CH$_2$), 8.59 (m, 8).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.14; H, 8.66. Found: C, 66.00; H, 8.70.

Preparation of Cis,cis Diene–Diesters 2c, 3c, 5c, and 6c.—Diene–diesters **5c** and **6c** were obtained by preparative vpc of the photostationary mixtures obtained from acetone-sensitized irradiation of **5a** and **6a**, respectively. Each mixture contained ~12% of the desired cis,cis isomer at the photostationary state. Compounds **5c** and **6c** were both colorless liquids and were characterized on the basis of the following information.

Dimethyl *cis,cis*-undeca-2,9-diene-1,11-dioate (**5c**): ir (neat) 5.80 (C=O), 6.08, and 12.2 μ; nmr (CCl_4) τ 3.80 (d of t, 2, $J_{2,3} = J_{9,10} = 11.5$, $J_{3,4} = J_{8,9} = 6.5$ Hz, *cis*-CH=CHCO$_2$Me), 4.50 (d, 2, $J_{2,3} = J_{9,10} = 11.5$ Hz, *cis*-CH=CHCO$_2$Me), 6.35 (s, 6, CO$_2$Me), 7.37 (m, 4, allylic CH$_2$), 8.58 (m, 6).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 65.00; H, 8.33. Found: C, 64.76; H, 8.51.

Dimethyl *cis,cis*-dodeca-2,10-diene-1,12-dioate (**6c**): ir (neat) 5.80 (C=O), 6.09, 12.2 μ; nmr (CCl_4) τ 3.90 (d of t, 2, $J_{2,3} = J_{10,11} = 12$, $J_{3,4} = J_{9,10} = 7$ Hz, *cis*-CH=CHCO$_2$Me), 4.33 (d, 2, $J_{2,3} = J_{10,11} = 12$ Hz, *cis*-CH=CHCO$_2$Me), 6.37 (s, 6, CO$_2$Me), 7.37 (m, 4, allylic CH$_2$), 8.58 (m, 8).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.14; H, 8.66. Found: C, 66.08; H, 8.70.

Dimethyl *cis,cis*-octa-2,6-diene-1,8-dioate (**2c**)[23] was prepared by carbonation of the di(lithium salt) of 1,5-hexadiyne followed by esterification and hydrogenation. The following procedure is typical.

A solution of 1,5-hexadiyne (3.9 g, 50 mmol) in 500 ml of dry THF was cooled to 0° in a flame-dried 1-l. flask equipped with a dropping funnel and an overhead stirrer. Methyllithium (60 ml, 2 *M* in ether, 0.12 mol) was added at 0° during 1 hr with rapid stirring followed by stirring for an additional 2 hr at 0°. Next, excess dry CO_2 was bubbled through the reaction mixture for a period of 4 hr at 0°; THF was added periodically to replace that which had evaporated. The resulting heavy white slurry was then diluted with 400 ml of 0.6 *M* HCl and the subsequent clear yellow solution concentrated *in vacuo* to remove most of the THF. The aqueous solution was continuously extracted with 400 ml of ether for 24 hr and the resulting ether layer dried ($MgSO_4$) and concentrated *in vacuo* to yield 10 g of yellow oil. This material was dissolved in 250 ml of methanol containing 4 ml of concentrated sulfuric acid and refluxed for 6 hr. After neutralization, methanol was removed *in vacuo* to give 4.5 g of yellow solid, mp 51–55°. Recrystallization from ether–hexane gave 4.05 g (45%) of colorless crystals, mp 65–65.5°. The following data supports the structure dimethyl octa-2,6-diyne-1,8-dioate:[23] ir ($CHCl_3$) 4.44 (C≡C), 5.81 (C=O), 6.99, 7.79, 9.25 μ; nmr ($CDCl_3$) τ 6.32 (s, 6, CO$_2$Me), 7.40 (s, 4); mass spectrum parent (70 eV) *m/e* 194.

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.86; H, 5.15. Found: C, 61.83; H, 5.13.

Dimethyl octa-2,6-diyne-1,8-dioate (0.95 g, 4.9 mmol) and a mixture of 40 mg of synthetic quinoline and 40 mg of 5% palladium on barium sulfate in 20 ml of methanol was hydrogenated at atmospheric pressure. The uptake of hydrogen after 15 min was 250 ml (calculated 222 ml). Removal of methanol *in vacuo* followed by silica gel column chromatography to remove quinoline gave 0.90 g (92%) of a 9:1 mixture of **2c**:**2b** as determined by vpc. Pure dimethyl *cis,cis*-octa-2,6-diene-1,8-dioate (**2c**)[23] was obtained from this mixture by preparative vpc and exhibited the following spectra: uv max (MeOH) 223 nm; ir (neat) 5.79 (C=O), 6.05, 12.1 μ; nmr (CCl_4) τ 3.80 (d of t, 2, $J_{2,3} = J_{6,7} = 11.2$, $J_{3,4} = J_{5,6} = 7$ Hz, *cis*-CH=CHCO$_2$Me), 4.30 (d, 2, $J_{2,3} = J_{6,7} = 11.2$ Hz, cis CH=CHCO$_2$Me), 6.32 (s, 6, CO$_2$Me), 7.2 (m, 4).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.61; H, 7.07. Found: C, 60.40; H, 7.12

Dimethyl *cis,cis*-nona-2,7-diene-1,9-dioate (**3c**) was prepared in an analogous manner from hepta-1,6-diyne. The intermediate diyne–diester in this case was a liquid which showed the following spectra: ir (neat) 4.45 (C≡C), 5.80 (C=O), 6.99, 8.0, 9.26 μ; nmr (CCl_4) τ 6.33 (s, 6, CO$_2$Me), 7.50 (br t, 4, J = 7 Hz, C≡CCH$_2$), 8.12 (m, 2); mass spectrum parent (70 eV) *m/e* 208.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.48; H, 5.79. Found: C, 63.23; H, 6.00.

Hydrogenation and chromatography as before yielded pure **3c**: uv max (MeOH) 216 nm; ir (neat) 5.78 (C=O), 6.04, 12.2 μ; nmr (CCl_4) τ 3.85 (d of t, 2, $J_{2,3} = J_{7,8} = 12$, $J_{3,4} = J_{6,7} = 7$ Hz, *cis*-CH=CHCO$_2$Me), 4.30 (d, 2, $J_{2,3} = J_{7,8} = 12$ Hz, *cis*-CH=CHCO$_2$Me), 6.35 (s, 6, CO$_2$Me), 7.33 (m, 4, allylic CH$_2$), 8.44 (m, 2).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 62.37; H, 7.46.

Acetone-Sensitized Photolysis of 1,5 Diene–Diesters 2a–2c.—The results of photolysis of the trans,trans,cis,trans, and cis,cis diene–diesters **2a**, **2b**, and **2c**, respectively, were essentially identical. Each photolysis resulted in geometric isomerization and "crossed" internal cyclization to give a final product mixture consisting of adducts **7** and **8** in the ratio 65:35. Preparative runs were conducted at a concentration of ~5×10^{-2} *M* in acetone using a water-cooled quartz immersion well apparatus and a Hanovia 450-W type L lamp fitted with a Corex filter; under these conditions complete conversion to **7** and **8** occurred within

2 hr. Small-scale photolyses (photoproduct time dependence studies) were performed in quartz tubes situated externally (~7 cm) to the same lamp, filter, and immersion well apparatus. These analytical runs were carried out at a concentration of ~1 *M* in acetone using either *n*-octadecane or *n*-decanol as vpc internal standards; both internal standards were stable under the reaction conditions. The results of these kinetic runs (two runs per diene) are shown in Figure 1.

The products from each photolysis were isolated by preparative vpc and identified on the basis of their spectra. The structure of photoproduct **7** was deduced to be dimethyl bicyclo[2.1.1]hexane-5-*exo*,6-*endo*-dicarboxylate from the nmr data previously given and from the following information: mp 65–66°; ir (KBr) 5.80 (C=O) μ; mass spectrum parent (70 eV) *m/e* 198.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.07. Found: C, 60.54; H, 7.07.

Photoproduct **8** was shown to be dimethyl bicyclo[2.1.1]-hexane-5-*endo*,6-*endo*-dicarboxylate from the nmr data previously given and on the basis of the following: mp 83–85°; ir (KBr) 5.80 (C=O) μ; mass spectrum parent (70 eV) *m/e* 198.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.07. Found: C, 60.40; H, 7.12.

Acetone-Sensitized Photolysis of 1,6 Diene–Diesters 3a–3c.—The photolyses of diene–diesters **3a–3c** in acetone were carried out exactly as described for the 1,5 dienes **2a–c**. Again the reactions were those of cis,trans isomerization accompanied by internal [2 + 2] cycloaddition to give, in this case, the "straight" cyclized products **9** and **10**. All three 1,6-diene geometric isomers gave, within experimental error, identical 3:1 **9**:**10** mixtures after 2 hr (preparative runs) with no other products detectable by vpc. Small-scale kinetic runs gave the photoproduct time dependence plots shown in Figure 2.

Compound **9** was shown to be dimethyl *cis,anti,cis*-bicyclo-[3.2.0]heptane-2,3-dicarboxylate by comparison of its spectra with that of an authentic sample independently prepared by the photocycloaddition of dimethyl maleate and cyclopentene.[13] Hydrolysis of both gave the corresponding diacid, mp 178–80° (lit.[13] mp 178–179.5°); the mixture melting point was undepressed.

Analogously, photoproduct **10** was shown to be dimethyl *cis,trans*-bicyclo[3.2.0]heptane-2,3-dicarboxylate. Hydrolysis of **10** gave the corresponding diacid, mp 175–76° (lit.[13] mp 175–177°), whose mixture melting point with an authentic sample was, once again, undepressed.

The relative thermodynamic stabilities of photoproducts **9** and **10** were determined by thermal epimerization studies. Sealed-tube thermolysis of either **9** or **10** at 200° for 48 hr in the presence of a trace of water gave an equilibrium mixture of 9:10 of 1:7.4 ± 0.1. The identity of the thermolysis products was authenticated by ir; no other products were detectable by vpc.

Acetone-Sensitized Photolysis of 1,8 Diene–Diesters 5a–c and 1,9 Diene–Diesters 6a–c.—Photolysis of dilute acetone solutions of geometric isomers **5a–c** and their homologs **6a–c** through Corex led only to geometric isomerism. All six compounds were individually irradiated and in each case a photostationary ratio of *trans,trans*:*cis,trans*:*cis,cis* of 32:49:19 (±2%) was attained within 1 hr; prolonged irradiation led to polymer formation.

Direct Irradiation of Dimethyl *trans,trans*-Nona-2,7-diene-1,9-dioate (3a).—Diene–diester **3a** (0.25 g) in 200 ml of anhydrous methanol was irradiated through Vycor and the course of the reaction followed by vpc. Five new peaks in addition to starting material were noted corresponding to photoproducts **3b**, **3c**, **9**, **10**, and **11**. The latter three were the only detectable products left after 1.5 hr; the final ratio was 2.9:1:3.4 **9**:**10**:**11**.

Compounds **3b**, **3c**, **9**, and **10** were isolated by vpc and identified by spectral comparison with samples obtained previously. Photoproduct **11** was obtained by preparative vpc and further purified by Kugelrohr distillation. It was identified as dimethyl *trans,trans*-nona-3,6-diene-1,9-dioate on the basis of the following data: ir (neat) 5.75 (C=O), 10.3 μ; nmr (CCl_4) τ 4.56 (m, 4, vinyls), 6.45 (s, 6, CO_2Me), 7.10 (m, 4), 7.30 (m, 2); mass spectrum parent (70 eV) *m/e* 212. The nmr spectrum of 50 mg of **11** in the presence of 30 mg of tris(dipavalmethanato)europium showed the following signals: τ 3.9 (d of t, 2, $J_{3,4} = J_{6,7}$ = 15.5, $J_{2,3} = J_{7,8}$ = 6.5 Hz, C_3 and C_7 vinyls), 4.2 (d of t, 2, J = 15.5 and 6.5 Hz, C_4 and C_6 vinyls), 5.6 (m, 6, CO_2Me), 6.15 (m, 4, C_2 and C_8 methylenes), 7.07 (m, 2, C_5 methylene). Irradiation at τ 6.15 caused the doublet of triplets at τ 3.9 to collapse to a doublet (J = 15.5 Hz). Irradiation at τ 7.07 caused the doublet of triplets at τ 4.2 to collapse to a broad doublet (J = 15.5 Hz).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 62.28; H, 7.75.

Photolysis of **3a** in hexane under similar conditions led to the same five photoproducts. In this case the final (1.5 hr) photoisomer mixture consisted of compounds **9**, **10**, and **11** in the ratio 2:1:3.2.

Photolysis of Dimethyl *trans,trans*-Nona-2,7-diene-1,9-dioate (3a) in the Presence of Piperylene.—A hexane solution 9.4×10^{-3} *M* in dimethyl *trans,trans*-nona-2,7-diene-1,9-dioate (**3a**) and 0.15 *M* in piperylene was irradiated externally through Corex. This led to the formation and disappearance of geometric isomers **3b** and **3c** until, after 13 hr, only photoproducts **9**, **10**, and **11** remained in the ratio 2.2:1:2.3, respectively. These compounds were isolated by glpc and identified by comparison with previously obtained samples.

Direct Irradiation of Dimethyl *trans,trans*-Octa-2,6-diene-1,8-dioate (2a).—Diene–diester **2a** (0.25 g) in 200 ml of methanol was irradiated through Corex and the course of the reaction followed by vpc. This showed the formation and decay of the geometric isomers **2b** and **2c** along with the buildup of four additional products. After 14 hr, no **2b** or **2c** remained, and preparative vpc of the remaining mixture afforded photoproducts **7** and **8** (average ratio of 2.7:1, ~20% yield) along with two unknown compounds, **X** and **Y**, in a ratio of ~1:1. The spectra of **X** and **Y**, while not definitive, are compatible with geometric isomers possessing the basic dimethyl octa-3,5-diene-1,8-dioate structure. Photoisomer **X** showed ir (neat) 5.75 (C=O) μ; nmr (CCl_4) τ 3.8–4.5 (m, 4), 6.40 (s, 6, CO_2Me), 7.00 (d, 4, J = 6 Hz).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.61; H, 7.07. Found: C, 60.45; H, 7.12.

Photoproduct **Y** showed ir (neat) 5.75 (C=O) μ; nmr (CCl_4) τ 3.6–4.6 (m, 4), 6.40 (s, 6, CO_2Me), 6.90 (m, 4).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.61; H, 7.07. Found: C, 60.67; H, 7.30.

Similar results were obtained in the photolysis of **2a** in hexane. After 26 hr, the **7**:**8**:**X**:**Y** ratio was 1.8:1.2:1.9:2.6. A third unknown glpc peak was observed in this photolysis but was not investigated further.

Registry No.—**2a**, 4756-84-7; **2b**, 32347-19-6; **2c**, 32347-20-9; **3a**, 34333-79-4; **3b**, 34333-78-3; **3c**, 34333-77-2; **5a**, 36615-25-5; **5b**, 36615-26-6; **5c**, 36615-27-7; **6a**, 36615-28-8; **6b**, 36615-29-9; **6c**, 36615-30-2; **7**, 32426-60-1; **8**, 32426-61-2; **11**, 36615-33-5; dimethyl octa-2,6-diyne-1,8-dioate, 36612-10-9; dimethyl nona-2,7-diyne-1,9-dioate, 36612-11-0.

Acknowledgment.—We thank the National Research Council, the Research Corporation, and the University of British Columbia for financial support. Thanks are also due Mr. Kent C. Dooley for help in synthesis and some preliminary photolyses.

Mechanistic Studies in Organic Photochemistry. VI. Photodecarboxylation of Benzyl Esters

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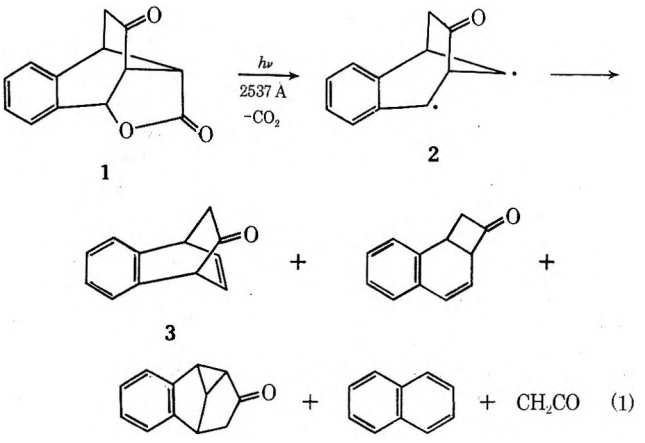
Irradiation of substituted γ-butyrolactones and substituted benzyl phenylacetates resulted in loss of CO_2 and formation of a carbon–carbon bond. Quantum yields for the reaction ranged from 0.03 to 0.25, depending on compound structure and the conditions of the reaction. The reaction could be sensitized with high-energy triplet sensitizers and quenched with cyclohexadiene, implicating the triplet excited state as the reactive state. Solvent effects, structural effects, effects of added nucleophiles, and the lack of stereospecificity for this reaction indicate radical intermediates prior to carbon–carbon bond formation. The similarity of solvent effects on the photostationary state of diphenylcyclopropanes (13 and 14) to those for the photodecarboxylation of diphenyllactones (11 and 12) implies a 1,3 diradical-like intermediate in the lactone reaction. Replacement of the benzyl moiety in benzyl phenylacetate with either an α-naphthyl or furfuryl moiety also resulted in photodecarboxylation. Allyl phenylacetate did not photodecarboxylate.

As part of our mechanistic study of the photorearrangements of benzobicyclo[2.2.2]octadienone (**3**), the lactone **1** was photolyzed in an effort to obtain the diradical **2**, a possible intermediate in triplet ketone rearrangement.[1a] We found that direct or sensitized irradiation of **1** resulted in a *quantitative* and efficient loss of carbon dioxide, leading to products arising from **2** (eq 1).[1] Decarboxylation is ordinarily a minor



pathway in the solution photochemistry of lactones[2,3] and esters.[4-6]

For simple esters, decarboxylation is one pathway available to the excited state; the relative importance of the process depends on the structure of the ester and the photolysis conditions.[4] Loss of carbon dioxide has been observed as the major photochemical pathway in the mercury-sensitized vapor-phase photolysis of simple lactones and butenolides,[5] the γ irradiation or photolysis of benzyl acetate in benzene solution,[6] photolysis of *p*-methoxybenzyl acetate,[7] and the photodecomposition of a dihydrosantonin.[8]

We wished to extend our study of the lactone **1** to simpler analogs to determine the importance of the strained bicyclic system and of the ketone function in the observed decarboxylation. Further, we hoped to develop synthetically useful applications of this process. To study the generality and utility of the reaction, a series of simple γ-phenyl-γ-butyrolactones and benzyl esters (the acyclic equivalent) was synthesized and their photochemistry studied.

Results and Discussion

Lactones. Preliminary Studies.—The simplest functional analog of lactone **1**, γ-phenyl-γ-butyrolactone[9] (**4**), upon direct irradiation (or acetone sensitization) led to loss of carbon dioxide and the formation of a single product in low yield. Continued irradiation led to product disappearance and polymer formation. The product was identified as phenylcyclopropane (**5**) by comparison of vpc, ir, and mass spectral data with those of an authentic sample.[10] To determine the influence of the phenyl substituent on the reaction pathway, the corresponding α-phenyl[11] (**6**) and β-phenyl[12] (**7**) derivatives were prepared and their photochemistry studied. Acetone-sensitized and direct irradiation of **6** and **7** gave no detectable carbon dioxide formation by the limewater test (a simultaneous photolysis of the γ isomer **4** showed considerable CO_2 evolution). These compounds were not investigated further.

In an effort to increase the yield of cyclopropane products and to evaluate the effect of other substituents on the lactone ring, α-cyano-γ-phenyl-γ-butyrolactone (**8**)[13] was prepared and photolyzed. Direct or sensitized irradiation of **8** also led to decarboxylation and the formation of two major products, *cis*- and *trans*-2-phenylcyclopropanecarbonitrile (**9** and **10**) by comparison with authentic samples. The yield of cyclopropane products was quite high; 44% of **9** and 48% of **10** were obtained from preparative photolysis in acetone at 2537 Å. The photochemistry of **4**, **6**, **7**, and **8** is presented in Chart I.

Since the lactone **8** could not be obtained in stereo-

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CHART I

PHOTOCHEMISTRY OF α-, β-, AND γ-PHENYLBUTYROLACTONE (4, 6, 7) AND α-CYANO-γ-PHENYL-γ-BUTYROLACTONE (8)

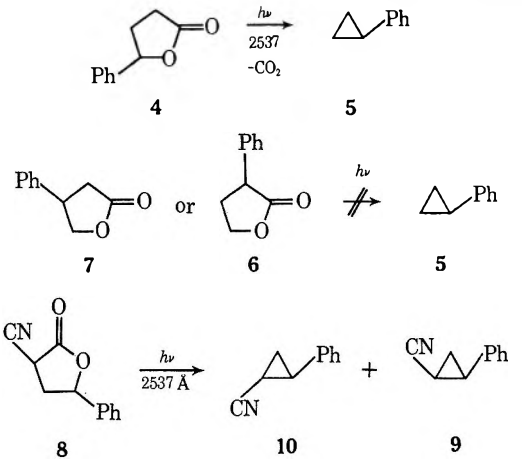
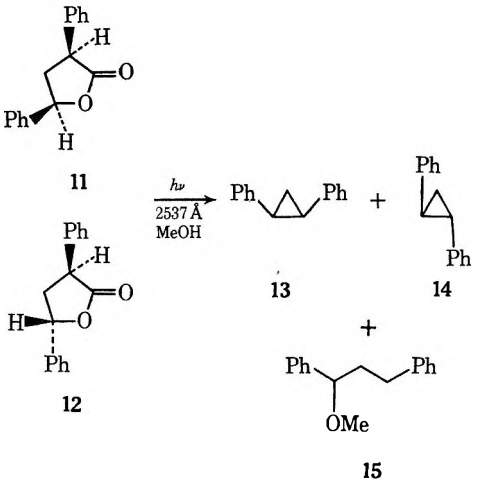


CHART II

PHOTOCHEMISTRY OF *cis*- AND *trans*-α,γ-DIPHENYL-γ-BUTYROLACTONE (11 and 12)



chemical purity, our study could not answer one question of paramount importance, *i.e.*, is the loss of CO_2 stereospecific? Stereospecificity might suggest a concerted process involving departure of CO_2 at the same time that the cyclopropane bond is formed,[14] while a lack of stereospecificity would require CO_2 loss followed by cyclopropane bond formation.

To resolve the concerted–nonconcerted question, the known[15] cis and trans isomers of α,γ-diphenyl-γ-butyrolactone (**11** and **12**) (Chart II) were prepared and studied. Photolysis of either **11** or **12** in methanol solution at 2537 Å led to the same mixture of three products (by vpc coinjection and by spectral analysis of the crude product mixtures). The products (in 50–60% yield) were isolated by column chromatography on silver nitrate–silica gel and characterized as *cis*-1,2-diphenylcyclopropane (**13**), the trans isomer **14**, and 1,3-diphenylpropyl methyl ether (**15**) by comparison with authentic samples.[16,17] The ether **15** was shown to be a product of secondary photolysis of **13** and **14**, since none of this compound could be detected by vpc at low conversion of **11**, while extended irradiation gave increased yields of **15** at the expense of **13** and **14**. Photolysis of lactones **11** and **12** in dioxane solvent gave only two major products, corresponding to the cyclopropanes. In all cases, however, minor amounts of secondary photoproducts of the cyclopropanes were observed; these have been described elsewhere.[18]

Observation of the isomeric cyclopropanes as primary photoproducts of both **11** and **12** at low conversion (Table I) suggests that CO_2 loss could not be a totally concerted process.

Lactones. Quantitative Results.—Quantitative studies of the photochemistry of the lactones were undertaken to obtain further information on the mechanism of the decarboxylation process. Quantum yields for disappearance, CO_2 evolution, and product appearance were determined (see Experimental Section for details) and are given in Table I.

TABLE I

QUANTUM YIELDS FOR DISAPPEARANCE, CO_2 EVOLUTION, AND PRODUCT APPEARANCE FOR γ-BUTYROLACTONES[a]

Lactone	dis[b,c]	CO_2[c,d]	Product[c]
γ-Phenyl (**4**)	0.026	0.020	0.0094 (**5**)
α-Cyano-γ-phenyl (**8**)	0.092	0.100	0.032 (cis, **9**) 0.045 (trans, **10**)
cis-Diphenyl (**11**)	0.045	0.026	0.010 (cis, **13**) 0.011 (trans, **14**)
trans-Diphenyl (**12**)	0.051 0.052 ± 0.005[e]	0.027	0.0064 (**13**) 0.0078 (**13**)[e] 0.0072 (**14**) 0.0075 (**14**)[e]

[a] Direct irradiation, dioxane solvent, 2537 Å. [b] Obtained by quantitative vpc. [c] Quantum yields at 20–30% conversion. The differences in quantum yields are due to the solvent addition products, which were not analyzed. [d] Trapped with tared Ascarite–Anhydrone scrubber. [e] Limiting values extrapolated to zero conversion.

The limiting value for the disappearance quantum yield of the *trans*-diphenyl lactone **12** indicates that secondary photolysis and internal quenching phenomena remain unimportant up to 30% conversion; the limiting values for the cyclopropanes **13** and **14** indicate that both are primary photoproducts.

In order to elucidate the effects of solvent on the mechanism, other solvents were utilized and these results are presented in Table II. In all cases, both lactones **11** and **12** gave both cyclopropanes **13** and **14** as primary photoproducts, although some solvents led to formation of several other products. Isomerization of the starting lactones was shown to be unimportant by vpc and by nmr analysis of recovered lactone from 20–30% conversion runs. These data clearly indicate that the reaction is primarily, if not completely, occurring *via* a nonconcerted pathway.

The results of the solvent study also indicate some effect of the solvent on the product ratio; there is, however, no clear pattern of retention *vs.* inversion or complete nonstereospecificity. In an effort to interpret the lactone solvent effects, the solvent effect on the photoequilibration of the cyclopropanes **13** and **14** was investigated.

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TABLE II

SOLVENT EFFECTS ON DISAPPEARANCE QUANTUM YIELD[a] AND RATIO[a,b] OF *cis*- AND *trans*-CYCLOPROPANE FOR DIPHENYL LACTONES

Lactone	Solvent	ϕ_{dis}	% cis (13)
cis (11)	10% MeOH–ether	0.12	58
	CH_3CN	0.074	46
	i-PrOH	0.061	52
	Dioxane	0.045	48
	Acetone[c,d]	0.042	45
trans (12)	10% MeOH–ether	0.026	54
	CH_3CN	0.042	37
	i-PrOH	0.070	34
	Dioxane	0.051	47
	Acetone[c,d]	0.040	45
	Cyclohexane[c,f]	*e*	55
	Hexane[c,f]	*e*	50
	95% ethanol	*e*	41

[a] Determined by quantitative vpc; 5% conversion at 2537 Å. [b] Extrapolated to zero conversion. [c] Several other products formed; cyclopropanes *ca.* 60% of total. [d] Sensitizer. [e] Not determined. [f] Estimated from triangulated areas in vpc.

Several reports on the photoisomerization of *cis*- and *trans*-1,2-diphenylcyclopropane appear in the literature.[17-22] Hammond and coworkers showed that the isomerization could be sensitized,[19,20] but found that the sensitization process involved singlet energy transfer (for naphthalene derivatives) since the quantum yield for sensitization paralleled the quenching of the fluorescence from the sensitizer.[21] The cyclopropanes **13** and **14** also are found to undergo isomerization on direct irradiation.[17,18,22] Some results for direct irradiation in various solvents are shown in Table III.

TABLE III

SOLVENT EFFECTS ON THE PHOTOEQUILIBRATION OF 13 AND 14

Solvent	Photostationary state, % cis
10% MeOH–ether[a]	72
10% MeOH–ether[b]	72
CH_3CN[a]	59
i-PrOH[a]	70
Dioxane[a]	72
MeOH[a]	67
Benzene[c]	61
Cyclohexane[c]	61

[a] Excess **13**, 2537 Å. [b] Excess **14**, 2537 Å. [c] Reference 18.

Each solvent studied leads to a photostationary state favoring the cis cyclopropane **13** in accord with the literature reports.[17-22] Similarly, photolysis of synthetic samples of *cis*- and *trans*-2-phenylcyclopropanecarbonitrile (**9** and **10**) gave a photostationary state containing 53% cis and 47% trans (from pure **9** or pure **10**, direct irradiation at 2537 Å in ether).

Table III shows, however, that the relative composition of the photostationary state is influenced by the solvent, although the effect is small. Although this process is not a true photoequilibrium, since formation of other products becomes important at long conversion, depleting the system of cis and trans isomers at varying rates,[18,22] low-conversion studies should allow evaluation of the ratio of the rate constants for closure of the suggested diradical intermediate[18] to cis cyclopropane (k_c) to that for closure to trans cyclopropane (k_t). These values are obtained from the relation in eq 2, which relates the concentration of cis and trans isomers at the steady state to the ratio of extinction coefficients at the wavelength of photolysis and the k_c/k_t ratio.[23]

$$\frac{[\text{cis}]}{[\text{trans}]} = \frac{\epsilon_{\text{trans}}}{\epsilon_{\text{cis}}} \cdot \frac{k_c}{k_t} \qquad (2)$$

Assuming that other photochemical processes are unimportant at short times and that thermal isomerization[24] is prevented by solvent deactivation, the solvent effect on the photostationary state should arise from effects on the k_c/k_t ratio or on the extinction coefficient ratio. Determination of the ratios of ϵ's gives the k_c/k_t ratio as a function of solvent (Table IV).

TABLE IV

COMPARISON OF k_{cis}/k_{trans} FOR PHENYL LACTONE PHOTOLYSES AND k_c/k_t FOR DIPHENYLCYCLOPROPANE PHOTOEQUILIBRIUM

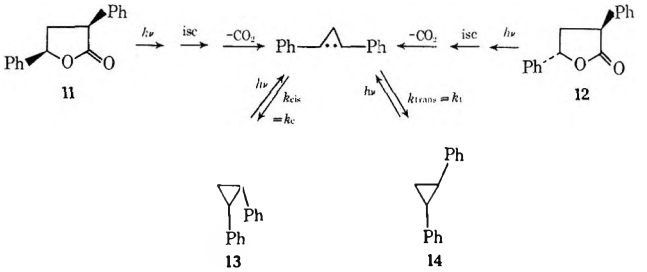
Solvent	k_{cis}/k_{trans}	k_c/k_t
cis-Diphenyl (11)		
10% MeOH–ether	1.38	0.63
CH_3CN	0.85	0.38
i-PrOH	1.08	0.54
Dioxane	0.92	0.52
trans-Diphenyl (12)		
10% MeOH–ether	1.17	0.63
CH_3CN	0.59	0.38
i-PrOH	0.52	0.54
Dioxane	0.89	0.52
Cyclohexane	1.22	0.35 (1.00)[a]
Cyanophenyl (8)		
Ether	0.67	0.71

[a] Reference 22, assuming that both diphenylcyclopropanes give the same intermediate.

The per cent composition of cyclopropane products from the lactones (at zero conversion) gives the k_{cis}/k_{trans} ratio directly (Chart III). If product formation

CHART III

PROCESSES INVOLVED IN PHOTOLYSIS OF DIPHENYL LACTONES AND DIPHENYL CYCLOPROPANES



in the lactones results from the same intermediate involved in the isomerization, the k_{cis}/k_{trans} ratio should equal the k_c/k_t ratio for the cyclopropanes. This

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(22) E. W. Valyocsik and P. Sigal, *J. Org. Chem.* **36**, 66 (1971).
(23) G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt and C. Dalton, *J. Amer. Chem. Soc.*, **86**, 3197 (1964).
(24) L. B. Rodewald and C. H. DePuy, *Tetrahedron Lett.*, 2951 (1964), and references cited therein.

equality holds if the singlet diradical and triplet diradical either are in equilibrium before closure to the cyclopropanes (a reasonable assumption in light of the reported[25] energy difference of ≤ 1 kcal for 1,3-diradicals) or have identical rate ratios for closure to the cis and trans cyclopropanes. The values for k_c/k_t and k_{cis}/k_{trans} are listed in Table IV.

In fact, as shown in Table IV, k_{cis}/k_{trans} varies from one to three times the k_c/k_t ratio. It is apparent, however, that the solvent effects show a qualitative parallel between the lactone photolyses and the diphenylcyclopropane photostationary state. Further, the similarity of the rate ratios for the lactones in all solvents studied suggests that the intermediate involved is neutral, rather than highly polar; it seems unlikely that a polar species would give the same relative yields of diphenyl cyclopropanes over a wide solvent polarity range.

The solvent effects listed in Table II for the ratio of diphenylcyclopropanes from the diphenyl lactones would appear, consequently, to originate in solvent effects on closure of the intermediate, rather than a change in mechanism with solvents. The origin of the solvent effect on the quantum yields of disappearance cannot be determined without further study, but presumably results from changes in rates of deactivation or intersystem crossing.

The discrepancy in the k_{cis}/k_{trans} and k_c/k_t ratios is not clearly understood. There are, however, three possible origins: (1) photoisomerization of the diphenylcyclopropanes and photodecarboxylation of the diphenyl lactones do not involve the same intermediate; (2) the cis and trans lactones lead to different intermediates (as has been proposed for the diphenylcyclopropane isomerization[22]); or (3) the photostationary state method does not lead to correct values for the k_c/k_t ratios. Further study will be necessary to determine the exact origin of the discrepancy in rate ratios, but the third possibility (above) seems most likely. The photochemistry of the diphenylcyclopropanes is complicated by several competing processes, and the absolute rates of formation of *cis*-1,2-diphenylcyclopropane from *trans*- and of *trans*- from *cis*- have not been determined (although Valyocsik and Sigal[22] report that the quantum yields for these processes are the same). It is possible that the photostationary state concentrations of cis and trans isomers do not accurately reflect the ratio of k_c and k_t.

The results obtained from photolysis of the various lactones (*vide supra*) permit several mechanistic conclusions: (1) efficient decarboxylation requires that the excited aromatic chromophore be adjacent to the γ_{CO} bond (since the α- and β-phenyl isomers **6** and **7** show no tendency to decarboxylate); (2) either cleavage of the γ_{CO} bond is irreversible or recombination is faster than bond rotation, since recovered diphenyl lactones show no stereoisomerization; and (3) CO_2 loss leads to a 1,3 diradical which can close to give both isomeric cyclopropane products (in the α,γ-disubstituted lactones.)

Esters. Preliminary Results.—Our studies on lactone photochemistry (*vide supra*) showed that photodecarboxylation is a general phenomenon for γ-phenyl γ-lactones. Since the diphenyl lactones **11** and **12** were found to decarboxylate with good efficiency, the acyclic isomers, benzyl phenylacetates, might also be expected to undergo photodecarboxylation.

The parent compound, benzyl phenylacetate (**16**), was readily obtained by the esterification of phenylacetic acid with benzyl alcohol and purified by distillation. Photolysis (Hanovia 450-W mercury arc, ≥ 2400 Å) in dioxane led to CO_2 expulsion and one major product in good yield by vpc analysis. Column chromatography gave 32% yield of dibenzyl (**17**) (57% based on recovered ester), a 44% yield of recovered **16**, and a mixture of high-polarity products. The dibenzyl was identified by spectral comparison, melting point, and mixture melting point with an authentic sample.[26] Similarly, the *p,p'*-dimethyl (**18**) and *p,p'*-dimethoxy (**19**) isomers were prepared and photolyzed; these also expelled CO_2 to give the corresponding dibenzyls, **20** and **21**, as products.

To test our earlier conclusion that a free diradical intermediate was involved in the photodecarboxylation process, the unsymmetrical ester, *p*-methylbenzyl *p*-methoxyphenylacetate (**22**), was synthesized and photolyzed. Again, CO_2 loss was observed, but vpc analysis indicated three products. These were isolated by column chromatography and preparative vpc and identified as **20**, *p*-methoxy-*p'*-methyldibenzyl (**23**), and **21** in a ratio of 1:2.5:1, respectively. The overall yield at 63% conversion was 99% based on recovered starting ester. These results are again in agreement with a radical process involving free intermediates, since a concerted process should lead to a greater yield of unsymmetrical product. These results are summarized in Chart IV.

As a further test of the generality and mechanistic course of the decarboxylation, meta-substituted derivatives were examined to determine if Zimmerman's[7] observation of a change in mechanism for benzyl acetates, from free radical to ionic processes,[7] would be duplicated in the benzyl phenylacetates.

The unsymmetrical di-meta-substituted derivatives **24** and **25** (Chart IV) were photolyzed in 20% aqueous dioxane at 2537 Å. Neither isomer showed any change in mechanism; both gave a mixture of the three possible dibenzyls (**26**, **27**, and **28**). No alcohol products, expected from trapping of an ionic intermediate by the water, could be observed by vpc or isolation of the photoproducts. These results again support a free-radical mechanism for decarboxylation. The dibenzyls, after isolation, were obtained in 60% yield (from **24**) and 74% yield (from **25**) based on recovered starting ester.

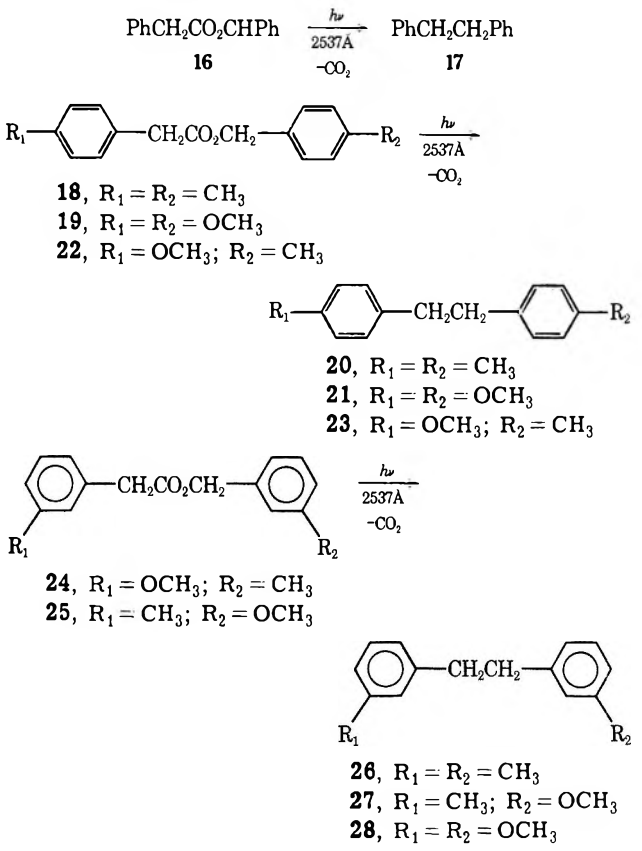
Esters **24** and **25** also were photolyzed in methanol saturated with sodium acetate ($\sim 1.4\ M$) in an effort to detect photosolvolysis products. Ester **24** showed no change in photochemical behavior as compared to a sample photolyzed in dry dioxane; the three dibenzyls **26**, **27**, and **28** comprised >95% of the volatile products. Ester **25**, however, showed five new products after irradiation (two major and three minor) in a combined yield of 20% of the volatile products, while the dibenzyls were formed in 80% yield; the ester was completely converted to products after 500 min. An

(25) (a) G. L. Closs and A. D. Trifunac, *J. Amer. Chem. Soc.*, **92**, 7227 (1970); (b) G. L. Closs, *ibid.*, **91**, 4552 (1969), and references cited therein.

(26) Authentic samples provided by Professor J. A. Landgrebe are gratefully acknowledged.

CHART IV

PHOTOCHEMISTRY OF BENZYL PHENYLACETATE (16) AND SUBSTITUTED DERIVATIVES



identical dark reaction of **25** resulted in 80% conversion of the ester in 420 min, with formation of two major products. These had the same retention times as the major new products in the photolysis sample (by vpc coinjection), suggesting that the additional products resulted from ground-state solvolysis, rather than a change in mechanism in the photolysis. This result supports the conclusion that radical formation and recombination, rather than a polar mechanism, is favored for the benzyl phenylacetates.

Since decarboxylation was found to be a general phenomenon for various benzyl phenylacetates, it was of interest to study esters of other aromatic or radical-stabilizing alcohols such as the allyl (**29**), furfuryl (**30**), and α-naphthylmethyl (**31**) esters of phenylacetic acid.

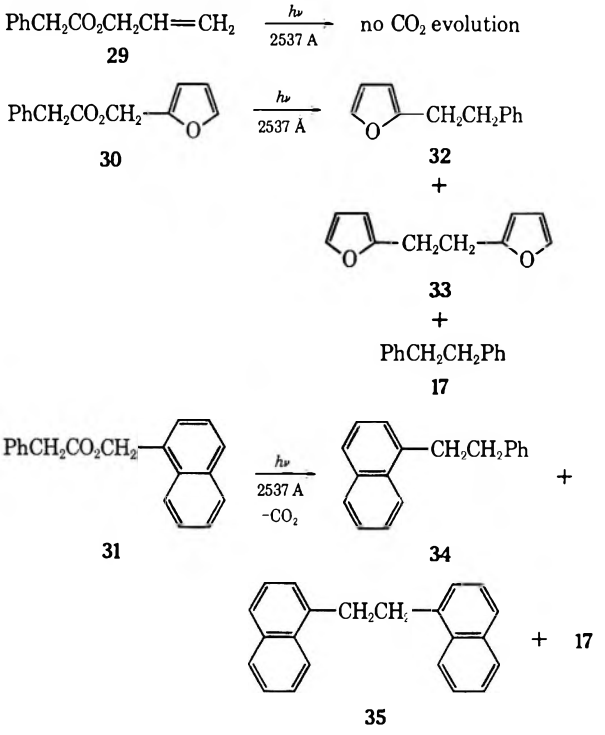
Photolysis of **29** under the usual conditions (dioxane solvent, 2537 Å) gave no detectable CO_2 evolution (limewater test), while vpc analysis indicated the formation of at least nine products, which were not investigated further.

The furfuryl ester **30**, however, did undergo decarboxylation upon direct irradiation (2537 Å) to give the three possible radical coupling products **17**, **32**, and **33** (Chart V).

The α-naphthylmethyl ester **31** was studied at both 2537 and 3000 Å, since the naphthalene chromophore will absorb at longer wavelengths than the chromophores previously employed. Irradiation at 2537 Å gave three products by vpc analysis, in a 1:10:1 ratio. These were isolated and characterized as 1-(α-naphthyl)-2-phenylethane (**34**), 1,2-di-α-naphthylethane (**35**), and dibenzyl (**17**), respectively. At

CHART V

IRRADIATION OF PHENYLACETATES



3000 Å, however, the product ratio had changed to 1:13:1.

The results for these three systems (Chart V) show that photodecarboxylation is a general process for esters of alcohols which are conjugated with aromatic or heteroaromatic systems.

Esters. Quantitative Studies.—Further mechanistic information was obtained by determination of the quantum yields for various benzyl phenylacetates. These values are presented in Table V.

TABLE V

QUANTUM YIELDS[a] FOR PHOTOLYSIS OF SUBSTITUTED BENZYL PHENYLACETATES

Ester	ϕ_{CO_2}[b,c]	ϕ_{dis}[d]	$\phi_{product}$[d]
16	0.031	0.033	0.023 (17)
18	*e*	0.25	0.22 (20)
19	0.19	0.25	0.21 (21)
24	*e*	0.075	0.012 (26)
			0.044 (27)
			0.012 (28)
25	*e*	0.23	0.028 (26)
			0.19 (27)
			0.032 (28)

[a] Direct irradiation, 2537 Å. [b] Trapped with tared Ascarite–Anhydrone scrubber. [c] Quantum yields at 20–30% conversion. [d] Obtained by quantitative vpc. [e] Not determined.

In all cases, the efficiency of decarboxylation is at least as high as that of the lactones. Both methyl and methoxy substituents lead to higher quantum yields as compared to the unsubstituted compounds. The efficiency of these reactions is within the range of synthetically useful processes.

Although the efficiency of the reaction is good, the formation of cross-coupling products reduces the synthetic potential. In an effort to overcome this problem, the effect of various solvents was studied, in an effort

to take advantage of the "cage effect," which has been extensively studied in free-radical systems.[27] The results for photolysis of *p*-methylbenzyl *p*-methoxyphenylacetate (22) are shown in Table VI.

TABLE VI
SOLVENT EFFECTS ON PRODUCT COMPOSITION FROM DIRECT IRRADIATION[a] OF 22[b]

Solvent	Di-*p*-CH_3 (20), %	*p*-OCH_3-*p'*-CH_3 (23), %	Di-*p*-OCH_3 (21), %
t-BuOH	15	68	17
95% EtOH	22	62	16
i-PrOH	14	71	15
Isooctane	20	61	19
Methylcyclohexane	22	61	17

[a] RPR-2537 Å lamps. [b] Determined by triangulation from vpc trace.

Table VI indicates that the yield of unsymmetrical product is highest in the alcohol solvents, while the hydrocarbon solvents lead to higher yields of cross-coupling products. In addition, it was observed that the efficiency of the process is highest for *tert*-butyl alcohol, followed by 95% ethanol and isopropyl alcohol. As has been noted in the lactone photolyses (*vide supra*), decarboxylation was much less efficient in hydrocarbon solvents and additional products were observed in the vpc trace.

To confirm the vpc results, a preparative photolysis of **22** was performed in isopropyl alcohol. Column chromatography and nmr analysis of the mixture indicated a 17:66:17 weight per cent ratio of products **20**, **23**, and **21**, respectively (60% yield based on recovered ester).

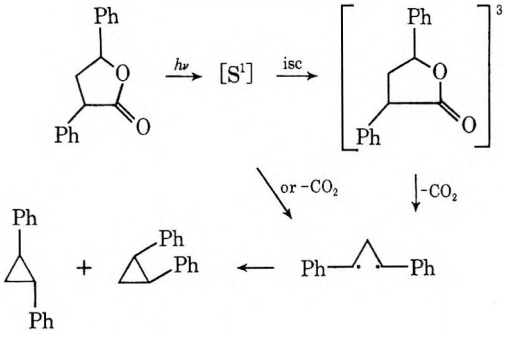
Results for lactone **1**[1] indicate that the decarboxylation process occurs *via* the triplet state, since the reaction can be sensitized with acetone, acetophenone, and benzophenone, and can be quenched with 1,3-cyclohexadiene. As shown above, the simpler lactones undergo decarboxylation upon sensitization with acetone, but at reduced efficiency. To determine the multiplicity involved in these simpler systems, the α-naphthyl ester **31** was investigated further.

The decarboxylation of ester **31** was quenched by 1,3-cyclohexadiene upon irradiation at 3130 Å. Formation of new products and low conversion precluded complete analysis of the quenching, but a Stern–Volmer plot for 1-(α-naphthyl)-2-phenylethane gave a slope of 43.6 l./mol, leading to a value of τ of 8.5×10^{-9} sec. Uv analysis indicated that the ester absorbed >99% of the light. These results suggest the involvement of the triplet state of **31**, although the observed lifetime of the excited state is shorter than typical triplet lifetimes.

From our study of the photodecarboxylation of benzyl esters and γ-lactones, we conclude that this process is general for esters (and lactones) in which an aromatic (or heteroaromatic) chromophore is conjugated with the ethereal C–O bond of the ester or lactone. Electron-donating substituents on the aromatic ring increase the efficiency of decarboxylation relative to benzyl phenylacetate. The quantum yields for the esters are within the range of synthetically useful processes.

The mechanistic studies above and previous results[28] lead us to conclude that the photodecarboxylation process observed occurs *via* discrete radical (diradical) intermediates which are formed by stepwise loss of CO_2, possibly from the triplet state of the ester or lactone, followed by recombination of the radicals (diradical) to give the observed products. Meiggs and Miller[28] have detected benzyl radicals in their study of the photolysis of methyl phenylacetate in agreement with our findings. The detailed mechanistic pathway is exemplified in Chart VI.

CHART VI
MECHANISM OF PHOTODECARBOXYLATION FOR LACTONES AND ESTERS



Experimental Section[29]

A. Synthesis. γ-Phenyl-γ-butyrolactone (4).—This was prepared by the method of Cromwell, *et al.*[9]

Phenylcyclopropane (5).—This was prepared by the method of Peterson and Skell.[10]

α-Phenyl-γ-butyrolactone (6).—This was prepared by the method of Pagliarini, *et al.*[11b]

β-Phenyl-γ-butyrolactone (7).—This compound was obtained by hydrolysis and decarboxylation[12] of a mixture of α-cyano-β-phenyl and α-cyano-γ-phenyl lactones prepared by reaction of styrene oxide with ethyl cyanoacetate.[13]

α-Cyano-γ-phenyl-γ-butyrolactone (8).[13]—Sodium metal (5.75 g, 0.25 g-atom) was dissolved in absolute ethanol (100 ml) under nitrogen in a flask fitted with mechanical stirring, dropping funnel, and reflux condenser with drying tube. The solution was cooled in ice, and ethyl cyanoacetate (28.3 g, 0.25 mol) was added during 10 min. Styrene oxide (30.0 g, 0.25 mol) was then added dropwise during 30 min. The solution was allowed to come to room temperature and stirred overnight, then heated to 60° for 8 hr. The excess ethanol was removed *in vacuo* and 100 ml of benzene was added to the residue, followed by 50 g of ice and 25 ml of concentrated HCl. The aqueous layer was washed with 4 × 100 ml of benzene, and the benzene solution was dried over magnesium sulfate and evaporated to afford 26.7 g (57%) of a mixture of the β-phenyl and γ-phenyl isomers[12] as a white crystalline solid, mp 73–82°. This was recrystallized repeatedly from 95% ethanol to give 1.5 g of white solid, mp 131–132°, assigned the structure α-cyano-γ-phenyl-γ-butyrolactone (8) from spectral evidence: nmr (acetone-d_6, TMS) δ 7.20 (m, 5 H), 5.48 (m, 1 H), 4.20 (m, 1 H), 2.64 (m, 2 H); ir (KBr) 4.40 (m), 5.62, 7.41, 8.48, 10.00, 10.72, 13.10, 14.25 μ (s); mass spectrum *m/e* (rel intensity) 187 (93), 143 (49), 116 (39), 115 (39), 107 (60), 105 (100), 79 (25), 78 (87), 77 (80), 52 (27), 51 (53), 50 (21), 39 (25); uv (95% ethanol) λ_{max} 2680 Å (ε 120), 2640 (210), 2580 (230), 2520 (180), 2480 sh (120), 2420 sh (90).

***cis*- and *trans*-2-Phenylcyclopropanecarbonitrile (9 and 10).**[30]—

(27) S. F. Nelson and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 143 (1966).

(28) T. O. Meiggs and S. I. Miller, *ibid.*, **94**, 1989 (1972).

(29) Melting points were obtained on a hot-stage apparatus calibrated with known samples, unless otherwise noted. Boiling points are uncorrected. The following spectrometers were used: nmr, Varian A-60; ir, Beckman IR-8; uv, Cary 14; mass, Varian MAT CH-2.

(30) M. Horak, J. Smejkal, and J. Farkas, *Collect. Czech. Chem. Commun.*, **28**, 228 (1963).

cis-2-Phenylcyclopropanecarboxylic acid[26] (516 mg, 3.18 mmol) was dissolved in 5 ml of 1 *N* sodium hydroxide and the water was removed under vacuum. Reagent, dry benzene (40 ml) was added, followed by 411 mg (3.23 mmol) of oxalyl chloride and two drops of pyridine. After the solution was stirred for 2 hr, 100 ml of cold concentrated ammonia was added, with stirring and ice cooling. The product mixture was extracted with 5 × 100 ml of ether and the ether extracts were dried and evaporated to give 383 mg (75%) of crude amide, nmr ($CDCl_3$, TMS) δ 7.3 (s), 2.0–0.8 (m), 0.7–0.4 (m). The crude amide was dissolved in 25 ml of dry reagent benzene, 5 ml of thionyl chloride was added, and the resulting solution was stirred at reflux for 5 hr and then poured into 50 ml of ice-cold concentrated ammonia. Extraction with 5 × 50 ml of ether gave 170 mg (50%) of crude *cis*-2-phenylcyclopropanecarbonitrile, which was chromatographed on a 1.9 × 30 cm column of Florisil to give 83 mg of pale yellow oil (fractions 13–30, 2% ether–hexane eluent). Preparative tlc (Merck silica gel F_{254}, 10% ethyl acetate–benzene, and micro distillation (90°, 40 mm) give the nitrile **9** as a water-white liquid: nmr (CCl_4, TMS) δ 7.28 (s, 5 H), 2.39 (d of d, 1 H), 1.50 (m, 3 H), ir (CCl_4) 3.21 (sh), 3.23 (sh), 3.26 (m); 4.43 (s); 6.25, 6.64, 6.85 (m); 7.24, 7.47, 8.59, 8.93, 9.22, 9.48 (w), 9.66, 10.42 (m), 11.00, 12.05, 13.88 (sh w), 14.40 (s); 14.70 (sh w), 15.80 μ (w).

Similarly the trans isomer **10** was prepared from 502 mg (3.1 mmol) of the corresponding acid.[26,30] The crude amide (411 mg, 70%) had nmr ($CDCl_3$, TMS) δ 7.25 (m), 1.80–1.10 (m), 0.55 (m); ir (KBr) 2.97, 3.12, 6.13 (s), 6.92, 7.00, 13.38, 14.45 μ (m). Dehydration as above gave 295 mg (95%) of crude **10** purified by preparative tlc as above and sublimation (90°, 30 mm): mp 51–52° (capillary) (lit.[30] mp 49.5°); nmr (CCl_4, TMS) δ 7.18 (m, 5 H), 2.56 (m, 1 H), 1.48 (m, 3 H); ir (CCl_4) 3.21 (sh); 3.32, 3.27 (m); 4.44 (s); 6.21, 6.67, 6.85, 6.90 (sh, m); 7.19, 8.20, 8.51, 8.89 (w); 9.26, 9.48, 9.71, 10.64 (m); 10.81, 11.11, 13.89 (sh w); 14.39 μ (s).

***cis*- and *trans*-α,γ-Diphenyl-γ-butyrolactone (11 and 12).**—These were prepared by the method of Johnson and Riggs[15] as follows.

4-Oxo-2,4-diphenylbutyronitrile.[31]—This was prepared by the method of Davey and Tivey.[32]

4-Oxo-2,4-diphenylbutyric Acid.—The nitrile from above (90.0 g, 0.38 mol) was heated under reflux with a mixture of 300 ml of concentrated sulfuric acid, 400 ml of glacial acetic acid, and 120 ml of water. The mixture was cooled and poured onto crushed ice; the precipitate was filtered off and dissolved in ether. Extraction with bicarbonate solution followed by acidification of the extract with concentrated HCl gave 77.3 g (85%) of the acid, mp 152–155° after recrystallization from THF–hexane (lit.[15] mp 151.5–152.5°).

***cis*- and *trans*-α,γ-Diphenyl-γ-butyrolactone (11 and 12).**—To a solution of 31.5 g (0.13 mol) of the butyric acid in 500 ml of dry THF was added 15.6 g (0.69 mol) of lithium borohydride in 500 ml of THF; the solution was stirred overnight under nitrogen. Water (600 ml) was added carefully, followed by 300 ml of 10% sulfuric acid. The THF was removed *in vacuo* and the residual solution was extracted with ether to give 26.0 g (84%) of crude product, which was chromatographed on a 4.5 × 110 cm column of Davison Grade 950 silica gel, slurry packed with hexane, to afford (1-l. fractions): fractions 1 and 2, hexane eluent, nil; 3 and 4, 2% ether–hexane, nil; 5 and 6, 5% ether–hexane, nil; 7–19, 10% ether–hexane, 360 mg of residue; 20–28, 15% ether–hexane, 9.615 g of **12**; 29 and 30, 15% ether–hexane, 38 mg of a mixture of **11** and **12**; 31–46, 15% ether–hexane, 7.718 g of **11**.

The *cis*-α,γ-diphenyl-γ-butyrolactone (**11**) was crystallized from acetone–hexane, mp 106–107° (lit.[15] mp 107–107.5°). The trans isomer **12** was recrystallized from ether–hexane, mp 68–69° (lit.[15] mp 74°).

***cis*- and *trans*-1,2-Diphenylcyclopropane (13 and 14).**—These were prepared by the method of Beech, Turnbull, and Wilson.[16]

1,3-Diphenylpropyl Methyl Ether (15).—This was prepared according to the procedure of Irving, *et al.*[17]

Benzyl Phenylacetate (16).—This was prepared by the method of Wiessberger and Kibler.[33]

***p*-Methoxybenzyl *p*-Methoxyphenylacetate (19).**—This was prepared as above from 5.002 g (0.036 mol) of anisyl alcohol, 6.609 g (0.040 mol) of *p*-methoxyphenylacetic acid, and 106 mg of *p*-toluenesulfonic acid in 50 ml of benzene. After 3 hr, removal of the solvent gave 7.344 g (76%) of crude **18** as an off-white solid, mp 54–64°. The ester was recrystallized twice from acetone at Dry Ice temperatures to give 2.159 g of white needles, mp 66.5–67.5°. The recovered crude ester was recrystallized twice from 95% ethanol to give 2.449 g of lustrous plates: mp 68.5–69.0°; nmr ($CDCl_3$, TMS) δ 7.08 (m, 8 H), 5.08 (s, 2 H), 3.78 (s, 6 H), and 3.58 (s, 2 H); ir ($CHCl_3$) 3.27, 3.32 (sh); 3.36, 3.38 (m); 3.42 (s); 3.50 (m); 5.82, 6.21 (s); 6.31 (m); 6.65, 6.88, 6.95 (s); 7.05 (s); 7.30 (m); 7.70 (s); 8.20 (broad, s); 8.52 (sh); 8.80(s); 9.00 (sh); 9.72 (s); 10.80 μ (m); uv (dioxane) λ_{max} 2810 Å sh (ε 2640), 2750 (3120); mass spectrum (70 eV) *m/e* (rel intensity) 286 (10), 122 (24), 121 (100).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.48; H, 6.35.

***p*-Methylbenzyl *p*-Methylphenylacetate (18).**—The ester was prepared as above by acid-catalyzed dehydration of 3.000 g (0.020 mol) of *p*-methylphenylacetic acid, 2.440 g (0.020 mol) of *p*-methylbenzyl alcohol, and 208 mg of *p*-toluenesulfonic acid in 70 ml of benzene. Work-up as before and distillation gave 4.655 g (92%) of **19** as a water-white liquid, bp 137–141° (0.2 mm), which solidified in the receiver. The ester was recrystallized from 95% ethanol to constant melting point, 39.5–40°: nmr (CCl_4, TMS) δ 7.06 (s), 7.03 (s, 8 H), 4.98 (s, 2 H), 3.48 (s, 2 H), 2.30 (s, 6 H); ir (CCl_4) 3.20 (sh w); 3.25 (sh), 3.29, 3.36, 3.39, 3.45 (sh m); 5.30, 5.75 (sh), 6.20 (w); 6.61, 6.82 (sh), 6.90, 7.02 (sh), 7.25, 7.50, 7.70 (m); 8.00, 8.25 (s); 8.45 (m), 8.75 (broad, s), 9.75 (sh), 9.90 (sh), 10.18 (m); 10.62 μ (w); uv (dioxane) λ_{max} 2730 Å (ε 490), 2680 sh (480), 2640 (560), 2590 sh (420); mass spectrum (70 eV) *m/e* (rel intensity) 254 (10), 106 (29), 105 (100), 79 (23), 77 (31).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.48; H, 7.11.

***p*-Methylbenzyl *p*-Methoxyphenylacetate (22).**—Dehydration of a mixture of 5.003 g (0.041 mol) of *p*-methylbenzyl alcohol and 6.807 g (0.041 mol) of *p*-methoxyphenylacetic acid with 138 mg of *p*-toluenesulfonic acid catalyst in 35 ml of benzene gave 10.059 g (91%) of crude **22** which was distilled (177–183°, 1.0 mm), then recrystallized from ether at Dry Ice temperatures to give 5.379 g of **22** as white needles: mp 32–32.5°; nmr (CCl_4, TMS) δ 7.08 (s), superimposed on 6.92 (m, 8 H), 5.00 (s, 2 H), 3.71 (s, 3 H), 3.48 (s, 2 H), 2.32 (s, 3 H); ir (CCl_4) 3.31 (sh, m); 3.39 (s); 3.50 (m); 5.80, 6.20 (s); 6.30 (m); 6.63, 6.90, 7.30 (s); 7.60 (sh, m); 7.75, 8.15, 8.50, 8.85, 9.65, 10.25 (s); uv (95% ethanol) λ_{max} 2820 Å (ε 1310), 2750 (1540); mass spectrum (70 eV) *m/e* (rel intensity) 270 (17), 121 (100), 105 (67), 91 (54).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.72. Found: C, 75.76; H, 6.88.

***m*-Methylbenzyl *m*-Methoxyphenylacetate (24).**—As before, the ester was prepared by dehydration of 6.651 g (0.040 mol) of *m*-methoxyphenylacetic acid and 4.888 g (0.040 mol) of *m*-methylbenzyl alcohol with 188 mg of *p*-toluenesulfonic acid catalyst in 50 ml of benzene. Work-up and vacuum distillation gave 7.816 g (72%) of **24** as a water-white liquid: bp 158–160° (0.1 mm); nmr (CCl_4, TMS) δ 7.12 (m), 6.72 (m, 8 H), 4.98 (s, 2 H), 3.62 (s, 3 H), 3.49 (s, 2 H), 2.26 (s, 3 H); ir (CCl_4) 3.28, 3.31, 3.37, 3.51 (m); 5.77, 6.28, 6.31, 6.72, 6.85, 6.89, 6.99 (s); 7.30 (m); 8.00, 8.78 (s); 9.18, 9.25 (w); 9.50, 9.58 (s); 10.18, 11.43 (m); 14.52 μ (s); uv (dioxane) λ_{max} 2810 Å sh (ε 1900), 2730 (2270); mass spectrum (70 eV) *m/e* (rel intensity) 270 (21), 122 (73), 121 (47), 107 (32), 105 (100), 93 (22), 79 (36), 78 (21), 77 (46), 65 (24).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.52; H, 6.72. Found: C, 75.53; H, 6.44.

***m*-Methoxybenzyl *m*-Methylphenylacetate (25).**—Using the general procedure above, 5.529 g (0.040 mol) of *m*-methoxybenzyl alcohol, 6.001 g (0.040 mol) of *m*-methylphenylacetic acid, and 273 mg of *p*-toluenesulfonic acid in 50 ml of benzene gave (after work-up and distillation) 6.968 g (65%) of **25**: bp 163–166° (0.1 mm); nmr (CCl_4, TMS) δ 7.00 (m), 6.75 (m, 8 H), 4.98 (s, 2 H), 3.61 (s, 3 H), 3.48 (s, 2 H), 2.25 (s, 3 H),; ir (CCl_4) 3.28, 3.31, 3.37, 3.51 (m); 5.77, 6.28, 6.31, 6.72, 6.85, 6.89, 6.99 (s); 7.30 (m); 8.00, 8.78 (s); 9.18 (w); 9.50, 9.58 (s); 10.18, 11.43 (m); 14.52 μ (s); uv (dioxane) λ_{max} 2810 Å sh (ε 1920), 2730 (2280); mass spectrum (70 eV) *m/e* (rel intensity) 270 (24), 138 (70), 122 (21), 121 (100), 105 (85), 91 (30), 77 (24).

(31) E. P. Kohler and H. M. Chadwell, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 78.

(32) W. Davey and D. J. Tivey, *J. Chem. Soc.*, 1230 (1958).

(33) A. Weissberger and C. J. Kibler, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1943, p 610.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.52; H, 6.72. Found: C, 75.26; H, 6.63.

Allyl Phenylacetate (29).[34]—Phenylacetic acid (20.0 g, 0.15 mol) was dissolved in 150 ml of 1 *N* sodium hydroxide and the water was removed under vacuum. Benzene (300 ml) was added and the flask was fitted with a reflux condenser, addition funnel, and nitrogen inlet; then 19.872 g (0.16 mol) of oxalyl chloride was added dropwise. The solution was stirred for 3 hr (until gas evolution ceased), then divided into three equal parts. One portion of the solution was added slowly to a solution of 2.865 g (0.049 mol) of freshly distilled allyl alcohol in 50 ml of pyridine (distilled from barium oxide) in an ice bath. After stirring for 3 hr, the solution was poured into 200 ml of ice water and the aqueous layer was discarded. The benzene solution was washed with 200 ml of 10% sulfuric acid, 2 × 200 ml of 10% sodium bicarbonate, 200 ml of water, and 200 ml of brine, dried, and evaporated to give 4.871 g of crude ester which was distilled to give 3.223 g (37%) of **29**, bp 115–117° (10 mm) [lit.[34] bp 123° (15 mm)].

Furfuryl Phenylacetate (30).—A second portion of the phenylacetyl chloride solution (above) was added slowly to a pyridine solution of 4.812 g (0.049 mol) of freshly distilled furfuryl alcohol. The reaction mixture was worked up as above to give 8.839 g of material which, after distillation, afforded 4.857 g (46%) of **30**, bp 125–129° (0.6 mm), as a pale yellow oil. Treatment with decolorizing carbon gave the ester as a water-white liquid which yellowed rapidly: nmr (CCl_4, TMS) δ 7.22 (m, 1 H), 7.12 (s, 5 H), 6.20 (m, 2 H), 4.93 (s, 2 H), 3.44 (s, 2 H); ir (CCl_4) 3.20 (sh); 3.24 (sh); 3.28, 3.37 (sh w); 5.75 (s); 6.23 (w); 6.68 (m); 6.90, 6.98, 7.08 (sh, w); 7.32, 7.55 (sh); 7.32 (sh, m); 8.10, 8.70 (sh), 8.83 (s); 9.30 (w); 9.85 (sh), 10.25, 10.90 (m); 11.30 (w); 14.10 (sh), 14.42 μ (m); uv (95% ethanol) λ_{max} 2680 Å (ε 80), 2640 (160), 2470 (210), 2520 (170), 2470 (150); mass spectrum (70 eV) *m/e* (rel intensity) 216 (6), 91 (25), 81 (69), 31 (100), 29 (76).

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.19; H, 5.60. Found: C, 71.94; H, 5.36.

α-Naphthylmethyl Phenylacetate (31).—α-Naphthylmethanol was synthesized by reduction of 20.014 g (0.128 mol) of 1-naphthaldehyde with 2.476 g (0.065 mol) of $LiAlH_4$ in 400 ml of ether. After stirring for 30 min, the reaction was worked up to give 20.520 g of alcohol as a yellow solid which was sublimed (100°, 0.10 mm) to afford 18.553 g (92%) of white, crystalline α-naphthylmethanol, mp 56–58° (lit.[35] mp 59.5–60°).

The third portion of the phenylacetyl chloride solution (above) was added to a pyridine solution of 7.830 g (0.049 mol) of the α-naphthylmethanol. Work-up as before gave 5.540 g (41%) of the crude ester as a yellow oil, bp 198–206° (0.5 mm) [lit.[36] bp 212° (4–5 mm)].

B. Photochemical Studies. Irradiation of γ-Phenyl-γ-butyrolactone (4).—The lactone **4** (3.199 g, 0.020 mol) was dissolved in 60 ml of dioxane, and the solution was divided among four quartz photolysis tubes. After degassing for 30 min, the samples were irradiated in the merry-go-round with 15 RPR-2537 Å lamps. Vpc analysis (program: 100°, 4 min, 15°/min at 270°, 4 min) showed one major and several minor products; after 380 min, no increase in product concentration was observed although **4** continued to disappear. The major product was isolated by preparative vpc (5 ft × 0.375 in. 30% UC W-98 column, 110°) and showed ir and mass spectra identical with those of an authentic sample of phenylcyclopropane (**5**) prepared by the method of Peterson and Skell.[10]

Comparative Photolysis of α-, β-, and γ-Phenyl-γ-butyrolactones (6, 7, and 4).—Photolysis tubes were prepared, containing 74 mg of α-phenyl lactone **6**, 62 mg of β isomer **7**, and 87 mg of γ-phenyl lactone **4**, respectively, dissolved in 15 ml of spectrograde acetone. A fourth sample (acetone only) served as blank. The four samples were degassed, connected to limewater bubblers to detect CO_2 evolution,[37] and irradiated with 16 RPR-2537 Å lamps. After 300 min, only the γ-phenyl lactone showed a positive CO_2 test.

Photolysis of α-Cyano-γ-phenyl-γ-butyrolactone (8).—Lactone **8** (267 mg, 1.43 mmol) was dissolved in 100 ml of acetone; 15-ml aliquots were pipetted into six quartz tubes, and the samples were degassed and irradiated for 6 hr in the merry-go-round (16 RPR-2537 Å lamps). Vpc analysis as above showed two major products. Evaporation of the solvent gave 200 mg of material which was chromatographed on a 2.5 × 56 cm column of Davison Grade 950 silica gel, slurry packed with 5% ether–hexane, to afford (200-ml fractions) fractions 1–8, 5% ether–hexane eluent, nil; 9–14, 5% ether–hexane, 89 mg (48%) of *trans*-2-phenylcyclopropanecarbonitrile (**10**); 15–20, 5% ether–hexane, nil; 21–23, 50% ether–hexane, 80 mg (44%) of the cis isomer **9**.

The crude **10** from fractions 9–14 was further purified by chromatography on a 1.2 × 28 cm Florisil column, preparative tlc on silica gel (10% ethyl acetate–benzene eluent), and sublimation (90°, 40 mm) to give white crystals, mp 50.5–51.5°, mmp 49–51°, having nmr and ir spectra identical with those of an authentic sample (*vide supra*).

Anal. Calcd for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 84.01; H, 6.53; N, 9.74.

The crude **9** from fractions 21–23 was purified by column chromatography and preparative tlc as above, then micro distilled (80°, 35 mm) to give a water-white oil having nmr and ir spectra identical with those of an authentic sample of **9** (*vide supra*).

Anal. Calcd for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.75; H, 6.37; N, 9.95.

Photolysis of *cis*- and *trans*-2-Phenylcyclopropanecarbonitrile (9 and 10).—The isomeric nitriles (29 mg cis, **9**; 25 mg trans, **10**) were individually photolyzed in ether solvent (quartz tubes, merry-go-round, 16 RPR-2537 Å lamps). Aliquots were analyzed by vpc (column 170°). Both isomers were found to reach the same photostationary state, 46.8% trans, 53.2% cis. Some polymerization was observed in both samples, and a new product was formed in low yield. This product was not investigated further.

Preparative Photolysis of *cis*- and *trans*-α,γ-Diphenyl-γ-butyrolactone (11 and 12).—To obtain sufficient photoproduct for isolation and identification, the synthetic mixture of lactones **11** and **12** was used without separation. The mixture of **11** and **12** (1.051 g, 4.42 mmol) was dissolved in 120 ml of methanol, and the solution was divided among eight quartz tubes, degassed, and irradiated (merry-go-round, 16 RPR-2537 Å lamps). After 180 min, the solvent was removed under vacuum to give 880 mg of material which was chromatographed on a 2.5 × 54 cm column of Davision grade 950 silica gel, slurry packed with hexane, to afford (125-ml fractions) fractions 1–8, hexane eluent, nil; 9–12, 1% ether–hexane, nil; 13–16, 2% ether–hexane, nil; 17–19, 5% ether–hexane, nil; 20–22, 5% ether–hexane, 319 mg of a mixture of photoproducts (by vpc); 23–28, 5% ether–hexane, 15 mg of residue; 29–31, 20% ether–hexane, 33 mg of residue; 32–34, 20% ether–hexane, 183 mg of trans lactone **12**; 35–36, 20% ether–hexane, 9 mg of residue; 37–42, 20% ether–hexane, 289 mg of cis lactone **11** (44% recovery of starting material).

The mixture of photoproducts from fractions 20–22 was separated by chromatography on a 1.5 × 46 cm column of 20% silver nitrate on Davison silica gel, slurry packed with hexane, 75-ml fractions, to give fractions 1–5, 0.5% ether–hexane, nil; 6–10, 1% ether–hexane, 6 mg of residue; 11–16, 1% ether–hexane, 57 mg (12%) of *trans*-1,2-diphenylcyclopropane (**14**); 17–28, 1% ether–hexane, 84 mg (18%) of *cis*-1,2-diphenylcyclopropane (**13**); 29–42, 1% ether–hexane, and 43–53, 2% ether–hexane, 101 mg (18%) of 1,3-diphenylpropyl methyl ether (**15**). The photoproducts were identified by spectral comparison with authentic samples (*vide supra*).

Preparative Photolysis of Benzyl Phenylacetate (16).—The ester **16** (4.014 g, 0.0178 mol) was dissolved in 230 ml of dioxane, degassed for 30 min, and irradiated with the medium-pressure Hanovia lamp, Vycor filter (cutoff, 240 nm). Aliquots were taken at intervals for vpc analysis (column program: 110°, 4 min, 15°/min to 270°; 4 min). After 30 min, two new peaks appeared in the vpc; after 198 min, the ratio of new peaks to reactant was 1:16:45. The solvent was removed *in vacuo* to give 3.88 g of crude material. A 1.007-g portion of the crude product mixture was chromatographed on a 1.5 × 46 cm column of Davison grade 950 silica gel, slurry packed with hexane, 75-ml fractions (analyzed by vpc as above) to afford fraction 1, hexane eluent, nil; 2–3, hexane, 234 mg of dibenzyl (**17**); 4–8, hexane, 7 mg residue; 9, 10% ether–hexane, nil; 10–13, 10% ether–

(34) R. Louw and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, **86**, 147 (1967).

(35) K. Zielger, *Ber.*, **54**, 737 (1921).

(36) R. N. Chakravarti and R. C. Dhar, *J. Indian Chem. Soc.*, **30**, 751 (1953).

(37) T. R. Hogness and W. C. Johnson, "Qualitative Analysis and Chemical Equilibrium," 4th ed, Holt, Rinehart and Winston, New York, N. Y., 1954, p 523.

hexane, 438 mg of unreacted **16**; 14–20, 10% ether–hexane, 26 mg of a complex mixture of minor products. The column was washed with 200 ml of ethyl acetate and 200 ml of methanol to give an additional 156 mg of high-polarity products.

The remainder of the photolysis mixture was chromatographed as above to provide a combined total of 1.037 g (32%) of dibenzyl (**17**), 1.784 g (44%) of unreacted **16**, and 637 mg of a complex mixture of high-polarity minor products (probably solvent-derived coupling products, by analogy with the results of Zimmerman and Sandel[7]).

Photoproduct **17** was further purified by sublimation (47°, 0.01 mm) and recrystallization from 95% ethanol, mp 52–53° (mixture melting point unchanged).[25]

Photolysis of *p*-Methylbenzyl *p*-Methoxyphenylacetate (22).—The ester **22** (1.521 g, 5.63 mmol) was dissolved in 330 ml of dioxane and the solution was degassed for 30 min and irradiated with the Hanovia medium-pressure mercury arc (Vycor filter) for 180 min. Vpc analysis (column program: 110°, 2 min; 15°/min to 270°, 6 min) showed three products in a ratio of 1:2.5:1. The solvent was removed *in vacuo* to give 1.401 g of crude product, which was chromatographed on a 2.5 × 50 cm column of Davison grade 950 silica gel, slurry packed in hexane, to provide (200-ml fractions, analyzed by vpc as above) fractions 1–6, hexane eluent, 30 mg of residue; 7–11, 1% ether–hexane, 12 mg of residue; 12–14, 2% ether–hexane, nil; 15–19, 2% ether–hexane, 517 mg of a mixture of **20** and **21**; 20–24, 2% ether–hexane, 11 mg of residue; 25–30, 2% ether–hexane, 282 mg of **23**; 41–45, 4% ether–hexane, nil; 46–53, 10% ether–hexane, 562 mg (37%) of unreacted **22**; ethyl acetate and methanol washes as above gave 217 mg of high-polarity products.

The white, crystalline di-*p*-methoxydibenzyl (**21**) from fractions 25–30 had nmr (CCl_4, TMS) δ 6.95 (m, 8 H), 3.75 (s, 6 H), 2.81 (s, 4 H); ir (CCl_4) 3.31 (sh); 3.42, 3.50 (m); 6.22, 6.63 (s); 7.70 (m); 8.05–8.35 (broad, s); 8.50, 9.70 μ (s); mass spectrum (70 eV) *m/e* (rel intensity) 242 (20), 121 (100). Sublimation (120°, 0.1 mm) gave mp 124–127° (lit.[38] mp 125–126°).

Photoproducts **20** and **23** from fractions 15–19 were isolated by preparative vpc (5 ft × 0.375 in. 30% UC W-98, 220°). The di-*p*-methyldibenzyl (**20**) was further purified by sublimation (70°, 0.1 mm): mp 78–81° (lit.[39] mp 78–80°); nmr ($CDCl_3$, TMS) δ 7.02 (s, 8 H), 2.87 (s, 4 H), 2.32 (s, 6 H); ir ($CHCl_3$) 3.22, 3.26, 3.32 (sh m); 3.40 (s); 3.48, 6.62, 6.92 (m); 9.10, 9.80 (w); 12.3–14.0 μ (broad, s); mass spectrum (70 eV) *m/e* (rel intensity) 210 (24), 105 (100). The *p*-methoxy-*p'*-methyldibenzyl (**23**) was purified by sublimation (70°, 0.1 mm): mp 61–62.5°; nmr ($CDCl_3$, TMS) δ 7.05 (s) superimposed on 6.93 (m, 8 H), 3.69 (s, 3 H), 2.82 (s, 4 H), 2.28 (s, 3 H); ir ($CHCl_3$) 3.21, 3.27, 3.32 (sh, m); 3.40, 3.48, 3.50, 6.21 (s); 6.31 (m); 6.65 (s); 6.84, 6.88 (sh, m); 6.93, 7.70, 8.05–8.33, 8.52 (s); 9.10 (m); 9.70 (s); 12.15–13.95 μ (s); mass spectrum (70 eV) *m/e* (rel intensity) 226 (14), 121 (100), 105 (11).

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.64; H, 8.02.

Preparative photolysis of 536 mg (1.99 mmol) of **22** in isopropyl alcohol (30 ml) for 920 min with 15 RPR-2537 Å lamps gave 463 mg of material after removal of the solvent. Chromatography of the photolysate on a 1.5 × 52 cm column of Davison grade 950 silica gel (as above) afforded 223 mg of a mixture of **20** and **23**, 47 mg of **21** (total dibenzyl recovery 60%), and 21 mg (4%) of unreacted **22**. Nmr analysis indicated 58% formation of the unsymmetrical dibenzyl **23**.

Irradiation of *m*-Methylbenzyl *m*-Methoxyphenylacetate (24).—A solution of 262 mg (0.97 mmol) of **24** in 15 ml of 20% aqueous dioxane was degassed and irradiated in the merry-go-round (2537 Å). After 900 min, the solvent was removed to afford 216 mg of material which was chromatographed on a 1.5 × 50 cm column of Davison Grade 950 silica gel, slurry packed with hexane, to provide (75-ml fractions) fractions 1–5, hexane eluent, nil; 6–10, 1% ether–hexane, nil; 11–13, 2% ether–hexane, nil; 14–15, 2% ether–hexane, 95 mg of a mixture of **26** and **27**; 16–19, 2% ether–hexane, 6 mg of residue; 20–26, 5% ether–hexane, 28 mg of **28**; 27–29, 10% ether–hexane, nil; 30–33, 10% ether–hexane, 16 mg (6 mol %) of unreacted **24**. The total recovery of dibenzyl products was 60% based on unreacted starting material.

The products (**26**, **27**, and **28**) were identified spectroscopically. The di-*m*-methoxydibenzyl (**28**) from fractions 20–26 had nmr (CCl_4, TMS) δ 7.06 (m, 2 H), 6.65 (m, 6 H), 3.70 (s, 6 H), 2.84 (s, 4 H); ir (CCl_4) 3.28 (sh); 3.31 (w); 3.38 (m); 3.48, 3.51, 5.82 (w); 6.28, 6.30 (s); 6.72, 6.82, 6.88, 6.96 (w); 7.63 (sh, m); 7.95 (s); 8.40 (w); 8.60 (sh, m); 8.68 (s); 9.20 (m); 9.52 (s); 9.85 (sh, m); 11.48, 11.80 (w); 14.43 μ (m); mass spectrum (70 eV) *m/e* (rel intensity) 242 (44), 122 (21), 121 (100), 91 (48), 77 (21).

The mixture of di-*m*-methyldibenzyl (**26**) and *m*-methoxy-*m'*-methyldibenzyl (**27**) from fractions 14–15 showed nmr (CCl_4, TMS) 6.95, 6.65 (overlapping m's), 3.60 (s), 2.78 (s), and 2.25 (s). The products were separated by preparative vpc (8 ft × 0.375 in., 30% UC W-98, 200°) to obtain infrared and mass spectra of the pure product. Compound **26** had ir (CCl_4) 3.20 (sh, w); 3.30, 3.40, 3.48 (s); 5.18, 5.40, 5.63, 5.72 (w); 6.22 (s); 6.29, 6.73 (m); 6.92 (s); 7.28 (m); 7.47 (w); 7.95, 8.55 (m); 9.20, 9.75 (s); 11.17 (w); 11.38 (m); 14.39 (s) (identical with literature spectrum); mass spectrum (70 eV) *m/e* (rel intensity) 210 (14), 105 (100). Compound **27** had ir (CCl_4) 3.20 (sh, w); 3.28, 3.31 (m); 3.39 (s); 3.48, 3.51 (m); 6.24, 6.31 (s); 6.72, 6.83, 6.88, 6.96 (m); 7.25 (w); 7.93 (s); 8.40 (w); 8.50 (m); 8.68 (s); 9.20, 9.25 (w); 9.48, 9.55 (s); 10.05 (w); 11.40 (m); 11.80 (w); 14.40 (s); mass spectrum (70 eV) *m/e* (rel intensity) 226 (33), 121 (83), 105 (100).

Irradiation of *m*-Methoxybenzyl *m*-Methylphenylacetate (25).—As above, a solution of 308 mg (1.14 mmol) of **25** in 15 ml of 20% aqueous dioxane was degassed and irradiated at 2537 Å for 900 min. Removal of the solvent and chromatography as above gave fractions 14–15, 2% ether–hexane, 157 mg of di-*m*-methyldibenzyl **26** and *m*-methoxy-*m'*-methyldibenzyl **27** (nmr, ir spectra identical with those of fractions 14–15 above); 18–22, 5% ether–hexane, 34 mg of di-*m*-methoxydibenzyl (**28**) (nmr, ir spectra identical with those of fractions 20–26 above); no starting material was recovered (total 74% recovery of dibenzyl products). No photosolvolysis products[7] were detected by vpc or spectral analysis, or from column chromatography.

Irradiation in Methanol–Sodium Acetate.—As a further test of the radical character of the decarboxylation, the meta-substituted esters **24** and **25** were also irradiated in methanol saturated with sodium acetate (~1.4 *M*). Two samples were prepared in quartz tubes, containing 327 mg (1.21 mmol) of **24** and 328 mg (1.22 mmol) of **25**, respectively, in 15 ml of methanol saturated with sodium acetate. These were degassed and irradiated with 15 RPR-2537 Å lamps for 500 min. The methanol was removed *in vacuo* and 30 ml of benzene was added. After stirring for 4 hr, the benzene fraction was analyzed by vpc as above. Ester **24** showed 60% conversion to give >95% of the dibenzyl products **26**, **27**, and **28**, by vpc comparison with a standard sample of 208 mg (0.77 mmol) of **24** in 15 ml of dry dioxane. Ester **25** showed complete conversion, to give the dibenzyls (81% of volatile products) and two new major and three minor products (19%). A dark reaction was run with 263 mg of **25** in 20 ml methanol, saturated with sodium acetate, maintained at 42–43° for 420 min under nitrogen. Work-up and vpc analysis as above showed 70% conversion to two new products which had the same retention times as the major products in the photochemical run (by coinjection).

Photolysis of Allyl Phenylacetate (29).—A solution of 323 mg (1.83 mmol) of **29** in 15 ml of dioxane was degassed, attached to a linewater bubbler to detect CO_2 formation,[37] and irradiated at 2537 Å with continuous degassing. After 2020 min, the sample showed only traces of $CaCO_3$ in the bubbler; vpc analysis (column program 110°, 4 min; 20°/min to 270°, 4 min) showed four major and five minor products which were not investigated further.

Photolysis of Furfuryl Phenylacetate (30).—As above, 346 mg (1.60 mmol) of **30** was dissolved in 15 ml of dioxane, degassed, and irradiated at 2537 Å (limewater bubbler used to detect CO_2). After 15 min, the bubbler solution was opaque. At 2020 min, vpc analysis (as above) showed *ca.* 60% conversion to three products (relative areas 1:3:2). The solvent was removed and the residue (285 mg) was chromatographed on a 1.5 × 54 cm column of Davison Grade 950 silica gel, slurry packed with hexane, to give (75-ml fractions) fractions 1–5, hexane eluent, nil; 6–10, 1% ether–hexane, nil; 11–13, 2% ether–hexane, nil; 14–15, 2% ether–hexane, 52.9 mg of a mixture of bifurfuryl (**33**), 1-(2-furanyl)-2-phenylethane (**32**), and dibenzyl (**17**) (in order of increasing retention time); 16–17, 2% ether–hexane, nil; 18–20, 4% ether–hexane, nil; 21–26, 4% ether–hexane, 45

(38) E. M. Richardson and E. E. Reid, *J. Amer. Chem. Soc.*, **62**, 413 (1940).

(39) R. G. Helgeson and D. J. Cram, *ibid.*, **88**, 509 (1966).

mg (13%) of unreacted **30**. Both the ester **30** and the photoproducts **32** and **33**, appeared to decompose during chromatography.

The mixture of photoproducts **17**, **32**, and **33** from fractions 14–15 had nmr (CCl_4, TMS) δ 7.12 (broad s), 6.17 (d of d), 5.88 (s), 5.83 (s), 2.90 (s), 2.87 (s); ir (CCl_4) 3.22 (sh): 3.25 (m); 3.28, 3.37, 3.40 (s); 3.48 (m); 5.78 (w); 6.27 (m); 6.70, 6.90, 7.95, 8.03, 8.72, 9.30, 9.73, 9.90, 11.63, 14.40 μ (s). Mass spectra (70 eV) of the products were obtained with the gc/mass spectral interface. **33** had *m/e* (rel intensity) 162 (23), 81 (100), 53 (22); **32**, 172 (25), 91 (31), 81 (100), 65 (9), 53 (12); **17**, 182 (19), 91 (100), 65 (13).

Photolysis of α-Naphthylmethyl Phenylacetate (31).—As above, the irradiation of the ester was monitored by use of a limewater bubbler; 336 mg (1.22 mmol) of **31** in 15 ml of dioxane was degassed and irradiated (2537 Å). After 2900 min, vpc analysis (as above) showed three products (relative areas 1:10:1) in *ca.* 40% yield; limewater test was positive. Removal of the solvent and chromatography of the residue (327 mg) on a 1.5 × 52 cm column of Davison Grade 950 silica gel, slurry packed with hexane, gave (75 ml fractions) 1–6, hexane eluent, 3 mg residue; 7–10, 1% ether–hexane, 2 mg residue; 11–13, 2% ether–hexane, nil; 14–16, 2% ether–hexane, 114 mg (40%) of a mixture of dibenzyl (**17**), 5%, and 1-α-naphthyl-2-phenylethane (**34**), 95%; 17–18, 2% ether–hexane, 3 mg of residue; 19–22, 4% ether–hexane, nil; 23–27, 10% ether–hexane, 130 mg (39%) of unchanged **31**. The di-α-naphthylethane was present in only trace quantities. However, it was shown to be present by coinjection with a sample obtained from the RPR 3000 Å irradiation (*vide infra*).

The viscous oil from fractions 14–16 had nmr ($CDCl_3$, TMS) δ 7.22 (s) superimposed on 8.20–7.13 (m, 12 H), 3.18 (AA'BB', 4 H); ir ($CHCl_3$) 3.25, 3.31, 3.39 (s); 3.48 (m); 5.15, 5.37, 5.55 (w); 6.26, 6.70, 6.90, 7.20 (m); 8.60 (w); 9.30, 9.72, 9.85 (m); 10.38, 11.68 (w); 14.45 μ (s); mass spectra (70 eV, gc/mass spectral interface) **17**, *m/e* (rel intensity) 182 (12), 92 (9), 91 (100), 65 (15) (identical with authentic mass spectrum of dibenzyl); **34**, 232 (19), 142 (12), 141 (100), 115 (16), 91 (6).

Photolysis of **31** with the RPR-3000 Å lamps (568 mg **31**, 2.06 mmol, in 15 ml dioxane) led to a positive limewater test. Vpc analysis showed 54% conversion after 2850 min, with three products formed in a 1:13:1 ratio. The major product was identical with 1-α-naphthyl-2-phenylethane (**34**) by vpc coinjection. Dibenzyl (**17**) was also observed as a minor product. Removal of the solvent and addition of ether resulted in formation of white crystals of 1,2-di-α-naphthylethane (**35**), mp 161–163° (lit.[40] mp 161–162°).

Solvent Effects on the Photostationary State of *cis*- and *trans*-1,2-Diphenylcyclopropane.—Samples of synthetic *cis*- and *trans*-1,2-diphenylcyclopropane (**13** and **14**) were dissolved in 15 ml of solvent, degassed, and irradiated in the merry-go-round at 2537 Å. Aliquots were withdrawn at intervals for vpc analysis (column 200°). For each solvent, the photostationary state was reached from *ca.* 5% excess cis or from 5% excess trans. The results are summarized in Tables III and IV.

Quantum Yield Determinations. General Procedure.—A solution of the lactone or ester in 15 ml of solvent in a quartz tube was degassed, placed in the merry-go-round, and irradiated with the RPR-2537 Å lamps. Light output was monitored by potassium ferrioxalate actinometry by the method of Hatchard and Parker.[41] Samples were withdrawn at intervals and analyzed directly by vpc.

Quantum yields for carbon dioxide evolution were measured by passing oxygen-free dry nitrogen through the photolysis mixture. The effluent gas from the photolysis vessel was then passed through a tared Ascarite–Anhydrone (magnesium perchlorate) trap.

Registry No.—**4**, 1008-76-0; **8**, 33574-07-1; **9**, 5279-82-3; **10**, 5590-14-7; **11**, 20272-24-6; **12**, 20272-26-8; **16**, 102-16-9; **18**, 36707-18-3; **19**, 33574-08-2; **20**, 538-39-6; **21**, 16557-55-2; **22**, 33574-09-3; **23**, 36707-23-0; **24**, 36707-24-1; **25**, 36707-25-2; **26**, 4960-53-6; **28**, 36707-27-4; **30**, 36707-28-5; **31**, 36707-29-6; **32**, 36707-30-9; **33**, 36707-31-0; **34**, 36707-32-1.

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(40) N. P. Buu-Hoi and N. Hoan, *J. Org. Chem.*, **14**, 1023 (1949).

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Kinetic Control in the Formation of Dienamines. Cross-Conjugated Dienamines of $\Delta^{3(9)}$-4-Hydrindenones

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A series of $\Delta^{3(9)}$-4-hydrindenones gives, with pyrrolidine, pure cross-conjugated dienamines. Systematic attempts to demonstrate the presence or to prepare the isomeric linearly conjugated dienamines having the amine group at the terminus of the diene were unsuccessful. Since the stereoisomeric 2,3-dimethyl-$\Delta^{3(9)}$-4-hydrindenones (**11**) give the corresponding cross-conjugated dienamines without any interconversion, this is regarded as a direct evidence for kinetic control in the formation of these bicyclic dienamines as a group. This generalization is supported by synthesis of the dienamines with N-deuterated pyrrolidine. The high regiospecificity of the reaction is explained in terms of steric hindrance in the concerned bicyclic system.

The enamines of 2-methylcyclohexanone and related unsymetrical ketones are known to be generally formed by thermodynamic control process. The less-substituted olefin is formed by a fast equilibrium, with steric effect control.[1,2]

The formation of the dienamines of α,β-unsaturated ketones also seems to be thermodynamically controlled, but products generally appear as mixtures of several dienamines, among which linear forms are predominant or exclusive. The yields in cross-conjugated forms are dependent on the structure of the reacting ketone and, for each ketone, on the structure of the antagonist secondary amine.[3,4] The determining factors for the ratio between linear and cross-conjugated dienamines are steric effects.[5] However,

(1) G. Stork, A. Brizzilara, H. Landesman, J. Smuszkowicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(2) S. K. Malhotra and F. Johnson, *Tetrahedron Lett.*, 4027 (1965).

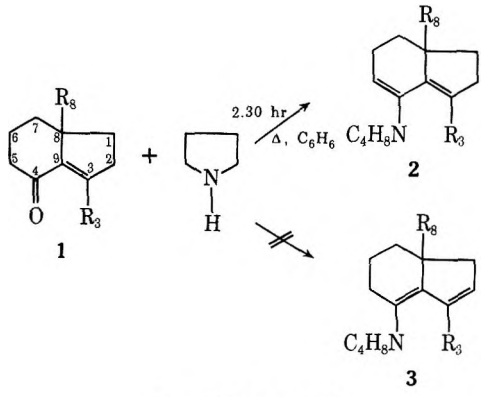
(3) G. Stork and G. Birnbaum, *ibid.*, 313 (1961).

(4) N. F. Firrell and P. W. Hickmott, *J. Chem. Soc. B*, 293 (1969).

(5) (a) F. Johnson, *Chem. Rev.*, **68**, 375 (1968); (b) P. W. Hickmott, B. J. Hopkins and C. T. Yoxall, *J. Chem. Soc., B*, 205 (1971).

as for other unsaturated systems,[6] a linear conjugation is probably better than a cross conjugation, and electronic effects also account for the observed equilibrium.

The behavior of cisoid unsaturated cyclohexanones is different. These ketones (2-alkylidenecyclohexanones or Δ^8-1-octalone) give mixtures of dienamines with a predominant cross-conjugated form.[8] The limit case is that of $\Delta^{3(9)}$-4-hydrindenones **1**, which afford with good yields pure cross-conjugated dienamines **2**.[7]



a, R_3 = H; R_8 = CH_3
b, R_3 = CH_3; R_8 = H
c, R_3 = R_8 = CH_3

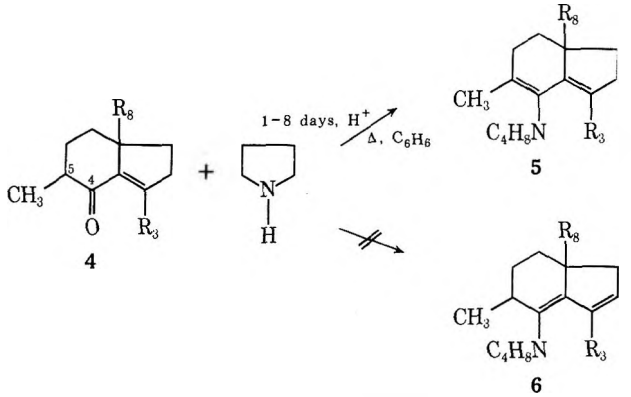
In the case of pulegone, we had observed an obvious kinetic control process followed by a slow equilibrium[3] since the ratio of different forms was time dependent.

In the present work we look over the control process in the formation of the pure cross-conjugated dienamines of $\Delta^{3(9)}$-4-hydrindenones **1**.

Results

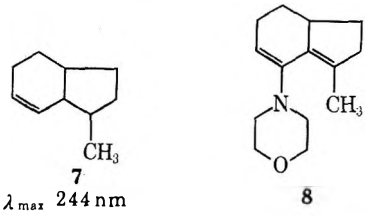
All the attempts to demonstrate the existence of an equilibrium between the cross-conjugated dienamines **2** and an uncertain linear form **3** lead to negative results.

I. Attempts of the Displacement of the Equilibrium toward the Linear Form.—The formation of pure cross-conjugated dienamines **2** formally appears similar to that of the less-substituted enamine from α-substituted cyclohexanone. Then we expected that the ketones **4** having a substituent on C_5 position could give a certain amount of linear dienamines **6**. In fact, in the three cases investigated, we have obtained pure cross-conjugated dienamines **5**. The reaction is more difficult than in the case of hydrindenones **1** and gives yields of only about 30–60% instead of 80–90% for **1**.



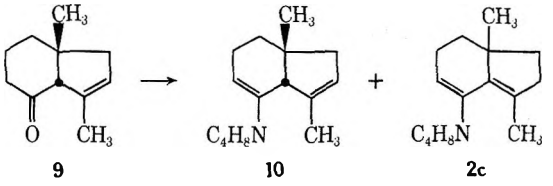
a, R_3 = H; R_8 = CH_3
b, R_3 = CH_3; R_8 = H
c, R_3 = R_8 = CH_3

On the other hand, it is known that the change of amine may modify the observed equilibrium between the dienamines.[4] Nevertheless, the 3-methyl-$\Delta^{3(9)}$-4-hydrindenone **1b** gives slowly (12-hr reflux in toluene with TsOH), with morpholine, a pure cross-conjugated dienamine **8**.



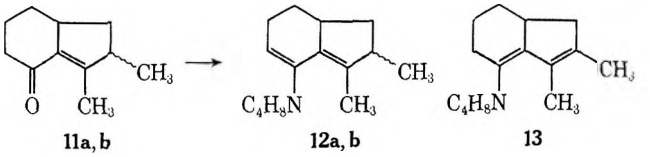
II. An Attempt of Direct Synthesis of the Linear Dienamine.—If the equilibrium between the cross-conjugated form and the expected linear form is slow, the direct synthesis of the linear dienamine could allow the study of the equilibrium.

The synthesis starts from the 3,8-dimethyl-Δ^2-4-hydrindenone **9**. This ketone is an α-substituted cyclohexanone and should give the dienamine with the less-substituted double bond (**10**), but the equilibrium



must be displaced, at least partially, by the presence of the C_2–C_3 double bond, since there is an important conjugation in the linear form **3c**, counteracting the steric effects. Then it would be possible to detect the formation of the dienamine **3c**. In fact, the reaction product of the ketone with pyrrolidine in excess (reflux in benzene with TsOH as a catalyst and distillation) is a mixture of the unconjugated dienamine **10** and the cross-conjugated dienamine **2c**, the latter being formed in small amounts. If this mixture is heated in benzene with TsOH, it evolves towards the pure cross-conjugated dienamine **2c**.

III. Direct Evidence of the Kinetic Control and Absence of the Equilibrium.—The two stereoisomeric hydrindenones **11a** and **11b** have two different stereoisomeric cross-conjugated dienamines **12a** and **12b**, but they have a common hypothetic linear dienamine **13**.



We have then investigated the case of the two separated pure ketones **11a** and **11b**. The experimental result is as follows. Each ketone gives a pure cross-conjugated dienamine by refluxing with pyrrolidine

(6) N. F. Phelan and M. Orchin, *J. Chem. Educ.*, **45**, 633 (1968).
(7) G. Dana and F. Weisbuch, *C. R. Acad. Sci., Ser. C*, **267**, 1154 (1968).
(8) C. Yamagami, F. Weisbuch, and G. Dana, *Tetrahedron*, **27**, 2967 (1971).

in benzene (without TsOH). The nmr data show that these two dienamines are different species. After distillation, these products are submitted to equilibrating conditions by a reflux for 24–48 hr in benzene with TsOH as a catalyst (10 mol % with respect to the dienamine). The dienamines remain pure and unchanged. They are then hydrolyzed, and each regenerated ketone is identical with the starting one (identification by nmr and vpc).

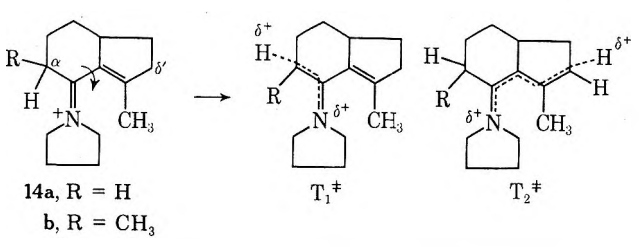
This result shows unambiguously that the two cross-conjugated dienamines **12a** and **12b** are not in equilibrium with each other, and that the linear dienamine **13** is not formed as an intermediate neither during the preparation of dienamines, nor during their acidic equilibration, even as an imperceptible trace. Then the reaction occurs under kinetic control, and the formation of the kinetic product is not followed by a thermodynamical equilibrium. This behavior is definitely different from that of the unsaturated transoid ketones (thermodynamic control process with fast equilibrium),[5] and from that of some less-strained cisoid ketones (kinetic control process followed by a slow equilibrium), as pulegone.[8]

The generalization of this result to the cases of the other hydrindenones **1** (or **4**) is supported by the synthesis or by the equilibration of the dienamines with deuteriopyrrolidine and a trace of deuterio-*p*-toluenesulfonic acid. If there was an equilibrating process involving the linear dienamines **3** (or **6**), we would have obtained di- and trideuterated dienamines **2** (or mono- and dideuterated dienamines **5**).

The experiments have been carried out in the case of hydrindenones **1c** and **4c** with pyrrolidine (50% d_1). The following results have been obtained: (a) synthesis of **2c**, 67.5% d_0 + 30% d_1 + 2.5% d_2; (b) equilibration of **2c** (3 hr in boiling benzene), 71% d_0 + 25% d_1 + 4% d_2; (c) equilibration of **5c** (1 hr in boiling benzene), 98% d_0 + 2% d_1; (d) synthesis of **12**, 68% d_0 + 29% d_1 + 3% d_2.

We observed that the precision of our measurements of isotopic abundance was about 2–4.5% (error relative to the theoretical values in natural samples, or error of reproducibility of the results with the same samples). As the dienamine **12** is formed with kinetic control, the small excess deuteration appears as insignificant (or arising from some slow unknown reaction), and we can say that the entire series reacts with kinetic control and does not involve the linear dienamine form with a noticeable rate.

This exclusive exchange of protons in the α position may be attributed to a hindered coplanarity of the double bonds of the intermediate immonium cations **14**.



14a, R = H
b, R = CH_3

$T_1^{\pm}$ $T_2^{\pm}$

Indeed these cations have been obtained as perchlorate salts of the corresponding dienamines, and their uv absorption spectra show a low conjugation between the two double bonds ($\epsilon \sim 6000$).

This lack of coplanarity would prevent the transmission of the positive charge from the N atom to the $C_{\gamma'}$ position[9] in the transition state ($T_2^{\pm}$).

Conclusion

The dramatic behavior observed in the formation of the cross-conjugated dienamines of $\Delta^{3(9)}$-4-hydrindenones results from a kinetic control process of the reaction caused by the hindered coplanarity of the intermediate immonium salt. This lack of coplanarity seems specific to this bicyclic system and is related to its particular strain.

This rigorous regiospecific reaction gives interesting synthetic intermediates, with good yields, allowing new possibilities of steroidal skeleton synthesis.[10]

Experimental Section[11]

The $\Delta^{3(9)}$-4-hydrindenones **1** are synthetized by the reduction of a mixture of cyclohex-2-en-1-one (or 3-methylcyclohex-2-en-1-one) with an α,β-unsaturated aliphatic aldehyde or ketone.[12]

The methyl-5 derivatives (ketones **4**) are obtained by normal reaction of methyl iodide with the dienamines **2**. (The yields are better than by the direct alkylation of the ketone by action of NaH or NH_2Na.) We obtained good elemental analyses after elimination of the residual starting ketone by a new reaction with pyrrolidine. (The residual starting ketone is not easily discernible either by vpc or by nmr.)

The structure and purity of the dienamines is demonstrated by mass spectral molecular weight determination and by nmr and ir spectroscopy (Table I).

4-Pyrrolidino-8-methyl-$\Delta^{3(9),4}$-hydrindane (2a).—A mixture of 22 mmol (3.3 g) of 8-methyl-$\Delta^{3(9)}$-4-hydrindenone **1a** and 75 mmol (5.4 g) of pyrrolidine is refluxed for 2.30 hr with 100 ml of benzene in a Dean–Stark separatory funnel; then benzene is evaporated under reduced pressure. The residue is then distilled and gives **2a**, bp 75° (0.05 mm), 4.35 g (yield 73%). The same result is obtained with TsOH as a catalyst (reflux 45 min only). *Anal.* Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.58; H, 10.39; N, 6.79.

Alkylation of the Dienamine 2a. Formation of the 5,8-Dimethyl-$\Delta^{3(9)}$-4-hydrindenone 4a.—A mixture of 15 mmol (3 g) of the dienamine **2a** and 20 mmol of methyl iodide (2.9 g) dissolved in 30 ml of dioxane is refluxed for 18 hr. The solution is hydrolyzed with acetic acid–sodium acetate–methanol buffer[13] (205 ml), neutralized with 35 g of NaOH in 120 ml of water, and diluted with 210 ml of water saturated with NaCl. The extraction with benzene yields **4a**, bp 100° (16 mm), 1.15 g (yield 50%). Nmr spectra show the presence of two geometrical isomers giving two triplets (J = 2.5 Hz) for the olefinic proton, δ_H (CCl_4) 6.15 (65%) and 6.32 ppm (35%). *Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.36; H, 9.71.

4-Pyrrolidino-5,8-dimethyl-$\Delta^{3(9),4}$-hydrindane (5a).—A mixture of 3.6 mmol (600 mg) of the preceding ketone **4a** and 14 mmol (1 g) of pyrrolidine is refluxed with 12 ml of benzene and 15 mg of TsOH for 18 hr. The product is distilled, bp 75° (0.01 mm), but appears with an important residual ketone. This product is evaporated *in vacuo* at 30° for 4 hr and gives the pure dienamine **5a**. *Anal.* Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.45. Found: C, 82.78; H, 10.49; N, 6.41.

4-Pyrrolidino-3-methyl-$\Delta^{3(9),4}$-hydrindane (2b).—A mixture of 174 mmol (26 g) of 3-methyl-$\Delta^{3(9)}$-4-hydrindenone (**1b**) and 520 mmol (37 g) of pyrrolidine is refluxed with 370 ml of benzene containing 40 mg of TsOH for 2.30 hr. Distillation of the product gives **2b**, bp 78° (0.01 mm), 33 g (yield 93%). *Anal.* Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.61; H, 10.42; N, 6.96.

The perchlorate of **2b** has mp 132.5–133° (crystallized from

(9) N. A. Firrell and P. W. Hickmott, *J. Chem. Soc. C*, 716 (1970).
(10) F. Weisbuch and G. Dana, *Tetrahedron Lett.*, 1511 (1969).
(11) With contribution of H. Guiguen.
(12) F. Weisbuch, *C. R. Acad. Sci., Ser. C*, **263**, 1234 (1966); Thesis, Paris, 1966.
(13) F. W. Heyl and M. E. Herr, *J. Amer. Chem. Soc.*, **75**, 1918 (1953).

TABLE I

SPECTROSCOPIC DESCRIPTION OF THE CROSS-CONJUGATED DIENAMINES

Compd	Mol wt m/e[a] at 8 eV	Ir,[b] cm^{-1}	Uv,[c] nm (ε)	Nmr,[d] δ, ppm
2a	203	1598	230 (11,800)	H(5) 4.57 (t, J = 4 Hz)
			271 (5500)	H(3) 5.53 (t, J = 2.2 Hz)
			Δλ +27	CH_3(8) 0.97 (s)
2b	203	1601		H(5) 4.60 (t, J = 3.8 Hz)
				CH_3(3) 1.87
2c	217	1605	231 (17,000)	H(5) 4.58 (t, J =
			260 (infl)	3.9 Hz)
				CH_3(3) 1.88
				CH_3(8) 0.98 (s)
5a	217	1605	242 (12,000)	H(3) 5.22
			283 (1700)	CH_3(5) 1.72
			Δλ +34	CH_3(8) 0.92 (s)
5b	217	1606	244 (15,500)	CH_3(5) 1.60
			285 (3100)	CH_3(3) 1.80
			Δλ +31	
5c	231	1608	246 (15,100)	CH_3(5) 1.60
			285 (2600)	CH_3(3) 1.77
			Δλ +31	CH_3(8) 0.89 (s)
8			235 (15,100)	H(5) 4.77 (t, J =
			250 (infl)	4 Hz)

[a] Mass spectra; the molecular weights have been determined with a spectrometer Hitachi-Perkin-Elmer RMU 6E MS. [b] Ir spectra are registered as films of pure material (polystyrene as reference) (Perkin-Elmer 137G). [c] Uv spectra are taken in dry cyclohexane solution (Spectralux double-beam spectrograph, SAFAS, Monaco). The Δλ increment of pyrrolidine group on the conjugation band is calculated from the λ_{max} observed for 3-methyl-$\Delta^{3(9),4}$-hydrindane **7**, as reference. [d] Nmr spectra are taken in dry CCl_4 solution at 60 MHz (Varian A 60); δ in ppm from internal TMS; s, singlet; t, triplet.

methanol and ether); ir 1636 and 1090 cm^{-1}; uv $\lambda_{max}^{CHCl_3}$ 288 nm (ε 5500); nmr ($CDCl_3$) δ_{CH_3} 2.87 ppm.

Alkylation of the Dienamine 2b. Formation of the 3,5-Dimethyl-$\Delta^{3(9)}$-4-hydrindenone 4b.—A mixture of 61 mmol (12.4 g) of the dienamine **2b** and 73 mmol (11 g) of methyl iodide, dissolved in 124 ml of dried dioxane, is refluxed for 17 hr. After being cooled, the solution gives a white solid mass which is hydrolyzed in the buffered solution[13] (820 ml) for 20 hr, diluted with 800 ml of water saturated with NaCl, neutralized with 150 g of NaOH in 450 ml of water, extracted with ether, and dried over Na_2SO_4. Distillation gives **4b**: bp 118–122° (20 mm); 9.4 g (yield 97%); ir $\nu_{C=O}$ 1680 cm^{-1}, $\nu_{C=C}$ 1629 cm^{-1}. The nmr spectrum of **4b** in solution in C_6H_6 shows two isomers characterized by their methyl doublets at 1.03 (J = 7.2 Hz, 40–45%) and 1.15 ppm (J = 6.2 Hz, 55–60%). *Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.40; H, 9.92.

4-Pyrrolidino-3,5-dimethyl-$\Delta^{3(9),4}$-hydrindane (5b).—A mixture of 37 mmol (6 g) of the hydrindenone **4b**, with a great excess of pyrrolidine (280 mmol) in 50 ml of benzene containing TsOH, is refluxed under a condenser containing molecular sieves (4 Å) for 48 hr. Distillation (0.05 mm) gives pure unreacted starting ketone, bp 40°, 3 g; intermediate, bp 40–78°, 1 g; and dienamine **5b**, bp 78–80°, 3 g. *Anal.* Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.45. Found: C, 82.96; H, 10.65; N, 6.51.

The perchlorate of **5b** has mp 137–166° (mixture of the two isomers which appear in the nmr spectrum); δ_{CH_3} ($CDCl_3$, TMS internal reference) 1.15 (29%) and 1.29 ppm (71%) (doublets); uv $\lambda_{max}^{CHCl_3}$ 289 nm (ε 6000); $\lambda_{max}^{CH_3OH}$ 288 nm (ε 6200).

4-Pyrrolidino-3,8-dimethyl-$\Delta^{3(9)4}$-hydrindane (2c).—The previous procedure gives with the 3,8-dimethyl-$\Delta^{3(9)}$-4-hydrindenone **1c** the dienamine **2c**, bp 82° (0.01 mm), yield 75%. *Anal.* Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.45. Found: C, 82.83; H, 10.69; N, 6.37.

4-Pyrrolidino-3,8-dimethyl-$\Delta^{2,4}$-hydrindane (10).—The same ketone **1c** contains 5–10% unconjugated form **9**, 3,8-dimethyl-Δ^{2}-4-hydrindenone,[12] which is separated as a pure isomer, by vpc on silicone SE-30 at 160°.

A mixture of 463 mg of the unconjugated ketone **9** and 800 mg of pyrrolidine is heated in 10 ml of benzene with TsOH for 4.15 hr in a Dean–Stark separatory funnel. The raw product, examined by nmr after distillation, shows (1) the unreacted ketone, about 22%, characterized by its olefinic proton (5.40 ppm) and angular methyl group (1.17 ppm); (2) the unconjugated dienamine **10**, about 55%, characterized by the two olefinic protons (4.37 ppm, triplet, J = 4 Hz, and 5.23 ppm, massive $\nu_{1/2}$ = 5 Hz) and the angular methyl (1.09 ppm); (3) the cross-conjugated dienamine **2c**, about 24%, characterized by its olefinic proton (4.59 ppm, triplet, J = 3.9 Hz) and the angular methyl (0.98 ppm). The residual ketone is evaporated *in vacuo*, and the dienamine mixture is dissolved in 10 ml of benzene with TsOH and refluxed for 12 hr. The nmr spectrum shows the cross-conjugated dienamine **2c** (about 85%) and the residual unconjugated dienamine **10** (15%).

The perchlorate of **10** has mp 218–219° (insoluble in $CHCl_3$); nmr (CD_3COCD_3, TMS internal reference) $\delta_{H(2)}$ 5.75 ppm (m), $\delta_{H(3)}$ 2.96 ppm (sharp singlet), $\delta_{CH_3(8)}$ 1.30 ppm (sharp singlet), $\delta_{CH_3(3)}$ 1.72 ppm.

Alkylation of the Dienamine 2c to Give 3,5,8-Trimethyl-$\Delta^{3(9)}$-4-hydrindenone 4c.—The procedure, used for **4b**, gives, with the dienamine **2c** the ketone **4c**: bp 110–113° (15 mm); yield 52%; ir $\nu_{C=O}$ 1680 cm^{-1}, $\nu_{C=C}$ 1627 cm^{-1}. *Anal.* Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18; Found: C, 81.00; H, 10.28. The nmr spectrum in C_6H_6 shows the formation of two isomers: (a) $\delta_{CH_3(8)}$ 0.85 ppm (s) and $\delta_{CH_3(5)}$ 1.17 ppm (d, J = 5.1 Hz), about 55%; (b) $\delta_{CH_3(8)}$ 0.91 ppm (s) and $\delta_{CH_3(5)}$ 1.06 ppm (d, J = 6.2 Hz), about 45%.

4-Pyrrolidino-3,5,8-trimethyl-$\Delta^{3(9),4}$-hydrindane (5c).—A 9.7-g sample of the pure ketone **4c** and 30 g of pyrrolidine are refluxed with molecular sieves in the condenser (as for **5b**) for 8 days in 120 ml of benzene with TsOH. Distillation gives 5.9 g of the unreacted ketone **4c** (high purity), bp 40° (0.01 mm), and 4.2 g of the dienamine **5c**, bp 76° (0.01 mm). *Anal.* Calcd for $C_{16}H_{25}N$: C, 83.11; H, 10.82; N, 6.06. Found: C, 83.03; H, 10.92; N, 6.18.

4-Pyrrolidino-2,3-dimethyl-$\Delta^{3(9),4}$-hydrindanes (12a and b).—The two starting stereoisomeric ketones **11a** and **b**, easily discernible by nmr spectroscopy owing to the doublets of the 2-methyl group, are separated by vpc on Apiezon N at 160° (length of the column 4 m, 30 μl for each injection) and obtained rigorously free from one another by a second fractionation.

The two dienamines, prepared as indicated, are characterized by the triplets of the olefinic proton in CCl_4: δ_H 4.57 ppm for the dienamine of the first predominant ketone and δ_H 4.68 ppm for the second one.

The experiments have been carried out with 280 mg of hydrindenone **11a**, the first isomer, and 110 mg of hydrindenone **11b**, the second isomer.

Anal. Calcd for $C_{15}H_{23}N$ (mixture of the two isomers)[7]: C, 82.89; H, 10.67; N, 6.45. Found: C, 82.80; H, 10.72; N, 6.52.

Registry No.—**2a**, 22508-86-7; **2b**, 22508-83-4; **2c**, 22508-84-5; **4a**, 36803-70-0; **4b**, 36803-71-1; **4c**, 36803-72-2; **5a**, 36803-73-3; **5b**, 36803-74-4; **5b** perchlorate, 36803-75-5; **5c**, 36803-76-6; **10** perchlorate, 36807-50-8; **12**, 36803-77-7.

The Reaction of Lead Tetraacetate with Unsymmetrical Ketones

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2-Butanone, when treated with lead tetraacetate (LTA) in acetic acid, gave 1-acetoxy-2-butanone as the major product. Similarly, 3-methyl-2-butanone and 2-octanone gave 1-acetoxy-3-methyl-2-butanone and 1-acetoxy-2-octanone as the major products. Phenylacetone, however, gave 1-acetoxy-1-phenyl-2-propanone as the major product. Similar results were obtained in propionic acid, propionoxy ketones being the major products, although minor amounts of acetoxy ketones were obtained. In trifluoroacetic acid, trifluoroacetoxy ketones were obtained, and the major products were 3-trifluoroacetoxy-3-methyl-2-butanone, 3-trifluoroacetoxy-2-octanone, and 1-trifluoroacetoxy-2-propanone. Deuterium exchange results indicate that the rates of substitution for the less and the more highly substituted positions for 2-octanone and isopropyl methyl ketone are about equal, while the rates of substitution for the more highly substituted position is favored in 2-butanone and phenylacetone. Enol acetates, when treated with LTA, yield acetoxy ketones, and the position of the acetoxyl group is dependent upon the position of the double bond in the parent enol acetate.

The treatment of carbonyl compounds with lead tetraacetate (LTA) is a well-known method for producing α-acetoxy ketones and aldehydes. Fuson[1] observed that carbonyl compounds, which exist primarily in their enol form, react with LTA with unusual ease.

The rapid reaction of enols seems to suggest a mechanism similar to that proposed for the oxidation of monohydric phenols[2-4] where the reaction is believed to proceed through a lead ester.

Evidence to support the intermediacy of the enol in the reaction comes from several sources. Ichikawa[5] observed that the rate of the reaction is dependent only upon the concentration of the ketone and not on that of LTA. Henbest and coworkers[6] observed that the rate of oxidation of ketones by LTA is strongly accelerated by BF_3. The rate enhancement is explained as a catalysis due to BF_3, which accelerates the formation of the enol. Recently Ellis[7] observed that the formation of the acetoxy derivative takes place at a position α to a carbonyl group even when other positions are available. He also presented evidence supporting the enolate anion as an intermediate for the acetoxy ketone.[7b]

In the course of studying this reaction with unsymmetrical ketones rather than with symmetrical ketones,[8-10] it became apparent that the orientation of the acetoxy group on the ketone is not the same as that reported for the acid-catalyzed bromination of unsymmetrical ketones.[11,12]

The orientation of the acetoxy group in the reaction of LTA with ketones favors the less substituted carbon rather than the more substituted carbon. This result motivated us to do a further study of this reaction.

Results

The ketones were treated with LTA in a 1:1 molar ratio in acetic acid or propionic acid at 100 ± 2° for 2 hr and in refluxing trifluoroacetic acid for 2 hr. The products were isolated by gas chromatography and analyzed by ir and nmr spectroscopy. The results are summarized in Table I. The reaction proceeded more rapidly in acetic acid than in benzene, and in neither case were any dimers found even though dimers have been reported in some cases.[10,13] After 2-octanone (**1**) was refluxed with LTA in benzene for 2 hr, 99% of the starting material was recovered and less than 1% of 1-acetoxy-2-octanone (**5**) was obtained.

2-Adamantanone, which cannot enolize, was treated with LTA. It was recovered unchanged, suggesting that an enol is a required intermediate in the formation of acetoxy ketones.

Since enols are clearly involved in the reaction, it seemed desirable to study the rates and orientation of enolization under our reaction conditions. If enolization is indeed the rate-controlling factor, this should be reflected in deuterium exchange studies. Nmr spectroscopy proved to be the best technique for studying the rates of enolization at these two positions for these ketones.

Several studies of the rates of substitution at enolic sites in ketones using nmr spectroscopy have already been reported.[12,14-17] In deuterated HCl, Rappe[12] found that the methylene group in methyl ketones is deuterated faster than the methyl group. However, certain methyne groups do exchange their protons more slowly than do the methyl groups. The effect is attributed to the steric hindrance from the branches on the methyne group.

Our deuterium exchange study indicated that 2-butanone had a faster rate of enolization for the methylene position than for the methyl position. For 2-octanone and 3-methyl-2-butanone, the rates of enolization for both positions were about equal, while for phenylacetone, the rate of enolization for the methylene group was greater than for the methyl group (Table II).

Comparison of Table I and Table II indicates that the

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TABLE I

PRODUCTS FROM THE OXIDATION OF KETONES WITH LTA

	In acetic acid[a]			In propionic acid			In trifluoroacetic acid		
Ketone	Total yield,[b] %	Ratio A^c (acetoxy ketone)	$1^d/K_{Br}$	Yield,[b] %	Ratio A (acetoxy ketone)	Ratio A^c (propionoxy ketone)	Total yield,[b] %	Ratio A^c (acetoxy ketone)	Ratio A^c (trifluoroacetoxy ketone[g])
2-Butanone	64[h]	1.68	0.37						
2-Octanone	81[i]	2.00	*e*	73[j]	2	1.6	36[k]		0.145
3-Methyl-2-butanone	60[l]	5.70	0.33 (0.91[f])	89[m]	8	6.2	40[n]	0.500	0.714
Phenylacetone	93[o]	0.236		53[p]	0.187	0.226	36[q]		

[a] At 100 ± 2° for 2 hr. [b] The total yields are based on the distilled products, and include the starting ketone recovered and diacetoxy ketones. [c] The ratio of the least substituted and the most substituted products (CH_3/CH_2 or CH). [d] Relative values obtained from Cardwell and Kilner[11] where $K_{Br} = K_{CH_2}/K_{CH_3}$ or K_{CH}/K_{CH_3}. [e] No K_{Br} value has been reported for 2-octanone; however, K_{Br} for 2-heptanone has been reported to be 1.5. Therefore $1/K_{Br}$ for 2-heptanone is 0.67.[11] [f] Rappe and Sachs reported a value of $K_{Br} = 1.1$ for methyl isopropyl ketone; therefore $1/K_{Br} = 0.91$. [g] Isolated as a mixture of trifluoroacetoxy ketone and hydroxy ketone. [h] 2-Butanone, 6%; 3-acetoxy-2-butanone, 12%; 1-acetoxy-2-butanone, 24%; diacetoxy ketone, 22%. [i] 2-Octanone, 29%; 3-acetoxy-2-octanone, 14%; 1-acetoxy-2-octanone, 28%; diacetoxy ketone, 10%. [j] 2-Octanone, 31%; 3-acetoxy-2-octanone, 2%; 3-propionoxy-2-octanone, 13%; 1-acetoxy-2-octanone, 4%; 1-propionoxy-2-octanone, 21%; diacetoxy ketone, 2%. [k] 2-Octanone, 13%; 3-trifluoroacetoxy-2-octanone, 15%; 1-hydroxy-2-octanone, 1%; 1-trifluoroacetoxy-2-octanone, 1%; 3-acetoxy-2-octanone, 5.5%. [l] 3-Methyl-2-butanone, 10%; 3-acetoxy-3-methyl-2-butanone, 6%; 1-acetoxy-3-methyl-2-butanone, 34%; diacetoxy ketone, 10%. [m] 3-Methyl-2-butanone, 58%; 3-acetoxy-3-methyl-2-butanone, 0.6%; 3-methyl-3-propionoxy-2-butanone, 3%; 1-acetoxy-3-methyl-2-butanone, 5%; 1-propionoxy-3-methyl-2-butanone, 17.5%; dipropionoxy ketone, 5%. [n] 3-Methyl-2-butanone, 6%; 3-methyl-3-trifluoroacetoxy-2-butanone, 14%; hydroxy ketone, 4%, 1-trifluoroacetoxy-3-methyl-2-butanone, 4%; 1-hydroxy-3-methyl-2-butanone, 6%; 3-acetoxy-3-methyl-2-butanone, 4%; 1-acetoxy-3-methyl-2-butanone, 2%. [o] Phenylacetone, 20%; 1-acetoxy-1-phenyl-2-propanone, 51%; 1-acetoxy-3-phenyl-2-propanone, 12%; diacetoxy ketone 10%. [p] Phenylacetone, 8.5%; 1-acetoxy-1-phenyl-2-propanone, 8.5%; 3-acetoxy-1-phenyl-2-propanone, 1.6%; 3-propionoxy-1-phenyl-2-propanone, 6.4%; 1-propionoxy-1-phenyl-2-propanone, 28%. [q] Phenylacetone, 26%; 1-acetoxy-1-phenylacetone, 15%; 3-acetoxy-1-phenylacetone, less than 0.5%; 1-trifluoroacetoxy-1-phenylacetone, 7%; 3-trifluoroacetoxy-1-phenylacetone, less than 0.5%.

TABLE II

RATES OF DEUTERIUM EXCHANGE FOR UNSYMMETRICAL KETONES IN ACETIC ACID-d_4 AT 100 ± 2°

Ketone	CH_3, $k \times 10^5$, sec^{-1}	CH_2 or CH, $k \times 10^5$, sec^{-1}	K_R[a]	k_D[b]
2-Butanone	1.2	2.1	0.571	0.57
2-Octanone	1.7	1.8	0.944	0.69
3-Methyl-2-butanone	1.6	1.5	1.066	1.25
Phenylacetone	3.1	6.9	0.449	

[a] $K_R = k_{CH_3}/k_{CH_2}$ or k_{CH_3}/k_{CH}. [b] Relative values reported by Rappe[12] in deuterium chloride, deuterium oxide, and dioxane.

products ratio and the enolization rates do not correspond well. These results suggest that enolization may not be the rate-determining step in the formation of acetoxy ketones.

Enol acetates, on treatment with LTA, also yield acetoxy ketones as well as lead diacetate and acetic anhydride.[18,19] In order to determine the relationship between the position of the double bond of the enol acetate and the acetoxy group in the product, isomerically pure enol acetates of ketones were prepared and treated with LTA in acetic acid at 100°. The results are summarized in Table III.

The results shown in Table III demonstrate that enol acetates lead rather specifically to just one or two possible products. These results might suggest that each acetoxy ketone comes from the appropriate enol acetate. However, enol acetates are eliminated as intermediates based on the fact that no enol acetates were found in the reaction mixture of LTA with ketones even though substantial amounts of enol acetates are recovered on treatment with LTA. Furthermore, the fact that just one of two possible acetoxy ketones was obtained implies that acetoxy ketones are stable and do not isomerize under the reaction conditions.

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Experimental Section[20]

LTA Oxidations of Ketones.—The ketones (2–10 g) were heated at 100° for 2 hr with equimolar amounts of LTA in 50–100 ml of the acids (acetic, propionic, trifluoroacetic). Ethylene glycol (2–5 ml) was added, the mixtures were diluted with water (300 ml), and the organic materials were extracted with 2–3 portions of ether. The ether solutions were washed with 10% Na_2CO_3 until neutral and dried, and the product mixtures were separated by gc after distillation. Structural assignments of new compounds were made on the basis of spectral data, and the results are summarized in Table I.

Preparation of Enol Acetates.—The ketones (0.15–0.35 mol) were refluxed for 24 hr with isopropenyl acetate (0.3–0.5 mol) and *p*-toluenesulfonic acid (0.15–0.2 g). The mixtures were concentrated by distillation, cooled, and added to an ice-cold mixture of hexane (100 ml) and saturated $NaHCO_3$ (100 ml). The mixtures were stirred rapidly and the temperature was not allowed to rise above 10°. The hexane layers were separated and dried, and the products were isolated by gc after distillation. Structural assignments were made on the basis of spectral data.

Reactions of Enol Acetates with LTA.—The enol acetates (0.5–2.5 g) were heated at 100° for 2 hr with equimolar amounts of LTA in 25–100 ml of acetic acid. The mixtures were worked up in the manner described for LTA oxidations of ketones and the products were similarly identified. Results are summarized in Table III.

Experimental Procedure for the Deuterium Exchange.—Solutions containing the ketone and deuterated acetic acid-d_4 (1:4, v/v) were placed in an nmr tube, and the tubes were sealed and heated in an oil bath at 100 ± 2°. The tubes were withdrawn at 1-hr intervals and the nmr spectra were taken. The rate of substitution was monitored using the nonenolizable protons as internal standards. The rate study was run in duplicate and the probe's temperature was kept at 47°. The rates

(20) Nmr spectra were recorded on a Varian A-60 spectrophotometer; chemical shifts are reported in τ values using tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer. Gas chromatography was performed on an F & M Model 720 thermal conductivity gas chromatograph using 2-, 4-, or 10-ft columns containing 20% silicone rubber on Chromosorb W, 20% ethylene glycol adipate (EGA) on Chromosorb W, and 10% Carbowax on Chromosorb W. Boiling points are uncorrected.

TABLE III

PRODUCTS FROM THE REACTION OF ENOL ACETATES OF THE KETONES 1, 2, AND 3 WITH LTA IN ACETIC ACID

Compd	Total yield, % (distilled)	Acetoxy ketone found	Product ratio, % Acetoxy ketone	Product ratio, % Enol acetate
(trans) $CH_3(CH_2)_4CH{=}C(OAc)CH_3$[a]	50	$CH_3(CH_2)_4CH(OAc)COCH_3$	22	78
(cis) $CH_3(CH_2)_4CH{=}C(OAc)CH_3$[b]	75	$CH_3(CH_2)_4CH(OAc)COCH_3$[c]	30	70
$PhCH{=}C(OAc)CH_3$[d]	81	$PhCH(OAc)COCH_3$	50	50
$PhCH_2C(OAc){=}CH_2$	72	$PhCH(OAc)COCH_2OAc$	64	36
$(CH_3)_2CH(OAc){=}CH_2$	63	$(CH_3)_2COCH_2OAc$	72	28
$(CH_3)_2C{=}C(OAc)CH_3$	68	$(CH_3)_2C(OAc)COCH_3$	5	95

[a] The trans isomer only. [b] Mixture of *cis*-2-octen-2-yl acetate and 1-octen-2-yl acetate (8.45:1). [c] A trace amount (<1%) of the 1-acetoxy-2-octanone was found. [d] The cis and trans isomers of this compound could not be separated on our columns.

TABLE IV

Compd[a]	Nmr spectra, τ	Compd[a]	Nmr spectra[b]
3-Acetoxy-2-octanone	9.1 (m, 3 H), 8.7 (m, 8 H), 7.91 (s, 3 H), 7.90 (s, 3 H), 5.2 (m, 1 H)	3-Propionoxy-3-methyl-2-butanone	8.9 (t, 3 H), 8.6 (s, 6 H), 7.95 (s, 3 H), 7.75 (q, 2 H)
1-Acetoxy-2-octanone	9.1 (m, 3 H), 8.7 (m, 10 H), 7.9 (s, 3 H), 7.7 (m, 2 H), 5.3 (s, 2 H)	1-Propionoxy-3-methyl-2-butanone	8.85 (m, 9 H), 7.65 (m, 3 H), 5.4 (s, 2 H)
3-Propionoxy-2-octanone	9.1 (m, 6 H), 8.8 (m, 8 H), 7.9 (s, 3 H), 7.6 (q, 2 H), 5.1 (m, 1 H)	3-Methyl-3-trifluoroacetoxy-2-butanone	7.81 (s, 3 H), 8.45 (s, 6 H)
1-Propionoxy-2-octanone	9.1 (m, 6 H), 8.8 (m, 10 H), 7.6 (q, 2 H), 5.85 (s, 2 H)	1-Trifluoroacetoxy-3-methyl-2-butanone and 1-hydroxy-3-methyl-2-butanone	5.68 (s, 0.764 H), 6.26 (s, 1.24 H), 6.33 (s, 0.62 H), 7.45 (m, 1 H), 8.83 (d, 6 H)
1-Hydroxy-2-octanone and 1-trifluoroacetoxy-2-octanone	7.9 (s, 3 H), 6.35 (s, 2 H), 2.7 (s, 5 H)	3-Acetoxy-2-butanone	8.75 (d, 3 H), 7.95 (s, 6 H), 5.05 (q, 1 H)
1-Propionoxy-1-phenyl-2-propanone	8.8 (t, 3 H), 7.95 (q, 2 H), 6.4 (s, 1 H), 2.7 (s, 5 H)	1-Acetoxy-2-butanone	8.9 (t, 3 H), 7.93 (s, 3 H), 7.7 (q, 2 H), 5.5 (s, 2 H)
1-Propionoxy-3-phenyl-2-propanone	8.8 (t, 3 H), 7.65 (q, 2 H), 6.3 (s, 2 H), 5.38 (s, 2 H), 2.7 (s, 5 H)	*trans*-2-octen-2-yl acetate	9.1 (m, 3 H), 8.7–8.8 (m, 8 H), 8.15 (s, 3 H), 7.92 (s, 3 H), 5.1 (t, 1 H)
1-Phenyl-1-trifluoroacetoxy-2-propanone	7.9 (s, 3 H), 4.0 (s, 1 H), 2.58 (s, 5 H)	*cis*-2-octen-2-yl acetate	9.1 (m, 3 H), 8.7 (m, 8 H), 8.2 (s, 3 H), 7.95 (s, 3 H)
3-Acetoxy-3-methyl-2-butanone	8.6 (s, 6 H), 7.95 (s, 6 H)	1-phenyl-2-propen-2-yl acetate	8.05 (s, 3 H), 6.5 (s, 2 H), 5.5 (s, 1 H), 5.3 (s, 1 H), 2.8 (s, 5 H)
1-Acetoxy-3-methyl-2-butanone	8.8 (d, 6 H), 7.8 (s, 3 H), 7.4 (m, 1 H), 5.4 (s, 2 H)	*cis*- and *trans*-1-phenyl-1-propen-2-yl acetate	7.9 (s, 6 H), 4.2 (s, ½H), 2.75 (s, 5 H)

[a] Satisfactory analytical data for C and H (±0.3%) were found for these compounds: Ed.

were calculated from the slopes of the first-order plots of ln c/c_0 *vs.* t by means of a least square determination (c_0 = initial concentration, c = concentration at time t).

Nmr data appear in Table IV.

Registry No.—LTA, 546-67-8; 2-butanone, 78-93-3; 2-octanone, 111-13-7; 3-methyl-2-butanone, 563-80-4; phenylacetone, 103-79-7; 3-acetoxy-2-octanone, 36959-98-5; 3-acetoxy-2-octanone, 36959-99-6; 3-propionoxy-2-octanone, 36906-00-6; 1-propionoxy-2-octanone, 36906-01-7; 1-acetoxy-1-phenyl-2-propanone, 19275-80-0; 1-acetoxy-3-phenyl-2-propanone, 36960-03-9; 1-propionoxy-1-phenyl-2-propanone, 36960-04-0; 1-propionoxy-3-phenyl-2-propanone, 36960-05-1; 3-acetoxy-3-methyl-2-butanone, 10235-71-9; 1-acetoxy-3-methyl-2-butanone, 36960-07-3; 3-propionoxy-3-methyl-2-butanone, 36960-08-4; 1-propionoxy-3-methyl-2-butanone, 36960-09-5; 3-acetoxy-2-butanone, 4906-24-5; 1-acetoxy-2-butanone, 1575-57-1; *trans*-2-octen-2-yl acetate, 36960-12-0; *cis*-2-octen-2-yl acetate, 36960-13-1; 1-phenyl-2-propen-2-yl acetate, 25522-54-7; *cis*-1-phenyl-1-propen-2-yl acetate, 19980-46-2; *trans*-1-phenyl-1-propen-2-yl acetate, 19980-44-0; 1-hydroxy-2-octanone, 7019-19-4; 1-trifluoroacetoxy-2-octanone, 36960-18-6; 1-phenyl-1-trifluoroacetoxy-2-propanone, 36960-19-7; 3-methyl-3-trifluoroacetoxy-2-butanone, 36960-20-0; 1-trifluoroacetoxy-3-methyl-2-butanone, 36960-21-1; 1-hydroxy-3-methyl-2-butanone, 36960-22-2.

The Reduction of Organomercurials. Stereospecific Replacement of Mercury by Deuterium[1]

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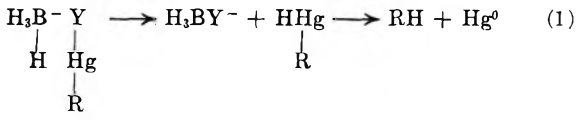
Sodium amalgam reduction of *cis*-8-acetoxymercuri- and *cis*-8-chloromercuridibenzobicyclo[2.2.2]octadien-7-ol acetates (**2** and **3**), *trans*-8-chloromercuridibenzobicyclo[2.2.2]octadien-7-ol (**4**), *cis,exo*-3-methoxy-2-norbornylmercuric chloride (**9**), *exo*-3-methoxy-*endo*-2-norbornylmercuric chloride (**10**), and *cis,endo*-3-methoxy-2-norbornylmercuric chloride (**11**) in alkaline deuterium oxide gives products with stereospecific retention during the replacement of mercury by deuterium. Sodium borodeuteride reduction of *trans*-8-chloromercuridibenzobicyclo[2.2.2]octadien-7-ol acetate (**5**), in addition to those compounds listed above, in aqueous base gives similar products but without stereospecific deuterium incorporation. Borodeuteride reduction of **3** and **4** in alkaline ethanol gives products without complete incorporation of deuterium. The results of these reductions are discussed briefly in mechanistic terms.

The work described in this paper arose from a need to determine rigorously the stereochemistry of oxymercuration products and to prepare specific isomers of β-deuterio alcohols.

During the early stages of this work, only a few papers regarding the specificity of the reduction of organomercurials had appeared. Bordwell and Douglass[4] studied reduction with borohydrides and established the stoichiometry (four mercurials per borohydride), source of hydrogen (only from BH_4^-), and lack of direct displacement character (neopentyl mercurials react readily). They attempted to determine the stereochemistry of the reaction by reducing *cis,exo*-3-hydroxy-2-chloromercurinorbornane with sodium borodeuteride. Only the exo-deuterated alcohol was found. A number of mechanisms were considered, but that shown in eq 1



(1)

seemed best to them. The final step was considered as an intramolecular extrusion to explain the retention observed. One example reported,[5] however, described at least one case where the reaction occurred with loss of stereochemistry.

Only one paper had considered the stereochemical course of the reduction of an organomercurial by sodium amalgam in deuterium oxide in which the substrate was not a norbornyl moiety. Thus, Wolfe and Campbell[6] studied the reduction of the product from the acetoxymercuration of 3,3,6,6-tetradeuteriocyclohexene. In this sterically unencumbered system, they found complete retention in the deuterated cyclohexanol. The cis isomer was not studied.

Several cases of retention with the sodium amalgam reduction of *exo*-2-mercurinorbornyl moieties had also been reported,[7] but the well-known preference for exo capture of norbornyl intermediates obscures interpretation of these results.

During the period of our investigation much interest has arisen in the oxymercuration–hydrodemercuration reaction.[8-12] This recent interest has prompted us to relay our results, which add the possibility of a stereospecific oxymercuration–deuteriodemercuration procedure for the preparation of stereospecific β-deuterio alcohols and alcohol derivatives to the regiospecificity already indicated,[9] and which also cast more light on the mechanism of the borohydride reduction.

Results

The Dibenzobicyclo[2.2.2]octadiene System.—With the view in mind of developing a general synthesis of 8-deuteriodibenzobicyclo[2.2.2]octadiene-7-ol derivatives, the oxymercuration and subsequent reduction of adducts derived from the readily available dibenzobicyclo[2.2.2]octatriene (**1**) were investigated. The syntheses of *cis*-8-acetoxymercuri- and *cis*-8-chloromercuridibenzobicyclo[2.2.2]octadien-7-ol acetates (**2** and **3**) and *trans*-8-chloromercuridibenzobicyclo[2.2.2]octadien-7-ol and 7-ol acetate (**4** and **5**) are straightforward and are described in the Experimental Section. Identification of the oxymercurial isomers **2**–**5** (and also the β-deuterio alcohols from their reduction) is facilitated by their simple pmr spectra.[13] Protons on the C-7,8 bridge have a 2.6 ± 0.7 Hz coupling constant with the C-1 and C-4 bridgehead protons. Cis protons at C-7 and C-8 couple with a constant of 8.8 ± 0.8 Hz and corresponding trans protons couple with a constant of 3.5 ± 1.1 Hz. Geminal protons at C-7 or C-8 are coupled with a constant of 13.1 ± 1.1 Hz. Protons cis and vicinal to acetoxy or hydroxy groups are shifted upfield about 0.3–0.4 ppm and protons trans and vicinal are shifted downfield about 0.7 ppm. Although the mercury group shifts the α proton downfield roughly

(1) Paper LXXV in series Bridged Polycyclic Compounds of University of Colorado group. Paper LXXIV: S. J. Cristol, G. C. Schloemer, D. R. James, and L. A. Paquette, *J. Amer. Chem. Soc.*, in press.

(2) Taken in part from the Ph.D. dissertation of J. J. M., University of California, 1966 (work done on norbornane system); *Diss. Abstr. B*, **28** (1), 112 (1967).

(3) National Science Foundation Trainee, 1968–1970. Taken in part from the Ph.D. dissertation of R. S. B., University of Colorado, 1970. (Work done on dibenzobicyclooctadiene system.)

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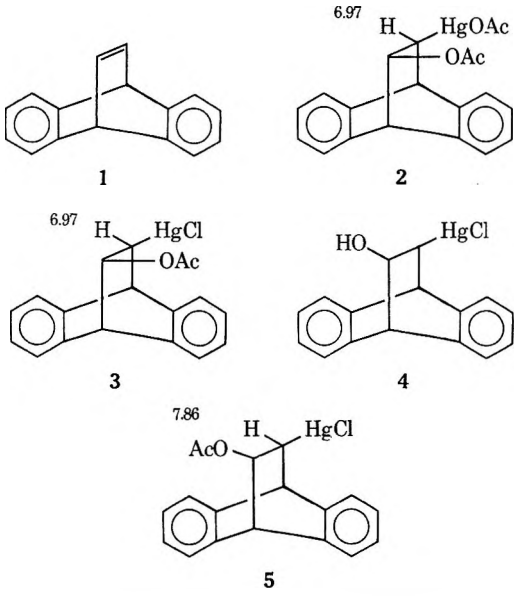
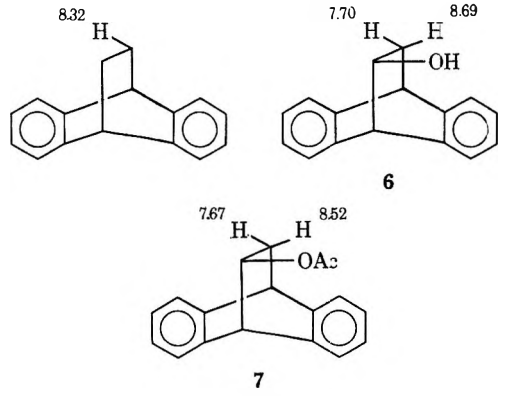
(12) G. M. Whitesides and J. San Filippo, Jr., *ibid.*, **92**, 6611 (1970).

(13) S. J. Cristol, T. W. Russell, J. R. Mohrig, and D. E. Plorde, *J. Org. Chem.*, **31**, 581 (1966).



0.6 ppm, similar effects of β-oxy functional groups are observed. The data of importance are shown on the structural formulas. Spectra were run in $CDCl_3$, and the chemical shift values, in τ units, are given.

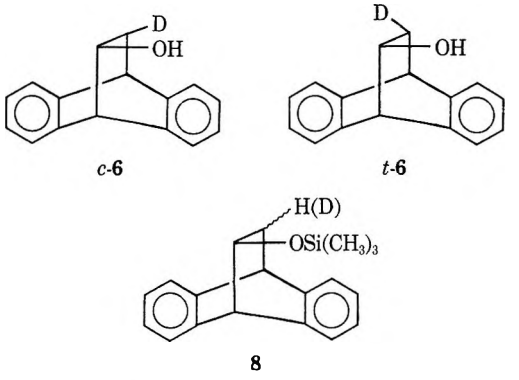


Compound **4** was not sufficiently soluble in $CDCl_3$ and its spectrum was therefore run in DMSO-d_6. The coupling constants of **4** (see Experimental Section) and its conversion to **5** attest to its assigned structure.

Reduction of mercurials **2**–**5** by either sodium borohydride or sodium amalgam gave good yields of either dibenzobicyclo[2.2.2]octadien-7-ol (**6**)[14] or its acetate (**7**).[14] The pmr spectra of **6** and **7** show good separation of the geminal C-8 protons. Thus, if a deuterium is placed at the C-8 position by either sodium borodeuteride or sodium amalgam reduction in deuterium oxide of the mercurials **2**–**5**, stereochemical analysis of the resulting **6**-*d* or **7**-*d* can be made by integrating the pmr signal of these regions.

Reductions with sodium amalgam were carried out in 1 *M* NaOD in D_2O solution with a large excess of the reducing agent for relatively long periods of time. Consequently, regardless of the mercurial (**2**–**5**) reduced, because of the hydrolysis of the ester only alcohol **6**-*d* was isolated as the product. Reduction of *cis*-acetoxyalkylmercuric acetate (**2**), *cis*-acetoxyalkylmercuric chloride (**3**), and *trans*-acetoxyalkylmercuric chloride (**5**) with sodium borodeuteride in 1 *M* NaOH in water–tetrahydrofuran (1:1) solution gave mostly acetate **7**-d_1 with short reaction times and mixtures of alcohol **6**-d_1 and acetate **7**-d_1 with longer times. Pmr analysis of the stereochemistry of the incorporated deuterium could be made either on the mixture of **6**-d_1 and **7**-d_1 or on the product **6**-d_1 after transesterification of the acetate part with sodium methoxide in methanol or after reduction with lithium aluminum hydride.

The pmr spectra of the product alcohols **6**-*d* were easily interpreted in terms of a mixture of *cis*-8-deuteriodibenzobicyclo[2.2.2]octadien-7-ol (*c*-**6**) and *trans*-8-deuteriodibenzobicyclo[2.2.2]octadien-7-ol (*t*-**6**). However, it became evident that about 10% of undeuterated **6** was being formed in the aqueous THF system and that a sensitive method of determining the amount of deuterated product was needed. Mass spectral analysis of **6** is unsatisfactory, since a retro Diels–Alder reaction completely removes the bridge and no molecular ion is observed. The trimethylsilyl ether (**8**) gives a peak ($M - 15^+$) by loss of methyl which is suitable for the determination.[15] Alcohol **6** is easily converted to trimethylsilyl ether **8** with *N*,*N*-bis(trimethylsilyl)acetamide, and the relative amount of **6** in mixture with *c*-**6** plus *t*-**6** may be calculated from the mass spectrometric measurement. Controls with synthetic mixtures of **6**, *c*-**6**, and *t*-**6** showed an accuracy of better than ±2%. Ratios of *c*-**6** to *t*-**6** in the mixtures which contained no more than 13% **6** may be determined to approximately ±5% by pmr.



Details of the procedures used are given in the Experimental Section. Reductions with sodium borodeuteride were carried out first in aqueous tetrahydrofuran (THF), prompted by the initial communication of Brown and Goeghegan,[16] in view of its technical ease, but it soon became evident that this procedure did not lead to stereospecific replacement of mercury by deuterium. Indeed, as the data in Table I show, reductions of *cis*- and *trans*-β-acetoxy mercurials **3** and **5** lead to almost identical mixtures of *t*-**6** and *c*-**6** with perhaps a small degree of retention predominating (over the 2:1 *t*-**6** to *c*-**6** average result). These data, plus those on the reduction of **2** and **4**, suggest the existence of a long-lived intermediate unable to maintain configuration in the borohydride reductions (*vide infra*), and also make clear the inappropriateness of this procedure for stereospecific labeling with deuterium.

Table I also contains data on the reduction of **2**, **3**, and **4** with sodium amalgam in deuterium oxide containing sodium deuterioxide. These reactions were stereospecific, with complete retention observed.

(14) K. Alder and H. Rickert, *Justus Liebigs Ann. Chem.*, **543**, 1 (1939).

(15) S. J. Cristol, R. J. Bopp, and A. E. Johnson, *J. Org. Chem.*, **34**, 3574 (1969).

(16) H. C. Brown and P. Goeghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967).

TABLE I

REDUCTION OF DIBENZOCYCLO[2.2.2]OCTYLMERCURIALS IN AQUEOUS SOLVENT SYSTEMS WITH SODIUM BORODEUTERIDE OR WITH SODIUM AMALGAM

Substrate	Reducing agent	Solvent	% D	*t*-6, %	*c*-6, %	Yield, %
2	$NaBD_4$	H_2O–THF (NaOH)	94	75	25	52 as 6-*d*[a]
3	$NaBD_4$	H_2O–THF (NaOH)	91	66	34	88 as 7-*d*[b]
4	$NaBD_4$	H_2O–THF (NaOH)	91	80	20	79 as 6-*d*[b]
5	$NaBD_4$	H_2O–THF (NaOH)	92	70	30	100 as 6-*d*[b]
2	Na/Hg	D_2O (NaOD)	97	0	100	49 as 6-*d*[a]
3[c]	Na/Hg	D_2O (NaOD)	96	14[c]	86[c]	65 as 6-*d*[a]
4	Na/Hg	D_2O (NaOD)	96	100	0	55 as 6-*d*[a]

[a] Yield after recrystallization. [b] Crude yield. [c] The reduction was stereospecific with retention. The sample of 3 was contaminated with approximately 15% of 5.

Sodium borohydride reductions may be carried out in alcohol solvents, and we decided to see if a solvent change might lead to a change in stereoselectivity of deuterium incorporation. To this end, the sodium borodeuteride reduction was conducted in ethanol solvent containing 1 *M* NaOH. The reduction was noticeably slower in this solvent than in aqueous THF, but was still rapid. To our surprise, analysis showed extensive incorporation of hydrogen in the product (Table II). The deuterated product amounted to

TABLE II

REDUCTION OF DIBENZOBICYCLO[2.2.2]OCTYLMERCURIALS WITH SODIUM BORODEUTERIDE IN ETHANOL

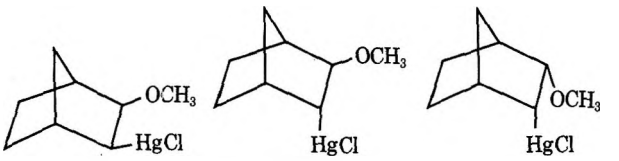
Compd	Time,[a] hr	% D	*t*-6, %	*c*-6, %
3	0	53	84	16
	1	60	69	31
4	0	49[b]	96[b]	4[b]
	1	38[b]	93[b]	7[b]

[a] Time that the sodium borodeuteride was stirred in the solvent system prior to addition of the mercurial. [b] Average of two experiments.

only 50 ± 10% of the product (only the alcohols 6 and 6-*d* were obtained in this solvent regardless of the mercurial substrate, alcohol or acetate). Because of the complication of large amounts of 6 and therefore smaller amounts of *c*-6 and *t*-6 in the products of these reductions, the analytical method for *c*-6 and *t*-6 is not so reliable as in the reductions in aqueous THF. Thus we do not know whether the variations in these results (Table II) from those in aqueous THF (Table I) are real, or whether the *c*-6:*t*-6 ratio appears different because of the magnitude of the experimental error.

The amount of deuterium incorporation was not changed when the borodeuteride was added to the solution of the mercurial, or when the mercurial was added to a borodeuteride solution which had aged for 1 hr. Furthermore, reduction of dibenzobicyclo[2.2.2]octadien-7-one to 7-deuteriodibenzobicyclo[2.2.2]octadien-7-ol in ethanol and 1 *M* NaOH with sodium borodeuteride gave a product containing 95% deuterium, demonstrating that our results are not due to hydrogen exchange between borodeuteride and solvent. The results are discussed later.

The Norbornyl System.—Most of the stereochemical work was carried out on three norbornyl adducts: *cis,exo*-3-methoxy-2-norbornylmercuric chloride (**9**), *exo*-3-methoxy-*endo*-2-norbornylmercuric chloride (**10**), and *cis,endo*-3-methoxy-2-norbornylmercuric chloride (**11**). The *cis,exo*-mercurial is the principal product of treatment of norbornene with mercuric acetate in methanol (followed by NaCl precipitation), while **10** and **11** result from acid-catalyzed isomerization of **9**.

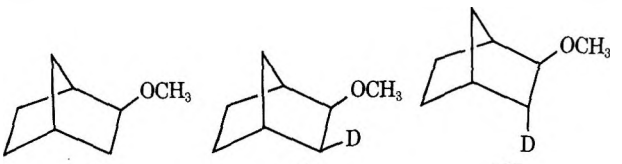


9 **10** **11**

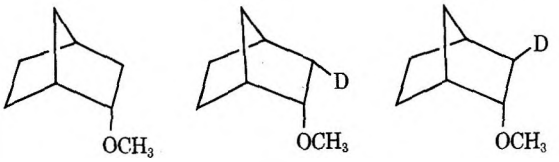
Stereochemical assignments for **9**, **10**, and **11** are based on the results of reduction by borohydride and on pmr analysis. Reductions of **9** and **10** gave only the exo isomer of 2-methoxynorbornane (**12**), and small amounts of norbornene. Reduction of **11** gave only 2-*endo*-methoxynorbornane (**13**) as the organic ether product. The ethers were isolated by glpc and were identified by spectral comparisons with samples of *exo*- and *endo*-2-methoxynorbornane obtained by methylation of the corresponding alcohols.

In the organomercurials, the proton at C-3, α to methoxy, is readily observed in the pmr spectra. The splitting pattern of this proton defines the stereochemistry of the 2-chloromercuri group. The simple doublet (J = 6.5 Hz) observed for H-3 of **9** indicates a single substituent at C-2 with an endo proton. The assigned structure of **10** is based on the simplicity of the H-3 resonance (doublet, J = 2.8 Hz) which indicates endo substitution at C-2. The eight-line pattern of the H-3 resonance of the mercurial **11** (J = 9.5, 3.8, 1.3 Hz) is interpreted as due to the coupling of an exo proton at C-3 with an exo proton at C-2 (J = 9.5 Hz), a proton at C-4 (J = 3.8 Hz), and a long-range coupling with exo H-5 (J = 1.3 Hz).

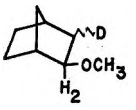
Reduction of **9** and **10** with deuterium incorporation led to *cis*-3-deuterio-*exo*-2-methoxynorbornane (*c*-**12**) and *trans*-3-deuterio-*exo*-2-methoxynorbornane (*t*-**12**).



12 *c*-**12** *t*-**12**



13 *c*-**13** *t*-**13**



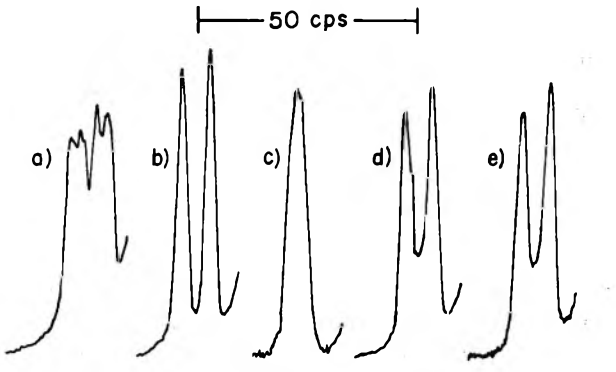
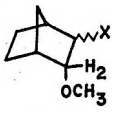


Figure 1.—Resonances of H_2 in the 100-MHz nmr spectra of *exo*-methoxynorbornanes in trifluoroacetic acid: (a) undeuterated compound; (b) $Na(Hg)/D_2O$ reduction product of *cis,exo*-methoxymercurial; (c) $Na(Hg)/D_2O$ reduction product of *trans*-methoxymercurial; (d) borodeuteride reduction product of *cis,exo*-methoxymercurial; (e) borodeuteride reduction product of *trans*-methoxymercurial. All peaks are centered at τ 6.40 and are on the edge of the absorption of the methoxyl protons (τ 6.54) which is not shown.

By using arguments such as those described for the pmr identification of the stereochemistry of **9** and **10**, one may interpret the shape of the resonance for the proton α to the methoxy group in **12**-*d* as indicative of the exo or endo nature of the proton at C-3 (Figure 1). The actual analysis of the ratio of *c*-**12** to *t*-**12** was made from comparison of the infrared spectra of the product with those of synthetic mixtures. As little as 3% of undeuterated **12** could have been detected easily in the infrared spectrum of a mixture; none was observed.

The deuterated products from the *cis,endo*-methoxymercurial **11** showed more complicated pmr absorptions for the exo proton at C-2 (Figure 2). Sodium amalgam reduction of **11** in deuterium oxide gave a sample of **13**-*d* in which the resonance for the exo proton at C-2, α to the methoxy group, was simplified from that of undeuterated **13** from a doublet of triplets (J = 9.7, 3.6 Hz) with an additional splitting of *ca.* 1 Hz to a doublet of doublets (J = 9.7, 3.6 Hz). Thus one of the 3.6-Hz couplings was lost. This must be due either to a deuterium in the endo position at C-3 or to a deuterium at the C-1 bridgehead. The former is the only logical conclusion, and the product may thus be identified as *endo*-3-deuterio-*endo*-2-methoxynorbornane (*c*-**13**). Sodium borodeuteride reduction of **11** gives a sample of **13**-*d* in which the absorption for the proton at C-2, α to methoxy, is a narrow, complex multiplet ($W_{1/2}$ = 9.3 Hz). This pattern may be confidently assigned to *exo*-3-deuterio-*endo*-2-methoxynorbornane (*t*-**13**).

Since pure samples of *c*-**12** and *t*-**12** were available from the sodium amalgam reductions of **9** and **10**, infrared analysis of the mixtures of these obtained from the borodeuteride reduction of **9** and **10** are accurate to ±3%. This accuracy was not possible for the reduction products of **11**, as a pure sample of *exo*-3-deuterio-*endo*-2-methoxynorbornane (*t*-**13**) was not available. However, the pmr spectral results make it clear that *t*-**13** was the principal product of borodeuteride reduction of **11**. The results of the reductions are summarized in Table III.



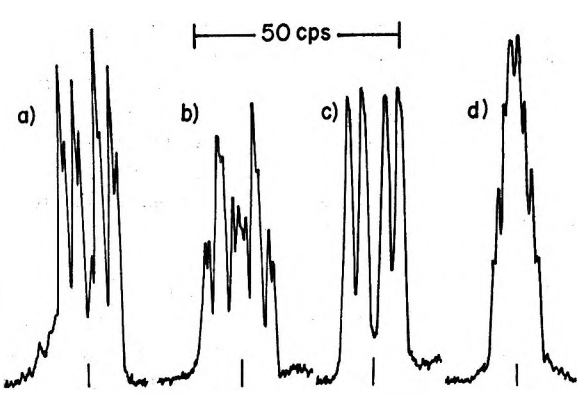


Figure 2.—Resonances of H_2 in the 100-MHz nmr spectra of *endo*-methoxynorbornanes in carbon disulfide: (a) X = *endo*-HgCl, superimposed on Hg^{199} side band of H_3 resonance; (b) X = H; (c) X = D, $Na(Hg)/D_2O$ reduction product of *cis,endo*-methoxymercurial; (d) X = D, borodeuteride reduction product of *cis,endo*-methoxymercurial. Shifts are from internal TMS.

TABLE III
REDUCTION OF NORBORNYLMERCURIALS IN AQUEOUS SYSTEMS WITH SODIUM AMALGAM AND SODIUM BORODEUTERIDE

Substrate	Reducing agent	Solvent	*c*-**12**, %	*t*-**12**, %
9	Na/Hg	D_2O (NaOD)	100	0
10	Na/Hg	D_2O (NaOD)	0	100
9	$NaBD_4$	H_2O (NaOH)	80	20
10	$NaBD_4$	H_2O (NaOH)	84	16
			t-**13**, %	*c*-**13**, %
11	Na/Hg	D_2O (NaOD)	0	100
11	$NaBD_4$	H_2O (NaOH)	major	minor

Sodium borodeuteride reduction of **9** and **10** in methanol gave deuterated **12** in the same product ratios (*c*-**12**:*t*-**12**) as in water. The reactions in methanol solution were slower and base was not necessary to suppress olefin formation. No undeuterated **12** could be observed in these products.

The borodeuteride reductions in methanol were carried out in the presence of 2 M sodium methoxide to ensure dissolution of the mercurials. When the reductions were quenched prior to completion of the reaction, unreacted mercurial was recovered from the aqueous phase by acidification with hydrochloric acid. After partial conversion, the unreacted mercurial was recovered and found to be unchanged starting material.

Results and Discussion

At the time this work was begun, little information was available regarding either the stereochemistry of reductive demercurations or detailed mechanisms. In the intervening time, a number of papers[10-12] have appeared on borohydride reductions, from which it has become clear that stereospecificity in the replacement of mercury by hydrogen (or deuterium) does not generally obtain. Our results confirm this lack of stereospecificity. The borohydride reaction is technically

the easier of the two methods under discussion and would appear to us to be the method of choice for reduction,[9] except when deuterium is to be introduced stereospecifically and/or quantitatively (see below) or when a rearranging radical[10-12] is an intermediate.

While study of the mechanisms of the reductions was not a major impetus for our work, we are in a position to make some statements about them. For the borohydride reduction, the work of Pasto,[10] of Jackson,[11] and of Whitesides[12] clearly implicate alkyl radical intermediates, presumably produced *via* the intermediacy of an alkylmercuric hydride (eq 2), as originally suggested

$$RHgX + BH_4^- \longrightarrow RHgH \quad (2)$$

by Bordwell[4] (eq 1). Pasto[10] has proposed that the alkylmercuric hydride decayed to product *via* a cage process (eq 3). Our attempt to trap the 3-*exo*-meth-

$$RHgH \longrightarrow [R\cdot \cdot HgH] \longrightarrow RH + Hg \quad (3)$$

oxynorbornyl radical (produced from the RHgD species) with *p*-diisopropylbenzene failed, as did Pasto's attempt[10] to trap the 3-hydroxy-2-butyl radical with undisclosed reagents. Pasto's result suggested the cage process to him.

Whitesides[12] has proposed an alternative mechanism in which the chain propagation steps 4 and 5 are in-

$$R\cdot + RHgH \longrightarrow RH + RHg\cdot \quad (4)$$

$$RHg\cdot \longrightarrow R\cdot + Hg \quad (5)$$

volved.[17] This appears to us to be an attractive alternative, as it accounts for the large amount of undeuterated material produced from **3** and **4** in ethanol (trapping of the free radical by the active α-hydrogen atoms in ethanol); see Table II. The significantly smaller (but still measurable) amount of nonlabeling in aqueous tetrahydrofuran in borodeuteride reductions (Table I) may be related to the speed of the overall reaction—that in ethanol is much slower than that in aqueous THF. It seems reasonable to assume that the rate constant for formation of the alkylmercuric hydride (eq 2) is less in ethanol than that in aqueous THF, while later steps should show little solvent dependence. Therefore, the steady-state concentration of RHgH should be lower in ethanol than in aqueous THF, and, since the rate of eq 4 depends upon RHgH concentration while that of reaction with solvent does not, the lesser deuteration in ethanol may be explained. These speculations are amenable to testing, as are alternative mechanisms, but, in the absence of additional experimental data, further speculation appears unwarranted. Our present preference for the chain process over the cage process may be regarded as tentative in those cases where solvent (or other) capture has not been observed, and it is possible that both processes compete. In any case, use of borodeuteride reduction, even for nonstereospecific deuteration, offers the prospect of incomplete deuteration, when solvents with active hydrogen atoms are present.[18]

When it is necessary to place a deuterium into a molecule stereospecifically, sodium amalgam reduction in D_2O is definitely the method of choice, although somewhat more tedious. In all our cases, which included epimeric examples, as well as in the earlier example, 100% retention of configuration was observed in the replacement of a carbon–mercury bond by a carbon–deuterium bond, and almost complete deuterium incorporation was observed (Table I).

The results of the sodium amalgam reduction are consistent with a mechanism involving two closely linked one-electron transfer steps at the amalgam surface, followed by hydrolysis of the anionic intermediate (eq 6). This is closely analogous to the mechanism

$$RHgCl \xrightarrow[-NaCl]{Na} RHg\cdot \xrightarrow[-Na^+]{Na} RHg^- \xrightarrow[-OH^-]{H_2O} RH + Hg \quad (6)$$

proposed[19] for electrolytic reduction of alkylmercuric salts with the last step expanded into two distinct steps. The hydrolysis step can be envisioned as direct electrophilic substitution on carbon, and, by analogy with known electrophilic substitution of organomercurials,[20] retention of configuration is rationalized.

It would clearly be of interest to use sodium amalgam reductions on the dehydronorbornyl–nortricyclyl system to see if the rearrangements observed[10-12] with borohydride reduction can be avoided, as homoallyl and cyclopropylcarbinyl anions seem less prone to rearrangements than the corresponding radicals.[21]

Experimental Section

Preparation of *cis*-8-Acetoxymercuridibenzobicyclo[2.2.2]-octadien-7-ol Acetate (2) and *cis*-8-Chloromercuridibenzobicyclo-[2.2.2]octadien-7-ol Acetate (3).[22]—In a 500-ml, round-bottom flask was placed 4.08 g (20 mmol) of dibenzobicyclo[2.2.2]octatriene (1)[23] and 6.38 g (20 mmol) of mercuric acetate in 200 ml of glacial acetic acid. The solution was stirred at room temperature. After 2 days, a 50-ml aliquot was removed and evaporated on a Rotovac with reduced pressure and a hot water bath. Carbon tetrachloride was twice added to the oil and evaporated to give a white solid. The solid was dissolved in benzene and decolorized with activated charcoal, and the benzene was removed by boiling as heptane was added until crystallization began. Recrystallization from benzene–heptane gave 1.23 g (47%) of **2** as large, clear crystals: mp 200–202°; pmr ($CDCl_3$)[24] τ 2.5–3.0 (m, 8, aromatic H), 4.78 (d of d, 1, J = 3 Hz, 8.5 Hz, H-7), 5.36 (d, 1, J = 3 Hz, H-1), 5.53 (d, 1, J = 2 Hz, H-4), 6.97 (d of d, 1, J = 2, 8.5 Hz, H-8), and 8.07 ppm (s, 6, $OCOCH_3$ and $HgOCOCH_3$); ir (KBr) 1730, 1626, 1222, and 1020 cm^{-1}. Mercury-199 satellites were generally difficult to verify, since usually one of the patterns fell under or close to another peak in the spectrum. The tentative couplings with various protons follow: H-4, 72 Hz; H-1, 30 Hz; H-8, 208 Hz; and H-7, 104 Hz.

Anal. Calcd for $C_{20}H_{18}HgO_4$: C, 45.94; H, 3.47. Found: C, 45.80; H, 3.39.

After 3 days the remaining 150 ml of the acetic acid solution was evaporated on a Rotovac at reduced pressure and elevated temperatures to give a clear oil. Sodium chloride (1.76 g, 30 mmol) was added in a small amount of water. Methanol was added to cause a homogeneous solution, and then more water was added (final volume 400 ml) to precipitate the product. Filtration and recrystallization from acetone–water gave 5.82 g (78%) of **3** as small white crystals. Analogous preparations gave crystals, mp 180.5–182.5° and 186–189°. In all cases, the material melted to a milky, viscous liquid which decomposed as the temperature increased: pmr ($CDCl_3$)[24] τ 2.5–3.0 (m, 8, aromatic H),

(17) Whitesides[12] apparently succeeded in trapping 20% of norbornyl radical with di-*tert*-butyl nitroxide in aqueous tetrahydrofuran.

(18) Whitesides[12] has noted that their reductions proceeded with only 78–85% deuterium incorporation.

(19) R. E. Benesch and R. Benesch, *J. Amer. Chem. Soc.*, **73**, 3391 (1951).

(20) For references see F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N. Y., 1968.

(21) S. J. Cristol and P. K. Freeman, *J. Amer. Chem. Soc.*, **83**, 4427 (1961); S. J. Cristol and R. V. Barbour, *ibid.*, **88**, 4262 (1966); **90**, 2832 (1968); S. J. Cristol and R. W. Gleason, *J. Org. Chem.*, **34**, 2363 (1969).

(22) V. L. Sokolov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1285 (1968).

(23) S. J. Cristol and N. L. Hause, *J. Amer. Chem. Soc.*, **74**, 2193 (1952).

(24) Pmr intensities are corrected for Hg-199 satellites.

4.74 (d of d, 1, J = 3.2, 8.5 Hz, H-7), 5.35 (d, 1, J = 3.2 Hz, H-1), 5.51 (d, 1, J = 2.4 Hz, H-4), 6.97 (d of d, 1, J = 2.4, 8.5 Hz, H-8), and 8.10 ppm (s, 3, $OCOCH_3$); ir (KBr) 1739, 1727, 1232, and 1015 cm^{-1}. Mercury-199 couplings were again only tentatively assigned (see above): H-4, 75 Hz; H-1, 32 Hz; H-8, 197 Hz; and H-7, 106 Hz.

Anal. Calcd for $C_{18}H_{15}ClHgO_2$: C, 43.29; H, 3.03. Found: C, 43.43; H, 3.06.

In later preparations, it was found convenient to add the solid sodium chloride directly to the acid solution and then add water to precipitate **3**. When **3** was prepared in this manner, there appeared a small, poorly resolved peak at τ 7.90 ppm, which was not removed by our recrystallization procedure. This is attributed to the trans adduct **5** and amounted to 15–19% of the adduct (pmr estimate).

Preparation of *trans*-8-Chloromercuridibenzobicyclo[2.2.2]-octadien-7-ol (4).[23]—Dibenzobicyclo[2.2.2]octatriene (**1**) (4.08 g, 20 mmol) was dissolved in 50 ml of acetone, and 50 ml of water containing 3 ml of acetic acid was added. To the resulting suspension was added 6.88 g (20 mmol) of mercuric acetate. The mixture was stirred at room temperature for 1 day as the precipitate dissolved. Sodium chloride (2.36 g, 40 mmol) was added and a precipitate formed. After 3 hr of stirring, the suspended precipitate was filtered to give 4.76 g of white powder. (In some analogous preparations, water was added before the precipitate was filtered, and the product contained unreacted **1**. Olefin **1** was then removed from the product by trituration with ether.) Recrystallization from nitromethane gave two crops (1.13 g, 22%) of fine, white crystals. This material was combined with that of another preparation, and the 3-g sample was recrystallized from 250 ml of nitromethane to give two crops (1.7 g) of small, white crystals: mp 255° (the material does not completely liquefy, but either decomposes or sublimes to a fine, white powder at the top of the capillary tube); pmr[24] [DMSO-d_6, shifts are given in hertz (60 MHz pmr) from the pattern for DMSO-d_5] −300 to −270 (m, 8, aromatic H), −137 to −106 (m, 4, H-1, H-4, H-7, and OH), and 32 Hz (4-line, 1, apparent couplings of J = 3.6 and 2 Hz, H-8). When D_2O was added to the pmr sample, one of the protons at −137 to −106 Hz was "washed out." Double irradiation experiments showed that when the pattern around −137 to −106 Hz was irradiated, the four-line pattern at 32 Hz became a singlet.

Anal. Calcd for $C_{16}H_{13}ClHgO$: C, 42.02; H, 2.87. Found: C, 42.10; H, 2.93.

Preparation of *trans*-8-Chloromercuridibenzobicyclo[2.2.2]-octadien-7-ol Acetate (5).—A solution of 1.0 g (2.2 mmol) of **4** in 12.0 ml of pyridine and 12.0 ml of acetic anhydride was heated at reflux for 1.2 hr and then stirred at room temperature overnight. The solution was poured onto about 200 ml of ice. The precipitate formed was extracted into 200 ml of chloroform. The solution was washed twice with 200-ml portions of water, once with 100 ml of 10% Na_2CO_3 (aqueous), once with 100 ml of water, and finally with 100 ml of saturated NaCl (aqueous). The chloroform layer was dried ($MgSO_4$) and evaporated on a Rotovac. Decolorization with activated charcoal and recrystallization from acetone–water gave 846 mg (77%) of **5** as small, white crystals: mp 244–245° (melted to a milky liquid); pmr[24] ($CDCl_3$) τ 2.5–3.0 (m, 8, aromatic H), 4.67 (t, 1, J = 3.4 Hz, H-7), 5.51 (d, 1, J = 2 Hz, H-4), 5.54 (d, 1, J = 3.4 Hz, H-1), 7.86 (d of d, 1, J = 3.4, 2 Hz, H-8), and 8.13 ppm (s, 3, $OCOCH_3$); ir (KBr) 1718, 1706, 1255, 1242, and 1030 cm^{-1}.

Anal. Calcd for $C_{18}H_{15}ClHgO_2$: C, 43.29; H, 3.03. Found: C, 43.27; H, 2.93.

Preparation of Dibenzobicyclo[2.2.2]octadien-7-yl Trimethylsilyl Ether (8).[15]—A 150-mg sample of alcohol **6** and 0.7 ml of *N,N*-bis(trimethylsilyl)acetamide [BSA, Eastman Organic Chemicals, redistilled, bp 69–72° (33 mm)] were combined in a 10 × 0.5 (i.d.) cm Pyrex tube, and the tube was sealed in a flame. The mixture was heated on a water bath for about 10 min until all of the **6** had dissolved (apparently, temperature and time are not critical if solution is obtained). The tube was opened and placed in a 45 × 0.9 (i.d.) cm Pyrex tube with one end closed off and jacketed in a length of steel tubing. The end containing the sample was placed horizontally in a Kugelrohr oven at 95–100°, and a vacuum (*ca.* 0.2 mm) was applied until all of the material had sublimed onto the cooler part of the tube outside of the oven. In this way, 151 mg (75%) of **8** was obtained: mp 96–98° (lit.[15] 93–95°). Pmr data are presented in ref 15.

Anal. Calcd for $C_{19}H_{22}OSi$: C, 77.50; H, 7.53. Found: C, 77.83; H, 7.59.

The above procedure was scaled down for the analyses of **6** obtained in the reductions by using about 10 mg of **6** and 0.2–0.3 ml of BSA. The mass spectrum of **8** at 70 eV on a direct probe inlet showed a base peak at m/e 178. The only other peaks over 2% of base were found at m/e (rel intensity) 28 (5), 32 (2), 73 (3), 151 (3), 152 (2), 176 (4), 177 (3), 178 (100), 179 (15), and 205 (3). The M^+ peak was present at m/e 294, but was too small to measure. The $M - 15^+$ peak was at m/e 279, represented about 1.5% of the base peak, and gave a measurable peak height of 80–150 mm. At least four scans of the $M - 15^+$ region were made in each analysis. The values for the undeuterated material (relative to m/e 279 = 100%) are tabulated below and compared with the calculated values for $C_{18}H_{19}OSi$. The averages are for a series of nine scans of the region m/e 274–281. The value for the m/e 280 peak varied from +2.6 to −1.2 of the average shown, with all but one of these values within 1.2 of the average.

	Rel intensity	
m/e	Obsd	Calcd
274–278	0	
279	100	100
280	25.9	24.9
281	8.7	5.2

Sodium Amalgam Reduction of *cis*-8-Acetoxymercuridibenzobicyclo[2.2.2]octadien-7-ol Acetate (2).—A 375-mg (0.72 mmol) sample of **2**, 5 g of freshly prepared 2% sodium amalgam, and 2.0 ml of 2 *M* NaOD in D_2O were stirred rapidly with a magnetic stirrer in a 10-ml round-bottom flask, fitted with a $CaSO_4$ drying tube. After 1 day, an additional 3 g of the amalgam was added. After another day, some chloroform was added to the reaction mixture, and the mixture was filtered through a glass fiber pad. The chloroform layer was separated, washed with saturated NaCl (aqueous), and dried ($MgSO_4$). Evaporation on a Rotovac gave crude 6-*d*, which was purified by preparative tlc (silica gel G, 20 × 20 × 0.25 cm plate, developed with 9% ether in benzene) and recrystallized (activated charcoal treatment) from ethanol–water to give 78 mg (49%) of 6-*d* as white crystals: mp 131–139°; pmr ($CDCl_3$ with D_2O) τ 2.5–3.0 (m, 8, aromatic H), 5.6–6.0 (m, 3, H-1, H-4, and H-7), and 7.73 ppm (very broad d, 1, J = 8.5 Hz, H-8 trans). Without D_2O in the pmr sample, the OH absorption showed up at τ 8.78 ppm.

The trimethylsilyl ether 8-*d* was prepared: mp 96–97°; mass spectrum m/e (rel intensity) 279 (2.5), 280 (78.8), 281 (17.6), 282 (4.9).

The data are consistent with a product 6-*d* containing 97% deuterium. Essentially all of the product is *c*-6.

Sodium Amalgam Reduction of *trans*-8-Chloromercuridibenzobicyclo[2.2.2]octadien-7-ol (4).—A 229-mg sample of **4**, 7.0 g of freshly prepared 2% sodium amalgam, and 2.0 ml of 1.66 *M* NaOD in D_2O were stirred for 3 days in a 10-ml, round-bottom flask fitted with a magnetic stirrer and $CaSO_4$ drying tube. About 5 ml of carbon tetrachloride was added, and about 1 hr later the mixture was filtered and the residual amalgam and mercury were washed well with chloroform. The combined organic layers were separated and washed with water. The solution was dried ($MgSO_4$) and evaporated on a Rotovac to give 76 mg of a white solid. Decolorization with activated charcoal in methanol and recrystallization from ethanol–water gave 61 mg (55%) of 6-*d*: mp 138–140°; pmr ($CDCl_3$ with D_2O) τ 2.5–3.0 (m, 8, aromatic H), 5.6–6.0 (m, 3, H-1, H-4, and H-7), and 8.72 ppm (very broad s, 1, H-8 cis). Without the D_2O in the pmr sample, the OH absorption shows up at the same position as H-8 cis.

The trimethylsilyl ether 8-*d* was prepared: mp 93–96.5°; mass spectrum m/e (rel intensity) 279 (5.9), 280 (134.6), 281 (37.0), 282 (10.7).

The data are consistent with alcohol 6-*d*, containing 96% deuterium. Essentially all of the product is *t*-6.

Sodium Amalgam Reduction of *cis*-8-Chloromercuridibenzobicyclo[2.2.2]octadien-7-ol Acetate (3).—A 250-mg (0.5 mmol) sample of **3** (containing about 15% of **5**), 7 g of freshly prepared 2% sodium amalgam, and 2.0 ml of 1.66 *M* NaOD in D_2O were treated as described above for **4** to give 72 mg (65%) of 6-*d*, mp

145–146°. Another recrystallization from the same solvent gave a sample of **6**-*d*, mp 139–140.5°.[25]

The trimethylsilyl ether **8**-*d* was prepared: mp 96–97°; mass spectrum *m/e* (rel intensity) 279 (4.6), 280 (99.2), 281 (25.2), 282 (7.8).

The data are consistent with **6**-*d* containing 96% deuterium. Integration of pmr intensities showed that the deuterated product was 86% *c*-**6** and 14% *t*-**6**.

Sodium Borodeuteride Reduction of *cis*-8-Acetoxymercuridibenzobicyclo[2.2.2]octadien-7-ol Acetate (2).—To a 525-mg (1.0 mmol) sample of mercurial **2**, in 2 ml of 2 *M* NaOH and 2 ml of THF, was added 21 mg (0.5 mmol) of sodium borodeuteride (Alfa Inorganics, Inc.) and the mixture was stirred for 2.5 hr. The product mixture was decanted from 174 mg (87%) of metallic mercury into water and was extracted with ether. The ether layer was washed with water and dried ($MgSO_4$). Evaporation on a Rotovac gave 287 mg of crude product. Pmr analysis of this product showed about 74% of the acetate **7**-*d* and 26% of the alcohol **6**-*d*. The entire product was transesterified with sodium methoxide in methanol to give 201 mg of a yellow oil, which was purified by preparative tlc (20 × 20 × 0.25 cm plate, silica gel G, developed with 9% ether in benzene). The crude yield of alcohol **6**-*d* from the plate was 150 mg (68%). Decolorization with activated charcoal and recrystallization from ethanol–water gave 115 mg (52%) of **6**-*d*, mp 141–142.7°.

The trimethylsilyl ether **8**-*d* was prepared: mp 94.5–96.5°; mass spectrum *m/e* (rel intensity) 279 (8.1), 280 (121.9), 281 (32.8), 282 (9.4).

The data are consistent with 94% deuterium incorporation in **6**. Pmr data integrations show that the deuterated product was 75% *t*-**6** and 25% *c*-**6**.

Sodium Borodeuteride Reduction of *cis*-8-Chloromercuridibenzobicyclo[2.2.2]octadien-7-ol Acetate (3).—A 250-mg (0.5 mmol) sample of mercurial **3** (containing about 15% **5**) and 10 mg (0.25 mmol) of sodium borodeuteride were placed in a 5-ml, round-bottom flask with a magnetic stirrer and 2 ml of THF. After about 30 sec, 2.0 ml of 2 *M* NaOH (aqueous) was added and a rapid reaction occurred. After 15 min, chloroform was added and the mixture was filtered. The chloroform layer was separated and dried ($MgSO_4$). Liquid mercury (91 mg, 91%) was obtained. Evaporation of the chloroform solution gave 121 mg (88%) of acetate **7**-*d*. Purification by preparative tlc (20 × 20 × 0.25 cm plate, silica gel G developed with 5% ether in benzene) gave 76 mg (57%) of **7**-*d* as an oil: pmr ($CDCl_3$) τ 2.5–3.0 (m, 8, aromatic H), 4.9 (five-line m, 1, H-7), 5.47 (d, 1, J = 3 Hz, H-1), 5.75 (d, 1, J = 2.6 Hz, H-4), 7.70 (very broad d, 0.40, H-8 trans), 8.12 (s, 3, $OCOCH_3$), and 8.48 ppm (very broad s, 0.60, H-8 cis). Lithium aluminum hydride reduction and recrystallization of the product from ethanol–water gave 25 mg of alcohol **6**-*d*, mp 147.5–148.5° (remelts at 137.5–139°).

The trimethylsilyl ether **8** was prepared: mp 95–96.5°; mass spectrum *m/e* (rel intensity) 279 (12.4), 280 (124.0), 281 (32.9), 282 (10.1).

The data are consistent with acetate **7**-*d* and alcohol **6**-*d* containing 91% deuterium. The deuterated product comprises 63% *t*-**6** and 37% *c*-**6**.

Sodium Borodeuteride Reduction of *trans*-8-Chloromercuridibenzobicyclo[2.2.2]octadien-7-ol (4)—A 229-mg (0.5 mmol) sample of mercurial **4** and 10 mg (0.25 mmol) of sodium borodeuteride were placed together with 2 ml of THF in a 5-ml, round-bottom flask fitted with a magnetic stirrer. After about 1 min, 2.0 ml of 2 *M* NaOH (aqueous) was added, and a rapid reaction occurred as the solution became black. After 15 min, chloroform was added and the product was filtered from 78 mg (78%) of metallic mercury. The chloroform layer was separated and dried ($MgSO_4$). Evaporation of the chloroform on a Rotovac and decolorization of the residue with activated charcoal in methanol, followed by evaporation, gave 88 mg (79%) of crystalline alcohol **6**-*d*. Recrystallization from ethanol–water gave alcohol **6**-*d*, mp 138–140°.

The trimethylsilyl ether **8**-*d* was prepared: mp 96–97°; mass spectrum *m/e* (rel intensity) 279 (13.5), 280 (129.6), 281 (34.4), 282 (10.1).

The data are consistent with a sample of 91% deuterated **6**. The deuterated product is 80% *t*-**6** and 20% *c*-**6** (pmr integrations).

Sodium Borodeuteride Reduction of *trans*-8-Chloromercuridibenzobicyclo[2.2.2]octadien-7-ol Acetate (5).—A 200-mg (0.39 mmol) sample of the mercurial **5** and 11 mg (0.25 mmol) of sodium borodeuteride were stirred together in a 5-ml, round-bottom flask with 2 ml of THF for about 30 sec. Sodium hydroxide (2 *M* aqueous, 2 ml) was added and a rapid reaction took place. After 15 min, chloroform was added, and the reaction was decanted from 70 mg (90%) of metallic mercury into 25 ml of water. The reaction mixture was extracted three times with 25-ml portions of chloroform, which were washed with 25 ml of water and 25 ml of saturated NaCl (aqueous). The combined chloroform extracts were dried ($MgSO_4$), and the chloroform was evaporated on a Rotovac to give 118 mg (109%) of a yellow oil. The pmr spectrum showed mostly acetate **7**-*d*. The acetate was reduced with lithium aluminum hydride to give 84 mg (100%) of the crude alcohol **6**-*d*. Repeated recrystallization from aqueous ethanol gave **6**-*d*, mp 138–149°.

The trimethylsilyl ether **8**-*d* was prepared: mp 95.8–97°; mass spectrum *m/e* (rel intensity) 279 (11.0), 280 (125.3), 281 (31.7), 282 (8.2).

The data are consistent with acetate **7**-*d* and alcohol **6**-*d*, which are 92% deuterated. The deuterated product consists of 70% *t*-**6** and 30% *c*-**6** (pmr integrations).

Sodium Borodeuteride Reduction of Dibenzobicyclo[2.2.2]-octadien-7-one.—A 25-mg (0.625 mmol) sample of sodium borodeuteride and 34 mg (0.125 mmol) of mercuric chloride were placed in 5 ml of 0.93 *M* NaOH in ethanol and stirred for 1 hr. The mercury salt partially oxidized some of the borodeuteride. Dibenzobicyclo[2.2.2]octadien-7-one (220 mg, 1.0 mmol) was added, and 18 hr later the reaction was worked up to give only alcohol **6**-*d*.

Pmr analysis of the crude sample showed no evidence of undeuterated **6** and could be interpreted entirely in terms of 7-deuteriodibenzobicyclo[2.2.2]octadien-7-ol: pmr ($CDCl_3$) τ 2.5–3.0 (m, 8, aromatic H), 5.70 (s, 1, H-1), 5.80 (t, 1, J = *ca.* 2.7 Hz, H-4), 7.78 (broad d of d, 1, J = 2.5, 13 Hz, H-8 trans), 8.52 (s, 1, OH), and 8.75 ppm (d of d, 1, J = 2.7, 13 Hz, H-8 cis). Recrystallization from ethanol–water gave crystals of **6**-*d*, mp 141–143°. The trimethylsilyl ether **8**-*d* was prepared: mp 95.5–97.5°; mass spectrum *m/e* (rel intensity) 279 (5.0), 280 (95.6), 281 (25.3), 282 (7.1). The product thus contained 95% deuterated **6**.

Sodium Borodeuteride Reduction of *trans*-8-Chloromercuridibenzobicyclo[2.2.2]octadien-7-ol (4) in Basic Ethanol. Experiment 1.—Sodium borodeuteride (6 mg, 0.14 mmol) and 100 mg (0.22 mmol) of mercurial **4** were combined and stirred in a 5-ml round-bottom flask. Absolute ethanolic sodium hydroxide (1.0 ml, 1.0 *M*) was added and the reaction slowly blackened. After 1 hr, the clear supernatant solution was decanted from 36 mg (82%) of metallic mercury into 30 ml of water (the mercury was washed with $CHCl_3$) and extracted with three 30-ml portions of chloroform. The chloroform layers were washed once with 30 ml of cold water and once with 30 ml of saturated NaCl (aqueous). The combined chloroform layers were dried ($MgSO_4$) and evaporated on a Rotovac to give 49 mg (100%) of crude **6**. The crude product was recrystallized from ethanol–water to give 30 mg (61%) of alcohol **6**, mp 138–139°.

The trimethylsilyl ether **8** was prepared: mp 95.8–97.1°; mass spectrum *m/e* (rel intensity) 279 (110.2), 280 (156.2), 281 (46.2), 282 (13.5).

The data are consistent with 54% deuterium incorporation in the product. The deuterated product appeared to contain 98% *t*-**6** and 2% *c*-**6**. A duplicate run gave 44% deuterium incorporation, with 94% *t*-**6** and 6% *c*-**6**.

Experiment 2.—A 6-mg (0.14 mmol) sample of sodium borodeuteride was dissolved in 1.0 ml of 1.0 *M* ethanolic NaOH and stirred at room temperature for 1 hr. A 100-mg (0.22 mmol) sample of mercurial **4** was added, and the reaction slowly darkened. After 1.2 hr, some of the metallic mercury had beaded, but a black sludge was present. Chloroform was added along with some water, and the reaction mixture was filtered through a tared funnel. The yield of mercury was 39 mg (97%). The product in the filtrate was worked up as in experiment 1 above. Evaporation of the solvents on a Rotovac gave 54 mg (110%) of crude **6**. The crude product was decolorized with activated charcoal and recrystallized from ethanol–water to give 31 mg (63%) of **6**, mp 136–138°.

(25) In a number of instances during this study, **6** was obtained melting in the range 145–148°. These alcohols had solution ir spectra and pmr spectra identical with those of samples which melted in the 138–142° range. Mixture melting points were made in some instances and melted over the whole range. Remelting of the mixture melting point sample, or of the samples of the higher melting **6**, gave melting points in the 138–142° range. Therefore, **6** forms homomorphs.

The trimethylsilyl ether **8** was prepared: mp 96–97°; mass spectrum *m/e* (rel intensity) 279 (134.5), 280 (129.3), 281 (37.7), 282 (10.3).

The data are consistent with a sample of alcohol **6** with 41% deuterium incorporation. Although the pmr data suggest that the deuterated product consists of 100% *t*-**6** and 0% *c*-**6**, the ir spectrum of this alcohol showed the presence of some *c*-**6**. A duplicate run gave 35% deuterium incorporation, with 86% *t*-**6** and 14% *c*-**6**.

Sodium Borodeuteride Reduction of *cis*-8-Chloromercuridibenzobicyclo[2.2.2]octadien-7-ol Acetate (3) in Basic Ethanol.—A 250-mg (0.5 mmol) sample of mercurial **3** was dissolved in 4.0 ml of 0.93 *M* ethanolic NaOH. To the stirred solution was added 10 mg (0.25 mmol) of sodium borodeuteride, and the mixture was stirred for 1 hr at room temperature. The reaction mixture was decanted from 90 mg (90%) of metallic mercury through glass wool into 30 ml of water. Work-up as above gave 112 mg (101%) of crystalline product, identified from its pmr spectrum as mainly alcohol **6**. There was no sign of the acetate **7**. Two recrystallizations from ethanol–water gave a sample of **6**, which contained some **1** (this does not interfere with pmr or mass spectral analysis), mp 143–145°.

The trimethylsilyl ether **8** was prepared: mp 94–96.5°; mass spectrum *m/e* (rel intensity) 279 (84.9), 280 (116.0), 281 (30.4), 282 (7.6).

The data are consistent with the formation of alcohol **6** with 53% deuterium incorporation. The deuterated products consist of 84% *t*-**6** and 16% *c*-**6** (pmr integration).

In a similar experiment, 10 mg (0.25 mmol) of sodium borodeuteride was stirred with 4.0 ml of 0.93 *M* ethanolic NaOH for 1 hr before 250 mg (0.5 mmol) of **3** was added. Work-up gave 114 mg (103%) of crude **6** and 92 mg (92%) of mercury. The crude **6** was recrystallized twice from ethanol–water to give 42 mg of alcohol **6**, again containing some **1**, mp 137–142°.

The trimethylsilyl ether **8** was prepared: mp 95.5–97°; mass spectrum *m/e* (rel intensity) 279 (53.6), 280 (94.1), 281 (25.0), 282 (6.9).

The data are most consistent with alcohol **6** containing 60% deuterated species. The deuterated product consisted of 69% *t*-**6** and 31% *c*-**6** (pmr integration).

***exo*-3-Methoxy-*exo*-2-norbornylmercuric Chloride (9).**—A mixture of 318.7 g (1.0 mol) of mercuric acetate, 96.1 g (1.0 mol) of norbornene, and 30 ml of concentrated sulfuric acid in 1 l. of methanol was stirred for 1 hr, cooled to 5°, and then poured into 2 l. of cold, 1 *M* aqueous sodium chloride. The precipitate was filtered, washed with water, and dried; the crude yield was 351.2 g (97%), mp 119–121.5°. Crystallization from ethanol gave 305 g (84%), mp 123–124.5° (lit.[26] mp 122–123°). The 100-MHz pmr spectrum (pyridine) shows the following peaks: τ 6.75 (d, 1, J = 6.5 Hz, H-3), 6.84 (s, 3, $-OCH_3$), 7.40 (d of d, 1, J = 6.5, 2.4 Hz, H-2), 7.53 (broad m, 2, H-1 and H-4), and complex absorption between 8.3 and 9.4 (6 protons). Hydrogen–mercury coupling constants were measured in deuteriochloroform: $J_{Hg^{199}-H_2}$ = 192 Hz; $J_{Hg^{199}-H_3}$ = 82 Hz.

Analysis of the crude product by nmr indicated it to be 96% *cis,exo*-3-methoxy-2-norbornylmercuric chloride and 4% *cis,exo*-3-acetoxy-2-norbornylmercuric chloride. When oxymercuration was carried out in the absence of acid, the product was 38% acetoxy- and 62% methoxymercurial. When the mixture from oxymercuration in the absence of acid was treated for 1 hr with 1 equiv of sulfuric acid prior to work-up, the distribution was 8% acetoxy- and 92% methoxymercurial. The analyses were performed by comparison of the methoxy protons at τ 6.8 with the acetoxy protons at τ 8.0.

The preparations of *exo*-3-methoxy-*endo*-2-norbornylmercuric chloride (**10**) and *cis,endo*-3-methoxy-2-norbornylmercuric chloride (**11**) by acid-catalyzed rearrangement of **9** will be described in a forthcoming publication.

Reduction of *cis,exo*-3-Methoxy-2-norbornylmercuric Chloride (9) with Sodium Borohydride.—A well-stirred slurry of 3.0 g (8.3 mmol) of **9** in 20 ml of 1.2 *M* aqueous sodium hydroxide was cooled in an ice bath and 110 mg (2.9 mmol) of sodium borohydride was added in one portion. The ice bath was removed and the mixture was stirred for 2 hr. The mixture was then extracted three times with *n*-pentane and the aqueous and organic phases were separated from 1.59 g (95%) of mercury. The organic phase was washed twice with water, twice with cold 3 *M* sulfuric acid, and again with water and then dried ($MgSO_4$). Vpc analysis on the pentane solution showed less than 1% norbornene. Solvent was removed through a 15-in. Podbielniak column and the product was distilled to give 0.71 g (68%) of **12**, bp 57° (26 mm). The pmr and ir spectra of the product were identical with those of authentic *exo*-2-methoxynorbornane (**12**).

Reduction of *exo*-3-Methoxy-*endo*-2-norbornylmercuric Chloride (10).—Reduction of 0.5 g (1.4 mmol) of the mercurial with sodium borohydride (0.7 mmol) in 2 *M* aqueous sodium hydroxide as described above for the *cis,exo*-mercurial gave mercury in 94% yield and a 62% yield of pure (ir) *exo*-2-methoxynorbornane (**12**).

Infrared Analyses.—All samples analyzed were purified by preparative gas chromatography. Isomer distributions were determined by matching the spectra of the unknown mixtures with those of known mixtures. The accuracy is estimated at ±3%. The following bands were used for the analyses: *exo*-2-methoxynorbornane, 7.84 (m), 8.23 (m), 9.75 (w), 10.3 (s), 11.1 (m), and 11.9 μ (m); *endo*-2-methoxynorbornane, 8.15 (m), 9.4 (s), 10.1 (m), 10.25 (s), and 12.4 μ (m); *cis,exo*-3-deuterio-2-methoxynorbornane, 9.78 (s), 9.95 (m), 11.2 (s), 12.6 (w), 12.9 (w), and 13.6 μ (m); *endo*-3-deuterio-*exo*-2-methoxynorbornane, 8.28 (m), 9.92 (w), 10.35 (s), 11.0 (s), 11.35 (w), 13.15 (m), and 13.85 μ (m).

Gas chromatographic analyses and isolations were performed on a Wilkens Model A-90-P3 chromatograph with a 5-ft, 20% Carbowax 20M column. Relative thermal conductivities were corrected by analysis of known mixtures.

Reduction of *cis,exo*-3-Methoxy-2-norbornylmercuric Chloride (9) with Sodium Amalgam in Deuterium Oxide.—A mixture of 5.0 g (13.8 mmol) of **9** and 45 g (43 mmol of sodium) of 2% sodium amalgam with 30 ml of 2 *M* NaOD in D_2O was shaken vigorously for 16 hr. The mixture was extracted three times with ether and the organic phase was washed three times with water, dried ($MgSO_4$) and then reduced in volume to about 2 ml on a 15-in. Podbielniak column. Vacuum transfer of the residual solution left no residue. Vpc analysis indicated a mixture of 79 mol % methoxynorbornane and 21% norbornene. Separation of the products by preparative vpc gave 1.14 g (65%) of the ether: pmr (trifluoroacetic acid) τ 6.40 (d, 1, J = 6.7 Hz, H-2), 6.54 (s, 3, $-OCH_3$), 7.7 and 7.9 (H-1 and H-4), and complex absorption at 8.2–9.2. Infrared analysis showed only the exo-3-deuterated ether *c*-**12**.

Sodium Amalgam Reduction of *cis,endo*-3-Methoxy-2-norbornylmercuric Chloride (11).—A mixture (0.91 g) composed of approximately 80% of the cis,endo isomer and 20% of *syn*-7-chloromercuri-*exo*-2-methoxynorbornane, mp 49–54°, was treated with 3.5 equiv of 2% sodium amalgam as described above for the reduction of the *cis,exo*-methoxymercurial. The ethers were separated from about 1% of norbornene by preparative vpc and were obtained in 55% yield. In the pmr spectrum (CS_2), H-2 of the endo isomer appears as a doublet of doublets (J = 9.7, 3.6 Hz) at τ 6.45 and the methoxy protons appear at 6.9. The *endo*-2-methoxynorbornane (*c*-**13**) had deuterium only in the endo 3-position.

Sodium Amalgam Reduction of *exo*-3-Methoxy-*endo*-2-norbornylmercuric Chloride (10).—A 1.8-g (5 mmol) sample of **10** was reduced with 23 g of 2% sodium amalgam (20 g-atoms of sodium) in 20 ml of 2 *M* NaOD in D_2O as described above for **9** to give 0.359 mg (57%) of methoxynorbornane which was free of undeuterated and exo 3-deuterated ether by ir analysis. When a mixture of 97% of this product and 3% of the ether from the cis,exo mercurial was subjected to ir analysis, the latter was detectable. In the pmr spectrum in trifluoroacetic acid, H_2 appears as a broad singlet ($W_{h/2}$ = 5.2 Hz) at τ 6.4. The remaining protons absorb in the positions cited above for *exo*-3-deuterio-*exo*-2-methoxynorbornane. The product is *t*-**12**.

Reduction of *cis,exo*-3-Methoxy-2-norbornylmercuric Chloride (9) with Sodium Borodeuteride.—A 3-g (8.3 mmol) sample of **9** in 20 ml of D_2O containing six sodium hydroxide pellets was treated with 0.12 g (2.8 mmol) of sodium borodeuteride and worked up after 2 hr as described above for the borohydride reduction. There was obtained 1.48 g (88%) of mercury and 0.82 g (78%) of 3-deuterio-*exo*-2-methoxynorbornane, bp 53° (21 mm). Infrared analysis showed this to be a mixture composed of 80% *exo*- (*c*-**12**) and 20% *endo*-3-deuterio-*exo*-2-methoxynorbornane (*t*-**12**). In the pmr spectrum in trifluoroacetic acid, H_2 appears as a broad doublet (J = 6.3 Hz) at τ 6.40. The bridgehead and methylene protons absorb in the same positions

(26) M. J. Abercrombie, A. Rodgman, K. R. Barucha, and G. F. Wright, *Can. J. Chem.*, **37**, 1328 (1959).

as in the product of sodium amalgam reduction but show distinct differences in the splitting patterns.

Reduction of 8.3 mmol of **9** with 2.39 mmol of sodium borodeuteride in 20 ml of 2 *M* methanolic sodium methoxide was worked up after 2 hr by separating the mixture from a 73% yield of mercury and pouring it into 100 ml of water. The aqueous phase was extracted with three portions of pentane. The pentane solution was worked up as described above to give a 63% yield of the ether, bp 51–52° (21 mm). Infrared analysis indicated 81% of the exo-3- (*c*-**12**) and 19% of the endo-3-deuterated ether (*t*-**12**) and no undeuterated compound. It was determined that 3% of the latter could have been detected. The aqueous phase from the work-up was titrated to pH 2 with hydrochloric acid. The precipitate was extracted with chloroform and the solution was evaporated to dryness to leave 0.648 g (22%) of **9**, mp 120–122.5°, free of trans isomer (**10**) by ir analysis.

Reduction of *cis,exo*-3-Methoxy-2-norbornylmercuric Chloride (9) with Sodium Borodeuteride in the Presence of Diisopropylbenzene.—A solution of 2.0 g (5.54 mmol) of **9** and 2.5 g (15.4 mmol) of *p*-diisopropylbenzene (Shell Chemical Corp.) in 15 ml of 0.7 *M* methanolic sodium methoxide was treated with 0.082 g (1.92 mmol) of sodium borodeuteride and worked up after 3.5 hr as described above. Mercury was obtained in 82% yield. The ether was partially separated from the aromatic hydrocarbon by fractionation on a 15-in. Podbielniak column and further purified by preparative vpc and was obtained in 71% yield. Infrared analysis showed no undeuterated material. Acidification of the aqueous phase gave 0.255 g (13%) of unchanged mercurial.

Reduction of *exo*-3-Methoxy-*endo*-2-norbornylmercuric Chloride (10) with Sodium Borohydride and Borodeuteride.—A 2.02-g (5.6 mmol) sample of **10** in 20 ml of D_2O containing seven sodium hydroxide pellets was reduced with 0.24 g (5.6 mmol) of sodium borodeuteride and worked up after 2.5 hr in the manner described above for reduction of the cis,exo mercurial. Mercury was obtained in 96% yield. The organic products (72% yield) were 84% *exo*-3-deuterio- (*c*-**12**) and 16% *endo*-3-deuterio-*exo*-2-methoxynorbornane (*t*-**12**) by ir analysis.

Reduction of 0.5 g (1.4 mmol) of the mercurial with 0.026 g (0.7 mmol) of sodium borohydride in 5 ml of heavy water containing two sodium hydroxide pellets gave, after 2 hr, a 94% yield of mercury and a 62% yield of *exo*-2-methoxynorbornane (**12**) which was undeuterated (ir analysis).

A mixture of 1.0 g (2.77 mmol) of **10** and 0.0146 g (0.35 mmol) of sodium borodeuteride in 10 ml of 2 *M* methanolic sodium methoxide gave, after 2 hr, 0.116 g (41% based on borodeuteride) of free mercury and 0.738 g of unchanged **10**, mp 89.5–92°, free of **9** (ir analysis). A small amount of the reduction product was isolated by vpc for ir analysis and found to be 82% *exo*-3-deuterio- (*c*-**12**) and 18% *endo*-3-deuterio-*exo*-2-methoxynorbornane (*t*-**12**). No undeuterated ether was detected.

Reduction of *cis,endo*-3-Methoxy-2-norbornylmercuric Chloride (11) with Sodium Borodeuteride.—A 1.0-g (2.77 mmol) sample of pure **11** was reduced with sodium borodeuteride in basic deuterium oxide as described above for the borodeuteride reduction of the cis,exo isomer. Mercury was isolated in 97% yield. Methoxycyclohexane was added to the organic phase as an internal standard and the yield of methoxynorbornane by vpc analysis, assuming equal thermal conductivities, was 109%. The bulk of the product was isolated by preparative vpc. In the pmr spectrum in carbon disulfide, H-2 absorbed at τ 6.45, methoxy protons at 6.84, H-1 and H-4 at 7.68 and 7.92, and the remaining seven hydrogens between 8 and 9.2. H-2 appears as an eight-line multiplet with $W_{h/2}$ = 9.3 Hz. Double irradiation of the downfield bridgehead proton (2.594 kHz, offset at 157 Hz, 100–200 mV input) simplified absorption of H-2 to a broad doublet of doublets with J = 3.0 and 1.3 Hz.

Registry No.—**2**, 36807-31-5; **3**, 20556-05-2; **4**, 20556-07-4; **5**, 36807-34-8; *c*-**6**, 21438-85-7; *t*-**6**, 36807-36-0; *c*-**7**-*d*, 6372-64-1; *t*-**7**-*d*, 36807-38-2; **8**, 21438-92-6; **8**-*d*, 36794-38-4; **9**, 36807-39-3; **10**, 36807-40-6; **11**, 36807-41-7; **12**, 10395-53-6; *c*-**12**, 36807-43-9; *t*-**12**, 36807-44-0; **13**, 10395-55-8; *c*-**13**, 36807-46-2; *t*-**13**, 36807-47-3; mercury, 7439-97-6; deuterium, 7782-39-0; sodium borodeuteride, 15681-89-7; sodium amalgam, 11, 110, 524.

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Reduction with Trichlorosilane. IV. Ether from Acetal[1]

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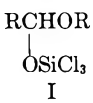
The reduction of acetals derived from formaldehyde, acetaldehyde, acetone, and diethyl ketone to the corresponding ethers with trichlorosilane under γ irradiation has been studied. An acetal reacts at first with chlorosilane to give an α-chloro ether, which is in turn reduced with the silicon hydride under γ irradiation. The present study, especially the reduction of mixed acetal containing a triethylsilyl group, makes clear the reduction sequence of an ester through an acetal type intermediate mentioned in our preceding paper.

Our previous paper reported the reduction of aliphatic esters to dialkyl ethers with trichlorosilane under free-radical conditions.[2] There we considered that the reduction proceeds *via* an acetal type intermediate I. If



I

this consideration were true, it might be expected that acetals, in general, are reduced with trichlorosilane to give the corresponding ethers. Furthermore, it might also be expected that the elucidation of the reduction mechanism of acetals may add to understanding the mechanism of the reduction of esters. From these viewpoints, acetals of formaldehyde, acetaldehyde, acetone, and diethyl ketone and some mixed acetals were allowed to react with trichlorosilane in the present paper. Although several papers reported that acetals can be reduced to ethers with lithium aluminum hydride[3] and sodium borohydride,[4] the present method will provide a new synthetic route to ethers in high yields.

Results and Discussion

A degassed mixture of acetal and trichlorosilane was irradiated with γ rays in a sealed tube. The results are summarized in Table I, which indicates comparatively

(1) Paper III in this series: R. Nakao, T. Fukumoto, and J. Tsurugi, *J. Org. Chem.*, **37**, 76 (1972).

(2) J. Tsurugi, R. Nakao, and T. Fukumoto, *J. Amer. Chem. Soc.*, **91**, 4587 (1969).

(3) E. L. Eliel, V. G. Badding, and M. N. Rerick, *ibid.*, **84**, 2371 (1962). and references cited therein.

(4) J. R. Dias and G. R. Pettit, *J. Org. Chem.*, **36**, 3485 (1971).

TABLE I

REDUCTION OF ACETALS TO ETHERS WITH TRICHLOROSILANE[a]

Registry no.	Run	Acetal	Product (yield, %)
77-76-9	1	$(CH_3)_2C(OCH_3)_2$	$(CH_3)_2CHOCH_3$[d] (85), HCl_2SiOCH_3 (90)
36749-09-4	2	$(C_2H_5)_2C(OC_2H_5)_2$	$(C_2H_5)_2CHOC_2H_5$[e] (89), $HCl_2SiOC_2H_5$ (95)
534-15-6	3	$CH_3CH(OCH_3)_2$	$C_2H_5OCH_3$[f] (79), HCl_2SiOCH_3 (94)
	4[b]	$CH_3CH(OCH_3)_2$	$C_2H_5OCH_3$ (61), HCl_2SiOCH_3 (34) Cl_3SiOCH_3 (58)
105-57-7	5	$CH_3CH(OC_2H_5)_2$	$C_2H_5OC_2H_5$ (82), $HCl_2SiOC_2H_5$ (96)
462-95-3	6[c]	$H_2C(OC_2H_5)_2$	$CH_3OC_2H_5$ (85), $HCl_2SiOC_2H_5$ (92)
10471-14-4	7	CH_3CHOCH_3 | OC_2H_5	$C_2H_5OC_2H_5$ (52), HCl_2SiOCH_3 (50) $C_2H_5OCH_3$ (35), $HCl_2SiOC_2H_5$ (43)
17841-50-8	8	$CH_3CHOC_2H_5$ | $OSi(C_2H_5)_3$	$C_2H_5OC_2H_5$ (93), $HCl_2SiOSi(C_2H_5)_3$ (96)

[a] Trichlorosilane/acetal = 3; dose rate = 0.3 Mrad/hr, total dose = 5.1 Mrad. [b] Trichlorosilane/acetal = 1. [c] Irradiated after mixing and standing for 5 days. [d] Registry no., 598-53-8. [e] Registry no., 36749-13-0. [f] Registry no., 540-67-0.

high yields of dialkyl ethers from several types of acetals. Besides the products cited in Table I, tetrachlorosilane was always found among the products when a 3:1 molar ratio of trichlorosilane/acetal was used. Although the mixed acetal, $CH_3CH(OCH_3)OC_2H_5$ of run 7, yields two types of ether, the mixed acetal, $CH_3CH(OC_2H_5)OSi(C_2H_5)_3$ of run 8, gave predominantly diethyl ether. The formation of tetrachlorosilane and the products from the latter mixed acetal will be discussed later in this paper.

We found that simple mixing of trichlorosilane with acetaldehyde dimethylacetal (3:1 molar ratio) caused eq 1 to shift to the right-hand side, because the formation of α-chloro ether and complete disappearance of the acetal were confirmed by nmr. The quantitative formation of dichloromethoxysilane was further confirmed by glpc. Identification and determination of α-chloroethyl methyl ether by glpc were unsuccessful because of its sensitivity to the decomposition. The results confirmed by nmr and glpc indicate that eq 1 proceeds quantitatively immediately after the simple mixing except run 6 for ethylal.[5] The reduction of acetal with trichlorosilane then turned out to be the reduction of α-chloro ether with trichlorosilane. After γ irradiation of the mixture, nmr spectra showed that ethyl methyl ether was produced together with the complete disappearance of the spectra of α-chloro ether and maintenance of the spectra of dichloromethoxysilane. This result indicates eq 2 for γ-induced reduction.

$$CH_3CH(OCH_3)_2 + HSiCl_3 \longrightarrow CH_3CHClOCH_3 + HCl_2SiOCH_3 \quad (1)$$

$$CH_3CHClOCH_3 + HSiCl_3 \xrightarrow{\sim\sim} CH_3CH_2OCH_3 + SiCl_4 \quad (2)$$

A number of papers[6] reported the reduction of alkyl chlorides to alkanes with trichloro- and trialkylsilanes. These reactions are believed to proceed by a radical chain mechanism. We irradiated the mixture of trichlorisilane and acetaldehyde dimethylacetal (3:1 molar ratio) in a Pyrex tube with uv lights for 1 hr and obtained a 51% yield of ethyl methyl ether. We also obtained an 86% yield of the ether by uv irradiation (for 1 hr) of the same mixture containing 2 molar % of di-*tert*-butyl peroxide/acetal. From Figure 1, which will be mentioned later, the G value (number of molecules formed per 100 eV of energy absorbed) is calculated as 5000. These results clearly support a radical chain mechanism.

The two-step sequence, chlorination of acetal to α-chloro ether and reduction of α-chloro ether to ether, is supported by the results shown in Table II. Chlorinating agents such as tetrachlorosilane and acetyl chloride[7] combined with triethyl- or triphenylsilane can yield methyl ethyl ether from acetaldehyde dimethylacetal, while triethyl- or triphenylsilane alone cannot. Dimethylchlorosilane (run 3, Table II) can behave similarly to trichlorosilane. Tetrachlorosilane (runs 4 and 5, Table II) also chlorinated the acetal similarly to eq 1. Acetyl chloride (run 6, Table II) is well known[7] to give α-chloro ether from acetal as indicated in eq 3. Methyl acetate,[8] expected to be produced in eq 3, was found in 75% yield by glpc. The two-step sequence was further supported by the following result. The mixture of trichlorosilane with chloromethyl ethyl ether (purified

TABLE II

REDUCTION OF ACETALEDHYDE DIMETHYLACETAL TO METHYL ETHYL ETHER WITH SILICON HYDRIDES COMBINED WITH CHLORINATING AGENTS[a]

Run	Chlorinating agent (mol)	Silicon hydride (mol)	Yield, %
1		$HSi(C_2H_5)_3$ (1)	0
2		$HSi(C_6H_5)_3$ (1)	0
3		$HClSi(CH_3)_2$ (2)	68
4	$SiCl_4$ (1)	$HSi(C_2H_5)_3$ (1)	83
5	$SiCl_4$ (1)	$HSi(C_6H_5)_3$ (1)	64
6	CH_3COCl (1)	$HSi(C_2H_5)_3$ (1)	71

[a] Dose rate = 0.3 Mrad/hr, total dose = 5.1 Mrad.

$$RR'C(OR'')_2 + CH_3COCl \longrightarrow RR'CClOR'' + CH_3COOR'' \quad (3)$$

(5) γ irradiation of the mixture of run 6 immediately after the mixing did not give ethyl methyl ether. After the mixture was left for a sufficient time period, γ irradiation gave a high yield of ethyl methyl ether as indicated in run 6, Table I. This may be attributed to the slower rate of eq 1 in the case of ethylal, because immediately after the mixing chloromethyl ethyl ether could not be detected by nmr. Chlorination was accelerated by adding a very small amount of water to the reduction system.

(6) (a) R. N. Haszeldine and J. C. Young, *J. Chem. Soc.*, 4503 (1960); (b) R. A. Jackson, *Advan. Free-Radical Chem.*, **3**, 231 (1969); (c) I. M. T. Davidson, *Quart. Rev., Chem. Soc.*, **25**, 111 (1971).

(7) L. Summers, *Chem. Rev.* **55**, 301 (1955).

(8) Methyl acetate is reduced to ethyl methyl ether with trichlorosilane under γ irradiation, but is not reduced with triethylsilane. Therefore, methyl acetate remained unaltered under the conditions of run 6, Table II.

commercial material) gave an 87% yield of ethyl methyl ether under γ irradiation.

The two-step sequence at first glance seems to require 2 mol of trichlorosilane to reduce 1 mol of acetal, because both eq 1 and 2 consume each 1 mol of trichlorosilane. However, run 4, Table I, indicates that an equimolar amount is sufficient. Since eq 1 is fast, 1 mol of trichlorosilane is consumed by eq 1. The reduction of α-chloro ether must be performed with dichloromethoxysilane produced in eq 1. As seen in run 4, Table I, the amount of dichloromethoxysilane decreases as compared with other runs, and trichloromethoxysilane was found anew instead of tetrachlorosilane. This result suggests that eq 4 proceeds under γ

$$CH_3CHClOCH_3 + HCl_2SiOCH_3 \xrightarrow{\gamma} CH_3CH_2OCH_3 + Cl_3SiOCH_3 \quad (4)$$

irradiation. Figure 1 shows yields of ethyl methyl ether by the reductions of 3:1 and 1:1 molar ratios of trichlorosilane/acetaldehyde dimethylacetal. This result indicates that dichloromethoxysilane can reduce α-chloro ether, but more slowly than trichlorosilane can.

As a summary, the reduction in the presence of a 2:1 or more molar ratio of trichlorosilane/acetal proceeds *via* eq 1 and 2. On the other hand, equimolar amount of trichlorosilane leads to the sequence indicated by eq 1 and 4.

Frainnet, *et al.*,[9] reported the reduction of acetals with trialkylsilanes in the presence of zinc chloride as a catalyst. The reduction sequence, which had not been mentioned by them, seems to differ from ours.

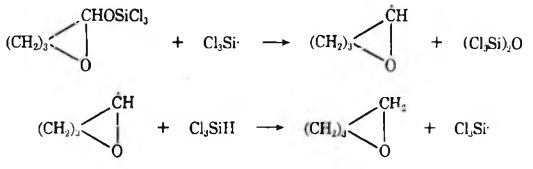
Connection with the Reduction of Esters.—It seems interesting to discuss the reduction of ester to ether in connection with the present results. In our previous paper[2] on the reduction of alkyl aliphatic esters we reported that the reduction proceeds *via* eq 5 and 6. In

$$RCOR' + HSiCl_3 \xrightarrow{\gamma} RCHOR' \quad (5)$$
(RCOR': O; RCHOR': OSiCl$_3$)

$$RCHOR' + HSiCl_3 \longrightarrow RCH_2OR' + Cl_3SiOSiCl_3 \quad (6)$$
(RCHOR': OSiCl$_3$)

this sequence we considered mixed acetal as an intermediate, and held eq 6 ambiguous. Later, in part III of this series, we proposed a sequence[10] for the reduction of lactones with trichlorosilane. However, on the basis of the results of the present paper, this sequence should be corrected to eq 7 and 8 (X = Cl). In the present paper, as a model of mixed acetal containing the trichlorosilyl group, which is very susceptible to moisture, we used in run 8, Table I, the mixed acetal containing the triethylsilyl group. The mixture of the latter acetal with trichlorosilane gave diethyl ether and triethylsiloxydichlorosilane both in nearly quantitative

(9) E. Frainnet and C. Esclamadon, *C. R. Acad. Sci.*, **254**, 1814 (1962).

(10)


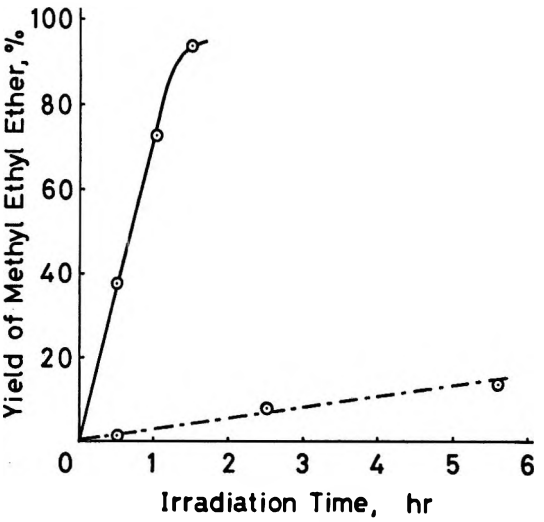


Figure 1.—Reduction of acetaldehyde dimethylacetal with trichlorosilane for various irradiation times. Dose rate = 0.3 Mrad/hr: -·⊙·-, $HSiCl_3$/acetal = 1; —⊙—, $HSiCl_3$/acetal = 3.

yields under γ irradiation (X = C_2H_5, R = CH_3, and R′ = C_2H_5 in eq 7 and 8).

$$RCHOR' + HSiCl_3 \longrightarrow RCHClOR' + HCl_2SiOSiX_3 \quad (7)$$
(RCHOR': OSiX$_3$)

$$RCHClOR' + HSiCl_3 \xrightarrow{\gamma} RCH_2OR' + SiCl_4 \quad (8)$$

As a summary, the reduction of ester to ether in the presence of a 3:1 or more molar ratio of trichlorosilane can be concluded to proceed *via* eq 5, 7, and 8. However, in the presence of a 2:1 molar ratio of trichlorosilane the reduction proceeds *via* eq 5, 7, and 9, because our previous paper reported that ethyl acetate and trichlorosilane (1:2.2 molar ratio) gave hexachlorodisiloxane besides diethyl ether. Equation 9 is quite similar to eq 4.

$$CH_3CHClOC_2H_5 + HCl_2SiOSiCl_3 \xrightarrow{\gamma} CH_3CH_2OC_2H_5 + Cl_3SiOSiCl_3 \quad (9)$$

Experimental Section

All boiling points are uncorrected. Gas chromatographies were determined by a Yanagimoto GCG-5DH with a 2.5-m column containing 25% silicon DC-200 on Celit 545 and a 3-m column containing 30% dioctyl phthalate on Celit 545 both using helium as a carrier gas. Nmr spectra were recorded on a JNM 3H-60 with tetramethylsilane as an external standard. Mass spectra were recorded on a Shimadzu-LKD 9000.

Materials.—Diethyl ketone diethylacetal was prepared by the method of Fife[11] from diethyl ketone and triethyl orthoformate, bp 155° (lit.[12] bp 154°). Acetaldehyde methyl ethylacetal was prepared by the modified procedure of Juvet.[13] Acetaldehyde diethyl acetal (0.6 mol) and methanol (0.2 mol) were refluxed in the presence of 1 drop of 12 *N* hydrochloric acid for 30 min. After neutralization with sodium hydroxide, two distillations gave the acetal: bp 83° (lit.[13] bp 84.5°); nmr (neat) δ 1.15 (t, 3, CH_2CH_3), 1.20 (d, 3, $CHCH_3$), 3.20 (s, 3, OCH_3), 3.45 and 3.50 (2 q, 2, CH_2), 4.55 (q, 1, CH). Acetaldehyde ethyl (triethyl)silylacetal[14] was synthesized by the addition reaction of

(11) T. H. Fife and L. Hagopian, *J. Org. Chem.*, **31**, 1772 (1966).

(12) Beilstein's "Handbuch der Organichen Chemie," Vol. 1, 1918, p 680.

(13) R. S. Juvet, Jr., and J. Chiu, *J. Amer. Chem. Soc.*, **83**, 1560 (1961).

(14) M. F. Shostakovskii, K. A. Andrianov, I. A. Shikhiev, and D. A. Kochkin, *Dokl. Akad. Nauk SSSR*, **93**, 681 (1953); *Chem. Abstr.*, **49**, 1542a (1955).

TABLE III
NMR SPECTRA OF REACTION MIXTURES

Mixture (molar ratio)	Reaction condition[a]	Spectra of products (molar ratio)
$CH_3CH(OCH_3)_2$ (1), $HSiCl_3$ (3)	Simple mixture	$CH_3CHClOCH_3$ (1) δ 2.01 (d, 3, CCH_3), 3.73 (s, 3, OCH_3), 5.84 (q, 1, CH);[b] HCl_2SiOCH_3 (1) δ 3.94 (s, 3, OCH_3), 5.82 (s, 1, SiH); $HSiCl_3$ (2) δ 6.40 (s, 1, SiH)
$CH_3CH(OCH_3)_2$ (1), $HSiCl_3$ (3)	Irradiation	$C_2H_5OCH_3$ (1) δ 1.41 (t, 3, CCH_3), 3.51 (s, 3, OCH_3), 3.62 (q, 2, CH_2); HCl_2SiOCH_3 (1) δ 3.93 (s, 3, OCH_3), 5.79 (s, 1, SiH); $HSiCl_3$ (1) δ 6.38 (s, 1, SiH)
$(CH_3)_2C(OCH_3)_2$ (1), $HSiCl_3$ (3)	Simple mixture	$(CH_3)_2CClOCH_3$ (1) δ 2.10 (s, 6, CCH_3), 3.70 (s, 3, OCH_3); HCl_2SiOCH_3 (1) δ 3.95 (s, 3, OCH_3), 5.82 (s, 1, SiH); $HSiCl_3$ (2) δ 6.40 (s, 1, SiH)
$(CH_3)_2C(OCH_3)_2$ (1), $HSiCl_3$ (3)	Irradiation	$(CH_3)_2CHOCH_3$ (1) δ 1.35 (d, 6, CCH_3), 3.48 (s, 3, OCH_3), 3.35–3.9 (m, 1, CH); HCl_2SiOCH_3 (1) δ 3.92 (s, 3, OCH_3), 5.79 (s, 1, SiH); $HSiCl_3$ (1) δ 6.35 (s, 1, SiH)
$H_2C(OC_2H_5)_2$ (1), $HSiCl_3$ (3)	A or B	$H_2ClOC_2H_5$ (1) δ 1.53 (t, 3, CH_3), 4.01 (q, 2, OCH_2C), 5.74 (s, 2, $ClCH_2O$); $HCl_2OSiOC_2H_5$ (1) δ 1.62 (t, 3, CH_3), 4.32 (q, 2, OCH_2C), 5.85 (s, 1, SiH); $HSiCl_3$ (2) δ 6.42 (s, 1, SiH)
$CH_3CH(OCH_3)_2$ (1), $SiCl_4$ (3)	Simple mixture	$CH_3CHClOCH_3$ (1) δ 2.11 (d, 3, CCH_3), 3.82 (s, 3, OCH_3), 5.91 (q, 1, CH); Cl_3SiOCH_3 (1) δ 4.11 (s, 3, OCH_3)
$CH_3CH(OCH_3)_2$ (1), HCl_2SiCH_3 (3)	Simple mixture	$CH_3CHClOCH_3$ (1) δ 1.92 (d, 3, CCH_3), 3.64 (s, 3, OCH_3), 5.78 (q, 1, CH); $HClSi(OCH_3)CH_3$ (1) δ 0.70 (d, 3, J = 2 Hz, $SiCH_3$), 3.74 (s, 3, OCH_3), 5.31 (q, 1, J = 2 Hz, SiH); HCl_2SiCH_3 (2) δ 1.07 (d, 3, J = 2 Hz, $SiCH_3$), 5.77 (q, 1, J = 2 Hz, SiH).

[a] A, allowing the mixture to stand for 5 days; B, adding a small amount of water to the mixture. [b] G. A. Olah and J. Sommer, *J. Amer. Chem. Soc.*, 90, 4323 (1968).

triethylsilanol to vinyl ether. A mixture of triethylsilanol[15] (0.2 mol), which was prepared by hydrolysis of triethylchlorosilane with aqueous sodium hydroxide, vinyl ethyl ether (0.4 mol), and hydrochloric acid (1 drop) was refluxed for 1 hr. The temperature of the mixture was raised to 55° at the later stage. After neutralization with sodium hydroxide, distillation gave the acetal, bp 81° (16 mm), $n^{20}D$ 1.4235 [lit.[14] bp 78–79° (15–16 mm), $n^{20}D$ 1.4232]. Other acetals, commercial materials, were distilled and stored in ampoules.

Trichlorosilane was treated with quinoline to remove hydrochloric acid and was distilled several times under vacuum.

The other reagents were purified by conventional methods.

Preparation of Standard Materials for Glpc and Nmr.—Standard materials for glpc and nmr were purified from the corresponding commercial materials by conventional methods except for the compounds cited below. Isopropyl methyl ether was prepared from methyl iodide and sodium isopropoxide by the conventional method, bp 32° (lit.[16] bp 32–33°). 1-Ethylpropyl ethyl ether was prepared by γ-induced reduction of diethyl ketone diethylacetal (0.15 mol) with trichlorosilane (0.45 mol). To the irradiated mixture was added aqueous sodium hydroxide for decomposition of chlorosilanes. Two distillations gave the ether: bp 106°; nmr (neat) δ 0.87 (t, 6, CCH_2CH_3), 1.14 (t, 3, OCH_2CH_3), 1.44 (m, 4, $CHCH_2CH_3$), 3.08 (m, 1, OCH), 3.42 (q, 2, OCH_2); mass spectrum (70 eV) m/e (rel intensity) 116 (0.2, M^+), 87 (54), 59 (100), 55 (37), 41 (23), 29 (29). Dichloromethoxysilane was prepared by methanolysis of trichlorosilane. A benzene solution of trichlorosilane (0.2 mol) was placed in a two-necked flask equipped with a dropping funnel and a reflux condenser which was fitted with a calcium chloride tube. Methanol (0.2 mol) was added dropwise for 1 hr with magnetic stirring at 0°. The resulting mixture was refluxed for 30 min for the completion of the reaction and the exclusion of hydrogen chloride produced. Dichloromethoxysilane was obtained by two distillations: bp 51° (lit.[17] bp 50.5°); nmr (neat) δ 3.88 (s, 3, OCH_3), 5.74 (s, 1, SiH). Dichloroethoxysilane was prepared in the same manner as mentioned above by using ethanol instead of methanol and toluene instead of benzene: bp 75° (lit.[17] bp 75.7°); nmr (neat) δ 1.53 (t, 3, CH_3), 4.23 (q, 2, OCH_2), 5.78 (s, 1, SiH). Triethylsiloxydichlorosilane was separated from the irradiated mixture of acetaldehyde ethyl (triethyl)silyl acetal and trichlorosilane. A degassed mixture of the acetal (0.1 mol) and trichlorosilane (0.3 mol) was irradiated by γ rays (dose rate = 0.3 Mrad/hr, total dose = 5.1 Mrad) in a Pyrex tube equipped with a breakable seal. After the irradiation, the mixture was distilled under vacuum. Triethylsiloxydichlorosilane was collected in a trap cooled by Dry Ice and the others (diethyl ether, tetrachlorosilane, and unchanged trichlorosilane) were trapped by liquid nitrogen. Five distillations gave a gas chromatographically pure sample, nmr (neat) δ 0.5–1.3 (m, 15, $SiCH_2CH_3$), 5.70 (s, 1, SiH).

Procedure for Irradiation.—A given amount of acetal and trichlorosilane or di-*tert*-butyl peroxide was degassed in a Pyrex tube or nmr sample tube by the same way as stated earlier.[1] The mixture was irradiated by γ rays from a ^{60}Co source or uv rays from a medium-pressure mercury lamp at room temperature.

Identification and Estimation of Products.—The products were identified by glpc or nmr and estimated by glpc, except for Figure 1. The yields of methyl ethyl ether in Figure 1 were estimated by comparison of nmr intensity of the methyl signal (δ 1.40, triplet) of the ether with that of the methyl absorption (δ 2.00, doublet) of unchanged α-chloroethyl methyl ether.

Nmr Spectra of the Products. A. From Acetals and Chlorosilanes.—Simple mixing of an acetal with a chlorosilane gave a superimposed spectrum which consisted of α-chloro ether, chloroalkoxysilane, and excess chlorosilane. When chlorosilane was trichlorosilane, γ irradiation changed the spectrum into that consisted of an ether, a dichloroalkoxysilane, and unchanged trichlorosilane with the disappearance of the spectrum of α-chloro ether. The nmr spectrum of each product is summarized in Table III.

B. From Acetaldehyde Dimethylacetal and Acetyl Chloride.—An equimolar mixture of the titled compounds, after standing for 4 days, gave a spectrum which consisted of the following four components: α-chloroethyl methyl ether, δ 1.83 (d, 3, CCH_3), 3.69 (s, 3, OCH_3), 5.78 (q, 1, CH) (relative ratio 0.8); methyl acetate, δ 2.08 (s, 3, CCH_3), 3.57 (s, 3, OCH_3) (relative ratio 0.8); unchanged acetal, δ 1.30 (d, 3, CCH_3), 3.33 (s, 6, OCH_3), 4.61 (q, 1, CH) (relative ratio 0.2); and unchanged acetyl chloride, δ 2.80 (s, 3, CH_3) (relative ratio 0.2).

Registry No.—Trichlorosilane, 10025-78-2.

Acknowledgment.—The authors wish to thank Dr. S. Kawamura and Mr. M. Chubachi for the nmr and mass spectral work, respectively.

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Influence of Solvent and Brominating Agent on the Steric Course of Bromine Addition to Substituted Cyclohexenes

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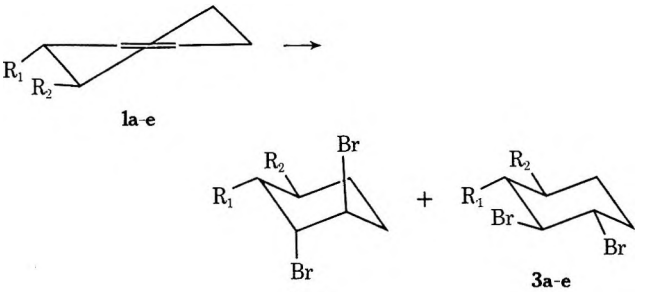
The addition of bromine to several 3- and 4-substituted cyclohexenes in chloroform always produces nonequilibrium mixtures of diaxial and diequatorial dibromides in ratios dependent on the size, position, and polarity of the substituent. 3-Substituted olefins yield higher amounts of diequatorial adducts than the corresponding 4-substituted compounds; particularly, 3-*tert*-butylcyclohexene gives the diequatorial dibromide as the major product. These results may be ascribed to a direct steric effect of the substituent in both the electrophilic and the nucleophilic steps of the addition, which is considered to proceed through the irreversible formation of cyclic bromonium ion intermediates. In contrast, the use of either ethyl ether as the solvent or pyridine perbromide and pyridinium hydrobromide perbromide as the brominating agents, or even the mere presence of tertiary amines in the reaction medium, always leads to a decrease in the amount of the diequatorial products. It is suggested that under these conditions the electrophilic attack could be a reversible prerate-determining step, the steric course of the addition being controlled by the steric interactions in the transition states of the nucleophilic step.

It is generally accepted[1] that the polar addition of bromine to nonconjugated alkenes is an anti stereospecific process, which involves the formation of cyclic bromonium ion intermediates, as was first postulated by Roberts and Kimball.[2] This belief has also recently been supported by stereochemical,[3] kinetic,[4] spectroscopic,[5] and thermochemical[6] evidence. On the basis of the results obtained with steroidal olefins[7-9] and related cyclohexene derivatives,[10] diaxial attack is considered to be strongly favored in the bromine addition to the cyclohexene ring. However, our investigations on the asymmetric bromination of 3- and 4-substituted cyclohexenes[11-13] have shown that diequatorial as well as diaxial dibromides are always produced; moreover, the presence of an asymmetric catalyst, such as a *Cinchona* alkaloid, causes, beside optical activity of the dibromides, a decrease in the amount of the diequatorial adducts. The asymmetric selection was attributed to the intervention of an alkaloid–bromine complex as the brominating agent; we therefore thought that also the use of a simple preformed amine–bromine complex, like pyridine perbromide, or the mere presence of bases in the reaction medium, could possibly change the ratio between diaxial and diequatorial adducts formed in the bromination of cyclohexene derivatives. We accordingly have undertaken an investigation of the steric course of these electrophilic additions to obtain some information about the influence of such factors as the nature and position of ring substituents and the solvent and the brominating agent employed. Two conformationally biased, 4- and 3-*tert*-butylcyclohexene (**1a** and **1b**), and three mobile systems, 4-methylcyclohexene (**1c**), methyl cyclohex-3-enecarboxylate (**1d**), and 3-methylcyclohexene (**1e**), have been studied.

Results

The ratios between the dibromides **2** and **3** obtained from **1a** and **1b** in various conditions are reported in Table I; the results of the brominations of **1c–e** are



a, R_1 = H; R_2 = *t*-Bu
b, R_1 = *t*-Bu; R_2 = H
c, R_1 = H; R_2 = Me
d, R_1 = H; R_2 = CO_2Me
e, R_1 = Me; R_2 = H

summarized in Table II. The halogenations with free bromine were carried out by adding solutions of Br_2 in $CHCl_3$ to solutions of the olefins in the various solvents at the temperatures reported; when auxiliary amines were used, they were added in equimolar amounts to the olefin solutions. To avoid the formation of mixed adducts arising from a nucleophilic attack by the solvent on the ionic intermediates, only nonpolar aprotic solvents were generally employed. The brominations with pyridine perbromide ($C_5H_5NBr_2$) and pyridinium hydrobromide perbromide ($C_5H_5NHBr_3$) were carried out by adding the solid brominating agents to solutions of the substrates; when such brominating agents were insoluble in the solvent used, the mixtures were stirred until the solid disappeared. Analyses of the products were performed both by nmr[14] and glpc; the two techniques gave identical results. Only the dibromides arising from **1b**, owing to easy thermal isom-

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(14) P. L. Barili, G. Bellucci, G. Berti, F. Marioni, A. Marsili, and I. Morelli, *J. Chem. Soc., Perkin Trans. 2*, 58 (1972).

TABLE I

Compd	Solvent	Temp, °C	Brominating agent	Added base	Ratio of 2:3
1a	$CHCl_3$	0	Br_2		94:6
	$CHCl_3$	−70	Br_2		95.5:4.5
	$CHCl_3$	0	Br_2	Et_3N	96:4
	$CHCl_3$	−70	Br_2	Et_3N	98:2
	$CHCl_3$	0	$C_5H_5NHBr_3$		>98:<2
1b	$CHCl_3$	0	Br_2		43:57
	$CHCl_3$	−70	Br_2		42:58
	$CHCl_3$	0	Br_2[a]		44:56
	$CHCl_3$	0	Br_2HBr[b]		45:55
	C_6H_6	7	Br_2		50:50
	Et_2O	0	Br_2		68:32
	CCl_4	0	Br_2		50:50
	$CHCl_3$	0	Br_2	Et_3N	63:37
	$CHCl_3$	0	Br_2	Quinuclidine	61:39
	C_6H_6	7	Br_2	Et_3N	59:41
	$CHCl_3$	0	Br_2	C_5H_5N	71:29
	$CHCl_3$	0	Br_2	C_5H_5N[c]	72:28
	$CHCl_3$	0	Br_2	2-MeC_5H_5N	72:28
	$CHCl_3$	0	Br_2	4-MeC_5H_5N	70:30
	$CHCl_3$	0	$C_6H_5NBr_2$		67:33
	CCl_4	0	$C_5H_5NBr_2$		71:29
	AcOH	20	$C_6H_6NHBr_3$		68:32
	$CHCl_3$	0	$C_5H_5NHBr_3$		73:27

[a] Added with bubbling oxygen. [b] 1 *M* solution of Br_2 in $CHCl_3$ saturated with HBr gas. [c] Fivefold excess with respect to **1b**.

TABLE II

Compd	Solvent	Temp, °C	Brominating agent	Added base	Ratio of 2:3
1c	$CHCl_3$	0	Br_2		87:13
	$CHCl_3$	−70	Br_2		93:7
	$CHCl_3$	0	Br_2HBr[a]		88:12
	Et_2O	0	Br_2		96:4
	$CHCl_3$	0	Br_2	C_5H_5N	97:3
	$CHCl_3$	0	Br_2	Et_3N	96:4
	CCl_4	0	$C_5H_5NBr_2$		98:2
	$CHCl_3$	0	$C_5H_5NHBr_3$		98:2
1d	$CHCl_3$	0	Br_2		90:10[b]
	$CHCl_3$	0	Br_2	Et_3N	93:7
	$CHCl_3$	0	Br_2	C_5H_5N	94:6
	$CHCl_3$	0	$C_5H_5NHBr_3$		94:6
1e	$CHCl_3$	0	Br_2		78:22
	$CHCl_3$	−70	Br_2		85:15
	Et_2O	0	Br_2		89:11
	$CHCl_3$	0	Br_2	Et_3N	88:12
	$CHCl_3$	0	Br_2	C_6H_6N	89:11
	CCl_4	0	$C_5H_5NBr_2$		92:8
	$CHCl_3$	0	$C_5H_5NHBr_3$		88:12

[a] 1 *M* solution of Br_2 in $CHCl_3$ saturated with HBr gas. [b] About 10% *cis*-3-hydroxy-*trans*-4-bromocyclohexane-1-carboxylic acid lactone is also formed.

erization[14] of **3b** to **2b** at the injection block temperature, could not be analyzed by glpc.

The additions took place entirely in an anti fashion under all of the conditions examined, to give mixtures of the corresponding diastereoisomeric trans dibromides **2** and **3**. As both **2** and **3** are stable under the reaction conditions, it may be excluded that **3** is formed by secondary isomerization of **2** through a "1,2 interchange."[14,15] This is also confirmed by the finding[11-13] that the chiral centers bearing the bromine atoms in the optically active dibromides **2** and **3** obtained by asymmetric bromination of **1a**, **1c**, **1d**, and **1e** have the same configuration; if compounds **3** were formed by isomerization of **2**, opposite configuration would have resulted. In the addition of free bromine to **1d** ~10% *cis*-3-hydroxy-*trans*-4-bromocyclohexane-1-carboxylic acid lactone and 5% another unidentified product were found beside the dibromo derivatives **2d** and **3d**. In the other cases no formation of products different from **2** and **3** (particularly cis dibromides) was observed, although the analytical procedures could have detected a 1% amount of them.

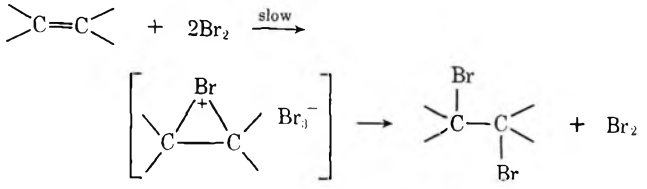
The reaction temperature appears to have no appreciable effect on the ratio between the diastereoisomeric adducts arising from the bromination in $CHCl_3$ of the biased substrates **1a** and **1b**; in contrast, by lowering the temperature the conformationally mobile systems **1c** and **1e** give higher ratios of **2** to **3**. The use of a basic solvent such as ethyl ether instead of $CHCl_3$ strongly decreases the formation of the diequatorial dibromides **3**, whereas benzene and CCl_4 have only little effect. The presence of tertiary amines in the reaction medium, or the use of pyridine perbromide or pyridinium hydrobromide perbromide as brominating agents, also leads to a decrease in the amount of the diastereoisomers **3**. In contrast, the presence of hydrogen bromide does not affect the steric course appreciably. The same trend is found in all of the olefins examined, although it is less evident in the case of **1a**, owing to its small tendency to give **3a**. The behavior of **1b**, which gives the highest amount of the diequatorial adduct, has been more thoroughly examined. The fact that the product composition does not change when oxygen is bubbled into the olefin solution during the addition of bromine provides evidence against a free-radical mechanism for the reaction. Pyridine derivatives are more efficient than aliphatic amines in inhibiting the formation of **3b**. However, within analogous sets, neither basic strength nor steric effects around nitrogen seem to be important, as both triethylamine and quinuclidine give substantially similar results, in spite of their different basicities and

(15) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, Amsterdam, 1968, p 373.

steric hindrances;[16] furthermore no differences are observed in the stereochemical results of the brominations by using different methyl-substituted pyridines as basic catalysts. Even the amount of base does not seem to be important, since, for example, a fivefold excess of pyridine does not appreciably change the results. No acetoxy bromides are formed in the run carried out with pyridinium hydrobromide perbromide in acetic acid, as shown by the absence of acetoxyl protons signals in the nmr spectrum. Finally, it is to emphasize that rather similar ratios of **2** to **3** are obtained from each olefin examined when one uses ethyl ether as the solvent and pyridine perbromide and pyridinium hydrobromide perbromide as the halogenating agent or when pyridine is present in the reaction medium.

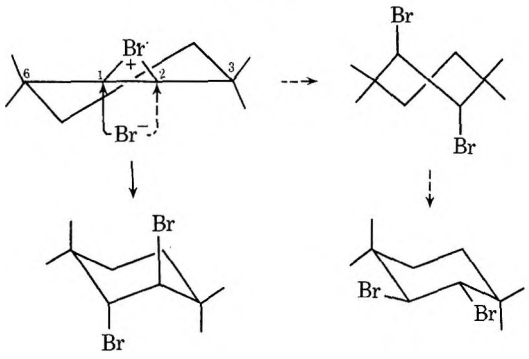
Discussion

The mechanism of the bromine addition to nonconjugated olefins in nonpolar solvents and in the absence of bromide ions is summarized as follows.[1]



According to Valls and Toromanoff[17] a cyclohexene bromonium ion may undergo two modes of ring opening (Scheme I): (1) nucleophilic attack antiparallel to the

Scheme I



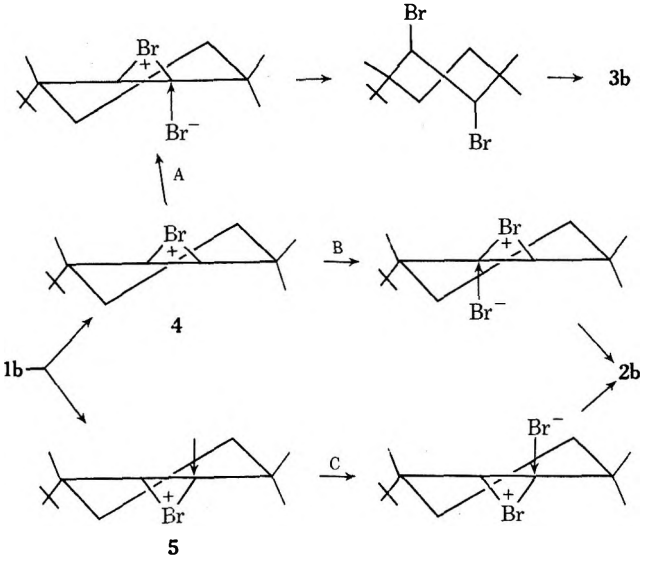
neighboring pseudoaxial bond at C-6, leading to the diaxial adduct through a prechair transition state, as indicated by the full arrow; (2) nucleophilic attack parallel to the pseudoaxial bond at C-3, leading to the diequatorial adduct through a preboat transition state, as indicated by the dotted arrow.

Whereas the configurations of the products arising from conformationally biased substrates should reflect the mode of the addition, little information can be obtained from conformationally mobile systems, because products which could be formed in unstable conformations will pass to the more stable ones, which no longer correspond to the addition mode. Therefore the steric course of the bromination of the biased compounds **1a** and **1b** will be discussed in more detail.

(16) W. L. Mosby in "Heterocyclic Systems with Bridgehead Nitrogen Atoms," A. Weissberger, Ed., Interscience, New York, N. Y., 1961, p 1335.
(17) J. Valls and E. Toromanoff, *Bull. Soc. Chim. Fr.*, 758 (1961).

The formation of 5% diequatorial dibromide **3a** beside diaxial isomer **2a** in the bromination of **1a** in $CHCl_3$ even at $-70°$ is consistent with a high but not exclusive preference for the antiparallel opening of both the *cis*- and the *trans*-bromonium ions arising from this olefin. In contrast, no diequatorial bromo chlorides were found in the addition of bromine chloride to **1a**.[18] On the other hand an excess of the diequatorial adduct **3b** is formed in the addition of free bromine to **1b** in $CHCl_3$ and substantial amounts of this diastereoisomer are obtained under all of the conditions employed. Some insight into the steric course of the bromination of **1b** may be obtained from the comparison with the epoxidation of the olefin followed by ring opening of the two epoxides, which may be considered as models for the bromonium ions. It has been shown[19] that **1b** reacts with peroxy acids to give a 9:1 ratio of trans to cis epoxide; while the latter is opened by hydrogen bromide in an exclusively diaxial way, the former undergoes prevalent nucleophilic attack on C-1 to give a diequatorial bromohydrin.[20] Similar results have been obtained also with hydrogen chloride.[21] The steric effect of the *tert*-butyl group should likewise hinder a cis electrophilic attack by bromine and favor a trans attack leading to the *trans*-bromonium ion **4**, which will be preferentially opened in a parallel mode by nucleophilic attack on C-1 (path A) to give an excess of the diequatorial dibromide **3b**. Antiparallel opening of both the *trans*- (**4**) and the *cis*-bromonium ion (**5**) (paths B and C) will afford the diaxial product **2b** (Scheme II).

Scheme II



A direct steric interaction between the *tert*-butyl group and the nucleophile in the transition state for the antiparallel opening of the *trans*-bromonium ion **4** may again account for the preference for path A over path B. Of course, both of these paths should be of higher energy than path C, involving opening of the *cis*-bromonium ion **5** through antiparallel attack on C-1,

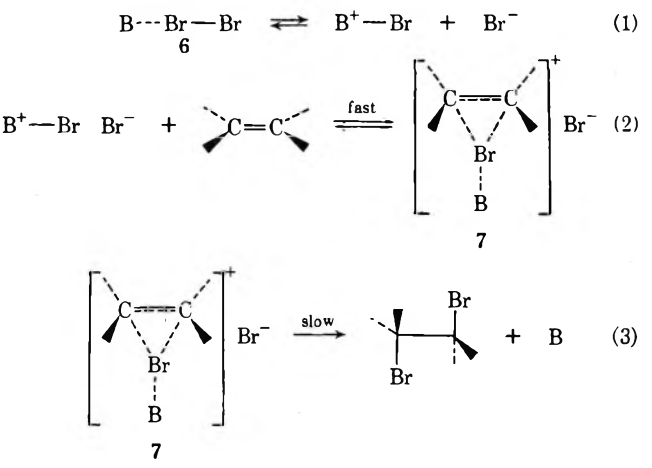
(18) H. J. Hageman and E. Havinga, *Recl. Trav. Chim. Pays-Bas.*, **85**, 1141 (1966).
(19) J.-C. Richer and C. Freppel, *Can. J. Chem.*, **46**, 3709 (1968).
(20) P. L. Barili, G. Bellucci, F. Marioni, A. Marsili, I. Morelli, and G. Ingrosso, *Chim. Ind. (Milan)*, **53**, 789 (1971).
(21) J.-C. Richer and C. Freppel, *Tetrahedron Lett.*, 4411 (1969).

far from the bulky alkyl substituent. However, if the formation of the bromonium ion intermediates is an irreversible step, as it is assumed for the bromination in nonpolar solvents,[1] the steric course of the addition will be controlled first by the relative rates of electrophilic attack on the two faces of the carbon–carbon double bond and then by those of the two alternative modes of nucleophilic opening of the bromonium ions. Whereas this scheme accounts well for the results of the bromination of **1b** in the absence of base, it does not explain the increase in the diaxial:diequatorial ratio when an amine or an ether is present in the system.

The increase in the amount of diaxial adduct **2b** must involve an increase of importance of either path B or path C over path A. It does not seem likely that path B is involved since the steric hindrance in the nucleophilic step should not be reduced appreciably in the presence of base.[22] Also the hypothesis, that the more polarized electrophilic bromine in the amine–bromine complex may be sufficiently smaller than Br_2 to displace the ratio of ions **4** to **5** in favor of the latter thus making path C more favorable, does not in our opinion appear sufficient to justify the observed increase in diaxial:diequatorial ratio. A third hypothesis which for the present we consider as the most acceptable is that the electrophilic step may be reversible when the reaction is conducted with a bromine–base complex.

If the bromonium ions were formed in a reversible prerate-determining step, the steric course of the addition could be controlled mainly by the difference in the transition-state free energies of the nucleophilic steps, provided that they are sufficiently slower than the formation of the bromonium ions and their reversal to the alkene. In the case of **1b**, since both paths A and B are less favored than path C, the *trans*-bromonium ion **4** would revert in part to the starting olefin and the reaction prevalently would proceed *via* the cis ion **5**, to give an excess of the diaxial dibromide 2b.

The crystal-structure determination of many amine–halogen addition compounds by X-ray diffraction has shown[23] that a halogen atom is bonded to nitrogen, the "outer" halogen being situated in a linear nitrogen–halogen–halogen arrangement as in **6**. Studies on amine–halogen complexes in solution have also been evidence of their N-donor-type structures.[24] Also ethers form similar addition compounds with halogens through one of the oxygen lone pairs.[23] The dissociation of eq 1 should simultaneously provide an electrophilic agent more effective than bromine itself and the nucleophile; interaction of the electrophilic moiety with the carbon–carbon double bond could establish the prerate-determining equilibrium shown in eq 2, leading to the ion pair **7**, in which the unipositive bromine may be bonded to both the base and to the olefinic carbon atoms. Slow collapse of **7** as outlined in eq 3 would give trans dibromides and free base. This is consistent with the observation that small added amounts of amines and ethers catalyze the halogenation of aro-



matic compounds.[25] Reversible formation of bromonium ions has recently been suggested[26] for the methoxybromination of 1-methyl-4-*tert*-butylcyclohexene in methanol as the solvent; reversibility of the electrophilic step has also been assumed to explain the steric course of the Woodward reaction on the same olefin[27] and of the hydroxymercuration of substituted cyclohexenes.[22,26] Work that is in progress in this laboratory has also shown similar trends in the steric course of the formation of bromohydrins and chloro bromides from **1b**: the presence of bases increases the percentage of electrophilic attack cis to the *tert*-butyl group.[28] One point that is still not clear is the reason why in the case of **1b** aliphatic amines appear to be less effective than pyridine derivatives in promoting diaxial addition.

The results obtained in the brominations with pyridinium hydrobromide perbromide are also consistent with a fast reversible formation of onium intermediates, if the reagent can dissociate to give some $C_5H_5NBr_2$.

In the case of 4-*tert*-butylcyclohexene (**1a**) the presence of base and the use of pyridinium hydrobromide perbromide affect the steric course in a much more limited way, even if in the same direction. The absence of a direct steric interaction between the substituent and the reaction site accounts for this smaller influence. However a certain shielding of the axial H at C-4, which according to the calculation of Altona and Sundaralingam[29] is tilted by ~15° toward the center of the ring, to the antiparallel attack of the nucleophile on the *cis*-bromonium intermediate **8** can justify the formation of some of the diequatorial adduct through parallel attack. Such shielding has been assumed as the cause for the preference for cis attack in the reaction of **1a** with peroxy acids[30] and diborane.[31] Since the C-5 axial H should exert a smaller shielding to the antiparallel attack on the *trans*-bromonium ion **9**, the reversibility of the first step can account for the in-

(22) D. J. Pasto and J. A. Gontarz [*J. Amer. Chem. Soc.*, **93**, 6909 (1971)] have proposed that the steric course of the oxymercuration of 3-substituted cyclohexenes is affected mainly by a torsional angle effect in the nucleophilic step involving the opening of the mercurinium ion. This is based on the assumption of a rather peculiar and unproved geometry for the mercurinium ion, which we do not think could apply to the bromonium ion.

(23) O. Hassel and C. Rømming, *Quart. Rev., Chem. Soc.*, **16**, 1 (1962).

(24) J. J. Eisch, *Advan. Heterocycl. Chem.*, **7**, 13 (1966).

(25) J. J. Eisch, *ibid.*, **7**, 4 (1966).

(26) D. J. Pasto and J. A. Gontarz, *J. Amer. Chem. Soc.*, **93**, 6902 (1971), footnote 49.

(27) P. L. Barili, G. Bellucci, B. Macchia, F. Macchia, and G. Parmigiani, *Gazz. Chim. Ital.*, **101**, 300 (1971).

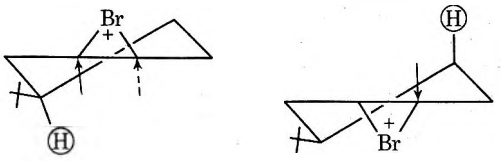
(28) In a paper by J.-C. Richer and C. Freppel, published after this manuscript was submitted [*Tetrahedron Lett.*, 2321 (1972)], about several types of additions involving iodine as the electrophile, the formation of the iodonium ions is considered as reversible, the nucleophilic step being controlled by torsional angle effects of the type advocated by Pasto and Gontarz.[22]

(29) C. Altona and M. Sundaralingam, *Tetrahedron*, **26**, 925 (1970).

(30) B. Rickborn and S. Y. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).

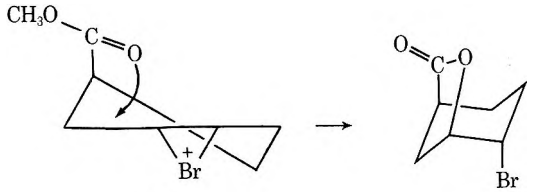
(31) D. J. Pasto and F. M. Klein, *ibid.*, **33**, 1468 (1968).

crease of the **2a** to **3a** ratio when the reaction is carried out in the presence of base. An exclusive formation of **2a** in the bromination of **1a** with $C_5H_5NHBr_3$ in pyridine has been reported by Pasto and Gontarz.[26] In support of our interpretation it can be mentioned that both the methoxybromination and the hydroxymercuration of **1a**, which have been assumed to proceed through reversible formation of onium intermediates,[26] give a slight excess of the products arising from the diaxial opening of the respective *trans*-onium ions, although the electrophilic attack should preferentially occur cis to the *tert*-butyl group.[30,31]



8 **9**

It is more difficult to rationalize the results obtained with the conformationally mobile substrates **1c–e** because of the necessity to take into account also the less stable conformers. While it would be possible to present an explanation which could fit into the same mechanisms proposed for **1a** and **1b**, we shall postpone its discussion until we have more evidence to support it. We want only mention at this point that the formation of bromolactone **11** in the bromination of the unsaturated ester **1d** is practically suppressed in the presence of base. This is also consistent with the mechanism shown in eq 1–3 for the bromination by amine–halogen complexes. Indeed, while the rather high localization of positive charge on the carbon atoms of the bromonium ion **10** may allow an intramolecular attack by



10 **11**

the poorly nucleophilic methoxycarbonyl group to give **11**, only the more nucleophilic bromide ion should be able to attack an intermediate of the type **7** in eq 2, owing to the greater delocalization of the positive charge and the smaller development of the carbon–bromine bonds.

Experimental Section

Starting Materials.—4-*tert*-Butylcyclohexene (**1a**) was prepared from the commercial mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanols according to the Sicher method.[32] 3-*tert*-Butylcyclohexene (**1b**) was obtained from 2-*tert*-butylcyclohexanone tosylhydrazone with butyllithium.[19] 4-Methylcyclohexene (**1c**) was prepared[33] by dehydration of mixed *cis*- and *trans*-4-methylcyclohexanols with $KHSO_4$. Methyl 3-cyclohexene-1-carboxylate (**1d**) was prepared by Fischer esterification of the commercially (Fluka AG) available acid. 3-Methylcyclohexene (**1e**) was purchased from Fluka AG.

All of the olefins were purified by distillation through a spinning band column and their purities checked by glpc.

Pyridine perbromide was prepared by mixing carbon tetrachloride solutions of equimolar amounts of bromine and dry pyridine at 0°. The red precipitate, collected, washed, and dried (mp 60–62°, lit.[34] mp 62–63°), was used without further purification.

Pyridinium hydrobromide perbromide was prepared by the Fieser method.[35]

Chloroform was purified by washing with 2 *N* NaOH, concentrated H_2SO_4, and H_2O and distillation. Rudi Pont Spectranalyzed reagent grade carbon tetrachloride was used without further purification. Ethyl ether was freed from peroxides by washing with a solution of ferrous sulfate. Benzene was washed with H_2SO_4, refluxed on sodium, and distilled.

Bromine was purified[36] by refluxing with calcium bromide and distillation.

Commercial anhydrous triethylamine was purified by distillation. Pyridine and 2-methyl-, 4-methyl-, and 2,6-dimethylpyridine were dried by refluxing with potassium hydroxide and fractionally distilled.

Bromination Procedures. A. With Br_2 in the Absence of Bases.—A 10% excess of a 1 *M* solution of Br_2 in $CHCl_3$ was added dropwise to a stirred solution of 1.5 mmol of the olefin in 5 ml of the appropriate solvent at the temperatures reported in Tables I and II. After the addition was complete, the solution was further stirred for 5 min, then washed with aqueous $NaHSO_3$ and H_2O, dried ($MgSO_4$), and evaporated at 30° (rotating evaporator). The residue was directly analyzed.

In the case of **1d**, the ir spectrum of the crude reaction mixture showed in addition to the strong carbonyl band at 5.8 μ typical of **2d** and **3d**, a weak band at 5.6 μ. Crystallization from pentane allowed to isolate a small amount of the bromolactone **17**, identified by comparison with an authentical sample.[37]

B. With Br_2 in the Presence of Bases.—A 10% excess of a 1 *M* solution of Br_2 in $CHCl_3$ was added to a solution of equimolar amount (1.5 mmol) of the olefin and the appropriate amine in 5 ml of $CHCl_3$. After stirring for 5 min the solution was washed with aqueous $NaHSO_3$, aqueous 2 *N* HCl, and H_2O, dried, and evaporated.

C. With $C_5H_5NBr_2$ or $C_5H_5NHBr_3$.—A 10% excess of the solid brominating agent was added to a solution of 1.5 mmol of the olefin in 5 ml of the appropriate solvent. The mixture was stirred for 15 min at 0° and then treated as described in B. $C_5H_5NBr_2$ is slightly soluble in CCl_4; the same happens for $C_5H_5NHBr_3$ in $CHCl_3$; however, in the presence of the alkenes, these reagents were completely dissolved after few minutes.

The bromination of **1b** with $C_5H_5NHBr_3$ in AcOH was carried out by stirring the reagents at 20° for 30 min, followed by dilution with water, extraction with ether, washing with H_2O, aqueous saturated $NaHCO_3$, and H_2O, and drying ($MgSO_4$).

In all cases the composition of the mixtures of **2** and **3** did not change after longer reaction times.

Methods of Analysis.—The glpc analyses of the reaction mixtures arising from **1a**, **1c**, **1d**, and **1e** were performed with a Carlo Erba Fractovap, Model G.V., column: 1% neopentyl glycol succinate (NPGS) on Chromosorb W, 80–100 mesh. The conditions were previously reported.[11,12,13] Nmr analyses of the same mixtures and of those of **2b** and **3b** were carried out with a JEOL C-60 HL spectrometer, by integration of the signals of the protons α to bromine.[14]

The results listed in Tables I and II were reproducible within ±2%.

Registry No.—**1a**, 2228-98-0; **1b**, 14072-87-8; **1c**, 591-47-9; **1d**, 6493-77-2; **1e**, 591-48-0; $CHCl_3$, 67-66-3; C_6H_6, 71-43-2; Et_2O, 60-29-7; CCl_4, 56-23-5; AcOH, 64-19-7; Br_2, 7726-95-6; $C_5H_5NHBr_3$, 36812-55-2; Br_2+HBr, 36748-62-6; $C_5H_5NBr_2$, 6081-86-3.

Acknowledgments.—We wish to thank Professor G. Berti for helpful discussion. This work was supported in part by a grant from Consiglio Nazionale delle Ricerche.

(32) J. Sicher, F. Šipoš, and M. Tichý, *Collect. Czech. Chem. Commun.*, **26**, 84 (1961).

(33) C. Harries, *Justus Liebigs Ann. Chem.*, **395**, 253 (1913).

(34) D. M. Williams, *J. Chem. Soc.*, 2783 (1931).

(35) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 967.

(36) P. Pascal, "Nouveau Traité de Chimie Minérale," Masson, Vol. 16, Paris, 1960, p 340.

(37) R. Grewe, A. Heinke, and C. Sommer, *Ber.*, **89**, 1978 (1956).

Molecular Rearrangements. XXIX. Exo/Endo Stereospecificity of Substituted Classical Norbornyl Cations. A Reassessment of "Hot" Carbonium Ions[1,2]

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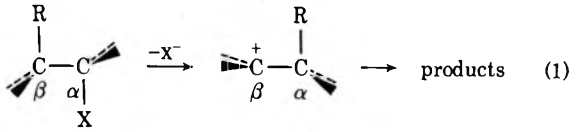
Received July 21, 1972

5-*endo*-Hydroxy-5-phenyl-2-*exo*-norbornylamine (5), 5-*exo*-hydroxy-5-phenyl-2-*exo*-norbornylamine (6), and 5-*exo*-hydroxy-5-phenyl-2-*endo*-norbornylamine (7) were treated with sodium nitrite in acetic acid–sodium acetate solution. From the product analyses of the reaction mixture (including glpc and carbon-14 isotope dilution measurements), it is concluded that (1) during reaction of 5 and 6, ~2% of SN2-like processes take place; (2) the exo/endo stereospecificity for attack on the classical ions formed from 5 and 6 is 160–650:1, whereas the exo/endo stereospecificity for attack on the classical ion E formed from 7 *after* Wagner–Meerwein rearrangement is only 8:1; (3) the production of 2-phenylnorbornane-2,5-*cis*,*endo*-diol-4-*d* (8) in 1.8% yield from 5-phenyl-5-*endo*-hydroxy-2-*endo*-norbornylamine-2-*d* (7) means that endo attack upon the *classical* cation E takes place after E has been formed by a Wagner–Meerwein rearrangement, and that 8 is not produced as a consequence of the Hückel–Kern pathway demonstrated in the production of borneol (19) from *endo*-fenchylamine (14); (4) the concept of a "hot" carbonium ion must now be altered, for, whatever the special character of the cations formed during the amine–nitrous acid reaction, this special character is not lost after Wagner–Meerwein rearrangement; and (5) the different behavior of presumably identical cations when they are produced remotely from different reactants is explained by counterion control in differently oriented ion pairs.

In a preliminary communication[2b] we demonstrated the special character of the cations generated during the amine–nitrous acid reaction by showing that a substituted secondary norbornyl cation can be attacked by solvent from the endo direction even after the cation in question has been formed by Wagner–Meerwein rearrangement. Hückel and Kern[3] had previously demonstrated the same phenomenon with the tertiary cations produced on Wagner–Meerwein rearrangement of the fenchylamines. There can now be no doubt, therefore, that carbonium ions formed on nitrous acid deamination can retain their special character after one[2b] or after several[2a] such Wagner–Meerwein or 6,2-hydride rearrangements,[4] and that they do not necessarily become equivalent to those ions produced on solvolysis of structurally identical compounds (identical, that is, except for leaving group).

Since the early work[5,6] on the stereochemistry of carbonium ion rearrangements, it has generally been assumed[7-9] that inversion of configuration at the migration terminus (C_α) is the predominant (or exclusive) stereochemical result (eq 1) of 1,2 shifts which

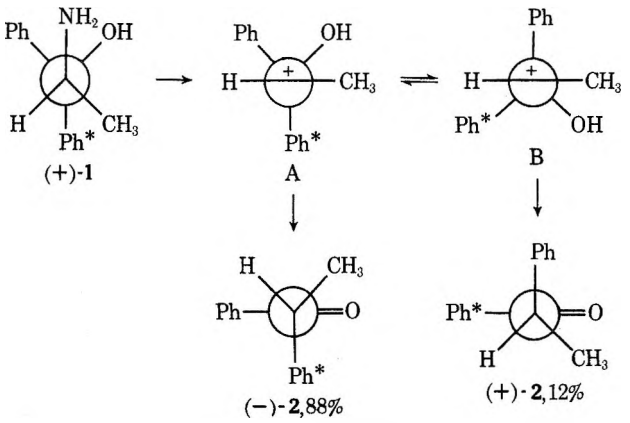


(1)

occur during solvolytic (X = halogen, OTs, OBs, etc.) or amine–nitrous acid (X = NH_2) reactions.[10] Although the assumption may be usually valid for 1,2 shifts occurring with solvolyses, it is demonstrably[11-16] untrue for the amine–nitrous acid and other reactions which proceed through decomposition of diazonium ions.[17]

In an isotopic investigation (with carbon-14) of McKenzie's original example,[5] we demonstrated[11] (Scheme I) that (1) inversion was not the only stereo-

SCHEME I[a]



[a] C_α is the front carbon atom of the Newman projection.

chemical consequence of the deamination of optically active 1,1-diphenyl-2-aminopropanol[18] and (2) whereas

(1) Research sponsored by the U. S. Atomic Energy Commission under contract with the Union Carbide Corporation; presented in part at the Symposium on Organic Reaction Mechanisms, Nagoya, Japan, Oct 19, 1971.

(2) (a) Paper XXVIII: C. J. Collins, I. T. Glover, M. D. Eckart, V. F. Raaen, B. M. Benjamin, and B. S. Benjaminov, *J. Amer. Chem. Soc.*, **94**, 899 (1972). (b) A portion of the research described in this paper was reported in preliminary form: C. J. Collins and B. M. Benjamin, *ibid.*, **92**, 3182 (1970).

(3) W. Hückel and H.-J. Kern, *Justus Liebigs Ann. Chem.*, **728**, 49 (1969).

(4) C. J. Collins, *Accounts Chem. Res.*, **4**, 315 (1971).

(5) (a) A. McKenzie, R. Roger, and G. D. Wills, *J. Chem. Soc. (London)*, 779 (1926); (b) H. I. Bernstein and F. C. Whitmore, *J. Amer. Chem. Soc.*, **61**, 1324 (1939).

(6) (a) P. D. Bartlett and I. Pöckel, *ibid.*, **59**, 820 (1937); **60**, 1585 (1938). (b) W. Hückel, *Nachr. Ges. Wiss. Gottingen, Math.-Phys. Kl., Fachgruppe* **2**, 59 (1941).

(7) See, for example, R. T. Morrison and R. N. Boyd, "Organic Chemistry," 2nd ed, Allyn and Bacon, Boston, Mass., 1966, p 883; also G. B. Butler and K. D. Berlin, "Fundamentals of Organic Chemistry," Vol. X, Ronald Press, New York, N. Y., 1972, pp 829–830.

(8) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957); A. Streitwieser, Jr., and W. D. Schaeffer, *J. Amer. Chem. Soc.*, **79**, 2888 (1957).

(9) D. J. Cram and J. E. McCarty, *ibid.*, **79**, 2866 (1957).

(10) See also P. I. Pollak and D. Y. Curtin, *ibid.*, **72**, 961 (1950); D. Y. Curtin, E. E. Harris, and E. K. Meislich, *ibid.*, **74**, 2901 (1952); D. Y. Curtin and E. K. Meislich, *ibid.*, **74**, 5518 (1952); D. Y. Curtin and P. I. Pollak, *ibid.*, **73**, 992 (1951); D. Y. Curtin and E. K. Meislich, *ibid.*, **74**, 5905 (1952).

(11) B. M. Benjamin, H. J. Schaeffer, and C. J. Collins, *ibid.*, **79**, 6160 (1957).

(12) B. M. Benjamin, P. Wilder, Jr., and C. J. Collins, *ibid.*, **83**, 3654 (1961).

(13) B. M. Benjamin and C. J. Collins, *ibid.*, **83**, 3662 (1961).

(14) C. J. Collins, M. M. Staum, and B. M. Benjamin, *J. Org. Chem.*, **27**, 3525 (1962).

(15) C. J. Collins, W. A. Bonner, and C. T. Lester, *J. Amer. Chem. Soc.*, **81**, 466 (1959).

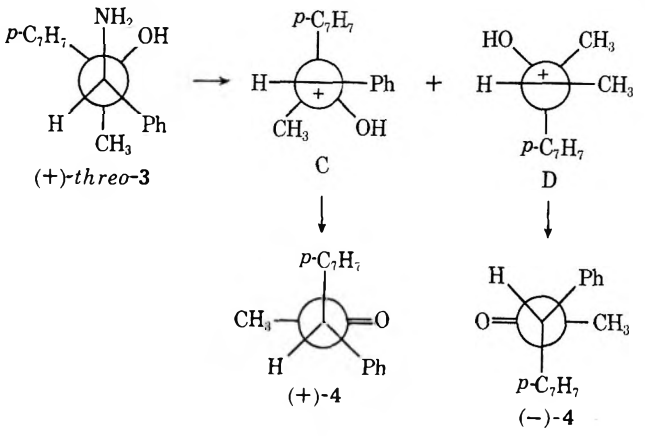
(16) C. J. Collins and B. M. Benjamin, *ibid.*, **85**, 2519 (1963).

(17) C. J. Collins, J. B. Christie, and V. F. Raaen, *ibid.*, **83**, 4267 (1961); C. J. Collins and J. B. Christie, *ibid.*, **82**, 1255 (1960).

(18) This was, in fact, obvious from the Experimental Section of the paper[5a] by McKenzie, Roger, and Wills.

88% of the ketonic product had been formed with migration of the labeled phenyl (Ph*) with inversion of configuration at the migration terminus (C_α), 12% had been formed through migration of the unlabeled phenyl (Ph) with retention of configuration at the migration terminus. Later we extended[12-14] these studies to show (Scheme II) that, when aryl migration with retention

SCHEME II

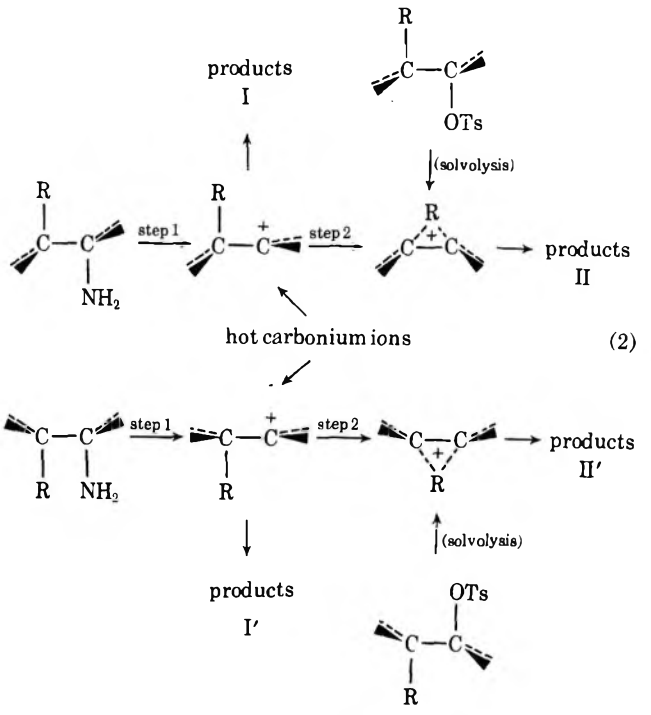


at C_α can take place through a trans transition state,[10] in which the bulky nonmigrating groups are trans one to the other, then *retention can predominate over inversion*. These important observations have not yet been completely appreciated.[7] The foregoing results clearly are in conflict (1) with the assumption[7-9] that inversion at C_α (eq 1) is the exclusive stereochemical result of such 1,2 shifts and (2) with Streitwieser's postulate[8] "that the diazonium ion rather than a carbonium ion is the branching point of the competing reactions" which take place on decomposition of aliphatic diazonium ions.

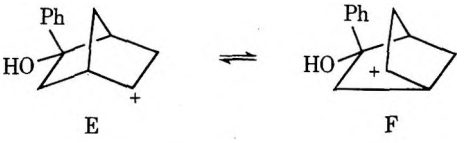
Some[11-14] of our earlier results are compatible with Winstein's proposal[19] of "hot" carbonium ion formation during amine–nitrous acid reactions. These "hot" carbonium ions were defined[19] as exhibiting no charge delocalization in their highly energetic states, thus explaining the lack of discrimination and multiplicities of products often observed.[4] The "hot" carbonium ion was visualized[19] as losing its excess energy very rapidly,[20] and after one Wagner–Meerwin rearrangement or one hydride shift was believed to become equivalent to those ions formed from solvolytic precursors; this means, for example, that, if a "hot" carbonium ion (as defined)[19,20] intervenes (eq 2) during the amine–nitrous acid reaction, then any rearrangement of atoms in the structure (step 2), whether it be Wagner–Meerwin or hydride shift, allows the ion sufficient time to lose its excess energy ("cool") and become equivalent to the cation formed (eq 2) on solvolysis. Thus, if a bridged ion results from solvolysis, then a bridged ion should result from a structurally related "hot" carbonium ion after a 1,2 shift.

(19) D. Semenow, C. H. Shih, and W. G. Young, *J. Amer. Chem. Soc.*, **80**, 5472 (1958), credit Professor Winstein with proposing a hot carbonium ion intermediate during the amine–nitrous acid reaction.

(20) E. Renk and J. D. Roberts, *ibid.*, **83**, 879 (1961), describe this process in a more colorful fashion by stating "it seems reasonable that any 'hot' allylcarbinyl cations formed by ejection of nitrogen from the corresponding diazonium ions would lose most if not all of their 'sizzle' upon 1,2-shift."

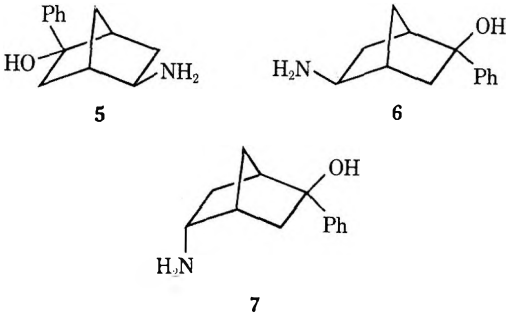


In our previous paper,[2a] we reported the fates of ions E and F after they were formed indirectly and remotely from precursors which suffered one or more 6,1,2 shifts



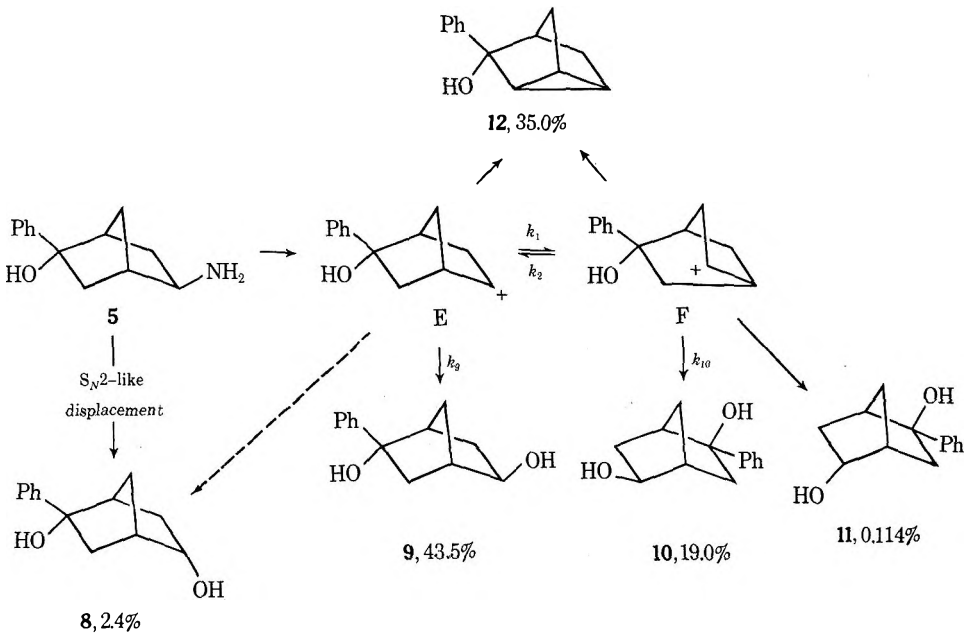
before either E or F could be produced. Using a combination of analytical techniques, including carbon-14- and deuterium-labeling methods, we were able to demonstrate that E and F maintain their classical, open carbonium ion properties even after several successive Wagner–Meerwein rearrangements and 6,1,2-hydride shifts, a result incompatible with the "hot" carbonium ion assumption—at least as originally stated.[19]

To gain more information on the properties of ions E and F when they are produced in a less circuitous fashion than that employed in our previous studies[2a] we turned our attention to the reaction with nitrous acid of the amines 5-*endo*-hydroxy-5-phenyl-2-*exo*-norbornylamine (**5**), 5-*exo*-hydroxy-5-phenyl-2-*exo*-norbornyl-



amine (**6**), and 5-*exo*-hydroxy-5-phenyl-2-*endo*-norbornylamine (**7**). Compound **5** when subjected to deaminating conditions[2] should lead directly to ion E, whereas **6** and **7** should produce ion F. It was our purpose to determine the stereospecificity for exo *vs.*

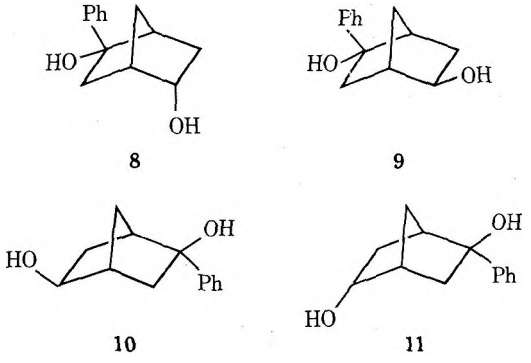
SCHEME III



endo attack on both E and F before and after Wagner–Meerwein rearrangement and also to study the effect on this stereospecificity of an exo *vs.* an endo leaving group (**6** *vs.* **7**).

Method and Results

The two exo amines **5** and **6** were prepared from the diols **8** and **11** which, in turn, were prepared by oxidation of **9**[21] and **10**,[21] respectively, with chromic acid followed by reduction of the ketones so obtained with



lithium aluminum hydride. The tosylates of **8** and **11** on treatment with sodium azide, followed by reduction, afforded **5** and **6**. Endo amine **7** was prepared from the ketone obtained from **10** by conversion to the corresponding oxime, followed by reduction with lithium aluminum hydride. These three amines were also prepared labeled in their phenyl groups with carbon-14.[2a]

The amine–nitrous acid reactions in acetic acid–sodium acetate solution were carried out as described previously.[2,17] In addition, one reaction of **5** was carried out using glacial acetic acid as the solvent. All three amines yielded five identifiable products. These were 3-phenyl-3-nortricyclenol (**12**) and the (secondary) monoacetates of the four 2-phenyl-2,5-norbornanediols **8–11**. For simplicity the products are shown in Schemes III–V as the free diols, since the isotope dilution analyses were carried out on product mixtures which had first been treated with lithium aluminum hydride. The products from **5–7** were determined by isotope-dilution methods,[22] and/or by spectral methods, and liquid column chromatography, and the results are given in Table I, together with certain product ratios,

TABLE I

YIELDS OF PRODUCTS AND PRODUCT RATIOS ON DEAMINATION OF AMINES **5–7**[a]

Products[b]	From **5** HOAc (glacial)	From **5** HOAc–NaOAc	From **6**, HOAc–NaOAc	From **7**, HOAc–NaOAc
		Yields, %		
12	43.5	35.0	29.6	17.2
8	3.4[c]	2.4[c]	0.039[c]	1.8
9	36.7	43.5	25.6	14.2
10	16.5	19.0	42.6	29.3
11	0.075[c]	0.114	2.2[c]	34.5
		Ratios		
9:**10**	2.2:1	2.3:1	1:1.7	1:2.1
9:**8**	10.5:1	18:1	650:1	8:1
10:**11**	220:1	166:1	19:1	1:1.2
8:**11**	45:1	21:1	1:56	1:19

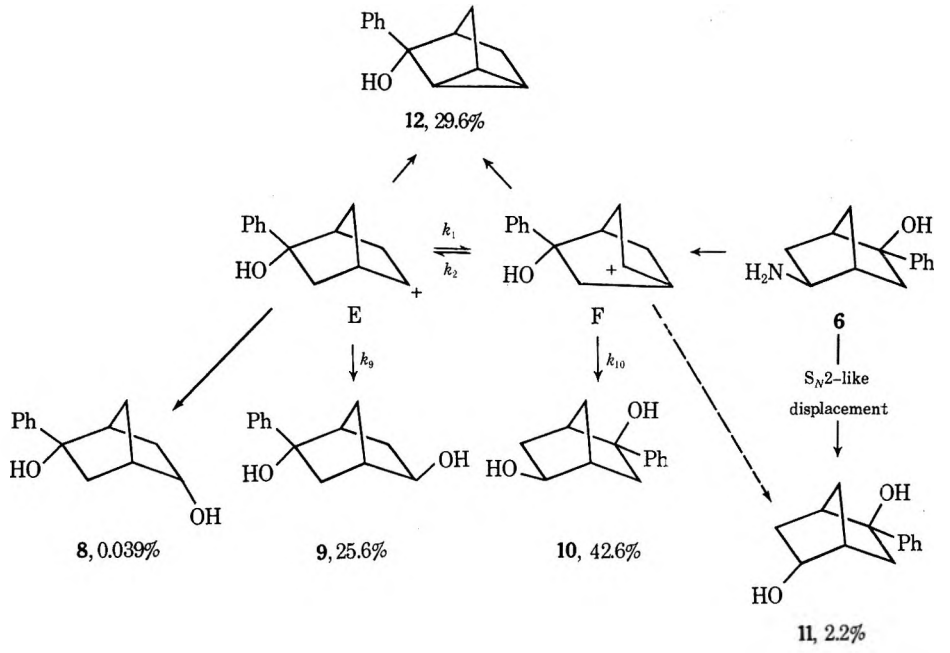
[a] Deaminations were performed at ambient temperature. Yields are normalized to 100%. [b] The monoacetates of **8–11** were obtained on deamination, and these were converted to the diols with lithium aluminum hydride. Smaller yields of three other compounds[a] resulting from hydride shift in the ions E and F were obtained. [c] These products were crystallized repeatedly with the addition of the hold-back carrier[23] until the radioactivity contents were constant.

whose significance will be discussed later. The results of the deaminations of **5**, **6**, and **7** are also shown graphically in Schemes III, IV, and V, respectively, so that the reactions carried out under like conditions (acetic acid–sodium acetate) can be more easily compared. We showed earlier[20,21] that under the reaction and work-up conditions all products are stable. Finally amine **7** labeled with deuterium in the exo-5 position was prepared and subjected to nitrous acid deamination; the

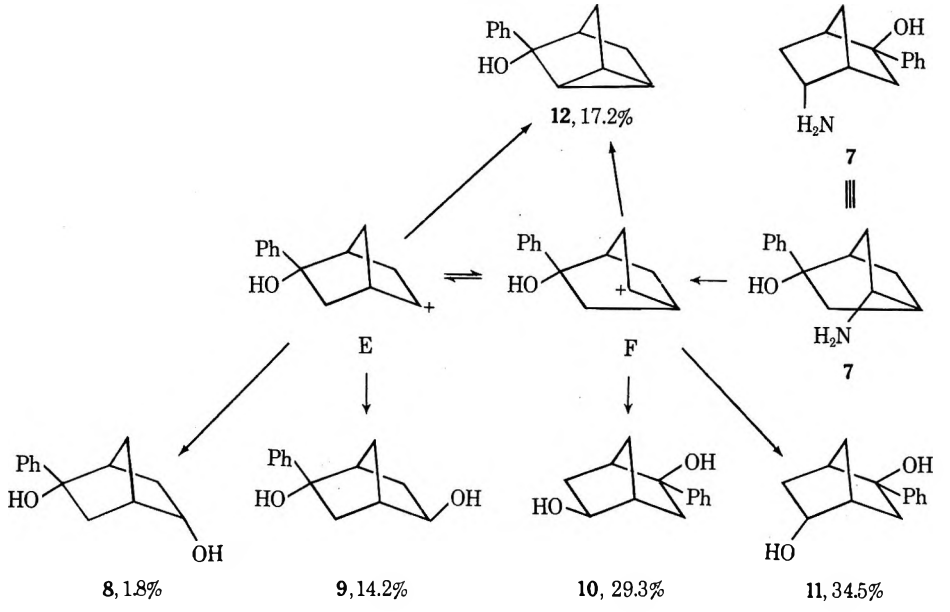
(21) C. J. Collins and B. M. Benjamin, *J. Amer. Chem. Soc.*, **89**, 1652 (1967).

(22) V. F. Raaen, G. A. Ropp, and H. P. Raaen, "Carbon-14," McGraw Hill, New York, N. Y., 1968, Chapter 2.

SCHEME IV



SCHEME V



deuterium distribution in the 2-*exo*-phenylnorbornane-2,5-*cis*,*endo*-diol (**8**-*d*) so obtained and isolated was established by nmr.

Discussion

The following conclusions can be drawn from the experiments just discussed.

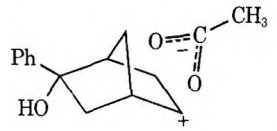
1.—Both amines **5** and **6** appear to undergo SN2 (or SN2-like) attack to yield, respectively, the acetates of diols **8** and **11**. Thus **5** yields 2% **8** acetate and **6** yields 2% **11** acetate on nitrous acid deamination in acetic acid-sodium acetate (Schemes III and IV). That these endo products result from SN2 processes follows from point 2.

2.—The exo/endo stereospecificity observed for **5** → **8** + **9** (18:1 **9**:**8**) is much greater than the exo/endo stereospecificity observed (166–220:1) for the process **5** → E → F → **10** + **11**. Ion E, after it has been produced by the process **6** → F → E → **8** + **9**, exhibits an exo/endo stereospecificity of 650:1 **9**:**8** much greater than that (18:1) observed when E is produced directly from **5**. These facts lead us to believe that the process **5** → **8** is predominantly SN2-like in character (the same argument is valid for the process **6** → **11**).

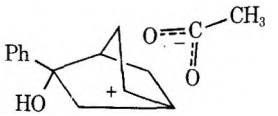
3.—Since the Wagner–Meerwein pair of cations E ⇌ F produce different ratios of **9**:**10** depending upon their origin from **5** or from **6**, we think they are best written as equilibrating classical ions (E ⇌ F). Thus, neglecting formation of **12** and the minor fractions of endo attack, when E is produced on deamination of **5**, it has a choice of rearrangement to F or collapse with exo counterion to yield the **9** acetate. Since the ratio of **9**:**10** is 2.3:1, E clearly undergoes collapse with counterion before complete equilibrium with F is attained. When F is produced from **6**, it has a similar choice (again neglecting the formation of **12** and small fractions of endo attack). It can collapse with exo counterion to yield the **10** acetate or it can rearrange

to E. Ion F obviously collapses with counterion to yield the **10** acetate before it has achieved equilibrium with E, and the ratio of **10**:**9** is 1.7:1.[23]

4.—The exo/endo ratios for attack on ions E and F *after* they have been formed (from **6** and **5**, respectively, Schemes III and IV) through Wagner–Meerwein rearrangement (650:1 **9**:**8**, 165:1 **10**:**11**) are smaller than the ratio (2000:1) for exo/endo attack during acetolysis of 2-*exo*-norbornyl tosylate.[24] Because the counterions formed during reaction of the exo amines **5** and **6** are, we think, [2,17] still exo to the positive charge, as in the ion pairs E-I and F-I, there will be a built-in preference for E-I and F-I to collapse to predominantly

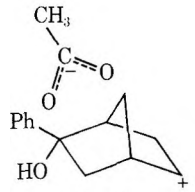


E-I

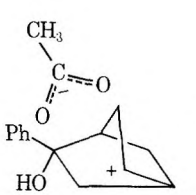


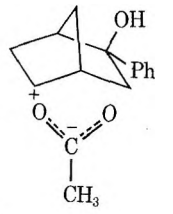
F-I

exo products. For this reason, the aforementioned ratios (165–650:1) are undoubtedly still much too large to be representative of the true exo/endo stereospecificities for the classical ions E and F. We therefore studied the reaction with nitrous acid of the endo amine **7** (Scheme V). Here the ion pairs should be



E-II



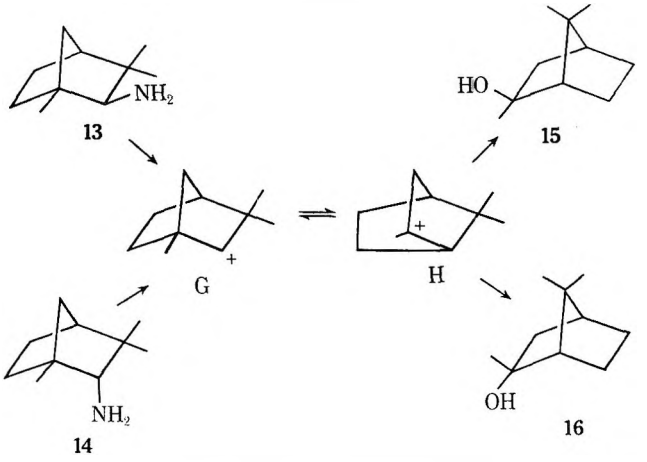


F-II

oriented somewhat as shown in structures E-II and F-II, and the serious bias for collapse to exo products exhibited by E-I and F-I should no longer be present. That ion F—formed directly from **7**—produces more endo product (**11** acetate) than exo (**10** acetate) in the ratio of 1.2:1 is a clear indication of counterion control in the ion pair F-II. After F-II has undergone Wagner–Meerwein rearrangement to E-II, the counterion is no longer in a position to attack directly the site of positive charge, and acetate ions or acetic acid molecules from the solvent should be more nearly under the influence of the steric requirements of E and F as they attack from exo or endo directions. The ratio (8:1) is the lowest yet observed for a substituted, secondary norbornyl cation in the absence of an SNi component and is overwhelming evidence that E has retained its classical character *after* having been formed from F by Wagner–Meerwein rearrangement.[25]

5.—Solvolyses of tertiary 2-norbornyl esters are now generally believed to be limiting [SN1(lim)].[26–31] The Hückel–Kern observation[3] that the *exo*- (**13**) and *endo*-fenchylamine (**14**) yield, among other products, mixtures of *exo*- (**15**) and *endo*-α-fenchene hydrate (**16**) (Scheme VI) provides us with a calibration for the

SCHEME VI



13 ⟶ 48% **15** + 2.8% **16**
14 ⟶ 13.5% **15** + 1.6% **16**

stereospecificity of attack on the tertiary α-fenchyl cation, H. Here exo attack is undoubtedly hindered somewhat by the *syn*-7-methyl groups, but there seems to be a leaving-group effect in that the endo amine **14** exhibits a lower exo/endo stereospecificity (8.5:1 **15**:**16**) than the exo amine **13**, where the ratio of **15**:**16** is 17.5:1. Comparing stereospecificities for the rearranged ion E from exo amine **6** (650:1 **9**:**8**, Scheme IV), and from endo amine **7** (8:1 **9**:**8**, Scheme V) we see again that the endo leaving group seems to reduce the stereospecificity for exo attack on ion E, just as in the Hückel–Kern[3] case. We believe the explanation just given in paragraph 4 applies to the Hückel–Kern results as well.

6.—Hückel and Kern[3] made another remarkable observation, for on nitrous acid deamination of *endo*-fenchylamine (**14**)—the complete results are shown in Scheme VII—they isolated borneol (**19**) in a yield of 3.5%. The simplest explanation here seems to be a 7,1–7,2-Wagner–Meerwein shift to give the cation K,

(23) When the tosylates corresponding to the amines **5** and **6** are hydrolyzed, **12** is also produced, but the major products **9** and **10** are formed in a 1.4:1 ratio of **9**:**10** from *both* reactants.[2a] If we assume that ions E and F go to 3-phenyl-3-nortricyclenol (**12**) in the same ratio whether **5** or **6** is the starting material, then for the deaminations of **5** and **6**, respectively (Schemes III and IV), we can derive the following equations.

$$(m_{10}/m_9)_5 = (k_{10}/k_9)[k_1/(k_2 + k_{10})]$$

$$(m_{10}/m_9)_6 = (k_{10}/k_9)[(k_1 + k_9)/k_2]$$

Making the substitutions $(m_{10}/m_9)_5 = 19/43.5$ and $(m_{10}/m_9)_6 = 42.6/25.6$, respectively, and assuming $k_9 = k_{10}$, then we can calculate that the equilibrium constant k_2/k_1 for F ⇌ E is 1.24, in excellent agreement with the value[2a] of 1.4 for the tosylates.

(24) H. C. Brown, J. H. Kawakami, and K. T. Liu, *J. Amer. Chem. Soc.*, **92**, 5536 (1970).

(25) The exo/endo ratio of 8:1 for attack on cation E is well within the range of stereospecificities for attack on secondary norbornyl compounds which have been shown by H. C. Brown and his coworkers to be primarily steric in origin. See, for example, H. C. Brown and K. T. Liu, *J. Amer. Chem. Soc.*, **92**, 200 (1970); H. C. Brown and J. H. Kawakami, *ibid.*, **92**, 201, 1990 (1970); H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **92**, 6914 (1970); H. C. Brown and K. T. Liu, *ibid.*, **93**, 7335 (1971), and references cited therein.

(26) S. Winstein, E. Grunwald, and H. W. Jones, *ibid.*, **73**, 2300 (1951).

(27) J. M. Jerkunica, S. Borčić, and D. E. Sunko, *Chem. Commun.*, 1489 (1968).

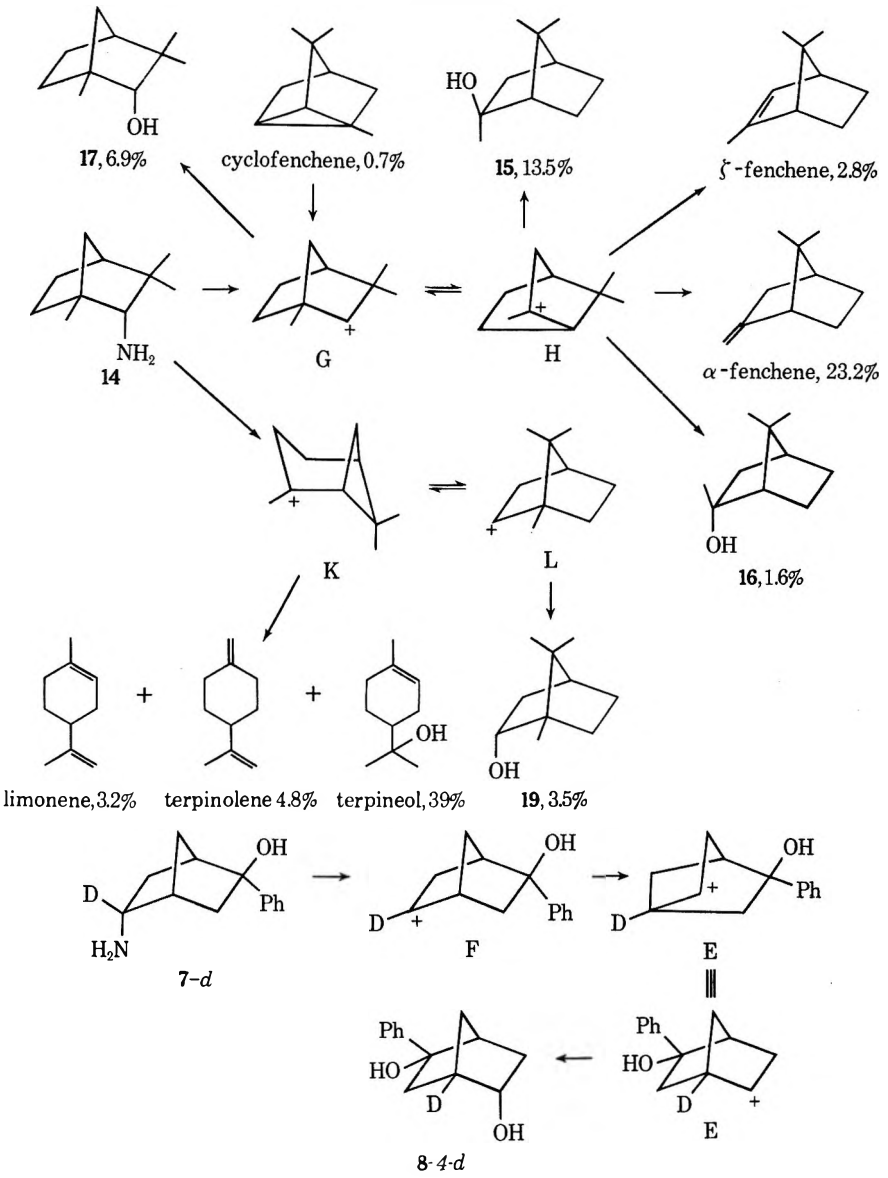
(28) J. P. Schaeffer, M. J. Dagani, and D. S. Weinberg, *J. Amer. Chem. Soc.*, **89**, 6938 (1967).

(29) H. C. Brown and S. Ikegami, *ibid.*, **90**, 7122 (1968); H. C. Brown and L.-T. Liu, *ibid.*, **89**, 466 (1967).

(30) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *ibid.*, **92**, 2538 (1970); J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *ibid.*, **92**, 2540 (1970).

(31) H. L. Goering and J. V. Clevenger, *ibid.*, **94**, 1010 (1972).

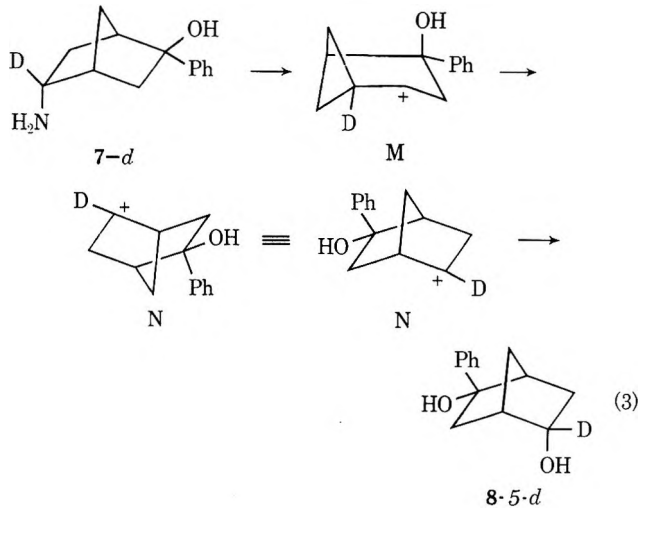
SCHEME VII



(4)

followed by another Wagner–Meerwein rearrangement to yield cation L, which then goes to borneol (**19**).

The isolation of borneol (**19**) from *endo*-fenchylamine (**14**) opens up the possibility that diol **8** is formed by a similar mechanism during deamination of **7**, as illustrated by eq 3. The two routes can be differentiated



(3)

by means of deuterium labeling, and this is also shown in eq 3 and 4. The amine–nitrous acid reaction with **7**-*d*, however, led to the usual reaction mixture from which diol **8**-*4*-*d* was isolated with deuterium only in the 4 bridgehead position, corresponding to the result expected through eq 4 and shown also in Scheme V.

7.—From the foregoing discussion it seems certain that the cations with which we are dealing can be considered to be special in some way. We have no evidence that they are of higher energy than if they had been formed on solvolysis, nor are we aware of any other data which *require* the formation of "hot" carbonium ions during the amine–nitrous acid reaction. "Hot" cations may in fact be unnecessary, for the usual scheme[32] of intimate, solvent-separated, and completely separated ion pairs (eq 5) produced on solvolyses

$$\begin{array}{ccccccc} \text{ROTs} & \rightleftharpoons & \text{R}^+\text{OTs}^- & \rightleftharpoons & \text{R}^+\|\text{OTs}^- & \rightleftharpoons & \text{R}^+ \quad \text{OTs}^- \\ & & & & & & \Big\downarrow \\ \text{ROAc} & \longleftarrow & \text{R}^+\text{OAc}^- & \rightleftharpoons & \text{R}^+\|\text{OAc}^- & & \end{array} \qquad (5)$$

(32) S. Winstein, E. Clippinger, A. H. Fainberg, and G. C. Robinson, *J. Amer. Chem. Soc.*, **76**, 2597 (1954); S. Winstein and A. H. Fainberg, *ibid.*, **80**, 459 (1958); S. Winstein, P. E. Kleindienst, Jr., and G. C. Robinson, *ibid.*, **83**, 885 (1961).

is much different from our picture[4,33] of ion pairing as it occurs during the amine–nitrous acid reaction (eq 6–13). During reaction in aqueous solution the hydroxide ion produced during eq 10 is also the counter-ion in collapse of the ion pair of eq 12 to carbinol product; that is, part of the leaving group becomes the entering group. When the reaction is carried out in acetic acid–sodium acetate medium, the situation must be somewhat different from that in eq 7–13. Acetyl nitrite is more probably the nitrosating agent,[34] and exchange of acetate for hydroxyl probably takes place before ionization of the diazonium hydroxide (eq 9).[35] Evidence for the latter proposal is to be found in the similarity of the stereochemical and isotopic results during the amine–nitrous acid reaction, in acetic acid–sodium acetate of 1,2,2-triphenylethylamine, and in the thermal decomposition, in the same medium, of *N*-acetyl-*N*-nitroso-1,2,2-triphenylethylamine.[17,36]

$$2HNO_2 \longrightarrow N_2O_3 + H_2O \quad (6)$$

$$N_2O_3 + RNH_2 \longrightarrow RNH_2{}^+NO + NO_2{}^- \quad (7)$$

$$RNH_2{}^+NO \longrightarrow RNHNO + H^+ \quad (8)$$

$$RNHNO \longrightarrow RN{=}NOH \quad (9)$$

$$RN{=}NOH \longrightarrow RN_2{}^+ + OH^- \quad (10)$$

$$RN_2{}^+ + OH^- \longrightarrow R^+ + OH^- + N_2 \quad (11)$$

$$R^+ + OH^- \longrightarrow ROH \quad (12)$$

$$R^+ \longrightarrow \text{other products} \quad (13)$$

Experimental Section

Pmr spectra were recorded using a Varian A-60 spectrometer. Chemical shifts are reported as δ values in parts per million downfield from TMS at 0. The chemical shifts are somewhat solvent dependent owing to the anisotropy of the phenyl substituent. Coupling constants are reported in hertz as line separations in cases where those line separations could obviously be measured, and they are not intended to represent computer refined values. Ir spectral data were recorded on a Beckman IR-8 spectrometer. Melting points were taken using a Kofler hot bench. Carbon–hydrogen analyses were performed by Huffman Laboratories, Inc., Wheatridge, Colo., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

2-*exo*-Phenyl-2-hydroxy-5-norbornanone.—Chromium trioxide (22 g) was cautiously and slowly added to 250 ml of cold pyridine while stirring. To the yellow complex was added 5 g of diol **9**.[21] The reaction mixture was stirred overnight. It was cooled in an ice–salt bath and 250 ml of cold, concentrated HCl was slowly added. This nearly neutral mixture was continuously extracted with ether for 24 hr. After the ether extracts were dried they were passed through a Norit pad and concentrated. Upon standing for 1 hr crystals formed. Recrystallization from ether containing a little hexane gave a pure product, mp 112°.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.39; H, 6.99.

2-*exo*-Phenylnorbornane-2,5-*endo*-diol (8).—The ketone described above (8.74 g) was treated with 1.5 g of $LiAlH_4$ in ether. The complex was decomposed with water and the ether layer was separated and concentrated. Large crystals formed. They were dissolved in ether and crystallization was allowed to take place again, mp 103°. A total of 6.11 g of pure crystals were obtained. The nmr spectrum (in pyridine) was as follows (in parts per million): hydroxyl hydrogens, 5.81 (2 H), concentration dependent; 5-exo hydrogen, 4.50 (1 H); 3-endo hydrogen, 2.75 (1 H); 3-exo and 6-endo 1 and 4 hydrogens, complex band centered near 2.4 (4 H); 6-exo hydrogen, several components centered near 1.9 (1 H); 7-syn and 7-anti hydrogens, complex pattern centered near 1.45 (2 H). The 5-exo hydrogen gives a broadened signal composed of five partially resolved peaks. The 3-endo hydrogen forms a pair of doublets, $J_{3\text{-endo},3\text{-exo}} = 12.8$ Hz and $J_{3\text{-endo},4} = 2.7$ Hz. The remaining signals are complex. Assignment of signals was aided by the spectrum of the 5-exo deuterated species.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 76.44; H, 7.90. Found: C, 76.25; H, 7.84.

2-*endo*-Hydroxy-2-phenyl-5-*exo*-norbornylamine (5).—Diol **8** (8 g) was treated with 9 g of *p*-toluenesulfonyl chloride in 40 ml of pyridine for 21 hr. The mixture was diluted with water and the product was extracted with 4–100-ml portions of ether. The ether extracts were washed successively with cold, diluted HCl and water. After the solution was concentrated, crystals formed, mp 130°. A second crop of crystals was recovered. A total of 14.3 g of pure tosylate was obtained.

Anal. Calcd for $C_{20}H_{22}O_4S$: C, 67.01; H, 6.19. Found: C, 66.80; H, 6.05.

A mixture made from 1.4 g of the tosylate from **8**, 1 g of sodium azide, and 10 ml of dimethyl sulfoxide was heated on the steam bath for 1 hr. Water was added and the product was extracted with ether. After the ether was evaporated, an oil remained which could not be caused to crystallize. It gave an nmr signal for the 5-endo hydrogen at 3.49 ppm which was a quartet with the peaks separated by 7.5 and 3.0 Hz ($CDCl_3$ solution). The five aromatic hydrogen signals appeared at 7.3 and the hydroxyl hydrogen signal appeared at 2.32 ppm. A group of signals for four hydrogens appeared between 2.0 and 2.7 and another group of signals for four hydrogens appeared between 1.0 and 1.5 ppm. No signals characteristic of the starting tosylate were detected. A strong absorption was present in the ir spectrum at 2100 cm^{-1} characteristic of azides.

The above azide was reduced with $LiAlH_4$ in ether. The complex was decomposed with water and the ether layer was separated. Upon evaporation of the ether, crystals formed. The compound was recrystallized from ether–hexane mixture, mp 105°.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.80; H, 8.43. Found: C, 76.71; H, 8.26.

Deamination of 5.—A sample of amine **5** dissolved in 50 ml of acetic acid was treated with 0.8 g of sodium nitrite. After 20 hr, products were worked up as described for amine **6**. Analysis of the mixture of carbinol products by nmr showed diols **9** and **10** to be present in the ratio of 2.22:1.

To exactly half of the mixture of products from the deamination of 2.1251 g of radioactive amine **5** (30.87 mCi/mol) was added 0.7401 g of nonradioactive diol **8**. After the compounds were converted to the diols by reducing the mixture with $LiAlH_4$, the products were separated by chromatography on alumina. In this way there was obtained 0.369 g of **12** (43.5%), 0.132 g of **10**[21] (15.7%), 0.315 g of **9** (37.3%), and 0.799 g of **8**. Compound **8** was crystallized from ether twice and assayed for carbon-14 content (1.153 mCi/mol). The yield of **8** was therefore 2.59%.

To the second half of deamination product described above was added 0.5760 g of nonradioactive **11**. After the materials were converted to a mixture of carbinols, the products were separated by chromatography. Compound **11** was recovered and crystallized twice from benzene. A few milligrams of **10** were added and the compound was crystallized again, dried, and assayed for carbon-14 content (0.0434 mCi/mol). Therefore the yield of **11** was 0.075%.

In another experiment 3.766 g of radioactive amine **5** (30.87 mCi/mol) was deaminated in 75 ml of acetic acid which was saturated with sodium acetate. The crude mixture of diol products obtained as above was analyzed by nmr. The ratio of **9**:**10** was found to be 2.22:1. To the gross product was added the following materials: 0.1825 g of **11**, 0.2431 g of **8**, 0.1144 g of **10**, and 0.3125 g of **9**. The compounds were separated by chromatography on alumina. The tricyclic alcohol **12** was isolated first (1.074 g, 35.0%). The diols obtained were recrystallized and the following data, millicurie/mole (%), were collected: diol **11**, 0.579 (0.114); diol **8**, 7.240 (2.43); diol **10**, 25.80 (19.0); diol **9**, 25.02 (43.5).

2-*endo*-Phenyl-2-hydroxy-5-norbornanone.—To a chromium trioxide–pyridine complex, prepared by cautious addition of 22 g of chromium trioxide to 250 ml of cold pyridine, was added 5 g of diol **10**.[21] The reaction mixture was stirred overnight. It was then cooled using an ice–salt bath and 250 ml of concentrated HCl was slowly added. The mixture was then continuously

(33) J. H. Ridd, *Quart. Rev. Chem. Soc.*, **15**, 418 (1961).

(34) We are indebted to Professor Theodore Cohen for this suggestion.

(35) See also E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group," Saul Patai, Ed., Interscience, New York, N. Y., 1968, Chapter 8, for discussions of stereochemical retention in such reactions.

(36) C. J. Collins and B. M. Benjamin, *J. Amer. Chem. Soc.*, **85**, 2519 (1963); C. J. Collins, W. A. Bonner, and C. T. Lester, *ibid.*, **81**, 466 (1959).

extracted with ether for 24 hr, at which time no more product could be recovered. Most of the ether was evaporated and the concentrated solution was passed through a Norit pad. Upon addition of hexane to the ether solution, crystallization of the ketone took place, mp 90°.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.54; H, 6.99.

2-*endo*-Phenylnorbornane-2-*exo*,5-*endo*-diol (11).—The preceding ketone (8.55 g) in ether solution was added to an ether solution of $LiAlH_4$ and the mixture was stirred at ambient temperature for 1 hr. Water was added until the precipitated alumina became grainy. The ether solution was separated by filtration and the alumina was washed thoroughly with fresh ether. When the solution was concentrated the diol crystallized. Recrystallization from ether produced a pure product, mp 109°. The nmr spectrum in pyridine solution is as follows (in parts per million): hydroxyl hydrogens, 6.0 (2 H), concentration dependent; 5 exo hydrogen, 4.38 (1 H); 3-endo hydrogen, 3.28 (1 H); 1-bridgehead, 4-bridgehead, and 7-syn hydrogens, 2.5 (3 H); 3-exo and 6-exo hydrogens, several peaks between 1.3 and 2.2 and partially overlapped by the 7-anti hydrogen, 1.47 (3 H); 6-endo hydrogen, 1.10 (1 H). The coupling constants are $J_{3\text{-endo},3\text{-exo}} = 13.0$, $J_{3\text{-endo},7\text{-anti}} = 2.3$, $J_{6\text{-exo},6\text{-endo}} = 13.3$, $J_{6\text{-endo},7\text{-syn}} = 3.2$, $J_{7\text{-syn},7\text{-anti}} = 8.5$ Hz. Analysis of the spectrum was aided by the spectrum of the 5-exo deuterated species. In the completely protonated form the signal for the 5-exo hydrogen was composed of five poorly resolved components and the signal for the 6-endo hydrogen appeared as a pair of poorly resolved triplets.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.35; H, 7.97.

2-*exo*-Hydroxy-2-phenyl-5-*exo*-norbornylamine (6).—Pure diol 11 (2.8 g) was dissolved in 15 ml of dry pyridine and 2.8 g of *p*-toluenesulfonyl chloride was added. When the solution was homogeneous, the flask was stoppered and allowed to stand overnight. The contents of the flask were then diluted with 150 ml of water and the aqueous solution was extracted with three 100-ml portions of ether. The ether extracts were washed separately with water, cold dilute HCl, and again with water. After evaporation of the ether, the compound could not be caused to crystallize. Analysis by nmr did not reveal the presence of starting diol. Without further purification the tosylate was placed in a flask with 15 ml of dimethyl sulfoxide and 15 ml of pyridine and 3 g of sodium azide was added. The mixture was heated to 110° for 3 hr. The solution was treated with water and the product was recovered by ether extraction. After the ether extracts were washed with water, the ether was evaporated and an oil remained. It did not crystallize. The nmr spectrum (in CCl_4) consisted of a broad triplet for the 5-endo hydrogen at 3.22 and signals for eight other hydrogens between 1.0 and 2.4 ppm. Five aromatic hydrogens appeared at 7.25 ppm. The hydroxyl hydrogen signal was removed by shaking the sample with a drop of D_2O. No signals characteristic of the tosylate precursor could be detected. The ir spectrum of the azide contained a strong absorption at 2100 cm^{-1}. The crude azide was treated with $LiAlH_4$ in ether solution. The complex was decomposed with water and the supernatant ether layer was removed and concentrated. Benzene was added and the amine crystallized, mp 118°.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.80, H, 8.43. Found: C, 76.83; H, 8.36.

The amine 6 was shown to be free of diol 11 as follows. To 0.2910 g of amine (30.59 mCi/mol) there was added 0.4254 g of nonradioactive diol 11. After the materials were brought into solution the diol was reisolated and found to be nonradioactive.

Deamination of 6.—To a solution of 2 g of amine 6 in 100 ml of glacial acetic acid there was added 2 g of solid sodium nitrite over a period of 2 hr. The reaction mixture was then stirred at room temperature for 20 hr and then diluted with water. The products were recovered by ether extraction. After the ether extracts were dried, they were combined, concentrated, and treated with $LiAlH_4$. Isolation of the mixed products was accomplished in the usual way. Integration of the nmr spectrum of the mixture of products showed the presence of diols 10 and 9 in the ratio of 1.67:1.

In another deamination experiment the acetic acid was saturated with anhydrous sodium acetate. The product from 1.569 g of amine 6 was treated with $LiAlH_4$ and the mixture of alcohols was chromatographed on alumina.[21] The following was recovered: 0.350 g of phenylnortricyclanol 12, 0.503 g of diol 10, and 0.303 g of diol 9. In a separate experiment using 1.0111 g of amine 6 labeled in the phenyl group with carbon-14 (30.59 mCi/mol) the deamination product was mixed with 1.1263 g of nonradioactive diol 11. The mixture was treated with $LiAlH_4$ after which 11 was recovered by chromatography on alumina. The diol was crystallized from benzene twice and its radioactivity content was determined. Following this, the sample of 11 was mixed with 40 mg of nonradioactive 12 and 33 mg of nonradioactive 10. It was chromatographed, crystallized, and assayed for carbon-14 content again (0.4349 mCi/mol). This corresponds to a yield of 0.0162 g, 22% of the reaction products. In a similar way the yield of 8 from 6 was found to be 0.039%.

Carbon-14 Labeled Amines 5 and 6.—To a solution of 25 g of 5-norbornen-2-ol in 200 ml of acetone cooled in an ice–salt bath there was added slowly 100 ml of cold chromic acid solution, prepared from 26 g of CrO_3 and 26 g of sulfuric acid, diluted to 100 ml with water. After stirring for 2 hr at room temperature most of the acetone was evaporated under vacuum. Water was added and the product, 5-norbornen-2-one, was recovered by ether extraction. Crude norbornenone was treated with equimolar amount of Grignard reagent prepared carbon-14-labeled bromobenzene. The complex was decomposed with concentrated ammonium chloride and the product was distilled under vacuum. In several preparations, the yield of 2-*exo*-phenyl-5-norbornen-2-ol[21] was usually <50%. Borohydration of the above phenylnorbornenol was carried out as described for the general reaction.[37] The solvent was composed of 600 ml of tetrahydrofuran and 250 ml of triglyme to prevent precipitation of the intermediate complex. Fractional crystallization of the mixture of products gave 29 g of phenyl-^{14}C-labeled 9, mp 163°, and 2-*exo*-phenylnorbornane-2-*endo*,6-*exo*-diol, mp 128°. The conversion of 9 to a mixture of 9 and 10 has been published.[21]

2-*exo*-Hydroxy-2-phenyl-5-*endo*-norbornylamine (7).—To a solution of 5 g of 2-*exo*-hydroxy-2-phenyl-5-norbornanone in 50 ml of pyridine was added 5 g of hydroxylamine hydrochloride. After the reaction mixture had been heated on the steam bath for 1 hr, most of the pyridine was evaporated in an air stream. Organic materials were extracted from the pasty mass by triturating it with ether. Crystals of 2-*exo*-hydroxy-2-phenyl-5-norbornanone oxime formed when the ether solution was concentrated. It recrystallized slowly from ether containing a little hexane, mp 128°.

Anaol Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96. Found: C, 72.09; H, 7.25.

Six grams of the above oxime was added to a solution of 2 g of $LiAlH_4$ in 250 ml of ether and the mixture was heated at reflux temperature for 20 hr. Water was added to decompose the complex and the ether solution was separated and concentrated. Amine was separated from neutral material by extracting it with cold dilute HCl. The acid was neutralized with sodium hydroxide and the amine was extracted with ether. Most of the ether was evaporated after which crystals formed. These crystals were collected on a filter and recrystallized, mp 157°. This compound was thought to be the secondary amine form by ring expansion of the six-membered norbornyl structure. Fractional crystallization from ether–hexane mixtures of the material in the filtrates gave a second compound, mp 81°. It slowly absorbed carbon dioxide when exposed to air.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.80; H, 8.43. Found: C, 76.56; H, 8.30.

Compound 7 containing deuterium in the 5-exo position was prepared by reducing the corresponding oxime with $LiAlD_4$.

Deamination of 7.—This amine (2 g) in 50 ml of acetic acid saturated with sodium acetate was deaminated by treating the solution with 2 g of sodium nitrite. The products were isolated and worked up in the same way as described for other deaminations. Chromatography on alumina of the mixture of carbinols gave the following yields of products: 283 mg of phenylnortricyclenol 12, 567 mg of diol 11 from endo attack, 480 mg of diol 10, 233 mg of diol 9. There was also obtained 99 mg of material which consisted in part of a mixture of ~30 mg of 8 and 30 mg of 7-phenylnorbornane-2-*exo*,7-*syn*-diol and some material which was not identified. Positive identification of the constituents of the 99-mg fraction was accomplished by rechromatographing it on alumina and comparing the nmr spectra of the fractions with the spectra of known compounds.

(37) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 31 (1963).

In another experiment 0.808 g of radioactive amine (59.35 mCi/mol) was deaminated. To the product, as diols, was added 50.0 mg of nonradioactive 8. The compounds were separated by chromatography on alumina and 633 mg of products were recovered. The last fraction containing 8 was rechromatographed after adding nonradioactive 9 and 7-phenylnorbornane-2-*exo*,7-*syn*-diol as hold-back carrier. Diol 8 was then crystallized and assayed for carbon-14 content (18.78 mCi/mol). This corresponds to a yield of 1.85%.

Deamination of 7-*exo*-5-*d*.—Amine 7 containing deuterium in the 5-exo position (9.5 g) was deaminated as described before. After the products had been separated and crystallized, their nmr spectra were then taken to determine the position of the deuterium label. The signal for the 5-exo hydrogen (4.38 ppm, pyridine solution) of 2-*endo*-phenylnorbornane-2-*exo*,5-*endo*-diol (11) was absent. Also the signal for the 6-endo hydrogen (1.10 ppm) was collapsed to a pair of doublets.

In the spectrum of 2-*endo*-phenylnorbornane-2-*exo*,5-*exo*-diol (10)[21] the signal for the 5-endo hydrogen (3.98 ppm) was missing. Diol 9, 2-*exo*-phenylnorbornane-2-*endo*,5-*exo*-diol, gave an nmr spectrum[2,21] in which the signal for the 4-bridgehead hydrogen (2.45 ppm) was missing and the signal for the 3-exo hydrogen (2.40 ppm) was collpased to a doublet.

The nmr spectrum of 2-*exo*-phenylnorbornane-2,5-*endo*-diol (8) was difficult to analyze. Therefore a sample of 8 weighing 100 mg was mixed with 50 mg of tris(dipivaloylmethane)europium and dissolved in deuteriochloroform. Under these conditions the spectrum was interpreted as follows (in parts per million): secondary hydroxyl hydrogen, 9.52 (br, 1 H); 2 and 6 aromatic hydrogens, 7.95 (m, 2 H); 3, 4, and 5 aromatic hydrogens, 7.45 (m, 3 H); 5-exo and tertiary hydroxyl hydrogens, unresolved, 6.98 (2 H); 3-endo hydrogen, doublet of doublets, 4.47 ($J_{3\text{-endo},3\text{-exo}}$ = 14.1, $J_{3\text{-endo},7\text{-anti}}$ = 2.8 Hz); the 3-endo hydrogen is partially overlapped by the 6-endo hydrogen, poorly resolved pair of triplets, 4.25 (2 H); 1- and 4-bridgehead hydrogens, unresolved 3.46 (2 H); 3-exo hydrogen, doublet of doublets, 3.03 ($J_{3\text{-exo},3\text{-endo}}$ = 14.1, $J_{3\text{-exo},4}$ = 4.4 Hz); the 3-exo hydrogen is partially overlapped by components of the 6-exo hydrogen, unresolved, 2.86 (2 H); 7-syn and 7-anti hydrogens, unresolved, 2.29 (2 H). In the spectrum for diol 8 derived from amine 7-*exo*-5-*d*, the signal for the bridgehead hydrogens at 3.46 ppm had an integrated intensity of 1.0. The signal for the 3-exo hydrogen collapsed to a pair of singlets with spacing of 14.1 Hz and the signal for the 5-endo hydrogen was narrower.

Registry No.—**5**, 29264-72-0; **6**, 29264-73-1; **7**, 29264-74-2; **7** oxime, 36808-83-0; **8**, 14518-60-6; **8** tosylate, 36808-85-2; **9**, 36808-86-3; **9** (phenyl-^{14}C), 36808-87-4; **11**, 36808-88-5; 2-*exo*-phenyl-2-hydroxy-5-norbanone, 36808-89-6; 2-*endo*-phenyl-2-hydroxy-5-norbanone, 36808-90-9.

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Sterically Controlled Syntheses of Optically Active Organic Compounds. XVI. Temperature Dependence of Hydrogenolytic Asymmetric Transamination[1]

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Temperature effects on the hydrogenolytic asymmetric transamination between ethyl pyruvate and optically active amines were studied. Definite temperature effects were observed between −20 and 65°. At relatively low temperature and when the optically active amine had an *R* configuration, the resulting alanine had an *R* configuration. The optical purity of (*R*)-alanine decreased as the reaction temperature increased and the configuration of analine inverted to the *S* configuration at higher temperature. Temperature effects using several optically active amines were studied. Within the context of these results, the possible steric course of the temperature-dependent asymmetric reactions is discussed. The differences of enthalpy of activation ($\Delta\Delta H^{\ddagger}_{S-R}$) and entropy of activation ($\Delta\Delta S^{\ddagger}_{S-R}$) between the formation of *S* amino acid and *R* amino acid were calculated at varying temperature. The results suggest that the entropy factor is very important in the inversion of configuration of the reaction product in the asymmetric synthesis.

Several studies on the hydrogenolytic asymmetric transamination between α-keto acids (or their esters) and optically active amino compounds have been reported.[2-8]

Generally, temperature is one of the most important factors in determining the molecular conformations that are involved in asymmetric syntheses. Some studies of the effect of temperature on asymmetric syntheses have been recorded in the literature.[9-15]

In a previous communication,[16] the temperature effect on the hydrogenolytic asymmetric transamination between ethyl pyruvate and optically active amines was reported. This investigation examines further the temperature dependence of hydrogenolytic asymmetric transamination. The optically active amines used were (*S*)-(−)- and (*R*)-(+)-α-methylbenzylamine, (*R*)-(+)-α-ethylbenzylamine, and (*S*)-(−)-α-(1-naphthyl)ethylamine. The reaction temperatures used were in the range of −20 to 65°. The hydrogenation reactions were carried out at 1 atm of hydrogen by using palladium hydroxide on charcoal suspended in absolute alcohol with agitation provided by a magnetic stirrer. One series of the hydrogenation reactions

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Table I
Temperature Effect in Hydrogenolytic Asymmetric Transamination

Reaction[a]	Amine[b]	Temp, °C	Yield, %	Configuration	Alanine, $[\alpha]^{25}D$, deg, 5 N HCl	Optical purity,[c] %	DNP-alanine, $[\alpha]^{25}D$, deg, 1 N NaOH	Optical purity,[d] %
1	(R)-(+)-Me	+65	72	S	+5.3	36	+41.0	28
2	(R)-(+)-Me	+50	70	S	+6.1	42	+56.9	40
3	(R)-(+)-Me	+35	61	S	+5.0	34	+51.1	36
A 4	(R)-(+)-Me	+20	65	S	+1.3	9	+14.3	10
5	(R)-(+)-Me	+10	52	R	−2.1	14	−19.6	14
6	(R)-(+)-Me	0	52	R	−4.3	29	−49.5	34
7	(R)-(+)-Me	−10	68	R	−5.7	39	−56.7	39
8	(R)-(+)-Me	−20	54	R	−6.3	43	−81.4	57
1	(S)-(−)-Me	+65	68	R	−4.2	29	−44.9	31
2	(S)-(−)-Me	+50	63	R	−6.0	41	−62.4	43
3	(S)-(−)-Me	+35	68	R	−5.3	37	−53.2	37
B 4	(S)-(−)-Me	+20	58	R	−0.7	5	−6.0	4
5	(S)-(−)-Me	+10	65	S	−0.3	2	+16.0	11
6	(S)-(−)-Me	0	58	S	+2.5	17	+47.6	33
7	(S)-(−)-Me	−10	50	S	+5.1	35	+66.4	46
8	(S)-(−)-Me	−20	50	S	+8.3	57	+86.0	60
1	(R)-(+)-Et	+65	68	S	+5.1	35	+58.8	41
2	(R)-(+)-Et	+50	81	S	+8.0	55	+79.6	55
3	(R)-(+)-Et	+35	61	S	+6.0	41	+62.6	44
C 4	(R)-(+)-Et	+20	58	S	+1.4	10	+22.2	15
5	(R)-(+)-Et	+10	56	R	+2.6	18	−24.3	17
6	(R)-(+)-Et	0	54	R	−2.6	18	−26.2	18
7	(R)-(+)-Et	−10	54	R	−3.0	20	−42.1	29
8	(R)-(+)-Et	−20	58	R	−4.8	33	−60.7	42
1	(S)-(−)-Naph	+65	74	R	−0.7	5	−17.5	12
2	(S)-(−)-Naph	+50	74	R	+0.4	3	−2.8	2
3	(S)-(−)-Naph	+35	52	S	+3.5	24	+36.6	25
D 4	(S)-(−)-Naph	+20	52	S	+7.2	49	+73.1	51
5	(S)-(−)-Naph	+10	56	S	+8.1	56	+81.5	57
6	(S)-(−)-Naph	0	58	S	+9.3	64	+95.1	66
7	(S)-(−)-Naph	−10	38	S	+7.1	48	+82.2	57
8	(S)-(−)-Naph	−20	54	S	+8.5	58	+99.2	69
1	(R)-(+)-Me	+65	81	S	+3.3	23	+34.7	24
2	(R)-(+)-Me	+50	63	S	+1.8	12	+15.0	10
E 3	(R)-(+)-Me	+35	58	R	−4.4	30	−53.4	37
4	(R)-(+)-Me	+20	65	R	−3.1	21	−74.4	52
5	(R)-(+)-Me	+10	58	R	−8.8	60	−100.3	70
6	(R)-(+)-Me	0	52	R	−8.9	61	−102.7	71
7	(R)-(+)-Me	−10	49	R	−10.0	68	−105.1	73

[a] Absolute ethanol was used as a solvent in reactions A, B, C, and D. Ethyl acetate was used in reaction E. [b] (R)-(+)-Me, (R)-(+)-α-methylbenzylamine; (S)-(−)-Me, (S)-(−)-α-methylbenzylamine; (R)-(+)-Et, (R)-(+)-α-ethylbenzylamine; (S)-(−)-Naph, (S)-(−)-α-(1-naphthyl)ethylamine. [c] Defined as $[\alpha]D$ obsd/$[\alpha]D$ lit. × 100; (S)-(+)-alanine, $[\alpha]^{25}D$ −14.6° (5 N HCl). [d] Defined as $[\alpha]D$ obsd/$[\alpha]D$ lit. × 100; DNP-(S)-(+)-alanine, $[\alpha]^{25}D$ +143.9° (1 N NaOH).

was carried out with ethyl acetate as the solvent. The results are summarized in Table I and in Figures 1 and 2.

The consumption curves of hydrogen at different temperatures are shown in Figure 1. The hydrogenation reaction in ethanol suspension takes place rapidly at temperatures higher than 0°. At temperatures below −20°, the hydrogenation reaction proceeds slowly. At −30°, the rate of the hydrogenation reaction was very slow. When ethyl acetate was substituted for the ethanol, the hydrogenation reaction at −20° was extremely slow.

In reactions A and B reported in Table I and Figure 2, alanine was prepared by using (R)-(+)-α-methylbenzylamine and (S)-(−)-α-methylbenzylamine at temperatures from −20 to 65°. Within this temperature range, the optical activity of alanine that was prepared from (R)-(+)-α-methylbenzylamine was opposite in sign and almost identical in magnitude with that of the alanine that was prepared from (S)-(−)-α-methylbenzylamine (Figure 2). At lower temperature, the configuration of alanine that was prepared from the (R)-(+) amine was found to be R (optical purity 57% at −20°). As the temperature of the reaction was increased, the optical activity decreased sharply. The optical activity of alanine became zero at about 17°. The configuration of alanine then inverted and the optical activity of (S)-alanine increased steadily until a maximum was reached at about 45–50° (optical purity 45% at 50°). Finally, the optical activity of alanine decreased at higher temperatures (Figure 2). The sigmoidal shapes of optical purity curves of alanine prepared from the other optically active amines are similar.

Formation of optically active compounds in the asymmetric synthesis is due to the difference between the rates of formation of the two diastereomers from the starting material (substrate*). The rates of formation of the diastereomeric activated complexes are determined by the difference of the free energies of

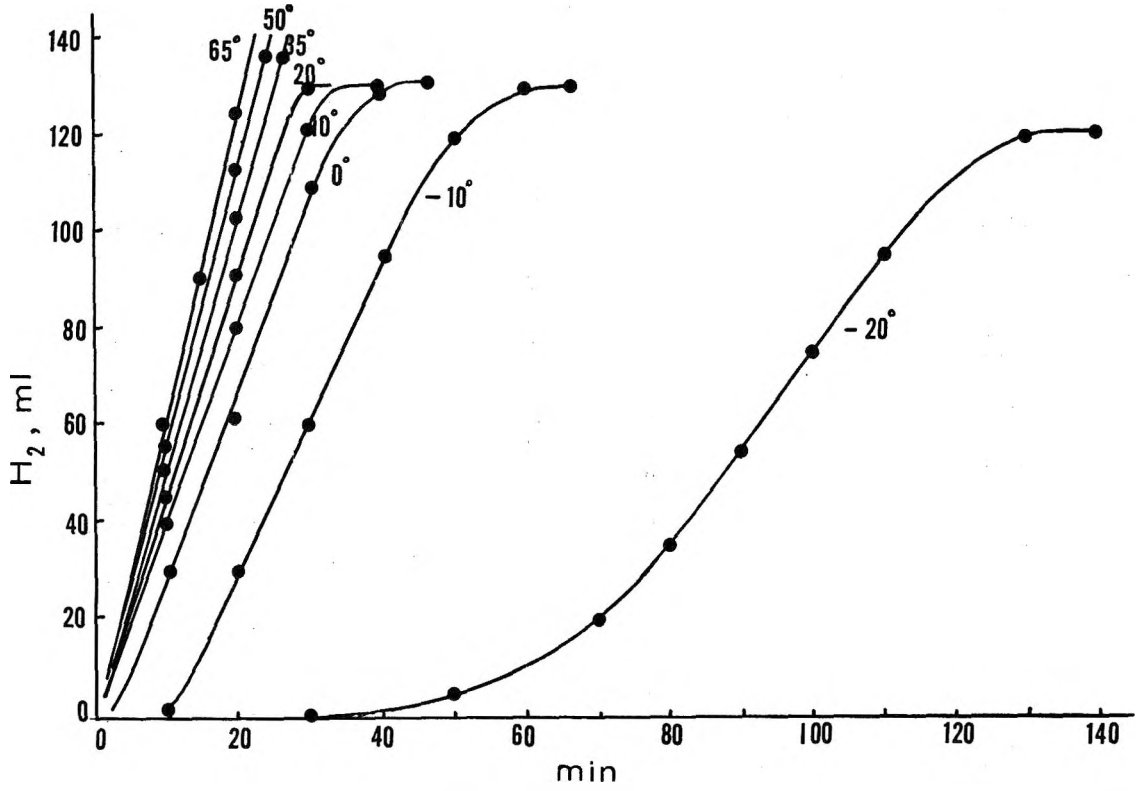
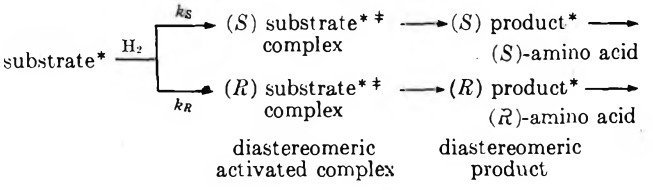


Figure 1.—Hydrogen consumption in the hydrogenation and hydrogenolysis of the Schiff base prepared from ethyl pyruvate and (*S*)-(−)-α-methylbenzylamine (reaction B).

activation ($\Delta G^{\pm}$) for the two diastereomeric transition states. According to the transition-state theory,[17]



the rate of formation of the [(*S*) substrate* complex]$^{\pm}$ is expressed as follows.[10,17-20]

$$k_S = \kappa_S \frac{kT}{h} e^{-\Delta G_S^{\pm}/RT}$$

If we assume that the transmission coefficient κ_S is equal to κ_R, the (*S*) product*/(*R*) product* is expressed as shown below.

$$\frac{(S)\text{ product}^*}{(R)\text{ product}^*} = (S)/(R) = k_S/k_R =$$

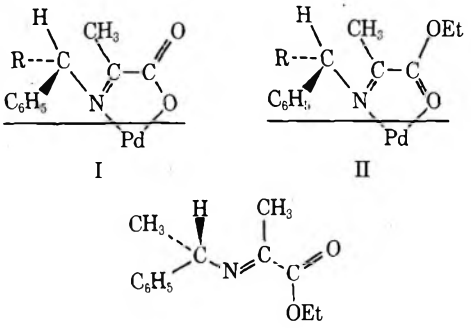
$$\exp \frac{\Delta S_S^{\pm} - \Delta S_R^{\pm}}{R} \exp \frac{-(\Delta H_S^{\pm} - \Delta H_R^{\pm})}{RT}$$

$$= \exp \frac{\Delta\Delta S^{\pm}_{S-R}}{R} \exp \frac{-\Delta\Delta H^{\pm}_{S-R}}{RT}$$

$$\log (S)/(R) = \log k_S/k_R = \frac{\Delta\Delta^{\pm}_{S-R}}{2.3R} - \frac{\Delta\Delta HS^{\pm}_{S-R}}{2.3RT}$$

Figure 3 shows the plot of log (*S*/*R*) against $1/T$ from the result obtained in the asymmetric transamination reactions. From this plot, $\Delta\Delta H^{\pm}_{S-R}$ and $\Delta\Delta S^{\pm}_{S-R}$ at varying temperatures were calculated. These are summarized in Table II. At low temperatures (−20 to 10°), $\Delta\Delta H^{\pm}_{S-R}$ is low; however, $\Delta\Delta S^{\pm}_{S-R}$ is higher. At relatively higher temperatures (10–50°), $\Delta\Delta H^{\pm}_{S-R}$ increases some, but $\Delta\Delta S^{\pm}_{S-R}$ increases considerably. At higher temperatures (50–65°), the signs of $\Delta\Delta H^{\pm}_{S-R}$ and $\Delta\Delta S^{\pm}_{S-R}$ change and their absolute values both decrease except for the case using (*S*)-(−)-α-(1-naphthyl)ethylamine. These results strongly suggest that the temperature-dependent asymmetric synthesis is largely controlled by the entropy factor ($\Delta\Delta S^{\pm}_{S-R}$). This indicates that the conformations of two diastereomers in the transition state are quite different and the entropy of activation of one diastereomer which leads to (*S*)-amine-(*S*)-amino acid is much lower than that of other diastereomers (*S*)-amine-(*R*)-amino acid which resulted in the formation of (*R*)-amino acid.

On the other hand, in the previous paper from this laboratory, a possible steric course of the hydrogenolytic asymmetric transamination was discussed.[5,8] As shown in structure I or II, the possible preferred conformation



III

(17) S. Glasston, K. J. Laidler, and H. Eyring, "The Theory of Rate Process," McGraw-Hill, New York, N. Y., 1941.

(18) E. I. Klabunovskii and E. S. Levitine, *Russ. Chem. Rev.*, **39**, 1035 (1970).

(19) The $\Delta G^{\pm}$ of the equation includes external factors such as solvents and catalysts, which cause a change in the free energy of activation of the reactions; *cf.* Chapters 4 and 8 of ref 17.

(20) C. A. Eckert, *Ind. Eng. Chem.*, **59**, 20 (1967).

TABLE II

$\Delta\Delta H^{\pm}_{S-R}$ AND $\Delta\Delta S^{\pm}_{S-R}$ OF THE REACTIONS AT VARYING TEMPERATURES

		−20 to 0°		0–35°		50–65°	
Chiral center	Solvent	$\Delta\Delta H^{\pm}_{S-R}$, kcal mol^{-1}	$\Delta\Delta S^{\pm}_{S-R}$, cal mol^{-1} deg^{-1}	$\Delta\Delta H^{\pm}_{S-R}$, kcal mol^{-1}	$\Delta\Delta S^{\pm}_{S-R}$, cal mol^{-1} deg^{-1}	$\Delta\Delta H^{\pm}_{S-R}$, kcal mol^{-1}	$\Delta\Delta S^{\pm}_{S-R}$, cal mol^{-1} deg^{-1}
(*R*)-(+)-Me	EtOH	4.1	13.8	7.2	25.0	−3.1	−7.7
(*S*)-(−)-Me	EtOH	−5.4	−18.0	−7.2	−25.0	2.7	10.2
(*R*)-(+)-Et	EtOH	3.6	14.6	6.1	21.6	−4.0	−9.9
(*S*)-(−)-Naph	EtOH	−2.2	5.3	−6.6	−20.6	−6.6	−20.6
(*R*)-(+)-Me	ACOEt	1.1	0.4	8.9	28.0	3.1	9.4

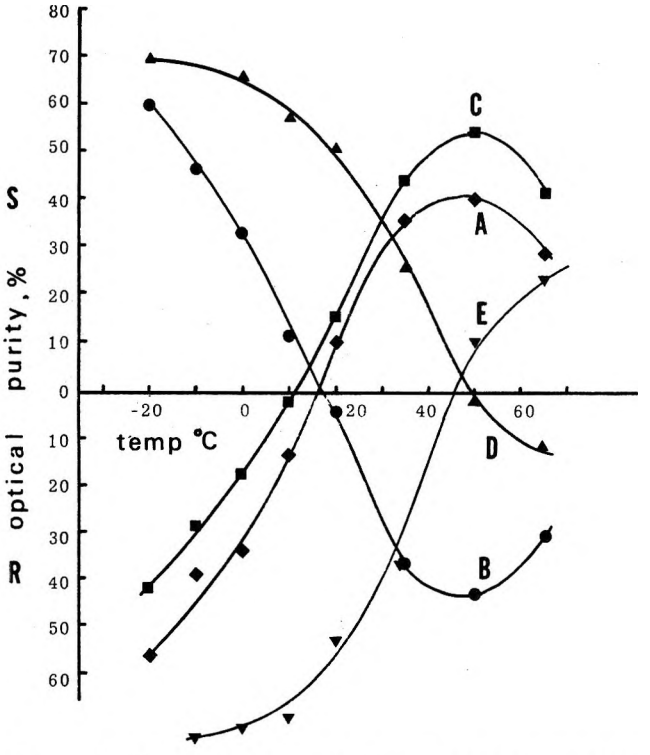


Figure 2.—Temperature effect in hydrogenolytic asymmetric transamination: A, (*R*)-(+)-α-methylbenzylamine, in ethanol; B, (*S*)-(−)-α-methylbenzylamine, in ethanol; C, (*R*)-(+)-α-ethylbenzylamine, in ethanol; D, (*S*)-(−)-α-(1-naphthyl)ethylamine, in ethanol; E, (*R*)-(+)-α-methylbenzylamine, in ethyl acetate.

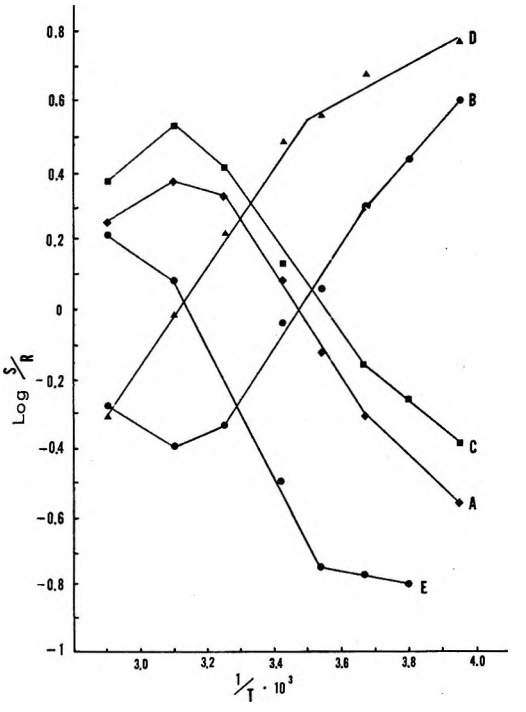


Figure 3.—Temperature dependence of hydrogenolytic asymmetric transamination.

of the substrate at room temperature could be a five-membered cyclic complex with the catalyst (chelation hypothesis) depending on whether the substrate is an acid (I) or its ester (II). These chelated substrates with the catalyst could then be adsorbed on the catalyst surface at the less bulky side of the molecule and the catalytic hydrogenation reaction would take place. The proposed steric course was supported by the results obtained in the study of various optically active amines and also in the study of the solvent effect on the asymmetric synthesis.[6,8]

In reaction C in Table I and Figure 2, the optical purity of alanine prepared from (*R*)-(+)-α-ethylbenzylamine is lower than that of alanine prepared from (*R*)-(+)-α-methylbenzylamine at a lower temperature. On the other hand, the optical purity of alanine prepared from (*S*)-(−)-α-(1-naphthyl)ethylamine is much higher at lower temperatures. These findings could be explained by the possible steric course proposed earlier (chelation hypothesis).[5,8] The preferred conformation of the substrate on the catalyst surface at lower temperatures would be structure II. The five-membered cyclic intermediate (II) with the catalyst would then be adsorbed at the less bulky side of the molecule and then hydrogenation would take place in a two-step mechanism. The participation of structure II would decrease as the reaction temperature increased. Concomitantly, the participation of the nonchelated structure III would increase. At higher temperature the preferred conformation would be structure III, which was hydrogenated without forming a five-membered substrate–catalyst complex (one-step mechanism). The decrease in optical purity at higher temperatures could be explained by the thermal agitation of the conformation of the substrate molecule.

If this is the case, the temperature dependence of the optical purity of alanine using α-methylbenzylamine, α-ethylbenzylamine, and α-(1-naphthyl)ethylamine can be understood without any contradiction in the results of the present and previous studies. At a relatively low temperature, the optical purity of alanine prepared from (*R*)-(+)-α-methylbenzylamine (reaction A) is higher than that of alanine prepared from (*R*)-(+)-α-ethylbenzylamine (reaction C), because the relative bulkiness of phenyl residue to methyl residue (reaction A) is larger than that of phenyl residue to ethyl residue (reaction C) in structure II. At a relatively high temperature (40–50°), the optical purity of alanine prepared from (*R*)-(+)-α-ethylbenzylamine (reaction C) is higher than that of alanine prepared from (*R*)-(+)-α-methylbenzylamine (reaction A). This could be

explained by the fact that the relative bulkiness of the ethyl group to the hydrogen is larger than that of the methyl group to the hydrogen in structure III. Similarly, at a relatively low temperature, the optical activity of alanine from (*S*)-(−)-α-(1-naphthyl)ethylamine (reaction D) is much higher than that of alanine from (*S*)-(−)-α-methylbenzylamine (reaction B). This could be explained by the fact that the naphthyl group is much bulkier than the phenyl group in structure II. Even at a relatively higher temperature, the stronger interaction of the naphthyl group with the catalyst might stabilize the conformation of structure II. Structure III would contribute to the inversion of configuration of the product at higher temperature. However, the relative bulkiness of the naphthyl group is so large that the sterically controlled effect based on the relative bulkiness of the hydrogen and methyl group in structure III might not function effectively. The thermal molecular movement of the substrate at higher temperature (>50°) would also result in lower optical purity.

All reactions described above were carried out by using absolute alcohol as the solvent. The reaction E in Figure 2 shows a temperature effect of alanine from (*R*)-(+)-α-methylbenzylamine in alcohol and in ethyl acetate. A definite solvent effect of varying temperatures is observed. At a relatively low temperature, the optical purity of alanine prepared in ethyl acetate is much larger than that of alanine prepared in ethanol. This could be explained by the solvent effect that is discussed in the previous paper.[6,8] At a relatively low temperature, the preferred conformation would be structure II in a solvent that has a low dielectric constant. Interactions between substrate and catalyst would be stronger in a less polar solvent than in a polar solvent. As indicated by the experimental results for reaction E, even at a relatively higher temperature (~45°), the preferred conformation of the substrate would be structure II.

This explanation of the steric course of the asymmetric reactions is consistent with the experimental values of $\Delta\Delta H^{\ddagger}_{S-R}$ and $\Delta\Delta S^{\ddagger}_{S-R}$ at varying temperatures.

In order to avoid possible fractionation of partially optically active alanine during the course of isolation and purification, the crude alanine that was isolated by the use of an ion exchange column was converted to a DNP derivative. The DNP-alanine was then purified by using Celite column chromatography[21] without fractionation of the optical isomers.[5,8]

(21) J. C. Perrone, *Nature (London)*, **167**, 513 (1951); A. Court, *Biochem. J.*, **58**, 70 (1954).

Experimental Section

All hydrogenation and hydrogenolysis were carried out in a three-neck flask at 1 atm with magnetic stirring. The palladium hydroxide on charcoal catalyst used in all experiments was from a single preparation. Hydrogenolysis was carried out with a Parr 3910 shaker-type hydrogenation apparatus. All optical activity measurements were carried out on a JASCO-ORD-CD-UV 5 spectropolarimeter. The accuracy of reaction temperatures is about ±1°.

All experimental procedures were similar to those described in an earlier paper[8] except for the hydrogenation apparatus and reaction temperature.

The specific rotations of optically active amines used follow: (*R*)-(+)-α-methylbenzylamine, $[\alpha]^{25}D$ +41.5° (benzene); (*S*)-(−)-α-methylbenzylamine, $[\alpha]^{25}D$ −42.3° (benzene); (*R*)-(+)-α-ethylbenzylamine, $[\alpha]^{25}D$ +21.7° (benzene); (*R*)-(+)-α-(1-naphthyl)ethylamine, $[\alpha]^{25}$ +88.0° (benzene).

Alanine from Ethyl Pyruvate and (*R*)-(+)-α-Methylbenzylamine (Reaction A, 1).—Ethyl pyruvate (0.58 g, 0.005 mol) and (*R*)-(+)-α-methylbenzylamine (0.61 g, 0.005 mol) were dissolved in 30 ml of benzene at room temperature. The precipitated water was removed by adding anhydrous sodium sulfate. The benzene solution was evaporated under reduced pressure after filtration. The remaining crude Schiff base was dissolved in 30 ml of absolute ethanol and the solution was subjected to hydrogenation at 1 atm by the use of 0.5 g of palladium hydroxide on charcoal at 65°. The hydrogenated and hydrogenolyzed product was hydrolyzed by refluxing with 30 ml of 6 *N* HCl for 5 hr and was dried under reduced pressure. The dried hydrolysate was dissolved in 10 ml of water and the solution was applied to a Dowex 50 × 2 column (hydrogen type, 50–100 mesh, 25 × 1.8 cm) and eluted with 1.5 *N* aqueous ammonia: yield 320 mg (72%); $[\alpha]^{25}D$ +5.25° (*c* 4.53, 5 *N* HCl); optical purity, 36%. After recrystallization from water and ethanol, an elemental analysis of alanine was carried out. *Anal.* Found: C, 40.70; H, 7.82; N, 15.44.

A part of the unrecrystallized alanine was converted to DNP-alanine in a conventional manner. The DNP-alanine obtained was purified by the use of a Celite column treated with pH 7 citrate–phosphate buffer (0.2 *M*).[21] These procedures are similar to those described in earlier reports.[5,8]

DNP-alanine had mp 168–169° dec, $[\alpha]^{25}D$ +41.0° (*c* 2.39, 1 *N* NaOH), optical purity 28.5%. The DNP-alanine was recrystallized from ether and petroleum ether (bp 30–60°) for elemental analysis, mp 172–174°. *Anal.* Found: C, 42.50; H, 3.58; N, 16.46.

Registry No.—(*R*)-(+)-α-Methylbenzylamine, 3886-69-9; (*S*)-(−)-α-methylbenzylamine, 2627-86-3; (*R*)-(+)-α-ethylbenzylamine, 3082-64-2; (*R*)-(+)-α-(1-naphthyl)ethylamine, 3886-70-2; (*S*)-alanine, 56-41-7; (*R*)-alanine, 338-69-2; (*S*)-DNP-alanine, 1655-52-3; (*R*)-DNP-alanine, 6367-22-2.

Acknowledgments.—This work was support by Grant No. NGR 10-007-052 from the National Aeronautics and Space Administration. The authors wish to express their thanks to Professor Yuzo Inouye of Kyoto University, to Mr. Tameo Iwasaki and Dr. W. Dale Snyder of this institute, and to Dr .Kazuo Matsumoto of Tanabe Seiyaku Co. Ltd. for valuable discussions. Thanks are extended also to Mr. Charles R. Windsor for amino acid analyses.

Synthesis of Lignans. I. Nordihydroguaiaretic Acid[1]

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Received April 27, 1972

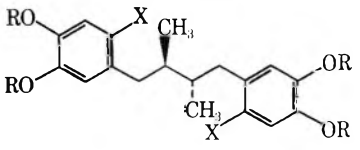
The novel alkylation of the sodium enolate of propioveratrone (**4**) with α-bromopropioveratrone (**5**) in liquid ammonia gave the racemic diketone **9**. A mechanism for the stereoselectivity of this alkylation is proposed and the structural requirements of the reaction are discussed. Cyclodehydration of **9** to the furan **8** followed by hydrogenation *via* the all-cis tetrahydrofuran **25** afforded nordihydroguaiaretic acid (NDGA) tetramethyl ether (**2**). A pronounced solvent effect on the hydrogenation was observed. Demethylation of **2** with concentrated hydrobromic acid afforded NDGA (**1**) in good yield and high purity. An alternate route to **2** *via* the alcohol **28** is also described.

Nordihydroguaiaretic acid (**1**), more commonly known as NDGA, is a phenolic lignan found in the resinous exudates of many plants, especially *Larrea divaricata*, the creosote bush of the southwestern United States.[2] Its structure was established by synthesis,[3] and there was strong chemical evidence[4] that the naturally occurring optically inactive NDGA was the meso rather than the racemic form.

Several syntheses of NDGA have appeared in the literature[3-8] and in patents,[6,9] but all involve low-yield reactions, lengthy reaction sequences, or expensive starting materials. The creosote bush has remained the only commercial source of NDGA, which has been used as an antioxidant in foods.

This report presents a practical synthetic route to NDGA utilizing a novel and highly stereoselective alkylation reaction to form the lignan carbon skeleton.

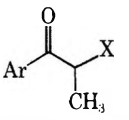
In order to obtain an unequivocal confirmation of the configuration[4] of natural NDGA, the tetramethyl ether **2**,[5] prepared from commercial NDGA,[10] was brominated, affording the dibromo derivative **3**.[5] A



1, R = X = H (NDGA)
2, R = CH_3; X = H
3, R = CH_3; X = Br

single-crystal X-ray analysis[11] confirmed that NDGA (**1**) has the meso configuration.

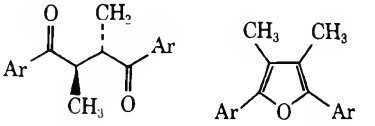
Acylation of veratrole with propionyl chloride using chloroform as solvent gave a higher yield (93%) of purer product, 3,4-dimethoxypropiophenone (**4**), than previously reported methods.[12,13] Bromination of **4** in refluxing chloroform then gave α-bromo-3,4-dimethoxypropiophenone (**5**), again in considerably better yield (95%) than by the methods previously described.[13]



Ar = 3,4-dimethoxyphenyl

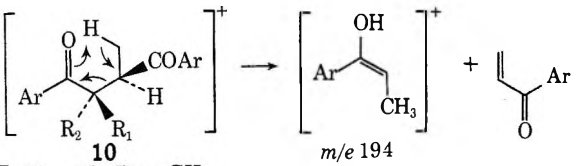
4, X = H
5, X = Br
6, X = Cl

Heating **5** with copper powder in refluxing xylene has been reported[14] to give 2,3-diveratroylbutane (**7**) in 28% yield, but, using a variety of copper powders and solvents, we could obtain the rather insoluble compound **7** in no more than 7% yield. Column chromatography of the mother liquors led to crystalline mixtures containing a second diketone (**9**) contaminated with **7**. Dehydration of either **7** or **9** afforded the furan **8** in high yields. From the data to be presented, it is clear that **7** and **9** are the expected meso and racemic diketones, respectively.



7 (meso) **8** **9** (racemic)

Support for the assignments of relative configuration to **7** and **9** came from their mass spectra,[15] which showed that a fragment ion at *m/e* 194 was much stronger in the spectrum of **7** than in that of **9**. This ion presumably arises by a rearrangement fragmentation,[16] the transition state (**10**) for which is sterically more favorable when R_1 = H and R_2 = CH_3 (**7**) than when R_1 = CH_3 and R_2 = H (**9**).



10 *m/e* 194

7, R_1 = H; R_2 = CH_3
9, R_1 = CH_3; R_2 = H

(1) Presented in part at Metrochem 69, New York, N. Y., May 1, 1969, and at the Annual Meeting of the Phytochemical Society of North America, Banff, Alberta, Canada, Aug 20, 1969.

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(4) A. W. Schrecker, *J. Amer. Chem. Soc.*, **79**, 3823 (1957).

(5) G. Schroeter, L. Lichtenstadt, and D. Irineu, *Ber.*, **51**, 1587 (1918).

(6) S. V. Lieberman, G. P. Mueller, and E. T. Stiller, *J. Amer. Chem. Soc.*, **69**, 1540 (1947); U. S. Patent 2,456,443 (Dec 14, 1948).

(7) M. P. Gerchuk and V. M. Ivanova, *Khim. Nauka Prom.*, **3**, 685 (1958).

(8) J. G. Blears and R. D. Haworth, *J. Chem. Soc.*, 1985 (1958).

(9) I. A. Pearl, U. S. Patent 2,644,822 (July 7, 1953).

(10) Wm. J. Stange Co., Paterson, N. J.

(11) J. S. McKechnie and I. C. Paul, *J. Chem. Soc. B*, 699 (1969). We thank Dr. Paul for performing this analysis.

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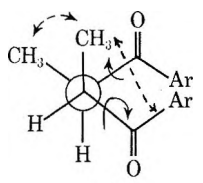
(13) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 809 (1938).

(14) J. R. Atkinson and R. D. Haworth, *ibid.*, 1681 (1938).

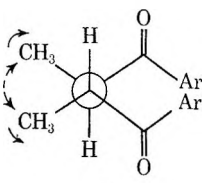
(15) Dr. F. Vane, Hoffmann-La Roche Inc., unpublished results.

(16) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1966, p 123.

Examination of the infrared spectra of these diastereomeric diketones showed some striking differences. The carbonyl absorption frequencies in the infrared spectra of the following compounds were measured in dilute carbon tetrachloride solution: propiophenone (1692 cm^{-1}), *p*-methoxypropiophenone (1685 cm^{-1}), 3,4-dimethoxypropiophenone (**4**, 1681 cm^{-1}), the racemic diketone (**9**, 1669 cm^{-1}), and the meso diketone (**7**, 1662 cm^{-1}). The lowering of the frequency by 11 cm^{-1} from propiophenone to **4** is clearly the result of electron enrichment of the carbonyl group of **4** by the strongly electron-donating methoxyl substituents, but the further lowering of the frequency by 12 cm^{-1} in **9** must be due to strong interaction (and therefore close proximity) between the two aroyl groups of **9**. Even stronger aroyl–aroyl interaction must exist in the meso diketone **7**. Such aroyl–aroyl interactions can be understood best in terms of the conformations of the diketones shown below (**7a** and **9a**), in which



7a



9a

the planar aroyl groups lie in approximately parallel planes and in close proximity.

Inspection of Dreiding models of these molecules also suggests that, in the meso diketone conformer **7a**, one of the methyl groups interacts sterically not only with the other methyl group, but also strongly with the ortho hydrogen atom on the nearer aryl group, as indicated by the dotted arrows. Both of these interactions are relieved best by slight rotations of the C–aroyl bonds, as indicated by the solid arrows. Such a conformational adjustment is done at the expense of forcing the aroyl groups into closer proximity, which is compatible with the infrared data. On the other hand, the methyl–methyl interaction in the racemic diketone conformer **9a**, shown by the dotted arrow, is easily relieved by slight rotation about the central carbon–carbon bond, and this motion tends to decrease the aroyl–aroyl overlap.[17]

The observed differences in the pmr spectra of these diketones are also understood in terms of such conformations. On the average, the methyl groups of the meso diketone conformer **7a** are closer to, and therefore more shielded by, the aroyl groups than are the methyl groups of the racemic diketone conformer **9a**. Accordingly, the signals for the methyl protons are found at higher field for **7a** than for **9a**. Base-catalyzed equilibration of either diketone led to mixtures of **7** and **9**, their ratio depending on the solvent as shown in Table I.

A better method of preparing the meso diketone **7** was sought in the reaction of the sodium enolate of **4** with the bromo ketone **5**. However, in DMSO the reaction gave the racemic diketone **9** in low yield. When the alkylation reaction was carried out in liquid ammonia at −33°, the pure racemic diketone **9** was obtained in 90% yield.

(17) No attempt is made to assess the absolute magnitude of aroyl–aroyl (or aryl–aryl) overlap in these compounds, but only the relative overlap as it is affected by these simple conformational adjustments from the ideal completely staggered conformations drawn in the diagrams above.

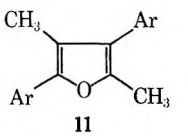
TABLE I

Starting material	Solvent	Base	Time, hr	Temp, °C	Ratio, 9:7[a]
7	C_2H_5OH–CH_3OH–C_6H_6 (4:4:1)	$NaOCH_3$	1	Reflux	1.9
9	C_2H_5OH–CH_3OH–C_6H_6 (4:4:1)	$NaOCH_3$	1	Reflux	2.2
7	DMSO	KO-*t*-Bu	1	22	3.6
9	DMSO	KO-*t*-Bu	1	22	3.9
7	C_6H_6	KO-*t*-Bu	1	40	2.8
9	C_6H_6	KO-*t*-Bu	1	40	2.4

[a] Differences in ratios in the same solvent systems are within experimental error.

As expected from the preceding analysis of the steric interactions in the two diastereomeric diketones, the racemic form **9** was found in each case to be slightly favored over the meso form **7**. However, the observed difference in stability does not account for the highly stereoselective alkylation of **4** by **5** to give the racemic diketone almost exclusively.

The novel and highly stereoselective alkylation of **4** by **5** in liquid ammonia seems to have rather specific structural requirements. When the α-chloro ketone **6** was used in place of **5**, the major product isolated (*ca.* 15% yield) was the furan **11**, perhaps arising *via* cyclization of an intermediate such as **12** resulting from a Darzens-type condensation. When the substituted acetophenones **13** and **14** were condensed under the same conditions, the reaction took yet another course, affording **15** and **16** in low yields along with recovered **13**, but none of the expected diketone **17**.



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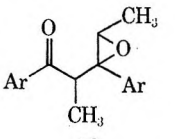

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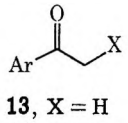
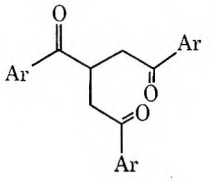


13, X = H
14, X = Br



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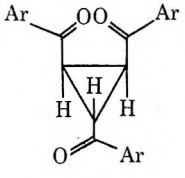
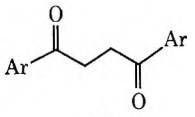


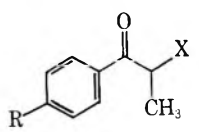
16



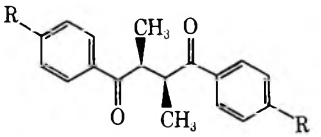
17

Assignment of structures **15** and **16** was based mainly on elemental analysis, and pmr and mass spectra. The presence of three, rather than two, pmr signals for the methoxy groups of **16** supports the trans configuration assigned.

On the other hand, the condensation proceeded normally with the pairs of propiophenone derivatives **18**–**19** and **20**–**21**, giving in each case the corresponding racemic diketones, **22** and **23**, in good yields. The meso diketones were not detected.

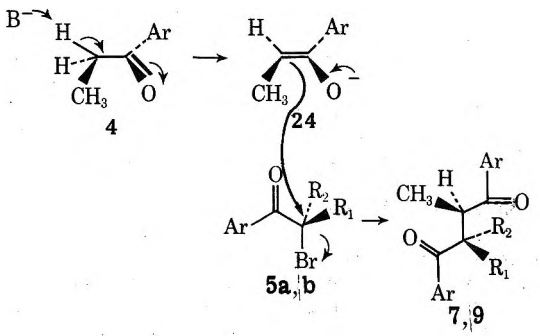


18, R = X = H
19, R = H; X = Br
20, R = OCH_3; X = H
21, R = OCH_3; X = Br



22, R = H
23, R = OCH_3

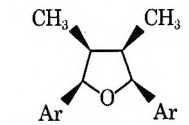
CHART I



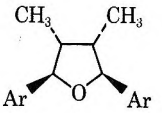
5a, $R_1 = H$; $R_2 = CH_3$ **7**, $R_1 = H$; $R_2 = CH_3$ (meso)
5b, $R_1 = CH_3$; $R_2 = H$ **9**, $R_1 = CH_3$; $R_2 = H$ (racemic)

The stereoselective formation of the racemic diketones in these reactions may be rationalized by the following proposed mechanism. Formation of the enolate from **4** should give predominantly the trans enolate **24**. Reaction of **24** with either enantiomer **5a** or **5b** from either above or below **24** is possible, but it would be sterically more favorable when the aroyl group of **5** is farthest from the aroyl group of **24**, and the methyl group of **5** is toward the oxygen of **24** rather than toward the aryl group. Thus, in the example illustrated in Chart I, reaction would be more likely to occur with **5b** than with **5a**, and displacement of bromide by the enolate with Walden inversion would lead to one enantiomer of the racemic diketone **9**. In like manner, and with equal probability, approach of **5** on the top side of **24** would preferentially form the other enantiomer of **9**, with the net result that the product is predominantly the racemic form.

Catalytic hydrogenation of the furan **8** was reported[8] to give either NDGA tetramethyl ether (**2**) or the all-cis tetrahydrofuran **25** depending on conditions, but no yield was given for the first case, and 70% was reported for the second. During extensive efforts[18] to hydrogenate **8** directly to **2**, an improved procedure for the preparation of **25** in 89% yield was developed, but none of the catalysts or conditions studied gave **2** in significant yields.



25



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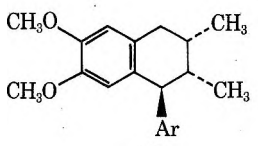
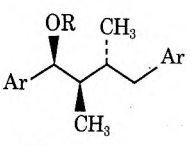


27



28, R = H
29, R = $COCH_3$

Galgravin (**26**), prepared by acid-catalyzed isomerization of **25**, is reported to be more easily hydrogenated to **2** with palladium oxide than is the furan **8**.[8] A series of similar hydrogenation experiments, summarized in Table II, was conducted on **8** and **25**, and disclosed a remarkable solvent effect on the ratio of the two products formed, **2** and racemic isogalbulin (**27**).[19] The formation of **27** may be the result of desorption of the intermediate alcohol **28** from the catalyst followed by its cyclodehydration in solution. Relatively nonpolar solvents such as THF may cause less desorption of **28**; so relatively more **2** is formed.

TABLE II

Substrate	Catalyst	Solvent	Temp, °C	Time, hr	Products, % 2	27
8[c]	PdO	AcOH	25	71	28[a]	58[a]
25[c]	PdO	AcOH	25	2	25[a]	75[a]
25	PdO	MeOH	25	20	5[a]	95[a]
25	PdO	EtOAc	25	23	74[a] 56[b]	26[a]
25	PdO	THF	25	45	79[a] 76[b]	21[a]
25	PdO	C_6H_6	25	24	No reaction	
8	PdO	THF	75 (1500 psig)	0.5	81[a]	18[a]

[a] Determined by gas chromatography. [b] Isolated crystalline. [c] Conditions similar to those reported by Blears and Haworth.[8]

As seen from the last entry in Table II, the use of tetrahydrofuran (THF) as a solvent and palladium oxide as a catalyst, along with elevated temperature and pressure, permitted the direct conversion of **8** to **2** in good yield. There seems to be no advantage in the stepwise conversion of **8** to **25** to **2**.

Unfortunately, only fresh palladium oxide, finely powdered, gave good results. A more convenient and reliable catalyst system was sought. Palladium chloride catalyzed the reduction of **8** to **2** but the hydrogen chloride liberated by the reduction of the catalyst caused the formation of 25% of isogalbulin (**27**). The addition of inorganic buffers minimized the formation of **27** and increased the activity of the catalyst, allowing the hydrogenation of **8** to **2** consistently in 65–75% yield. Synthetic **2** was identical with the tetramethyl ether of natural NDGA.

Finally, demethylation of **2** with refluxing concentrated hydrobromic acid afforded, in nearly quantitative yield, NDGA (**1**), identical with a purified sample of the natural product.

An alternative route to **2** involves reductive ring opening[19,20] of **25** by a solution of sodium in liquid ammonia and tetrahydrofuran to give the alcohol **28**, which is probably an intermediate in the hydrogenations of **8** and **25** already described. Cyclization of **28** by a very mild acid treatment[20] gave racemic isogalbulin (**27**) in good yield. Hydrogenolysis of the acetate **29** gave **2**. However, this longer route to **2** seems to have no advantages over the direct hydrogenation of **8**.

Experimental Section

Microanalyses were performed by Dr. F. Scheidl and associates of the Hoffmann-La Roche Inc. microchemical laboratory. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Spectra were recorded on standard instruments by the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc., or on a Perkin-Elmer Model 237B Infracord. Unless otherwise noted, pmr spectra were recorded at 60 MHz. Chemical shifts are expressed as δ values (parts per million downfield from tetramethylsilane as internal reference) and coupling constants (J) are expressed in cycles per

(18) We thank Mr. D. Wagner, Hoffmann-La Roche Inc., for assistance with the high-pressure hydrogenation experiments.

(19) A. J. Birch, B. Milligan, E. Smith, and R. N. Speake, *J. Chem. Soc.*, 4471 (1958).

(20) N. S. Crossley and C. Djerassi, *ibid.*, 1459 (1962).

second. Thin layer chromatograms (tlc) were used routinely for following reactions and separations, and were performed on Brinkmann F254 silica gel plates, which were examined under long- and short-wave ultraviolet light and were then sprayed with a 1:1 mixture of 85% phosphoric acid and concentrated nitric acid and warmed gradually on a hot plate. Gas chromatographic analyses were carried out on a 4 ft × 0.25 in. o.d. copper column packed with 1.1% SE-30 + 0.2% Versamid 900 on AW/DMCS Chromosorb G, 60–80 mesh, installed in an instrument equipped with a thermal conductivity detector, using helium as a carrier and operating at 220–250°.

Purification of NDGA (1).—Commercial NDGA[10] was recrystallized three times from 36% aqueous acetic acid to give tan-colored material, mp 183–184°. This was sublimed at 175–180° (0.03 mm) to afford large white and some yellow crystals. The white crystals were hand picked and ground in a mortar, giving pure NDGA: mp 185–186° (lit.[5] mp 184–185°); optically inactive; ν_{max} (KBr) 3470, 3310, 3200, 1612, 1530, 1520, 790, 755 cm^{-1}; nmr (CD_3OD) δ 0.78 (6 H, d, J = 6 Hz), 1.66 (2 H, poorly resolved q, J = 6 Hz), 2.12 (2 H, unsymmetrical q, J = 13, J' = 9 Hz), 2.61 (2 H, unsymmetrical q, J = 12, J' = 6 Hz), 4.98 (4 H, broad s), 6.36–6.75 (6 H, m); λ_{max} (CH_3OH) 283, 218 mμ (ϵ 6660, 13,400).

NDGA Tetramethyl Ether (2) from Commercial NDGA.—Addition of potassium hydroxide solution (16 g of KOH in 50 ml of water and 75 ml of methanol) to a solution of NDGA[10] (20.0 g, 0.0663 mol) in methanol (60 ml) at room temperature under nitrogen gave a dark solution to which dimethyl sulfate (67 g, 0.532 mol) was added with stirring over a period of 15 min. The temperature during the addition was maintained at 35–40°, and enough potassium hydroxide solution was introduced periodically to maintain pH 8–9. The reaction mixture was stirred at room temperature for 18 hr and then poured into water. The precipitate was collected by filtration, washed with water, and dried to provide 22.7 g (96%) of tan-colored solid, mp 93–98°. Purification of the product by elution from Florisil with benzene–chloroform (1:1) followed by several recrystallizations from methanol afforded analytically pure product: optically inactive; mp 100–102° (lit.[5] mp 100–101°); ν_{max} (KBr) 1610, 1595, 1525, 1265, 1240, 1160, 1140, 1025 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (6 H, d, J = 6 Hz), 1.50–3.00 (6 H, m), 3.87 (12 H, s), 6.60–6.84 (6 H, m); λ_{max} (CH_3OH) 279, 228 mμ (ϵ 6080, 16,400).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.77; H, 8.48.

***meso*-1,4-Bis(2-bromo-4,5-dimethoxyphenyl)-2,3-dimethylbutane (3).**—NDGA tetramethyl ether (2, 5.0 g, 14 mmol) was brominated in acetic acid[6] in 91% yield. After several recrystallizations from methanol the product had mp 131–132°. A sample of large, needlelike crystals, obtained by slow evaporation of a saturated methanol solution, was subjected to X-ray crystallographic examination[11] and found to be the meso isomer.

3,4-Dimethoxypropiophenone (4).—To a cooled, well-stirred slurry of anhydrous aluminum chloride (22.0 g, 0.166 mol) in chloroform (80 ml) at 0–5° under an atmosphere of dry nitrogen was added a solution of freshly distilled propionyl chloride (12.0 g, 0.13 mol) in chloroform (10 ml) at such a rate as to maintain a temperature of 0–5°. When the addition was complete (about 15 min), a solution of veratrole (13.8 g, 0.1 mol) in chloroform (10 ml) was added in the same manner over a 30-min period, during which time hydrogen chloride was slowly evolved. The reaction mixture became a nearly clear, yellow-green solution, which was stirred at 0–5° for 1 hr after completion of the addition. With continued stirring and cooling 3 *N* hydrochloric acid (100 ml) was then added *very* cautiously dropwise, keeping the temperature below 30°. When all the solids were dissolved, the phases were separated, the lower organic phase was washed with 3 *N* sodium hydroxide solution (50 ml) once, and the two aqueous solutions were back-extracted in succession with chloroform (50 ml). The combined chloroform solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness *in vacuo*, and the residue was crystallized from methanol (25 ml) by chilling overnight in a freezer to afford a first crop, 14.31 g (78.8% yield), mp 58.5–59.5°. A second crop, 3.84 g (20.0% yield), had mp 54–58°. An analytical sample had mp 58–59° (lit.[13] mp 59–60°).

α-Bromo-3,4-dimethoxypropiophenone (5).—A solution of bromine (65.4 g, 0.408 mol, 2% excess) in chloroform (100 ml) was added as rapidly as possible through an addition funnel to a refluxing solution of 3,4-dimethoxypropiophenone (4, 77.6 g, 0.40 mol) in chloroform (300 ml) with good agitation. The hydrogen bromide, which was rapidly evolved, was conducted from the top of the reflux condenser to a flowing water scrubber. When the addition was complete the solution was refluxed for 10 min to drive off most of the hydrogen bromide; then the solvent was removed under reduced pressure. Crystallization of the residue from methanol (200 ml) gave a first crop, 101.9 g (93.2% yield), mp 81–82°. A second crop, 2.3 g (2.2% yield), had mp 72–77°, and an analytical sample had mp 82–82.6° (lit.[13] mp 83–84°).

***meso*-2,3-Bis(3,4-dimethoxybenzoyl)butane (7). A.**—The procedure described by Atkinson and Haworth[14] was used, except that commercial copper powder was used in place of "freshly precipitated copper"[21] and a small crystal of iodine was added to the reaction mixture. Crystallization of the crude product from methanol afforded white crystals: mp 184.5–187.5° (lit.[14] mp 189–190°); 3.8% yield; nmr ($CDCl_3$) 1.15 (6 H, d, J = 6 Hz), 4.01 (14 H), 6.90–8.0 (6 H, m); *m/e* (rel intensity) 386 (10), 221 (2), 194 (2), 180 (2), 165 (100), 137 (3), 122 (2).

B.—α-Bromo-3,4-dimethoxypropiophenone (5, 2.73 g, 10 mmol), copper powder (2.73 g, 43 mmol), benzene (20 ml), and diphenyl ether (20 ml) were stirred together under a nitrogen atmosphere and solvent was distilled until the reaction temperature reached 150°. The reaction mixture was stirred at 150° for 18.5 hr; then it was filtered and the filtrate was chromatographed on activity I neutral alumina. Diphenyl ether was eluted with benzene, the crude diketone was eluted with benzene–ether (19:1 through 1:1) and more polar products were eluted with ethyl acetate. Crystallization of the diketone fraction gave fine white needles of 7, mp 186–190° (137 mg, 7.1% yield). Treatment of the mother liquors plus the ethyl acetate eluates with boiling ethanolic hydrochloric acid gave crude crystals of 8, mp 169.5–170.5° (lit.[14] mp 169–170°), 376 mg (20.4% yield).

3,4-Dimethyl-2,5-bis(3,4-dimethoxyphenyl)furan (8). A.—A solution of *meso*-2,3-bis(3,4-dimethoxybenzoyl)butane (7, 24 mg) in 10% ethanolic hydrochloric acid (5 ml) was refluxed for 15 min and cooled to provide colorless crystals of 8, mp 169–170.5° (lit.[14] mp 169–170°), 20 mg (87.4% yield).

B.—To a boiling solution of *rac*-2,3-bis(3,4-dimethoxybenzoyl)-butane (9, 38.6 g, 0.10 mol) in dichloromethane (100 ml) was added a 1% solution of hydrogen chloride in methanol (250 ml) slowly with continued boiling. After about 5 min crystals separated, and after the slurry was chilled a first crop was obtained, mp 170–171°, 30.20 g (82% yield). Concentration of the mother liquors afforded a second crop, mp 169.5–170.5°, 4.56 g (12.4% yield), and a third crop, mp 168.2–170.0°, 0.54 g (1.5% yield).

Racemic 2,3-Bis(3,4-dimethoxybenzoyl)butane (9).—To liquid ammonia (approximately 50 ml) was added powered ferric chloride (50 mg), then small pieces of sodium (0.51 g, 0.022 g-atom, 10% excess) were added and the blue color was allowed to dissipate over about a 20-min period. To the resulting gray suspension of sodamide was added solid 3,4-dimethoxypropiophenone (4, 3.88 g, 0.02 mol) in small portions and the mixture was stirred for about 5 min. Solid α-bromo-3,4-dimethoxypropiophenone (5, 5.46 g, 0.02 mol) was then added in small portions to the gray-green mixture, and the reaction mixture turned deeper green, then reddish, and finally tan colored. After the mixture was stirred for 1 hr, solid ammonium chloride (2.68 g) was added, followed by dichloromethane (50 ml), and the gray mixture was then warmed cautiously to room temperature to evaporate most of the ammonia. The mixture was filtered with suction, the residual solids were extracted twice with dichloromethane, and the combined filtered solutions were concentrated to about 50 ml in volume, diluted with methanol (75 ml), and further concentrated to about 50 ml in volume by boiling. The product crystallized on stirring and cooling, mp 137–141°, 6.96 g (90.3% yield). Recrystallization from methanol provided an analytical sample: mp 145–146°; ν_{max} (KBr) 3080, 1665, 1595, 1585, 1515, 1265, 1245 cm^{-1}; nmr ($CDCl_3$) δ 1.33 (6 H, d, J = 7 Hz), 3.92 (14 H, "d"), 6.9–8.0 (6 H, m); mass spectrum *m/e* 386 (11), 221 (2), 194 (<1), 180 (<1), 165 (100), 137 (3), 122 (4).

Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.37; H, 6.78. Found: C, 68.16; H, 6.83.

Base-Catalyzed Equilibration of Diketones 7 and 9.—A mixture of 7 (50 mg), methanol (20 ml), benzene (5 ml), ethanol (20 ml), and sodium methoxide (62 mg) was boiled gently for about 1 hr and then stored at room temperature overnight. The solution

(21) In one experiment "freshly precipitated copper" was used, but only traces of 7 could be detected in the product.

was boiled down to a volume of 15 ml, powdered magnesium sulfate (100 mg) was added to neutralize base, the mixture was filtered, and the filtrate was reduced to dryness under reduced pressure. Extraction of the residue twice with chloroform and removal of the solvent left a residue (48 mg) which was analyzed by nmr spectrometry (100 MHz), using the signals at δ 1.15 ppm (compound **7**) and 1.33 ppm (compound **9**) to determine the ratio of **9**:**7**, which was 1.87.

Similarly, **9** (50 mg) gave a mixture (48 mg) with a ratio of **9**:**7** = 2.17.

α-Chloro-3,4-dimethoxypropiophenone (**6**).—A solution of α-chloropropionyl chloride (50.1 g, 0.39 mol) in chloroform (50 ml) was added to a stirred slurry of anhydrous aluminum chloride (66.5 g, 0.50 mol) in chloroform (300 ml), while the temperature of the mixture was maintained at −5 to 0°. A solution of veratrole (41.4 g, 0.30 mol) in chloroform (40 ml) was then added dropwise while the same temperature was maintained. The dark solution was stirred for 4 hr at 0–5°, then for 1 hr at room temperature. Hydrochloric acid (3 *N*, 300 ml) was added very cautiously with ice-bath cooling, and the mixture was extracted and washed as described for compound **4** to afford 55 g of dark brown liquid. Column chromatography over activity I neutral alumina (600 g) afforded a fraction (6.47 g, eluted with hexane–benzene and benzene–chloroform mixtures) which solidified. Crystallization from hexane–benzene gave colorless needles (6.4 g, mp 57–60°). An analytical sample had mp 58.5–60.5°, ν_{max} (KBr) 1692 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73; Cl, 15.50. Found: C, 57.80; H, 5.47; Cl, 15.41.

2,4-Dimethyl-3,5-bis(3,4-dimethoxyphenyl)furan (**11**).—A solution of the enolate of **4** (3.88 g, 0.02 mol) was prepared in 75 ml of liquid ammonia as described above. The chloro compound **6** (4.57 g, 0.02 mol) was added rapidly and the reaction mixture was stirred for 5 hr. After addition of solid ammonium chloride (1.2 g) and dichloromethane (50 ml), the ammonia was allowed to evaporate. Extraction with dichloromethane gave a green, viscous liquid (8.7 g), the hexane-insoluble fraction of which was triturated with methanol to give a solid (0.935 g, mp 154–157°). Recrystallization from methanol afforded an analytical sample: mp 158–160°; λ_{max} (MeOH) 290 nm (ϵ 26,830), inflection 233 (18,950); nmr ($CDCl_3$) δ 2.17 (3 H, s), 2.35 (3 H, s), 3.90 and 3.95 (6 H, 2 s), 7.0 (6 H, m).

Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.87; H, 6.54.

3,4-Dimethoxyacetophenone (**13**).—By the same procedure used for the preparation of **4**, veratrole was acetylated to **13** in 82% yield, mp 48–50° (from benzene–hexane) (lit.[22] mp 48°).

α-Bromo-3,4-dimethoxyacetophenone (**14**).—Treatment of **13** (18.0 g, 0.10 mol) in chloroform (75 ml) with a solution of bromine (16.3 g, 0.102 mol) in chloroform (25 ml) at 25° gave 16.5 g (64% yield) of crude **14**. An analytical sample recrystallized from benzene–hexane had mp 80–81° (lit.[23] mp 80–81°).

1,2,3-Tris(3,4-dimethoxybenzoyl)propane (**15**).—A suspension of sodamide in liquid ammonia (50 ml) was prepared from sodium (0.51 g, 0.022 mol), and **13** (3.60 g, 0.02 mol) was added in small portions, followed by **14** (5.18 g, 0.02 mol). The mixture was stirred at −33° for 3 hr and worked up in the usual manner to afford 10 g of dark, viscous liquid, which was chromatographed over 250 g of neutral alumina. Several fractions solidified and were combined and crystallized from benzene–hexane to afford 1 g of **15**: mp 174–175°; ν_{max} (KBr) 1680 cm^{-1} (broad); λ_{max} (CH_3OH) 229, 276, 306 nm (ϵ 49,000, 33,520, 27,310); nmr ($CDCl_3$) 3.39 (4 H, q, J = 7, J' = 3 Hz), 3.88 and 3.93 (18 H, 2 s), 4.75 (1 H, t, J = 7 Hz), 6.8–8.0 (9 H, m); mass spectrum *m/e* 165 (base peak), 370 (M − ArCO, H), 536 (M$^+$).

Anal. Calcd for $C_{30}H_{32}O_9$: C, 67.15; H, 6.01. Found: C, 67.11; H, 6.01.

***trans*-1,2,3-Tris(3,4-dimethoxybenzoyl)cyclopropane** (**16**).—Fractional crystallization from the mother liquors of **15** afforded 150 mg of a second compound, **16**: mp 202–204°; ν_{max} (KBr) 1660 cm^{-1} (broad); λ_{max} (CH_3OH) 230, 280, 312 nm (ϵ 33,400, 24,530, 23,940); nmr ($CDCl_3$) δ 3.7–4.3 (21 H, m, with three strong singlets for $-OCH_3$), 6.8–8.1 (9 H, m); mass spectrum *m/e* 165 (base peak), 369 (M − ArCO), 534 (M$^+$).

Anal. Calcd for $C_{30}H_{30}O_9$: C, 67.40; H, 5.66. Found: C, 67.51; H, 5.61.

(22) H. Stephen and C. Weizmann, *J. Chem. Soc.*, **105**, 1046 (1914).

(23) C. Mannich and F. L. Hahn, *Ber.*, **44**, 1542 (1911).

Racemic 2,3-Dimethyl-1,4-diphenyl-1,4-butanedione (**22**).—Propiophenone (13.8 g, 0.1 mol) was added to a suspension of sodamide (0.13 mol) in liquid ammonia (200 ml) and stirred for 15 min before addition of α-bromopropiophenone (21.3 g, 0.1 mol). The reaction mixture was stirred for 30 min and the ammonia was replaced with methylene chloride. Extraction with methylene chloride gave 26 g of dark-colored liquid which was chromatographed over 100 g of Florisil. Elution with hexane–benzene mixtures gave a solid which after recrystallization from hexane weighed 10.0 g: mp 86–87°;[24] ν_{max} (KBr) 1680 cm^{-1}; nmr ($CDCl_3$) δ 1.27 (6 H, d, J = 6 Hz), 3.75 (2 H, m), 7.2–8.0 (10 H, m); mass spectrum *m/e* 266 (M$^+$).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.90; H, 6.89.

Boiling **22** in methanolic hydrogen chloride for a few minutes converted it to 2,5-diphenyl-3,4-dimethylfuran, mp 114–115° (lit.[25] mp 116°), in good yield.

α-Bromo-*p*-methoxypropiophenone (**21**).—Bromination of *p*-methoxypropiophenone in refluxing chloroform provided **21** in 86% yield, mp 66–69° (from methanol) [lit.[26] mp 68.5° (petroleum ether, bp 30–60°)].

Racemic 2,3-Bis(*p*-methoxybenzoyl)butane (**23**).—The condensation of *p*-methoxypropiophenone (16.4 g, 0.10 mol) with **21** (24.3 g, 0.10 mol) was carried out as described for compound **22** above. The product was crystallized from methanol to afford a cream-colored solid (22.1 g, 67% yield), mp 116–121°. An analytical sample melted at 124–127°: ν_{max} (KBr) 1660 cm^{-1}; nmr ($CDCl_3$) δ 1.30 (6 H, d, J = 6 Hz), 3.9 (8 H, strong s over m), 7.0 and 8.1 (8 H, aromatic AA'BB' pattern); mass spectrum *m/e* 135 (base peak), 326 (M$^+$).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.80; H, 6.64.

***all-cis*-3,4-Dimethyl-2,5-bis(3,4-dimethoxyphenyl)tetrahydrofuran** (**25**).—Hydrogenation of the furan **8** (36.8 g, 0.1 mol) over 10% palladium on calcium carbonate catalyst (5.0 g) in ethanol (1000 ml) at 125° under 1500 psig hydrogen for 3 hr, followed by filtration and removal of solvents, gave a white solid (35 g) which on recrystallization from methylene chloride–methanol gave a first crop, mp 127.5–130.0° (29.86 g, 80.4% yield). Concentration of the mother liquors gave a second crop, mp 125.5–128.0° (2.54 g, 6.8% yield), and a third crop, mp 124.5–127.5° (0.47 g, 1.3% yield). An analytical sample had mp 131–132° (lit.[8] mp 132–133°); nmr ($CDCl_3$) δ 0.62 (6 H, d, J = 7 Hz), 2.70 (2 H, m), 3.94 (12 H, s), 5.19 (2 H, d, J = 6.5 Hz), 7.0–7.17 (6 H, m).

Hydrogenations of 8 and 25. General Procedure.—A mixture of the compound to be reduced (0.2–3.68 g), catalyst (usually 0.2 g), and solvent (50 ml) was stirred magnetically under an atmosphere of hydrogen at the desired temperature. After filtration of the spent catalyst, the filtrate was examined by gas chromatographic analysis. For isolation of crude NDGA tetramethyl ether (**2**), the solvents were removed and the residue was crystallized from 10–20 times its weight of hexane.

NDGA Tetramethyl Ether (**2**). **A. From 8.**—The furan **8** (33.3 g, 90.5 mmol) in THF (500 ml) was hydrogenated over powdered palladium oxide (2.0 g) at 50° (1500 psig) for about 10 hr. Gas chromatographic analysis indicated 77.8% of **2** in the crude filtrate. Removal of solvent and crystallization of the residue (33.7 g) from hexane (550 ml) gave crude **2**, mp 91.5–95° (25.4 g, 78% yield).

B. From 25.—Compound **25** (745 mg, 2 mmol) in THF (50 ml) was hydrogenated over powdered palladium oxide (200 mg) at 25° (1 atm) for 46 hr. Gas chromatographic analysis indicated 78.5% of **2** in the crude filtrate. Removal of solvent and crystallization of the residue (848 mg) from hexane gave crystalline **2**, mp 93–95° (543 mg, 76% yield).

C. From 8, Using Palladium Chloride.—The furan **8** (4.00 g), palladium chloride (0.40 g), and sodium acetate (0.46 g) in tetrahydrofuran (100 ml) were shaken in a rocking autoclave at 75° under hydrogen at 50 psig for 10 hr. Gas chromatography indicated a yield of 79% of **2**, 85% of which could be isolated as described above.

NDGA (1) from 2.—Concentrated hydrobromic acid (860 g) was added under nitrogen to **2** (71.56 g, 0.201 mol) and the mixture was stirred and refluxed for 9 hr and allowed to cool to room

(24) The meso isomer melts at 67°: A. Wolf, German Patent 876,237 (May 11, 1953); *Chem. Abstr.*, **52**, 9227*b* (1958).

(25) R. E. Lutz and R. J. Taylor, *J. Amer. Chem. Soc.*, **55**, 1593 (1933).

(26) C. Hell and A. Hollenberg, *Ber.*, 682 (1896).

temperature overnight with continued stirring. The dark-colored solid product, collected by filtration, washed with water, and dried, had mp 174–182° (59.27 g, 97.5% yield). Recrystallization from about 1600 ml of 20% aqueous acetic acid with charcoal treatment gave a much lighter colored, but still gray-brown, crystalline product, mp 184–186° (45.74 g) (77% recovery, 75% yield). A second recrystallization with charcoal gave light tan crystals, mp 184–185.3° (91% recovery). After a third recrystallization the cream-colored crystals (95% recovery) had mp 184.5–186°, identical in all respects with purified natural NDGA, mmp 184–186°.

The overall yield of thrice-recrystallized product was 65%. No product of satisfactory quality could be recovered from the mother liquors.

Monoalcohol 28.—Sodium (4.37 g, 0.19 mol) was added to anhydrous liquid ammonia (1.1 l.) and stirred under reflux under a nitrogen atmosphere. After 1 hr a solution of the tetrahydrofuran **25** (18.6 g, 50 mmol) in THF (500 ml) was added. After 2.5 hr of stirring under reflux the ammonia was removed by warming the reaction mixture to room temperature. Addition of methanol (10 ml) and then water (400 ml), followed by extraction with chloroform, washing with water, drying over sodium sulfate, and removal of solvents, gave the crude product (22.0 g), which was crystallized from methanol to afford white crystals of **28**, mp 107.5–109° (16.34 g, 43.7 mmol, 87.4% yield). A second crop was collected to give a total of 17.96 g (48 mmol, 96% yield). An analytical sample was recrystallized from benzene–hexane: mp 110–111.3°; ν_{max} (KBr) 3570, 1258, 1238, 1135, 1130, 1025 cm^{-1}; λ_{max} (CH_3OH) 229, 269, 285 mμ (ϵ 16,553, 5824, 4883); nmr ($CDCl_3$) δ 0.84 (3 H, d, J = 6 Hz), 1.10 (3 H, d, J = 6 Hz), 1.80 (2 H, m), 1.98 (1 H, broad s, exchangeable with D_2O), 2.10 (1 H, q, J_1 = 13, J_2 = 10 Hz), 2.82 (1 H, q, J_1 = 13, J_2 = 3 Hz), 3.70–4.17 (12 H = 4 CH_3O), 4.70 (1 H, d, J = 6 Hz), 6.40–7.00 (6 H, m).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.74; H, 7.96.

Racemic Isogalbulin 27.—A slurry of **28** (2.52 g, 6.72 mmol) in ethanol (18 ml) was treated with concentrated hydrochloric acid (3 ml) and stirred for 4.5 hr at room temperature. The solution was poured into water and extracted with ether to give a crude product (2.84 g) which was crystallized from methanol with cooling. Recrystallization from hexane provided 1.71 g (4.8 mmol, 72.4%) of **27** as a white solid, mp 66.5–72°. An analytical sample was recrystallized successively from hexane, ethanol, and methanol: mp 70.5–72.5° (lit.[19] mp 86°); ν_{max} (KBr) 1470, 1262, 1250, 1150, 1140, 1109 cm^{-1}; λ_{max} (CH_3OH) 204, 232, 282, 287 mμ (ϵ 62,750, 16,500, 7100, 6600); nmr ($CDCl_3$) δ 0.97 (6 H, d, J = 7 Hz), 2.5 (4 H, m), 3.67–4.10 (13 H, m), 6.71 (5 H, m).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.86; H, 7.83.

Monoacetate 29.—To an ice-cold mixture of acetic anhydride (10 g) and pyridine (10 g) was added **28** (3.74 g, 10 mmol) and the mixture was stirred for 5 min before being allowed to warm to room temperature. After 2 hr the mixture was poured into water (200 ml), extracted with chloroform, washed with water, dried, and freed of solvent. The crude product (4.59 g) was crystallized from methanol to give 671 mg of starting material. Second and third crops gave a total of 2.75 g (6.62 mmol, 80.6% corrected yield) of **29**, mp 77–82°.

An analytical sample was recrystallized from hexane: mp 80–82°; ν_{max} (KBr) 1760, 1270, 1240, 1155, 1135, 1030 cm^{-1}; λ_{max} (CH_3OH) 229, 278, 285 mμ (ϵ 14,100, 4850, 3900); nmr ($CDCl_3$) δ 0.80 (3 H, d, J = 6 Hz), 1.07 (3 H, d, J = 6 Hz), 2.07 (3 H, s), 2.50 (4 H, m), 3.78–3.90 (12 H = 4 OCH_3), 5.80 (1 H, d, J = 8 Hz), 6.71 (6 H, m).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.48; H, 7.82.

All subsequent experiments gave a dimorphic form of **29**, mp 100–102°, the solution spectral properties of which were identical with those of the lower melting acetate. The lower melting dimorph was converted to the higher melting one by recrystallization from hexane and seeding with the higher melting solid. However, conversion of the higher melting to the lower melting dimorph could not be achieved.

Hydrogenolysis of 29.—A mixture of **29** (1.045 g, 2.5 mmol), ethyl acetate (50 ml), and powdered palladium oxide (100 mg) was hydrogenated at room temperature and 1 atm for 22 hr. Filtration and removal of solvent gave 1.015 g of oil which was crystallized from hexane to give 0.703 g (1.96 mmol, 79%) of crude **2** as a white solid, mp 93–95.5°. Gas chromatographic analysis of the sample showed that it contained 90.3% **2** and 9.7% **27**.

Registry No.—**1**, 27686-84-6; **2**, 24150-24-1; **3**, 36287-35-1; **6**, 36287-36-2; **7**, 36287-37-3; **9**, 27686-81-3; **11**, 36287-39-5; **15**, 36287-40-8; **16**, 36287-41-9; **22**, 36287-42-0; **23**, 36208-08-9; **25**, 27686-82-4; **27**, 36286-72-3; **28**, 36286-73-4; **29**, 36286-74-5.

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Synthesis of Sequence Peptide Polymers Related to Collagen[1,2]

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The sequence peptide polymers poly(Pro)-Gly, poly(Hyp(H))-Gly, poly(Ala)-Pro-Gly, poly(Pro)-Hyp(H)-Gly, poly(Ser(H))-Pro-Gly, and poly(Gly)-Gly-Hyp(H)-Gly have been prepared in high optical purity from the corresponding peptide *p*-nitrophenyl esters.[3] All residues were of the L configuration.

Polymers containing proline and hydroxyproline have been prepared ranging from the homopolymers through random copolymers to polymers with repeating sequences. Much of the interest in these polymers arises from their relationship to collagen.[6]

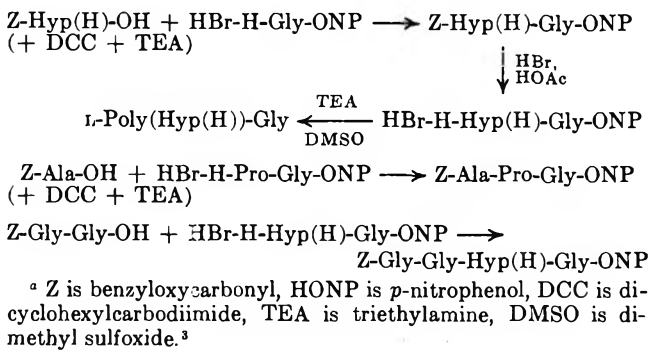
Among sequence polymers reported previously are poly(Gly)-Pro-Hyp,[7] poly(Pro)-Gly-Pro,[8] poly(Pro)-Ala-Gly,[9] poly(Gly)-Pro-Ala,[10] poly(Gly)-Pro-Gly,[10] poly(Pro)-Gly-Gly,[8a] and poly(Ala)-Pro-Gly.[11]

The present paper reports details of the synthesis of the repeating sequence polymers A–F, Table I. Some, such as poly-Pro-Hyp(H)-Gly, have collagen-related sequences, others such as poly-Pro-Gly do not. In this study we have paid special attention to the difficult questions of optical purity of intermediates and of polymers. Various physical studies on these polymers will be reported elsewhere.

Facile racemization of C-terminal residues *via* azlactone formation has been well documented,[12,13] but it is not so well known that C-terminal proline is also racemized under relatively mild conditons.[14] Evidence presented below indicates that polymerization of tripeptides by tetraethyl pyrophosphite can lead to racemization; yet this method has often been used for making collagen analogs.

In the present study we used the active ester route shown in Scheme I. The steps involve only those

SCHEME I[a]



[a] Z is benzyloxycarbonyl, HONP is *p*-nitrophenol, DCC is dicyclohexylcarbodiimide, TEA is triethylamine, DMSO is dimethyl sulfoxide.[3]

shown in previous work to be free of racemization.[5,13] We have further applied two direct criteria for evaluating optical purity. One is the rotations of intermediates (Table I); these are constant on recrystallization or on synthesis from independent batches of starting materials. The other is the rotations observed for hydrolyzed samples. According to the hydrolysis criterion all compounds in Table I are judged to be optically pure within the experimental error of 2–4%. According to the first criterion they are purer.

It is possible to compare one rotation value with a value from the literature. Poly(Pro)-Hyp(H)-Gly (Table I) had $[\alpha]^{25}D$ −400° (*c* 0.1, water). The reported value for a sample of the equivalent Gly-Pro-Hyp(H) was $[\alpha]D$ −280°, and what is described as a second form had $[\alpha]D$ −140°.[7] Poly(Pro)-Hyp(H)-Gly is rather poorly soluble in water while the reported poly(Gly)-Pro-Hyp was fairly soluble. The higher rotation and the lower solubility of polymer prepared by the *p*-nitrophenyl ester route suggests that it is of higher optical purity than polymer prepared using tetraethyl pyrophosphite.

Molecular weights (Table II) were measured by the Archibald method,[15] using both schlieren optics and the Rayleigh interference system, and also by full sedimentation equilibrium. Except for poly(Pro)-Hyp(H)-Gly in water, there is relatively little association. Number average molecular weights as measured in water with a differential vapor pressure "osmometer" are believed correct to ~10%. Dinitrophenylation of the amino end groups gave number average results which tended to be too high. The cause is not known with certainty, but, if there had been as much as 2–3% of benzyloxycarbonyl group as an impurity in the hydrobromide "monomer," then end group values would be close to those observed. Unfractionated condensation polymers such as those prepared by the *p*-nitrophenyl

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(2) With the technical assistance of E. Heimer.

(3) Abbreviation conventions are those recommended by IUPAC–IUB[4] extended so as to specify side-chain substitution explicitly. *Cf.* ref 5, footnote 6. All residues in the present work were of the L configuration.

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Table I

Rotations of Intermediates and Polymers[a]

No.	Compounds	Mol wt	Concn, %	Solvent	Drude terms: $a \times 10^{-1}$	Drude terms: λ_0, nm	Molar rotation, deg: At 589	At 546	Obsd[b]	Expected[b]
1	Z-Ala-OH	223.2	2	HOAc	−10.304	167.67 ± 6	−32.7	−38.3	13.6	14.7[c]
3	Z-Pro-OH	249.3	2	EtOAc	−32.025	185.66	−102	−121	(−71)[d]	−71.4
4	HBr-H-Hyp(H)-Gly-ONP	390.2	2	Water	−91.743	171.03	−289	−341	−71.3	−70.4
5	Z-Hyp(H)-Gly-ONP	443.4	2	DMF	−67.923	220.79	−228	−272	−68.4	−70.4
6	HBr-H-Pro-Gly-ONP	374.2	1.4	DMF	−32.107	162.77	−100	−118	−72.4	−71.4
7	Z-Pro-Gly-ONP	427.4	2	DMF	−81.213	219.70	−272	−325	−72.0	−71.4
8	HBr-H-Ala-Pro-Gly-ONP	445.1	2	CH_3OH	−106.73	218.34	−357	−427	−57.1	−57.2[e]
9	Z-Ala-Pro-Gly-ONP	498.5	0.5	CH_3CN	−123.21	232.49	−421	−505	−56.8	−57.2[e]
10	HBr-H-Pro-Hyp(H)-Gly-ONP	487.1	1	CH_3OH	−143.68	203.99	−471	−560	−144	−142
11	Z-Pro-Hyp(H)-Gly-ONP	540.5	1	CH_3OH	−179.26	218.38	−599	−716	−144	−142
12	HBr-H-Ser(H)-Pro-Gly-ONP	461.1	1	CH_3OH	−105.14	217.62	−351	−419	−56.1	−55.8[f]
13	Z-Ser(H)-Pro-Gly-ONP	514.5	1	CH_3CN	−96.554	230.31	−329	−394	−52	−55.8[f]
14	HBr-H-Gly-Gly-Hyp(H)-Gly-ONP	504.1	1	CH_3OH	−112.66	216.43	−375	−448	−67.2	−70.4
15	Z-Gly-Gly-Hyp(H)-Gly-ONP	557.5	1	HOAc	−99.169	219.58	−332	−397	−70.7	−70.4
A	Poly(Hyp(H))-Gly[g]	170.2	0.6	Water	−126.5	204.91	−414	−493	−71.5	−70.4
B	Poly(Pro)-Gly[g]	154.2	0.1	Water	−132.0	212.00	−440	−525	−72.5	−71.4
C	Poly(Ala-Pro-Gly)[g]	225.2	0.5	DCA	−131.1	206.75	−435	−513	−59	−57.2
D	Poly(Pro)-Hyp(H)-Gly[g]	267.3	0.5	DCA	−248.5	210.76	−820	−980	−146	−142
			0.1	Water	−326.0	201.18	−1060	−1250		
E	Poly(Ser(H))-Pro-Gly[g]	241.2	0.5	DCA	−98.4	219.89	−330	−394	−55.5	−55.8
F	Poly(Gly)-Gly-Hyp(H)-Gly[g]	284.3	0.1	Water	−86.8	205.62	−284	−339	−71	−70.4

[a] The reported Drude equation parameters summarize the optical rotations observed at 589, 578, 546, 435, and in some cases 365 nm. Temperature was 25°. The correlation uncertainty in a and λ_0 is ~1–1.5% relative.[h] The rotations at 589 and 546 nm are believed to be correct to at least 5% relative; most are good to 2% or better. DMF is dimethylformamide. DCA is dichloroacetic acid. [b] Check of optical purity. Peptide was hydrolyzed in 5 *N* HCl for 15 hr at 100°. The molar rotation is reported at 546 nm in 5 *N* HCl at 25°. Some compounds were also hydrolyzed under more vigorous conditions as a check. The expected value is that based on measurements on the amino acid plus simple derivatives, hydrolyzed as above. [c] Values reported by J. P. Greenstein and M. Winitz ("Chemistry of the Amino Acids," Wiley, New York, N. Y., p 116) were averaged by fitting to the Drude equation to give the following $[M]_{546}$ values: H-Ala-OH, 14.9; H-Hypro(H)-OH, −71.8; H-Pro-OH, −73.1°. [d] Estimated from hydrolysis at 120° for 10 hr. [e] $[M]_{546}$ summed for H-Ala-OH + H-Pro-OH = +14.3 − 71.5 = −57.2. [f] $[M]_{546}$ summed for H-Ser(H)-OH + H-Pro-OH = +15.7 − 71.5 = −55.8. [g] Based on elemental analyses for C and N, the following polymer contents (dry basis) were assigned: 92% A, 92% B, 90% C, 89% D, 95% E, 90% F. Water is not readily removed even on prolonged drying. The Drude a value, the molar rotations at 589 and 546 nm, and the observed rotation at 546 nm for hydrolyzed samples were all corrected to dry basis by the factor indicated. In this study several samples of each polymer were used and water contents varied from one to the next. [h] See ref 19b for further details.

Table II

Polymer Molecular Weight Determinations

Polymer	$\bar{V}$[a]	Wt av mol wt: Archibald[b]	FSE[c]	No. av mol wt: DVP[d]	DNP[e]	η[f]
Hyp(H)-Gly	0.667	9,800	8,300	3,700		
		12,800	9,400	5,300	8,000	0.335
			12,800	4,600	14,000	0.406
Pro-Gly	0.716	10,000	7,700	3,100	12,000	0.316
			14,200	5,300	20,000	0.432
Ala-Pro-Gly	0.723		2,500			0.275
Pro-Hyp(H)-Gly	0.701	45,000[g]	42,000		15,000	0.291
Ser(H)-Pro-Gly	0.685	11,000	10,000			0.286
Gly-Gly-Hyp(H)-Gly	0.656		17,000	5,000	30,000	0.443

[a] Partial specific volume, computed from residue values in Table III: H. K. Schachman in "Methods in Enzymology," Vol. IV, S. P. Colowick and N. O. Kaplan, Ed., Academic Press, New York, N. Y., 1957, p 70. [b] 1% solution in water, meniscus values, standard deviation of average ~15%. [c] Full sedimentation equilibrium, 0.1–1% solution in water, standard deviation of average ~8%. [d] Differential vapor pressure molecular weight using a vapor phase osmometer, in water; standard deviation of average ~15%. [e] Dinitrophenylation by "simplified" procedure; standard deviation of average ~15%. [f] Reduced viscosity in dichloroacetic acid at 30°. [g] Other preparations had mot wt 9800 and 23,000.

ester method should have a weight average molecular weight twice the number average.[16]

In spite of the marked tendency of proline peptides to form diketopiperazines,[17] it is interesting that 5–10% yields of the important dipeptide polymers poly(Pro)-Gly and poly(Hyp(H))-Gly can nevertheless be reproducibly obtained.

Proton magnetic resonance has proved especially valuable in monitoring the peptide syntheses and in evaluating the polymers. In most cases it is possible to check quantitatively for the presence of the amino acids and the protecting groups and to ascertain the presence of impurities.[18]

Experimental Section[19]

HBr-H-Hyp(H)-Gly-ONP (4).—Dry hydrogen bromide was passed through a solution of 9.0 g of Z-Hyp(H)-Gly-ONP in 50 ml of trifluoroacetic acid for 45 min. The solution was poured into 500 ml of dry ether; the slurry was stirred and filtered. The crude product was dried under vacuum, stirred with 100 ml of methanol, then filtered, and washed with ether. The yield was quantitative, mp 248° dec. Methylene chloride could be used in place of trifluoroacetic acid. This preparation consistently gave samples with bromide and *p*-nitrophenol titers within 1% (relative) of theory.

(16) P. J. Flory, "Principles of Polymer Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 325.

(17) M. Goodman and K. C. Stueben, *J. Amer. Chem. Soc.*, **84**, 1279 (1962).

(18) A table of the nmr resonance positions will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-4377. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(19) (a) Analyses, ultracentrifuge runs, and optical rotations were performed by Mrs. L. Ross. A few analyses were performed by F. Pascher, Bonn, Germany. Infrared spectra were run on a Perkin-Elmer Infracord (137) or on the Model 21. Nmr data reported in Table III were measured on a Varian A-60. (b) Further procedures are reported by R. J. Albers, N. F. Estrin, and D. F. DeTar, *Biochem. Preparations* **13**, 34 (1971).

Anal. Calcd for $C_{13}H_{16}N_3O_6Br$: C, 40.02; H, 4.13; N, 10.77; Br, 20.48, ONP, 35.39. Found: C, 39.33; H, 4.03; N, 10.81; Br, 20.25; ONP, 35.4.

The ir spectrum (137, KBr) showed 1760 (COONP), 1655 (amide), 1620 (w), 1580 (w), 1560, 1520 cm^{-1}.

Z-Hyp(H)-Gly-ONP (5).—To a stirred mixture of 20.0 g of dicyclohexylcarbodiimide, 26.3 g of HBr-H-Gly-ONP, and 170 ml of acetonitrile at 5° was added over a period of 25 min a solution of 28.0 g of Z-Hyp(H)-OH[20] and 9.11 g of triethylamine in 50 ml of acetonitrile. After 2 hr at room temperature the reaction was complete as judged from the disappearance of carbodiimide (ir). The urea was removed by filtration and extracted twice with 25-ml portions of methylene chloride. The combined solvents were reduced to one-third of their volume and poured into 2 l. of ice–water (pH 2). The product was filtered, dissolved in methylene chloride, and dried over $MgSO_4$, and solvent removed. (In some runs the initial product was an oil; this was taken up in methylene chloride as above.) The material solidified and was crystallized from 200 ml of methanol–ether. Further recrystallization from methanol gave 24 g (55%), mp 139–141°.

Anal. Calcd for $C_{21}H_{21}N_3O_8$: C, 56.88; H, 4.77; N, 9.48; ONP, 31.15. Found: C, 57.16; H, 4.91; N, 9.55; ONP, 30.8.

The ir spectrum (137, KBr) showed 1770 (COONP), 1690 (Z), 1660 (amide), 1610 (w), 1640 (w), 1595, 1520 cm^{-1}.

Poly(Hyp(H))-Gly (A).—To a solution of 10.0 g of HBr-H-Hyp(H)-Gly-ONP in 15.0 ml of dimethyl sulfoxide at 25° was added 3.60 ml of triethylamine. After 1 week 15 ml of ether was added causing copious precipitation. The solvent was decanted; the precipitate was extracted with ethyl acetate and then dialyzed for 3 days in water. Lyophilization gave 0.30 g (7%) polymer. The major product was presumably the diketopiperazine, which was not isolated.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.4; H, 5.9; N, 16.5. Calcd for 92% polymer–8% water: C, 45.4; H, 6.3; N, 15.1. Found: C, 45.6; H, 6.4; N, 15.1.

The ir spectrum (21, KBr) showed 3356, 3077 (w), 2924, 1639, 1543, 1443, 1328, 1198, 1078, 1028 cm^{-1}.

HBr-H-Pro-Gly-ONP (6).—Dry hydrogen bromide was passed through a stirred solution of 356 g of Z-Pro-Gly-ONP in 3 l. of dry methylene chloride (distilled from P_2O_5). The product was separated by filtration, washed with dry ether, with two 400-ml portions of acetonitrile, and with ether, and then dried under reduced pressure at 50° to give 291 g (94%) of hydrobromide, mp 197–198° dec.

Anal. Calcd for $C_{13}H_{16}N_3O_5Br$: C, 41.73; H, 4.31; N, 11.23; Br, 21.35; ONP, 36.9. Found: C, 41.34; H, 3.99; N, 11.13, Br, 20.97; ONP, 36.4.

The ir spectrum (137, KBr) 1760 (COONP), 1660 (amide), 1610 (w), 1590 (w), 1555, 1525 cm^{-1}.

Z-Pro-Gly-ONP (7).—To a stirred mixture of 148.5 g of dicyclohexylcarbodiimide, 190.0 g of HBr-H-Gly-ONP, and 2 l. of acetonitrile at 5° was added over a period of 20 min a solution of 200.0 g of Z-Pro-OH[21,22] and 67.3 g of triethylamine in 600 ml of acetonitrile. After 1 hr at room temperature, the mixture was filtered. The filtrate was reduced to half-volume and poured into 4 l. of ice–water adjusted to pH 2 (HCl). The oily precipitate solidified on stirring and was collected by filtration. The filter cake was extracted with two 200-ml portions of dimethylformamide and these were poured in ice–water at pH 2 (HCl). The combined precipitates were crystallized from methanol–water and then from ethyl acetate giving 211.0 g (70%) of product, mp 139–141°.

Anal. Calcd for $C_{21}H_{21}N_3O_7$: C, 59.01; H, 4.95; N, 9.83; ONP, 32.3. Found: C, 59.48; H, 5.26; N, 9.91; ONP, 31.3.

The ir spectrum (137, KBr) showed 1770 (COONP), 1690 (Z), 1660 (amide), 1610 (w), 1640 (w), 1595, 1520 cm^{-1}.

Poly(Pro)-Gly (B). i.—To a solution of 10.0 g of HBr-H-Pro-Gly-ONP in 10.0 ml of dimethyl sulfoxide at 25° was added 3.7 ml of triethylamine. The solution gelled in 5 min; an additional 5.0 ml of dimethyl sulfoxide was added. After 3 days, 120 ml of ethyl acetate was added causing precipitation of triethylamine hydrobromide and polymer. The precipitate was dissolved in methanol and reprecipitated with ether giving 2.1 g of white powdery solid. This was dialyzed with water for 2 days. Lyophilization gave 1.00 g of polymer.

ii.—Polymerization on the same scale was carried out in 14.0 ml of dimethyl sulfoxide for 3 days. The solvent was removed at room temperature under high vacuum, and the residue was dissolved in 25 ml of water and dialyzed against water. After 2 days neither *p*-nitrophenol nor triethylamine hydrobromide could be detected. The solvent was removed by lyophilization, giving 0.200 g of polymer.

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.5; H, 6.5; N, 18.2. Calcd for 96% polymer–4% water: C, 52.4; H, 6.7; N, 17.4. Found: C, 52.4; H, 7.2; N, 17.1.

The ir spectrum (21, KBr) showed 3390, 3077, 3040, 2882, 1639, 1527, 1439, 1323, 1235, 1187, 1157, 1020 cm^{-1}.

HBr-H-Ala-Pro-Gly-ONP (8).—Hydrogen bromide was passed through a suspension of 10.0 g of Z-Ala-Pro-Gly-ONP in 60 ml of acetic acid. The product was precipitated by pouring the solution into 500 ml of dry ether: yield 8.4 g (94%). This material was hydroscopic but upon stirring in warm ethyl acetate was converted to 8.2 g of nonhydroscopic material, mp 190° dec.

Anal. Calcd for $C_{16}H_{21}N_4O_6Br$: C, 43.16; H, 4.75; N, 12.58; Br, 17.95; ONP, 31.01. Found: C, 40.69; H, 4.73; N, 12.6; Br, 18.3; ONP, 29.1.

The ir spectrum (137, KBr) showed 1760 (COONP), 1690 (amide), 1600 (w), 1680 (w), 1510 cm^{-1}.

Z-Ala-Pro-Gly-ONP (9).—To a stirred mixture (5°) of 61.9 g of dicyclohexylcarbodiimide, 110.0 g of HBr-H-Pro-Gly-ONP and 2.2 l. of acetonitrile was added during 1 hr a solution of 72.1 g of Z-Ala-OH[23] and 41.0 ml of triethylamine in 1.1 l. of acetonitrile. After 4 hr at 5°, the mixture was filtered and the filter cake extracted with 250 ml of dimethylformamide. The combined solvents were reduced to one-half volume under reduced pressure and poured into 4 l. of ice–water (pH 2). The precipitate was collected, dissolved in 1 l. of warm methanol, and allowed to crystallize. The prouct was dried (107 g, 73%) and recrystallized from 2.5 l. of methanol to give 91.0 g (62%) of product, mp 155–156°.

Anal. Calcd for $C_{24}H_{26}N_4O_8$: C, 57.82; H, 5.26; N, 11.24; ONP, 27.7. Found: C, 57.5; H, 5.13; N, 11.2; ONP, 27.6.

The ir spectrum (137, KBr) showed 1740 (COONP), 1680 (Z), 1640 (amide), 1610 (w), 1580 (w), 1540, 1510 cm^{-1}.

Poly(Ala)-Pro-Gly (C).—To 6.22 g of HBr-H-Ala-Pro-Gly-ONP in 10.0 ml of dimethyl sulfoxide was added 1.81 ml of triethylamine. After 4 hr 5.0 ml more of solvent was added to promote stirring. This was continued for 4 days. The solvent was removed under vacuum at room temperature, and the residue was transferred to a dialysis bag with water. Some precipitation occurred; after 2 days the water was removed by lyophilization leaving on drying 1.30 g (41%) of polymer.

Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.2; H, 6.7; N, 18.7. Calcd for 89% polymer–11% water: C, 47.4; H, 7.1; N, 16.6. Found: C, 47.7; H, 7.1; N, 16.3.

The ir spectrum (21, KBr) showed 3390, 3077 (sh), 3000 (sh), 1645, 1546, 1379, 1342, 1238, 1198, 1110, 1076 cm^{-1}.

HBr-H-Pro-Hyp(H)-Gly-ONP (10).—Dry hydrogen bromide was passed through a solution of 7.0 g of Z-Pro-Hyp(H)-Gly-ONP in 40 ml of trifluoroacetic acid. This solution was poured into 500 ml of dry ether and stirred in the cold until the precipitate was filterable. The solid was washed with 10% acetonitrile in ether, dried under vacuum, and then stirred with 200 ml of warm ethyl acetate to give 5.4 g (85%) of product, mp 170° dec.

Anal. Calcd for $C_{18}H_{23}N_4O_7Br$: C, 44.36; H, 4.76; N, 11.50; Br, 16.40; ONP, 28.34. Found: C, 43.49; H, 4.63; N, 11.3; Br, 15.6; ONP, 26.2.

The ir spectrum (21, KBr) showed 1779 (COONP), 1684 (amide), 1647 (amide), 1621 (w), 1597 (w), 1567 (w), 1538 cm^{-1}.

Z-Pro-Hyp(H)-Gly-ONP (11).—To a mixture of 20.0 g of HBr-H-Hyp(H)-Gly-ONP, 10.8 g of dicyclohexylcarbodiimide, and 130 ml acetonitrile was added a solution of 14.6 g of Z-Pro-OH and 7.1 ml of triethylamine in 120 ml of acetonitrile over a period of 1 hr. After 4 hr the urea was removed and washed with acetonitrile. The solutions were combined and evaporated to dryness. The residue was slurried in 200 ml of ethyl acetate leving triethylamine hydrobromide undissolved. The product was precipitated by adding 400 ml of ether. After thorough drying, the product was slurried in water to remove traces of triethylamine hydrochloride which otherwise causes the material to become gummy: yield 11.0 g (46%), mp 90–92°.

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Anal. Calcd for $C_{26}H_{28}N_4O_9$: C, 57.77; H, 5.22; N, 10.37; ONP, 25.55. Found: C, 57.26; H, 5.36; N, 10.4; ONP, 24.7.

The ir spectrum (21, KBr) showed 1751 (COONP), 1681 (br, Z, amide), 1647 (amide), 1618 (w), 1594 (w), 1546 (w), 1524 cm^{-1}.

Poly(Pro)-Hyp(H)-Gly (D).—To a solution of 2.00 g of HBr-H-Pro-Hyp(H)-Gly-ONP in 4.8 ml of dimethyl sulfoxide was added 0.57 ml of triethylamine. During 4 hr 6.0 ml more of solvent was added as gelling caused the solution to become unstirrable. After 2 days the solvent was removed by lyophilization. The residue was extracted with ether, then dialyzed against water for 3 days. (After 2 days no bromide ion could be detected.) The polymer was separated by lyophilization and dried at 80° under high vacuum: yield 0.65 g (59%).

Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.9; H, 6.4; N, 15.7. Calcd for 95% polymer–5% water: C, 51.2; H, 6.6; N, 14.9. Found: C, 51.6; H, 6.7; N, 14.8.

The ir curve (21, KBr) showed 3413, 2923, 1633, 1546, 1445, 1401, 1333, 1195, 1159, 1081, 1026 cm^{-1}.

HBr-H-Ser(H)-Pro-Gly-ONP (12).—This preparation was similar to that of 10; the yield was quantitative, mp 202° dec.

Anal. Calcd for $C_{16}H_{21}N_4O_7Br$: C, 41.66; H, 4.59; N, 12.15; Br, 1732; ONP, 29.9. Found: C, 40.46; H, 3.97; N, 12.12; Br, 17.01; ONP, 29.5.

The ir spectrum (137, KBr) showed 1770 (COONP), 1680 (Z), 1640 (amide), 1610 (w), 1580, 1515 cm^{-1}.

Z-Ser(H)-Pro-Gly-ONP (13).—To a cold (5°) stirred mixture of 28.1 g of dicyclohexylcarbodiimide, 50.0 g of HBr-H-Pro-Gly-ONP and 1 l. of acetonitrile was added during 3.5 hr a solution of 35.0 g of Z-Ser(H)-OH and 17.0 ml of triethylamine in 500 ml of acetonitrile. After 1.5 hr the solids were separated and the filter cake was extracted twice with 200 ml of warm acetonitrile. The solvents were combined and taken to dryness; the residue was dissolved in 400 ml of warm ethyl acetate from which the product separated upon cooling and stirring for several hours. This material was washed with water (pH 2) and recrystallized from ethyl acetate giving 33.6 g (49%) of product, mp 142–144°.

Anal. Calcd for $C_{24}H_{26}N_4O_9$: C, 56.03; H, 5.09; N, 10.89; ONP, 26.8. Found: C, 55.69; H, 5.32; N, 10.85; ONP, 26.7.

The ir spectrum (137, KBr) showed 1770 (COONP), 1770 (Z), 1660 (amide), 1640 (amide), 1620 (w), 1530 cm^{-1}.

Poly(Ser(H))-Pro-Gly (E).—To a stirred solution of 6.00 g of HBr-H-Ser(H)-Pro-Gly-ONP in 10.0 ml of dimethyl sulfoxide was added 1.79 ml of triethylamine. After 3 days the solvent was removed by lyophilization. The residue was washed successively with 250-ml portions of ether, methanol, chloroform, and ether employing a preparative centrifuge (10,000 rpm). The polymer was dried under vacuum at 80° for 3 days: yield 1.90 g (61%).

Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.8; H, 6.3; N, 17.4. Calcd for 95% polymer–5% water: C, 47.3; H, 6.5; N, 16.6. Found: C, 47.3; H, 6.3; N, 16.5.

The ir spectrum (21, KBr) showed 3356, 3076, 2941, 1639, 1529, 1443, 1330, 1235, 1053 cm^{-1}.

HBr-H-Gly-Hyp(H)-Gly-ONP (14).—Hydrogen bromide was passed through a solution of 4.4 g of Z-Gly-Gly-Hyp(H)-Gly-ONP and 25 ml of trifluoroacetic acid for 1 hr. The solvents were evaporated at 25° and 300 ml isopropyl alcohol added. The precipitate was stirred in the cold overnight, collected, washed with additional isopropyl alcohol, then with ether, and dried at 50° under vacuum: yield 4.0 g, mp 212° dec.

Anal. Calcd for $C_{17}H_{22}N_5O_8Br$: C, 40.48; H, 4.37; N, 13.89; Br, 15.87; ONP, 27.38. Found: C, 40.17; H, 4.55; N, 13.84; Br, 15.57; ONP, 26.6.

The ir spectrum (21, KBr) showed 1767 (COONP), 1681 (amide), 1653 (amide), 1631 (amide), 1600, 1563, 1527, 1492 (w) cm^{-1}.

Z-Gly-Gly-Hyp(H)-Gly-ONP (15).—To a stirred mixture of 5.28 g of dicyclohexylcarbodiimide, 10.0 g of HBr-H-Hyp(H)-Gly-ONP, and 100 ml of acetonitrile at room temperature was added during 2 hr a solution of 8.52 g of Z-Gly-Gly-OH and 2.86 g of triethylamine in 200 ml of acetonitrile. The mixture was stirred for 18 hr and filtered. The filter cake was slurried in 100 ml of warm dimethylformamide which was filtered into 1.5 l. of ice–water (pH 2) and the mixture was stirred overnight. The precipitate was collected, dried, and recrystallized from methanol giving 5.0 g (35%) of product, mp 184–187°.

Anal. Calcd for $C_{25}H_{27}N_5O_{10}$: C, 53.86; H, 4.88; N, 12.56; ONP, 24.77. Found: C, 53.34; H, 5.04; N, 12.68; ONP, 25.0.

The ir spectrum (21, KBr) showed 1773 (COONP), 1695 (Z), 1661 (amide), 1621 (amide), 1595 (w), 1565, 1548, 1524 cm^{-1}.

Poly(Gly)-Gly-Hyp(H)-Gly (F).—To a stirred solution of 3.50 g of HBr-H-Gly-Gly-Hyp(H)-Gly-ONP and 7.0 ml dimethyl sulfoxide was added 0.96 ml of triethylamine. The solution was stirred for 3 days and then lyophilized. The residue was washed into a dialysis bag with water and dialyzed for 1 week against water. The water was removed by lyophilization, and the powders were dried at 80° for 2 days under vacuum to yield 0.90 g of polymer (46%).

Anal. Calcd for $C_{11}H_{16}N_4O_5$: C, 46.47; H, 5.67; N, 19.71; O, 28.14. Found: C, 46.4; H, 5.8; N, 18.63.

The ir spectrum (21, KBr) showed 3344, 2933 (sh), 1650, 1538, 1471, 1408, 1333, 1235, 1198 (w), 1160 (w), 1079, 1027 cm^{-1}.

Registry No.—**1,** 1142-20-7; **3,** 1148-11-4; **4,** 35016-72-9; **5,** 35006-40-7; **6,** 35016-73-0; **7,** 6464-84-2; **8,** 36358-38-0; **9,** 35006-34-9; **10,** 36358-40-4; **11,** 36358-41-5; **12,** 35761-25-2; **13,** 36358-43-7; **14,** 36358-44-8; **15,** 35006-39-4; A, 28186-03-0; B, 27252-06-8; C, 26523-49-9; D, 25734-60-5; E, 26523-51-3; F, 28186-05-2.

Nucleosides. LXXVIII. Synthesis of Some 6-Substituted Uracils and Uridines by the Wittig Reaction[1]

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Orotaldehyde (1) was treated with various alkylidene phosphoranes to afford α,β-unsaturated 6-substituted uracils. 6-Chloromethyluracil (7) was converted to the 6-triphenylphosphonium salt (8) by reaction with triphenylphosphine. This salt gave 6-styryluracil (2) when treated with benzaldehyde. With orotaldehyde, 8 afforded 1,2-bis(6-uracilyl)ethene (14), which was converted to 1,2-bis(6-uracilyl)ethane (15). With formaldehyde, 8 yielded 6-vinyluracil (9) which was polymerized to poly(6-vinyluracil) (13). Bromination of 9 afforded the 5-bromo analog 11 exclusively. With sodium bisulfite, 9 was converted quantitatively to the sodium salt of 2-(6-uracilyl)ethanesulfonic acid (12). Synthesis of 6-methylcytidine from N^4-acetyl-6-methylcytosine by the $Hg(CN)_2$–CH_3NO_2 procedure was achieved and the nucleoside was converted *via* a bisulfite adduct to 6-methyluridine, which was subsequently oxidized to tri-*O*-acetylorotidine aldehyde (21). With carbethoxymethylenetriphenylphosphorane, 21 was converted to the ethyl ester of *trans*-3-(6-uridinyl)acrylic acid (23).

Pyrimidine nucleosides containing a carbon substituent at C-6 have been generally difficult to synthesize. Simple examples of the C-6 methylated members of that group have been described recently.[2] More complex 6-alkylated nucleosides have been synthesized[3] by Claisen-type rearrangements of certain 5-allyloxy or 5-propynyloxy pyrimidine nucleosides to afford carbon to carbon 6-substituted derivatives bearing an hydroxy or ether function on C-5. A more general approach to various C–C 6-substituted nucleosides would be from the hiterto unknown uridine-6-carboxaldehyde ("orotidine aldehyde") by use of the Wittig reaction. Indeed, such a reaction was reported in the special case of 2-amino-4-hydroxy-5-phenylbutylpyrimidine-6-carboxaldehyde and its 2-acetamido derivative by Baker and Jordaan.[4] We report herein results on the use of the Wittig reaction on orotaldehyde (uracil-6-carboxaldehyde) and orotidine aldehyde as part of our general program dealing with the synthesis of nucleosides of potential biological interest. We also report a facile synthesis of 6-vinyluracil and its polymerization to poly(6-vinyluracil). The latter should be useful as a model system (with a polymethylene-type backbone) for use in binding studies with certain synthetic or naturally occurring polynucleotides.[5]

Attempts to condense orotaldehyde (1)[6] with ylides not stabilized by conjugation were unsuccessful. Thus, only trace amounts of 6-vinyluracial were detected, after chromatography, when 1 (Scheme I) was treated with methyltriphenylphosphonium bromide in dimethyl sulfoxide containing sodium methylsulfinylmethide. Better results were obtained, however, when 1 reacted with the stabilized ylide derived from benzyltriphenylphosphonium chloride in the presence of a threefold excess of phenyllithium in *N*,*N*-dimethylformamide (DMF) or with sodium methoxide to afford *trans*-6-styryluracil (2) in 51% yield. Trans isomerism in 2 was established by its pmr spectrum, which showed a characteristic coupling constant of 16.5 Hz for the vinylic protons. The corresponding cis isomer was not detected in the condensation products. The success of the reaction indicated that in spite of the charge in the anionic species of 1, the aldehyde was still susceptible to nucleophilic attack by the ylide. (It is reasonable to expect that most of 1 is ionized in such strongly basic medium.) Hydrogenation of 2 over palladium/charcoal afforded the known 6-phenethyluracil (3).[7] Reaction of 1 with an equimolar amount of carbethoxymethylenetriphenylphosphorane in DMF gave 4 as the trans isomer in 62% yield. A trace of the cis isomer (detected by tlc) was found in the reaction mixture. The pK_a of this ylide is ~9[8] (*i.e.*, its pK_a is comparable to that of 1) and, under the reaction conditions employed, appreciable amounts of the neutral form of the reactants present would favor condensation to 4. When DMF was replaced by ethanol as the solvent of reaction, the crystalline product isolated in 95% yield was found by pmr spectroscopy to consist of a 15:85 mixture of the cis and trans isomers of 4. The identity of each component in the mixture was determined by the different coupling constants of the vinylic protons: J_{trans} = 16.5 and J_{cis} = 13.0 Hz. These results are consistent with previous studies on the influence of the reaction medium on the stereoselectivity of the Wittig reaction with stabilized ylides[9] which concluded that "the proportion of the cis isomer is enhanced by the presence in the reaction solution of a Lewis acid such as a proton-donating solvent. . ."

Attempts were made to prepare certain 5-substituted orotaldehydes by oxidation of the corresponding 6-methyluracils with selenium dioxide. With 5-acetamido-6-methyluracil, no reaction occurred, while with the 5-nitro analog many side products were observed along with only trace amounts of the 6-aldehyde derivative. With 5-bromo-6-methyluracil, selenium dioxide oxidation did take place without side reactions. How-

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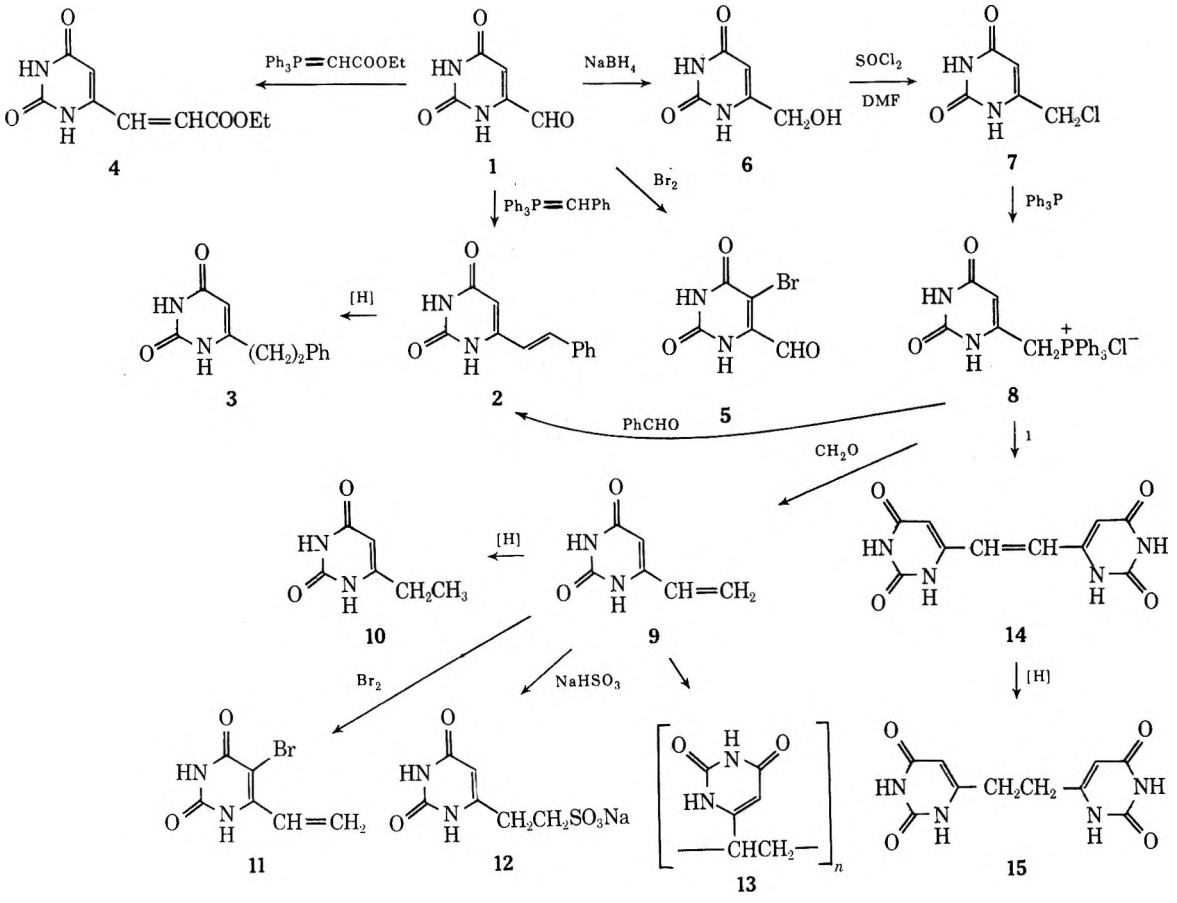
SCHEME I



ever, the formation of product was very slow. A more practical approach to 5-bromoorotaldehyde (**5**) was found in the direct bromination of **1** with 1 equiv of bromine in water.

An alternate route to α,β-unsaturated 6-substituted uracils was found by condensation of aldehydes with the pyrimidyl Wittig derivative (**8**) which was prepared conveniently from **1** *via* **6** and **7**. Reaction of **8** with benzaldehyde gave, as expected, the styryl derivative **2**. When treated under nitrogen with formaldehyde and then with a threefold molar excess of sodium ethoxide in ethanol, compound **8** afforded 6-vinyluracil (**9**) in good yield. An excess of base is required for this reaction because of prior ionization of an NH proton in **8** before formation of the ylide intermediate. Hydrogenation of **9** over palladium/charcoal afforded the known[10] 6-ethyluracil (**10**) which, in addition to pmr data, confirms the structure of **9**.

The chemical properties of 6-vinyluracil are of interest. Bromination of **9** with an equivalent amount of bromine in water yielded exclusively 5-bromo-6-vinyluracil (**11**). When treated with bisulfite, compound **9** was converted quantitatively into the sulfonate salt **12**. This addition, unlike that of uracil, is not reversible in alkali.[11] The structure of **12** was easily established by the uv spectrum, which is similar to that for 6-ethyluracil, and the pmr spectrum, which exhibits signals for four methylenic protons and the C-5 vinylic proton. Attempts to achieve a free-radical polymerization of **9** were precluded by its poor solubility in most organic solvents. It was possible, however, to prepare the silylated derivative of **9**, which polymerized directly in dioxane solution and in the presence of azobisisobutyronitrile as free-radical initiator to silylated poly(6-vinyluracil) which, after hydrolysis, afforded poly(6-vinyluracil) (**13**) as a sparingly soluble, partially hydrated amorphous solid. The uv spectrum of this polymer is similar, as expected, to that for 6-alkyluracils.

The phosphonium salt (**8**) reacted with orotaldehyde (**1**) in DMF in the presence of excess sodium ethoxide to afford the diuracilyl derivative (**14**) in good yield. The elemental analyses and uv properties are consistent with structure **14** although, owing to the poor solubility of this compound, pmr measurements could not be made to determine its geometrical isomerism. Hydrogenation of **14** in aqueous base over palladium/charcoal gave the expected 1,2-bis(6-uracilyl)ethane (**15**), which also exhibited poor solubility properties. [It should be noted that **15** is structurally similar to 1,2-bis(3,4-dioxopiperazin-1-yl)ethane, a compound which has demonstrated[12] antitumor activity.]

In order to apply the Wittig reaction to nucleosides, a synthesis of orotidine aldehyde (**21**) (Scheme II) was achieved from N^4-acetyl-6-methylcytosine. Condensation of the latter with tri-*O*-benzoyl-D-ribofuranosyl bromide by the $Hg(CN)_2$–nitromethane procedure[13]

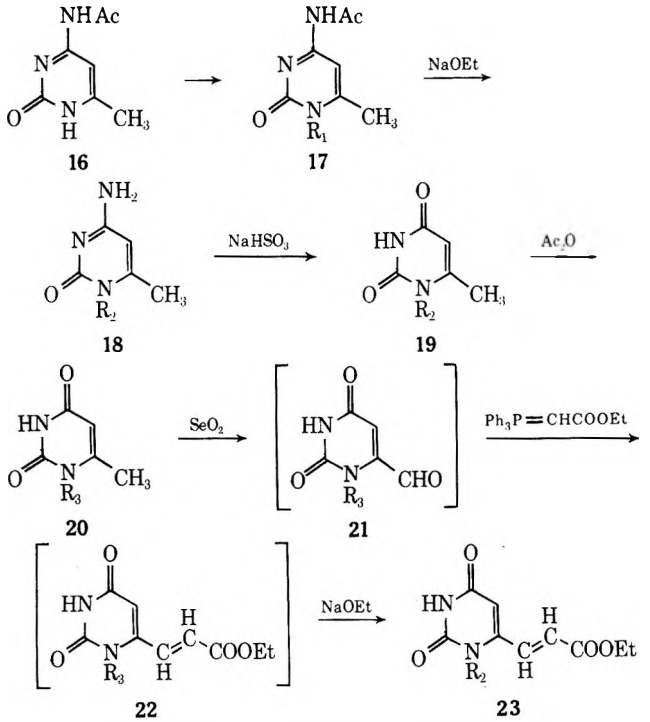
(10) (a) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens, *J. Chem. Soc.*, 4106 (1956); (b) R. Robinson and M. L. Tomlinson, *ibid.*, 1283 (1935).

(11) (a) R. Shapiro, R. E. Servis, and M. Welcher, *J. Amer. Chem. Soc.*, **92**, 422 (1970); (b) H. Hayatsu, Y. Wataya, K. Kai, and S. Iida, *Biochemistry*, **9**, 2858 (1970).

(12) A. M. Creighton, K. Hellmann, and S. Whitecross, *Nature (London)*, **222**, 384 (1969).

(13) (a) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965); (b) K. A. Watanabe and J. J. Fox, *J. Heterocycl. Chem.*, **6**, 109 (1969).

Scheme II



R_1 = tri-*O*-benzoyl-β-D-ribofuranosyl
R_2 = β-D-ribofuranosyl
R_3 = tri-*O*-acetyl-β-D-ribofuranosyl

gave the blocked N-1 ribosylated pyrimidine (**17**) which, without isolation, was deacylated to 6-methylcytidine (**18**) in good yield.[14] Formation of 6-methyluridine (**19**) from **18** was performed using a method developed for the deamination of cytidine by catalysis with bisulfite[11a] under more stringent conditions. The relatively slow rate observed for this reaction as compared with that for cytidine is presumed to be due to the steric hindrance at C-6 by the 6-methyl group. After acetylation of **19** the protected nucleoside **20** was oxidized with selenium dioxide in 11:1 dioxane–glacial acetic acid to the tri-*O*-acetylorotidine aldehyde **21**. If the oxidation was carried out in glacial acetic acid, glycosyl cleavage of the product **21** occurred with the formation of orotaldehyde (**1**), while omission of HOAc slowed the oxidation with selenium dioxide considerably. Aldehyde **21** was unstable and, even in chloroform, it decomposed on standing. A small sample of **21** was purified by preparative tlc to a syrup which exhibited the expected pmr singals in $CHCl_3$ (δ 9.53 for aldehydic proton). The crude product **21** was treated immediately with carbethoxymethylenetriphenylphosphorane in DMF to afford the α,β-unsaturated ester derivative **22** which, after treatment with sodium ethoxide, gave crystalline *trans*-3-(6-uridinyl)acrylic acid as the ethyl ester **23**. Proof of **23** as the trans isomer is based on its pmr spectrum, which exhibited a coupling constant for the vinylic protons of the side chain of 16.0 Hz.

Extension of this approach to the synthesis of variously 6-substituted pyrimidine nucleosides is now underway in our laboratories.

(14) Syntheses of 6-methylcytidine and 6-methyluridine have been reported[2] by other methods. However, the reported yields were lower and the isolation of product was more laborious.

Experimental Section

Melting points were obtained on a Thomas-Hoover apparatus (capillary method) for temperatures below 300° and are uncorrected. For higher temperatures, a Mel-Temp block was used. The pmr spectra were measured on a Varian A-60 spectrometer using TMS as internal standard. Chemical shifts are reported in parts per million (δ). Signals are described as s (singlet), d (doublet), t (triplet), q (quartet), or m (complex multiplet). Values given for coupling constants and chemical shifts are first order. Uv spectra were measured on a Unicam SP 800-B ultraviolet spectrophotometer. Thin layer chromatography was performed on silica gel GF_{254} (Merck); spots were detected by uv absorbance or by charring after spraying with 20% v/v sulfuric acid–ethanol. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Galbraith Laboratories, Knoxville, Tenn. All evaporations were carried out *in vacuo*.

6-Styryluracil (2). A. From Orotaldehyde (1).—A mixture of anhydrous orotaldehyde[6a] (0.70 g, 0.0050 mol) and triphenylbenzylphosphonium chloride (1.94 g, 0.0050 mol) was dissolved in 25 ml of dry DMF under a slow stream of nitrogen. To the solution was added 7.5 ml of a 2 *M* solution (~0.015 mol) of phenyllithium in benzene–ether (70:30). The mixture was heated for 30 min at ~90° and cooled to ambient temperature. The solution was neutralized with glacial acetic acid and evaporated to dryness. The crystalline residue was recrystallized from ethanol to afford 0.550 g (51%) of the product in two crops. One final recrystallization from glacial acetic acid gave an analytically pure sample of **2**: mp 345–350° dec; pmr (DMSO-d_6) δ 5.77 (1, s, H-5), 6.84 (1, d, CH=CHC_6H_5), 7.30–7.90 (6, m, CHC_6H_5), 10.83 (2, broad singlet, 2 NH's), J_{trans} = 16.5 Hz.

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.13; H, 4.76; N, 13.11.

B. From 8.—To a solution of **8** (*vide infra*) (2.12 g, 0.0045 mol) and 0.530 g (0.005 ml) of benzaldehyde in 100 ml of ethanol was added under a slow stream of dry nitrogen a solution of sodium ethoxide [from 0.350 g (0.0150 g-atom) of sodium metal] in 25 ml of ethanol. The mixture was heated to reflux for 15 min, cooled, and neutralized with glacial acetic acid. The crude product **2** (0.305 g, 31%) was collected by filtration and recrystallized from glacial acetic acid to give an analytically pure sample of **2** identical in all respects with the sample obtained by method A.

6-Phenethyluracil (3).—A solution of **2** (0.524 g, 0.00245 mol) in 200 ml of glacial acetic acid was hydrogenated at 1 atm over 20 mg of 10% Pd/C. After hydrogen uptake had ceased, the mixture was filtered through Celite and evaporated to dryness. The residue crystallized from glacial acetic acid in three crops to afford 0.461 g (87%) of product **3**. One more recrystallization from water–ethanol gave an analytical sample: mp 254–256° dec (lit.[7] mp 260–262°); pmr (DMSO-d_6) δ 2.30–2.90 (4, m, CH_2CH_2, overlapping DMSO), 5.33 (1, s, H-5), 7.25 (5, s, C_6H_5), 10.89 (2, broad singlet, 2 NH's).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.53; H, 5.71; N, 12.96.

***trans*- and *cis*-3-(6-Uracilyl)acrylic Acid Ethyl Ester (4).**—To a magnetically stirred suspension of anhydrous orotaldehyde (1.40 g, 0.0100 mol) in 30 ml of dry DMF was added 3.48 g (0.0100 mol) of carbethoxymethylenetriphenylphosphorane. The reaction was slightly exothermic. After 1.5 hr, ethanol (30 ml) was added to the clear solution, and the mixture was cooled at 0°. The crystalline product, collected by filtration, weighed 1.31 g (62%). One recrystallization from ethanol gave analytically pure material: mp 255–257°; uv $\lambda_{max}^{pH\ 1}$ 305 mμ (ε 10,900), $\lambda_{min}^{pH\ 1}$ 265 (3500), $\lambda_{max}^{pH\ 11}$ 336 (7900), $\lambda_{min}^{pH\ 11}$ 283 (1900); pmr (DMSO-d_6) δ 1.26 (3, t, CH_2CH_3), 4.22 (2, q, CH_2CH_3), 6.02 (1, s, H-5), 6.89 and 7.28 (2, two AB doublets, CH=CH), 10.95 and 11.15 (2, two broad singlets, 2 NH's), J_{trans} = 16.5 Hz.

Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.39; H, 4.76; N, 13.27.

The reaction was repeated on the same scale using 40 ml of ethanol instead of DMF as the solvent. The mixture was heated to reflux for 1.5 hr, chilled, and filtered. The crystalline product weighed 2.00 g (95%). Pmr measurements indicated that the product was a 15:85 mixture of the cis and trans isomers. No attempt was made to isolate each isomer from the mixture. Pmr signals corresponding to the cis isomer of the mixed spectrum are described as follows: pmr (DMSO-d_6) δ 1.09 (3, t,

CH_2CH_3), 4.23 (2, q, CH_2CH_3), 5.70 (1, s, H-5), 6.30 and 6.75 (2, two AB doublets, CH=CH), J_{cis} = 13.0 Hz.

When the reaction was performed in methanol, the final product (95% yield) consisted of a 1:4 mixture of the cis and trans isomers.

5-Bromorotaldehyde (5).—To a solution of orotaldehyde monohydrate (1.58 g, 0.0100 mol) in 500 ml of water was added dropwise a saturated solution of 1.70 g of bromine in water. After complete decolorization, the mixture was treated with sodium acetate trihydrate (1.36 g, 0.0100 mol), evaporated to a small volume, and chilled. The precipitate obtained in three crops was filtered and washed with cold water. The white crystalline product (5) weighed 1.85 g (78%). One recrystallization from water gave the analytical sample: mp 273–275° dec; uv $\lambda_{max}^{pH\ 1}$ 279 mμ (ε 7800), $\lambda_{min}^{pH\ 1}$ 241 (1400), $\lambda_{max}^{pH\ 11}$ 301 (6600), $\lambda_{min}^{pH\ 11}$ 253 (1600), $\lambda_{max}^{pH\ 14}$ 286 (6300), $\lambda_{min}^{pH\ 14}$ 253 (2400).

Anal. Calcd for $C_5H_3BrN_2O_2$: C, 27.42; H, 1.38; N, 12.79; Br, 36.49. Found: C, 27.32; H, 1.44; N, 12.84; Br, 36.47.

5-Bromorotaldehyde Phenylhydrazone.—As the pmr of 5 in DMSO-d_6 was complicated by what is presumed to be a dimeric structure, the phenylhydrazone derivative of 5 was prepared as a further confirmation of its structure: mp 264° dec; pmr (DMSO-d_6) δ 6.70–7.60 (5, m, C_6H_5), 7.93 (1, s, -CH=N), 11.21 (3, broad singlet, 3 NH's). When TFA was added the last signal resolved into two singlets at δ 10.79 (1 NH) and 11.45 (2 NH's).

Anal. Calcd for $C_{11}H_9BrN_4O_2$: C, 42.74; H, 2.93; N, 18.12; Br, 25.85. Found: C, 42.69; H, 2.89; N, 18.10; Br, 25.82.

6-Chloromethyluracil (7).—To a well-stirred suspension of very finely ground 6-hydroxymethyluracil monohydrate 6[15,16] (3.10 g, 0.0194 mol) in 20 ml of thionyl chloride was added 1 ml of $SOCl_2$ containing 8 drops of DMF. After an initial vigorous evolution of HCl gas the mixture was heated to reflux for 5–10 min. As the reaction proceeded the solids that precipitated on the flask walls were washed back into the mixture with 10 ml of thionyl chloride. It was found necessary occasionally to break big clumps as they formed. The mixture was then cooled to room temperature and diluted with 70 ml of diethyl ether and the crude product was collected by filtration and washed with ether (2.90 g, 93%). One recrystallization from hot acetic acid gave 1.45 g of pure material, mp 249–251° (lit.[17] mp 240° dec). A second crop, mp 244–248°, brought the total yield to 2.30 g (74%). This was used without further purification: pmr (DMSO-d_6) δ 4.40 (2, s, CH_2Cl), 5.70 (1, s, H-5), 11.11 (2, broad singlet, 2 NH's).

6-Uracilylmethylenetriphenylphosphonium Chloride (8).—A solution of 7 (3.60 g, 0.0225 mol) and triphenylphosphine (9.00 g, 0.0343 mol) in 250 ml of ethanol was heated to reflux for 16 hr. Another 3.2 g (0.0122 mol) of triphenylphosphine was then added and heating was resumed for another 3 hr while 100 ml of ethanol was removed by distillation. The clear solution was chilled and the crystalline product (7.25 g) was collected. Evaporation of the mother liquor afforded another crop to give a total yield of 9.00 g (84%). Two recrystallizations from ethanol gave the analytical material: mp 200° dec; uv $\lambda_{max}^{pH\ 1}$ 265.5 mμ (ε 8600), $\lambda_{min}^{pH\ 1}$ 246 (5400); pmr (DMSO-d_6) δ 1.05 (3, t, CH_3 of ethanol), 3.46 (2, q, CH_2 of ethanol), 5.18 (2, broad singlet, CH_2), 5.46 (1, s, H-5), 7.55–8.10 (15, m, 3 C_6H_5), 11.06 and 11.23 (2, 2 broad singlets, 2NH's). The presence of 1 mol of ethanol supports the analytical data.

Anal. Calcd for $C_{23}H_{20}N_2O_2PCl \cdot C_2H_5OH$: C, 64.03; H, 5.59; N, 5.97; P, 6.60; Cl, 7.56. Found: C, 63.32; H, 5.60; N, 5.98; P, 6.61; Cl, 7.84.[18]

6-Vinyluracil (9).—A mixture of the phosphonium chloride 8 (0.423 g, 0.0009 mol) and paraformaldehyde (0.135 g, 0.0045 mol) was suspended in 30 ml of absolute ethanol. To the stirred mixture, which was kept under nitrogen,[19] was slowly added ~0.003 mol of sodium ethoxide (from 75 mg of sodium metal) in 10 ml of ethanol. The mixture became yellow and then slowly decolorized as a precipitate formed. The suspension was then heated to 50° for 5 min, cooled to room temperature, neutralized with glacial acetic acid to pH 4–5, and filtered. After evaporation of the filtrate to a small volume some insoluble material that had precipitated was again removed and the clear solution was evaporated to dryness. The residue, which contains triphenylphosphine oxide in addition to 9, was partitioned between chloroform and water and the aqueous extract was treated with an excess of Dowex 50 W (H^+) resin. After filtration, the solution was evaporated to dryness and the crystalline residue was recrystallized from hot acetic acid to afford pure 9 in three crops (0.104 g, 83%). Another recrystallization from acetic acid gave an analytically pure sample: mp >350°; uv $\lambda_{max}^{pH\ 1}$ 296.5 mμ (ε 9200), $\lambda_{min}^{pH\ 1}$ 247 (1900), $\lambda_{max}^{pH\ 11}$ 307 (7000), $\lambda_{min}^{pH\ 11}$ 257 (1500), $\lambda_{max}^{pH\ 14}$ 308 (6300), $\lambda_{min}^{pH\ 14}$ 260 (1600); pmr (pyridine-d_6) quartet centered at δ 5.67 (1, $RCH_\alpha{=}CH_{trans}\ H_{cis}$) quartet centered at 6.27 (1, H_{trans}), quartet centered at 6.61 (1, H_α), ~12.5 (2, broad singlet, 2 NH's), J_{gem} = 2.5–3.0 Hz, J_{trans} = 17.5–18.0 Hz, J_{cis} = 8.5–9.0 Hz.

Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.94; H, 4.33; N, 20.13.

6-Ethyluracil (10).—Compound 9 (0.276 g, 0.0020 mol) was dissolved in 100 ml of hot water and catalytically reduced under hydrogen (1 atm) in the presence of 10% Pd/C at ambient temperature. The uptake was rapid (16 min) and quantitative. After concentration, the filtrate deposited a first crystalline crop (0.198 g) of 10, mp 204–207° (lit.[10b] mp 205°). A second crop (0.045 g) was obtained after further evaporation to give a total yield of 87%: pmr (DMSO-d_6) δ 1.09 (3, t, CH_3), 2.31 (2, q, CH_2), 5.31 (1, s, H-5), 10.75 (2, broad singlet, 2 NH's).

5-Bromo-6-vinyluracil (11).—To a vigorously stirred solution of 6-vinyluracil (0.138 g, 0.0010 mol) in 50 ml of water was added, dropwise, an aqueous solution of bromine (0.176 g, 0.0011 mol/10 ml H_2O). After 30 min the mixture was chilled and the white crystalline product was collected by filtration (0.130 g), decomposes slowly over 250°. Another crop of 11 (0.157 g, total yield 72%) was obtained after evaporation of the mother liquor: uv $\lambda_{max}^{pH\ 1}$ 305 mμ (ε 8600), $\lambda_{min}^{pH\ 1}$ 255 (1100), $\lambda_{max}^{pH\ 11}$ 327 (7000), $\lambda_{min}^{pH\ 11}$ 268 (1000), $\lambda_{max}^{pH\ 14}$ 325 (5900), $\lambda_{min}^{pH\ 14}$ 272 (1200); pmr (DMSO-d_6) quartet centered at δ 5.85 (1, $RCH_\alpha{=}CH_{trans}\ H_{cis}$), quartet centered at 6.32 (1, H_{trans}), quartet centered at 6.86 (1, H_α), 11.10 and 11.52 (2, 2 broad singlets, 2 NH's), J_{gem} = 0.5–1.0 Hz, J_{trans} = 17.5 Hz, J_{cis} = 11 Hz.

Anal. Calcd for $C_6H_5BrN_2O_2$: C, 33.21; H, 2.32; N, 12.91; Br, 36.82. Found: C, 33.08; H, 2.49; N, 12.93; Br, 36.85.

2-(6-Uracilyl)ethanesulfonic Acid (Sodium Salt) (12).—To a solution of 6-vinyluracil (0.138 g, 0.0010 mol) in 40 ml of water was added a solution of sodium bisulfite (0.125 g, 0.0012 mol) in 5 ml of water and the clear mixture was heated on the steam bath for 20 min. Uv measurements indicated that the $\lambda_{max}^{pH\ 1}$ at 307 mμ disappears as a new maximum at 261 mμ increases in intensity. Evaporation of the mixture and crystallization from water–methanol afforded 0.229 g (88%) of the crystalline sulfonate as the monohydrate in three crops: mp 318–321° dec with loss of water at 110°; uv $\lambda_{max}^{pH\ 1}$ 261 mμ (ε 8000), $\lambda_{min}^{pH\ 1}$ 229 (1500), $\lambda_{max}^{pH\ 11}$ 283 (7000), $\lambda_{min}^{pH\ 11}$ 242 (1400), $\lambda_{max}^{pH\ 14}$ 278 (6800), $\lambda_{min}^{pH\ 14}$ 244 (1600); pmr (DMSO-d_6) δ 2.74 (4, m, CH_2CH_2), 3.47 (2, very broad singlet, H_2O), 5.38 (1, s, H-5), 10.75 (2, broad singlet, NH's). The presence of 1 mol of H_2O supports the analytical data.

Anal. Calcd for $C_6H_7N_2O_5SNa \cdot H_2O$: C, 27.70; H, 3.48; N, 10.76; S, 12.32. Found: C, 27.43; H, 3.35; N, 10.62; S, 12.23.

Polymerization of 6-Vinyluracil.—To a suspension of 0.400 g (0.0029 mol) of 6-vinyluracil in 2 ml of dried acetonitrile was added 1 ml of *N,O*-bis(trimethylsilyl)acetamide (BSA). The container was sealed and the mixture was stirred while being heated at 50° until it became clear. Most of the solvent was then evaporated under a stream of dry nitrogen and excess BSA was removed under vacuum. The syrupy residue was dissolved in 5 ml of dry dioxane, and 10 mg of azobisisobutyronitrile was added. The clear solution was placed in a sealed tube and heated

(15) T. B. Johnson and L. H. Chernoff, *J. Amer. Chem. Soc.*, **36**, 1742 (1914); K. L. Nagpal, P. C. Jain, P. C. Srivastava, M. M. Dhar, and N. Anand, *Indian J. Chem.*, **6**, 762 (1968).

(16) Compound **6** was used as the crystalline monohydrate form. When, on one instance, it was dried and used in the anhydrous form no reaction took place. The apparent need for some water in the reaction mixture is not clear.

(17) P. Rambacher and N. Kaniss, *Angew Chem., Int. Ed. Engl.*, **7**, 383 (1968).

(18) Despite repeated recrystallization of compound **8** the C analysis was consistently lower than the value calculated. Since all other elemental analyses are in excellent agreement with the theoretical values, we feel justified to report the full analysis as presented here.

(19) A large amount of 6-methyluracil was formed as a side product of the reaction when anhydrous conditions and an inert atmosphere were not used.

to 60° for 16 hr. The viscous mixture was then dissolved in 5 ml of 1 *N* NaOH and to the solution was added 15 ml of water. All insoluble material was removed by centrifugation and the polymerized product was precipitated from the clear alkaline solution by neutralization with 5 ml of 1 *N* HCl. The amorphous solid was washed successively with distilled water, methanol, and finally ether. Each washing was performed by suspending the solid in the solvent used and magnetically stirring it for 5 min. It was then recovered by centrifugation and decantation. The product (**13**) obtained after drying *in vacuo* over phosphorus pentoxide weighed 0.386 mg (89% yield based on the analytically determined amount of hydration): uv $\lambda_{max}^{pH\ 1}$ 263 mμ (ε 5600), $\lambda_{min}^{pH\ 1}$ 233 (2000), $\lambda_{max}^{pH\ 11}$ 270 (4600), $\lambda_{min}^{pH\ 11}$ 243 (2000), $\lambda_{max}^{pH\ 14}$ 274 (4500), $\lambda_{min}^{pH\ 14}$ 243 (1900).

Anal. Calcd for $(C_6H_6N_2O_2 \cdot 0.65H_2O)_n$: C, 48.09; H, 4.92; N, 18.70. Found: C, 48.08; H, 4.87; N, 18.69.

1,2-Bis(6-uracilyl)ethene (14).—A solution of anhydrous orotaldehyde **1** (0.560 g, 0.0040 mol) in 20 ml of warm DMF was added slowly to a suspension of **8** (1.69 g, 0.0036 mol) in 60 ml of ethanol). To the clear solution was then added 20 ml of ethanol containing 10 mmol of sodium ethoxide (from 0.240 g of sodium metal). The mixture was heated to reflux for 5 min, cooled to room temperature, and neutralized with glacial acetic acid to pH ~7. The mixture was chilled and the amorphous solid was separated by centrifugation and decantation. It was washed with ethanol and with ether by the same technique. After drying over P_2O_5 the product weighed 0.68 g (76%). Compound **14** was insoluble in all the organic solvents tried and was purified by dissolving in 0.1 *N* NaOH and reprecipitating with an equal volume of 0.1 *N* HCl. The amorphous solid thus obtained was dried over phosphorus pentoxide *in vacuo*: mp >350°; uv $\lambda_{max}^{pH\ 14}$ 340 mμ (ε 14,300), $\lambda_{min}^{pH\ 14}$ 279 (3800), $\lambda_{max}^{pH\ 11}$ 342 (15,900), $\lambda_{min}^{pH\ 11}$ 283 (3800). (The insolubility of compound **14** precluded accurate uv measurements at lower pH values.)

Anal. Calcd for $C_{10}H_8N_4O_4$: C, 48.39; H, 3.25; N, 22.57. Found: C, 47.86; H, 3.66; N, 22.61.

1,2-Bis(6-uracilyl)ethane (15).—The previous experiment for the preparation of **14** was repeated on a 1-mmol scale. The solid which separated after neutralization (**14**) was resuspended without drying in 50 ml of water and redissolved with the addition of 2.5 ml of 1 *N* NaOH. The solution was hydrogenated at 1 atm over 10% Pd/C. After filtration through Celite, the solution was acidified with glacial acetic acid and the precipitated product was washed with ethanol, then with ether and finally collected by filtration (0.172 g, 76%). Compound **15** (mp >350°) was insoluble in all common organic solvents tried, including hot DMSO and DMF. One purification by the method described for **14** afforded an analytically pure sample of **15**: uv $\lambda_{max}^{pH\ 11}$ 282 mμ (ε 13,500), $\lambda_{min}^{pH\ 11}$ 242 (4200), $\lambda_{max}^{pH\ 14}$ 277 (13,200), $\lambda_{min}^{pH\ 14}$ 244 (4800).

Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.03; N, 22.39. Found: C, 47.85; H, 4.12; N, 22.36.

6-Methylcytidine by the Mercuric Cyanide–Nitromethane Procedure (18).—A mixture of N^4-acetyl-6-methylcytosine **16**[2b] (1.67 g, 0.010 mol) and mercuric cyanide (5.1 g, 0.020 mol) was suspended in 1 l. of redistilled nitromethane and the mixture was magnetically stirred and heated to reflux. After 100 ml of the solvent had distilled off, a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranoyl bromide (from 10.5 g of the 1-*O*-acetyl derivative, 0.020 mol) in 100 ml of dry benzene was added slowly to the refluxing mixture. All solids had dissolved by the end of the addition. Heating of the clear solution was continued for 2 hr. After the reaction mixture was cooled, 0.40 g of crystalline unreacted N^4-acetyl-6-methylcytosine precipitated and was recovered by filtration. The clear filtrate was evaporated to dryness and the residue was partitioned between chloroform and a 30% aqueous potassium iodide solution. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The syrupy residue was then dissolved in 200 ml of hot methanol containing sodium methoxide (from 0.100 g of sodium metal). The solution was heated to reflux for ~15 min, cooled to ambient temperature, and neutralized with glacial acetic acid. Evaporation to dryness afforded a syrup which was freed from methyl benzoate by two extractions with ether. The residue crystallized from methanol to afford, in two crops, 1.40 g of 6-methylcytidine (**18**) (71% yield based on unrecovered N^4-acetyl-6-methylcytosine). One recrystallization from methanol gave analytically pure material, mp 236–238° dec (lit.[2b] mp 236–238°). All its other physical constants were identical with those already reported for 6-methylcytidine.

6-Methyluridine (19).—To a solution of **18** (1.20 g, 0.0047 mol) and sodium bisulfite (4.85 g, 0.0467 mol) in 25 ml of water was added acetic acid to bring the pH to ~5. The solution was heated on a steam bath for 2.5 hr, cooled to ambient temperature, and treated with a concentrated aqueous solution of barium hydroxide (8.55 g, 0.500 mol). The mixture was then filtered from the precipitate of barium sulfite and the clear filtrate was passed through a short column of Dowex 50 W (H^+) (170 ml wet volume). After the column was washed free of all uv-absorbing materia., the eluate was evaporated to dryness and the residual water was azeotroped with ethanol. Crystallization of the residue from ethanol afforded crystalline 6-methyluridine (0.637 g, 53%) in two crops. The product was identical in all respects with an authentic sample of 6-methyluridine.[2] A study of the rate of deamination of cytidine under the conditions used here indicated that complete conversion to uridine had occurred after only 20 min.

***trans*-3-(6-Uridinyl)acrylic Acid Ethyl Ester (23).**—A solution of 6-methyluridine (1.976 g, 0.0077 mol) in 12 ml of acetic anhydride was heated to reflux for 2 hr. The reaction mixture was cooled to room temperature and treated with 3 ml of water. The solution was again heated for another 20 min and finally evaporated to dryness. The crystalline residue was recrystallized from toluene–ethyl acetate to afford 2.30 g (78%) of pure **2′,3′,5′-tri-*O*-acetyl-6-methyluridine (20)**: mp 152–153°; pmr ($CDCl_3$) δ 2.11 (9, m, $COCH_3$), 2.27 (3, s, CH_3 at C-6), 4.06–4.77 (3, m, H-4′ and H-5′), 5.48–5.90 (4, m, H-1′, H-2′, H-3′, and H-5), 9.70 (1, broad singlet, NH).

To a solution of **20** (1.152 g, 0.0030 mol) in 9 ml of dioxane–acetic acid (11:1) was added 1 g (0.009 mol) of selenium dioxide.[20] The well-stirred suspension was heated to reflux for 14 hr. Tlc of the supernatant solution (chloroform–methanol, 10:1) indicated the initial formation of an intermediate compound with R_f 0.48 (presumed to be the 6-hydroxymethyl derivative). As the reaction proceeded this initial product slowly disappeared as the final product **21** (R_f 0.57) increased in concentration. This aldehyde was detected by its absorbance under uv light and by spraying with a solution of dinitrophenylhydrazine hydrochloride. The mixture was diluted with benzene and filtered. The filtrate was evaporated to dryness and the residue was partitioned between water and chloroform. The organic layer was then dried over sodium sulfate. A small sample of the crude product was chromatographed on a 20 × 20 cm silica gel PF_{254} (2 mm) plate and the band corresponding to the aldehyde was eluted with ethyl acetate. After evaporation of the eluate and drying of the residue *in vacuo*, the pure sample of **21** was used for pmr measurements: pmr ($CDCl_3$) δ 2.10 (9, s, $COCH_3$), 4.09–4.61 (3, m, H-4′ and H-5′), 5.33–6.02 (2, m, H-2′ and H-3′), 6.34 (1, s, H-5), 6.52 (1, d, H-1′), 9.53 (1, s, CHO), 10.00 (1, broad singlet, NH), $J_{1',2'}$ = 2.5–3.0 Hz. Evaporation of the dried chloroform solution afforded **21** as a syrup which was dissolved immediately in 5 ml of dry DMF and treated with 1.22 g (0.0035 mol) of carboxymethylenetriphenylphosphorane under dry nitrogen. Tlc of the mixture after standing at room temperature for 16 hr indicated completion of the reaction. An excess of the phosphorane was destroyed by addition of 1 ml of 40% aqueous formaldehyde and the mixture was evaporated to dryness. The crude residue **22** was dissolved in 50 ml of ethanol containing sodium ethoxide (from 200 mg of sodium metal) and the deacetylation mixture was left standing overnight at room temperature. The stiff gelatinous mass was first diluted with an equal volume of ethanol and then treated with an excess of Dowex 50 W (H^+) with vigorous stirring. Solids dissolved as neutralization proceeded. After filtration, the clear solution was evaporated to dryness and the residue which contained the title compound **23** together with some triphenylphosphine oxide was freed of the latter by extraction with benzene and then ether. Tlc indicated the presence of **23** as the major product together with a minor component (possibly the cis isomer). Crystallization of the syrupy residue from ethyl acetate gave 0.189 g of **23** as white, stout prismatic crystals in three crops, mp 152–156°. The mother liquor was applied to two 20 × 20 cm silica gel PF_{254} (2 mm) plates which after chromatography in chloroform–methanol (10:1) and elution of the appropriate band with ethanol–

(20) Selenium dioxide (99%) was purchased from J. T. Baker Chemical Co., Phillipsburg, N. J.

ethyl acetate (20:80) yielded 0.220 g of pure **23** as a homogenous syrup (40% total yield). This syrup crystallized from ethanol as small aggregates of white, fibrous needles (110 mg in two crops, mp 152–156°). The two crystalline forms obtained for product **23** had identical physical properties (uv, pmr, analysis, tlc) except for their ir spectra (KBr). It was found possible to convert one form (prisms) to the other (fibers) by redissolving crystals of the former in hot ethanol and seeding the solution with crystals of the latter. The ir spectrum was found to have changed accordingly: uv $\lambda_{max}^{pH\ 1}$ 290 mμ (ε 7300), $\lambda_{min}^{pH\ 1}$ 259 (4600), $\lambda_{max}^{pH\ 11}$ 297 (6400), $\lambda_{min}^{pH\ 11}$ 264 (5200); pmr (DMSO-d_6) δ 1.27 (3, t, CH_3), 3.20–4.55 (7, m, H-2′, H-3′, H-4′, H-5′, and $COCH_2$), 4.60–5.40 (3, two doublets and one triplet, all exchangeable in D_2O, sugar OH's), 5.63 (1, d, H-1′), 5.97 (1, s, H-5), 6.61 and 7.54 (2, two AB doublets, CH=CH), 11.49 (1, broad singlet, NH), $J_{1',2'}$ = 5.0 Hz, J_{trans} = 16.0 Hz.

Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.01; H, 5.30; N, 8.09.

Registry No.—**2**, 36807-59-7; **3**, 13345-12-5; *cis*-**4**, 36807-60-0; *trans*-**4**, 36807-61-1; **5**, 22724-20-5; **5** phenylhydrazone, 36803-37-9; **7**, 18592-13-7; **8**, 36803-39-1; **9**, 36803-40-4; **10**, 15043-03-5; **11**, 36803-42-6; **12**, 36803-43-7; **13**, 36812-98-3; **14**, 36803-44-8; **15**, 36803-45-9; **20**, 36807-62-2; **21**, 36807-63-3; **23**, 36806-64-4.

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Interconversions of Hexofuranosyl Nucleosides. IV. Synthesis of Nucleosides Derived from 6-Deoxy-L-glucose[1]

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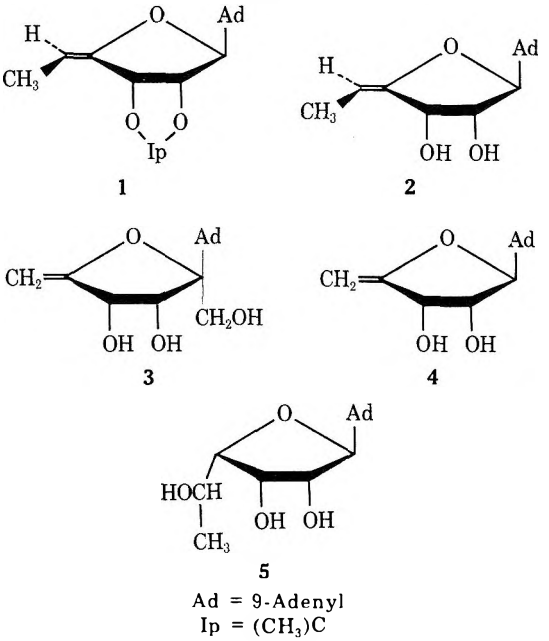
Acetolysis of 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose (**6**) in 10:1 acetic acid–acetic anhydride followed by reaction of the crude product with 6-benzamidochloromercuripurine and titanium tetrachloride in refluxing 1,2-dichloroethane, gave 9-(6-deoxy-β-L-glucofuranosyl)adenine (**8**) and 9-(6-deoxy-α-L-mannopyranosyl)adenine (**7**) in a ratio of 4:1, after removal of blocking groups. Similarly, acetolysis of 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-L-mannofuranose under the same conditions, followed by formation of the blocked nucleoside, afforded crystalline 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-β-L-glucofuranosyl)adenine (**9**) and not 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine, as had been previously reported. Acetolysis of **6**, removal of the blocking groups with base, and acetylation of the free sugars gave the crystalline anomeric 6-deoxy-1,2,3,4-tetra-*O*-acetyl-L-glucopyranoses (**11** and **12**) in good yield. 6-Deoxy-L-glucose was prepared in 62% yield from the β anomer **11**. Both **11** and the α anomer **12** were converted to 6-deoxy-2,3,4-tri-*O*-acetyl-α-L-glucopyranosyl bromide (**14**) by reaction with hydrogen bromide in acetic acid. The nucleoside, 9-(6-deoxy-β-L-glucopyranosyl)adenine, was prepared by reaction of **14** with 6-benzamidochloromercuripurine in boiling xylene followed by removal of the blocking groups with sodium methoxide.

In the previous article in this series[2] the synthesis of 9-(5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranosyl)adenine (**1**) (Chart I) was described. The deblocked nucleoside **2** was of interest because of its structural relationship to the nucleoside antibiotic, decoyinine (**3**), and to a biologically active analog of **3**, 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**4**).[3] However, removal of the isopropylidene group of **1** under the various acidic conditions attempted resulted in a complete degradation of the nucleoside because of its acid-unstable enol ether structure. The same problem arose in the preparation of **3** and **4**, but this was solved with use of the more acid-labile ethoxymethylidene blocking group in place of the isopropylidene group.[3] Therefore, a decision was made to prepare an alkoxymethylidene derivative of **2** with the expectation that this blocking group could be removed under conditions that would not hydrolyze the *N*-glycosyl bond.[4] To do this it was necessary to prepare alkoxymethylidene derivatives of 9-(6-deoxy-α-L-mannofuranosyl)adenine (**5**); therefore, a large quantity of **5** was required. Two routes leading to **5** have been reported,[5,6] but neither one is straightforward,

CHART I



Ad = 9-Adenyl
Ip = $(CH_3)C$

(1) This work was supported, in part, by Grant No. T-442 from the American Cancer Society.

(2) L. M. Lerner, *J. Org. Chem.*, **37**, 477 (1972).

(3) J. R. McCarthy, R. K. Robins, and M. J. Robins, *J. Amer. Chem. Soc.*, **90**, 4993 (1968).

(4) C. A. Dekker and L. Goodman in "The Carbohydrates," Vol. IIA, W. Pigman and D. Horton, Ed., Academic Press, New York, N. Y., 1970, p 1.

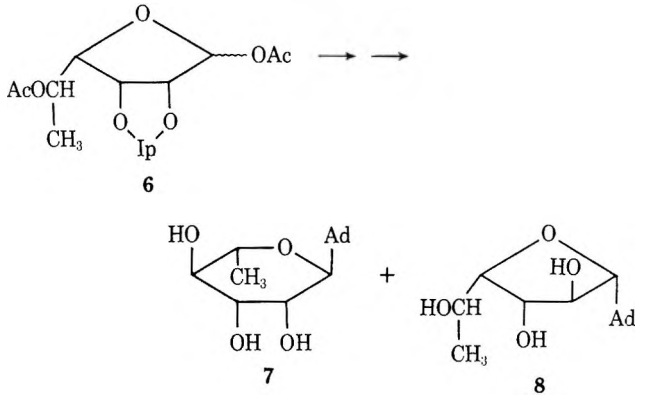
(5) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

(6) L. M. Lerner and Y. Y. Cheng, *Carbohyd. Res.*, **14**, 297 (1970).

gives high yields, or can be speedily accomplished. Therefore, an attempt was made to prepare **5** from 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose[6] (**6**) by acetolysis to form the impure tetraacetate, immediate formation of the blocked nucleoside, and subsequent removal of the blocking groups. A small amount of 9-(6-deoxy-α-L-mannopyranosyl)-adenine[7] (**7**) was also expected from this reaction sequence, but separation of **5** from **7** was not expected to present a serious problem.

Acetolysis of **6** gave a syrup which was coupled with 6-benzamidochloromercuripurine by the titanium tetrachloride method.[8] Removal of the blocking groups with sodium methoxide in methanol, separation of the nucleosides from unreacted sugars *via* their picrates,[7] and chromatography on an anion exchange column[9] afforded **7** and a nucleoside which was definitely not **5** in a ratio of about 1:4 (Chart II). This

CHART II



compound was identified as 9-(6-deoxy-β-L-glucofuranosyl)adenine (**8**), the enantiomer of which was first reported by Reist, *et al.*[10] Evidence for this identification is presented in Table I.

TABLE I

COMPARISON OF PHYSICAL PROPERTIES OF THE ENANTIOMERIC FORMS OF 9-(6-DEOXY-β-GLUCOFURANOSYL)ADENINE

Property	D form[a]	L form
Mp, °C	118–118.5	119.5–121
$[\alpha]_D$	−59.9°	+61.6°
Analysis	$C_{11}H_{15}N_5O_4 \cdot C_2H_5OH$	$C_{11}H_{15}N_5O_4 \cdot C_2H_5OH$
IO_4^- uptake	0.9 mole equiv/96 hr	0.81 mole equiv/96 hr 0.90 mole equiv/144 hr
Picrate mp, °C	204–208 dec	207–209 dec

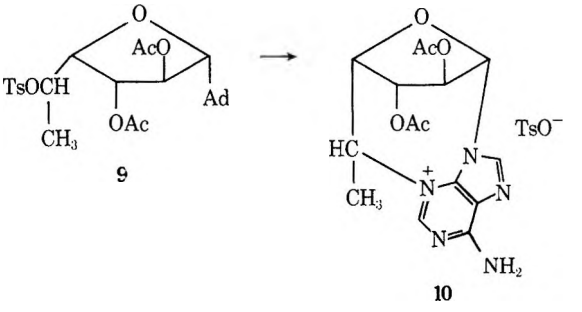
[a] Reference 10.

In addition, the infrared spectrum of **8** had the peaks reported for the D form and the ultraviolet spectrum indicated substitution at N-9 of the purine, a point which was not recorded for the D nucleoside.

The reason for the isolation of **8** instead of **5** is now understandable on the basis of some recent developments concerning epimerization at C-2 of carbohydrates. It has been reported[11,12] that acetolysis of aldofuranoses and their derivatives, which have cis hydroxyls at C-2 and C-3, under conditions quite similar to that described in this paper, resulted in epimerization at C-2. Some of this work had been based upon an older report by Jerkeman,[13] and two mechanisms[11,13] have been suggested to account for this phenomenon, both of which require a furanose ring and three adjacent hydroxyl groups with the two ring hydroxyls in a cis relationship. In the earlier paper,[13] it was suggested from chromatographic data that the only products were furanose acetates, but in the present work the isolation of **7** would indicate otherwise. It is important to note that in agreement with the previous reports and the mechanisms proposed for the acetolysis reaction, epimerization at C-2 only occurred with the furanose ring and not with the pyranose ring. During acetolysis an exchange of acetate groups occurred which allowed a portion of the furanose ring to rearrange to the pyranose form, and this portion of material was not converted into the L-gluco isomer. The 1:4 ratio of **7**:**8** should not be construed as being a real indication of the ratio of L-manno to L-gluco isomers because the sugars may have reacted to a different extent with the nitrogenous base.

Because of the nature of the reaction products isolated after acetolysis of **6** and formation of the nucleosides, a reexamination of the structure of a closely related product previously reported from this laboratory was felt to be necessary. Crystalline 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)-adenine was reported to be the product of a series of reactions which entailed acetolysis of 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-L-mannofuranose under the same conditions reported herein.[2] It appeared to be a good possibility that this nucleoside derivative was really 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-β-L-glucofuranosyl)adenine (**9**) (Chart III).[14] Evidence for this structure was obtained by

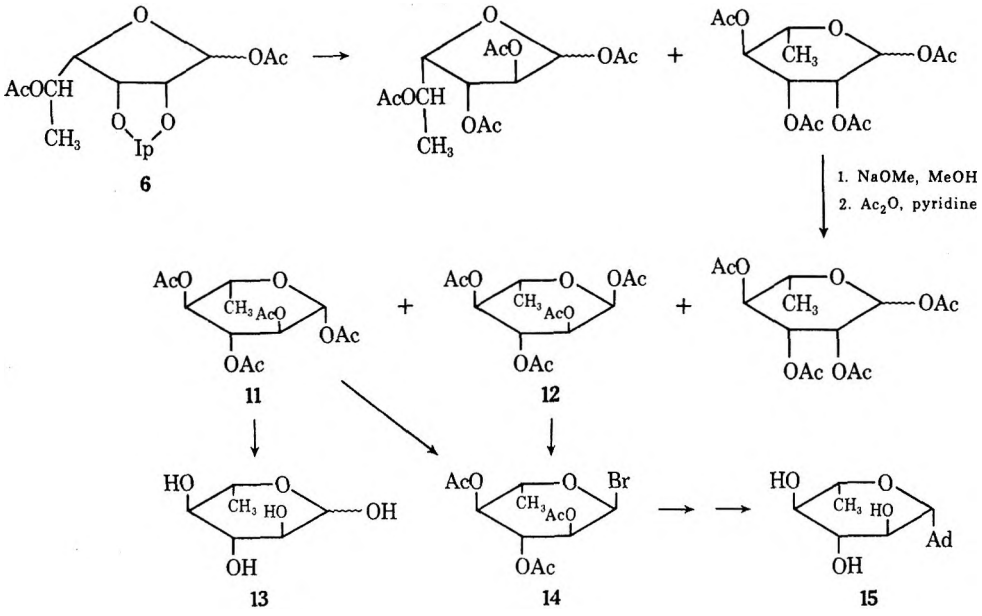
CHART III



formation of cyclonucleoside **10** in either boiling *N*,*N*-dimethylformamide or dioxane. The cyclonucleoside did not crystallize but it did show an expected ultraviolet maximum at 272 mμ and tosylate anion peaks at 1010 and 681 cm^{-1} in the infrared. Such a structure as **10** could not have formed unless the adenine ring and

(7) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).
(8) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 12 (1955); J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).
(9) C. A. Dekker, *J. Amer. Chem. Soc.*, **87**, 4027 (1965).
(10) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **23**, 1753 (1958).
(11) W. Sowa, *Can. J. Chem.*, **49**, 3292 (1971).
(12) G. J. F. Chittenden, *Carbohyd. Res.*, **22**, 491 (1972).
(13) P. Jerkeman, *Acta Chem. Scand.*, **17**, 2769 (1963).
(14) The author is indebted to Dr. Derek Ball for bringing the possibility of this to his attention. This information was also instrumental in the positive identification of **8**.

CHART IV



C-5′ were on the same side of the furanose ring. However, such evidence does not prove that the configuration of the sugar moiety is L-gluco, although it would be expected that the main product resulting from reaction of the sugar derivative with the mercuric chloride salt of the base would have a configuration at the anomeric carbon atom that is trans to the hydroxyl at C-2′.[15] Because **9** could not be converted to **8** without extensive degradation[2] and it was not feasible to prepare **9** from **8**, 100-MHz nuclear magnetic resonance spectroscopy was used[16] in order to gain further information in support of the structure of **9**, especially as concerned the relative configurations of C-2′ and C-3′. Salient features of the spectrum are shown in Table II.

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA FOR 9-(6-DEOXY-2,3-DI-*O*-ACETYL-5-*O*-*p*-TOLUENESULFONYL-β-L-GLUCOFURANOSYL)ADENINE (**9**)[a]

Position, τ	Intensity	Multiplicity	Assignment
1.78	1	Singlet	H-2
1.84	1	Singlet	H-8
2.25	2	Doublet	Tosyl protons ortho to sulfonate
2.61	2	Doublet	Tosyl protons ortho to methyl
2.70	2	Singlet	NH_2
3.89	1	Broad singlet	H-1′
4.24	1	Broad singlet	H-2′
4.64	1	Doublet (distorted)	H-3′
4.96	1	Multiplet	H-5′
5.65	1	Multiplet	H-4′
7.62	3	Singlet	Tosyl methyl
7.89, 7.94	6	Two singlets	Acetate methyls
8.73	3	Doublet	C-6′ methyl

[a] Obtained in DMSO-d_6 using tetramethylsilane as reference.

The nmr spectrum appeared to support the structure of **9**. The trans relationship of the H-1′ and H-2′ protons is supported by the singlets at τ 3.89 and 4.24. The broadening of the peaks may be due to long-range coupling and it is of interest to note that in a double resonance experiment, in which the peak due to H-4′ was irradiated, the broad singlet due to H-1′ broke into a doublet. The peak at τ 4.64 for H-3′ gave a doublet due to the expected coupling of H-3′ with H-4′ and supports the trans relationship of H-2′ and H-3′.[17] The assignments of the multiplets at τ 4.96 and 5.65 were made after double-resonance experiments in which irradiation at τ 5.65 caused the doublet due to H-3′ to collapse to a singlet and irradiation at τ 4.96 caused the doublet at τ 8.73 (C-6′ methyl) to collapse to a singlet.

Further proof of the identity of the sugar in the present experiments as 6-deoxy-L-glucose (**13**) resulted in the development of a very simple and practical preparation of this rare sugar (Chart IV). After acetolysis of **6**, the acetyl groups were removed under mild basic conditions, which resulted in a rearrangement of the ring structure to the pyranose form. The pyranoses (a mixture of **13** and 6-deoxy-L-mannose) were acetylated with acetic anhydride in pyridine and the anomeric tetraacetates **11** and **12** were fractionally crystallized. These compounds do not seem to have been previously reported, although their D enantiomers are known.[18,19] Both **11** and **12** were converted into 6-deoxy-2,3,4-tri-*O*-acetyl-α-L-glucopyranosyl bromide (**14**), and although the physical data for **14** were similar to those of the D form,[20] the compound was too unstable to get a reliable elemental analysis. Removal of the acetyl groups of **11** with methanolic sodium methoxide resulted in a 62% yield of **13**.

Condensation of **14** with 6-benzamidochloromercuripurine by the procedure of Davoll and Lowy[21] and removal of the blocking groups afforded a 55% yield of

(15) B. R. Baker, in Ciba Foundation Symposium, "Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957, p 120.

(16) Nmr spectra were obtained by Dr. Harry Agahigian of the Baron Consulting Co., Orange, Conn.

(17) J. D. Stevens and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1799 (1968).

(18) W. Schuepp and E. Hardegger, *Helv. Chim. Acta*, **53**, 1336 (1970).

(19) E. Hardegger and R. M. Montavon, *ibid.*, **29**, 1199 (1946).

(20) J. Compton, *J. Amer. Chem. Soc.*, **60**, 395 (1938).

(21) J. Davoll and B. A. Lowy, *ibid.*, **73**, 1650 (1951).

9-(6-deoxy-β-L-glucopyranosyl)adenine (**15**). Preparation of **15** directly from a crude syrupy mixture containing **11** and **12** using the titanium tetrachloride method of coupling did not offer any advantages, since purification of the product necessitated the use of chromatography.

Proof of structure of **15** was supported by an ultraviolet maximum at 260 mμ, indicating that the sugar was bonded to adenine at N-9. The compound consumed 1.8 molar equiv of periodate, which supported the pyranose ring. In order to ascertain the configuration at the anomeric carbon atom, a polarimetric investigation of the dialdehyde product **17** obtained after periodate oxidation was made. 9-(6-Deoxy-β-L-galactopyranosyl)adenine[22] (**16**) and **7** were used as reference compounds and the results are shown in Table III.

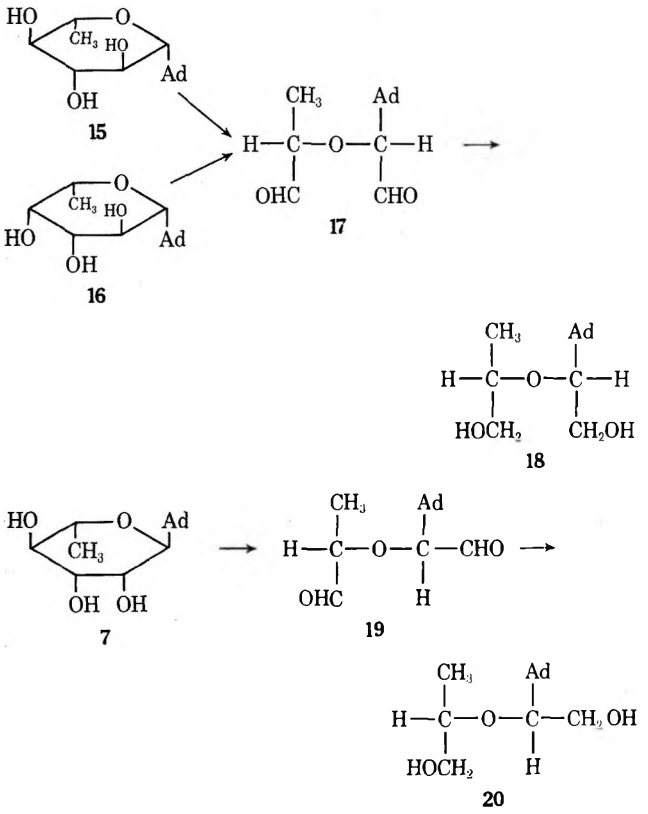
TABLE III
POLARIMETRIC STUDIES WITH NUCLEOSIDES

Nucleoside	$[\alpha]_D$ after IO_4^- oxidation[a]	$[\alpha]_D$ after $NaBH_4$ reduction[a]
15	−5°	−50°
16	−7°	−46° (−54°)[b]
7	−5°	+74° (+81°)[b]

[a] Based upon the calculated dry weight of the dialdehyde or dialcohol product. [b] Values in parentheses are for the pure crystalline dialcohols, ref 22.

It was expected that **15** and **16** would give the same dialdehyde **17**, whereas **7** would give the diasteromeric dialdehyde **19** (Chart V). However, the specific rotations were too close to each other and too near zero to be of any use in structure determination. Therefore, in a separate experiment, the dialdehydes were reduced with sodium borohydride to the known dialcohols[22] **18** and **20** and their specific rotations were determined. The results indicated that **15** had the β-L configuration.

CHART V



Experimental Section[23]

9-(6-Deoxy-β-L-glucofuranosyl)adenine[24] (**8**).—To an ice-cold mixture containing 10.9 g of 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose[6] (**6**), 224 ml of glacial acetic acid, and 22.4 ml of acetic anhydride was added, dropwise, 12.5 ml of concentrated sulfuric acid. After 48 hr at room temperature the reaction mixture was poured into 500 g of ice, and this was stirred vigorously until all of the ice had melted. Chloroform (100 ml) was added to the stirring mixture, the layers were separated, and the aqueous layer was extracted two additional times with 100-ml portions of chloroform. The chloroform extracts were combined and washed with cold water (five 300-ml portions), saturated sodium bicarbonate (two 300-ml portions), and once again with water. The chloroform solution was dried and evaporated, and traces of acetic acid were removed by evaporation of toluene, leaving an oil which weighed 8.4 g.

The oil (8.3 g, 25 mmol) was dissolved in 1200 ml of 1,2-dichloroethane to which 14.2 g (30 mmol) of 6-benzamidochloromercuripurine and 14.2 g of Celite-545 were added. A portion of the solvent (200 ml) was distilled, 3.3 ml (30 mmol) of titanium tetrachloride in 200 ml of 1,2-dichloroethane was added, and the mixture was refluxed for 22 hr.[8] The mixture was cooled, 500 ml of saturated sodium bicarbonate was added, and vigorous stirring was continued for 2 hr. The mixture was filtered through a pad of Celite-545, the filter cake was washed with 250 ml of warm 1,2-dichloroethane, the organic layer was separated, and the solvent was evaporated. The residue was dissolved in 200 ml of chloroform and washed with 30% aqueous potassium iodide (two 150-ml portions) and water (200 ml), and dried. Evaporation gave 12.1 g of a foam which was dissolved in 150 ml of methanol, treated with 10 ml of 1 *N* methanolic sodium methoxide, and heated at reflux for 1 hr. This solution was evaporated to dryness, dissolved in 100 ml of water, brought to neutrality with acetic acid, and washed with chloroform (three 50-ml portions). The aqueous layer was evaporated, leaving a red-colored residue which was dissolved in 50 ml of warm methanol and treated with 140 ml of 10% methanolic picric acid. A yellow precipitate formed immediately and the flask was chilled for 2 hr. The filtered product was washed with cold methanol and ether, giving 7.1 g.

The picrate was suspended in 1 l. of stirring hot water, the yellow color was discharged by addition of Bio-Rad AG1-X8 (CO_3^{2-}) resin, and stirring was continued for an additional 1.5 hr.[7] Filtration and evaporation of the water left a white foam which was redissolved in a small amount of water and placed on top of a column (31 × 2.4 cm) of Bio-Rad AG1-X2 (OH, 200–400 mesh) resin.[9] Elution of the column was carried out with 30% aqueous methanol and 10-ml fractions were collected and monitored by ultraviolet absorption at 254 mμ. Fractions 35–65 were combined and evaporated to dryness, and the product (550 mg, 8%) was crystallized from ethanol. This product was identified as 9-(6-deoxy-α-L-mannopyranosyl)adenine (**7**), mp 214–216°, $[\alpha]^{23}D$ −61° (*c* 1.1, H_2O). This compound did not depress the melting point upon admixture with an authentic sample[25] of **7**, the infrared spectra were identical, as also were the mobilities upon paper chromatography in two solvent systems.

Fractions 205–800 were pooled and evaporated, and crystallization occurred during this step to give 2.12 g (30%), which was recrystallized from ethanol to afford 1.94 g of **8** in three crops: mp 119.5–121°; $[\alpha]^{22}D$ +61.6° (*c* 0.813, H_2O); uv max (0.1 *N* HCl) 258 mμ (ε 14,500), (H_2O) 259 (14,450), (0.1 *N*

(22) L. M. Lerner and R. R. Rossi, *Biochemistry*, **11**, 2772 (1972).

(23) General methods and instrumentation are described in the first paper of this series: L. M. Lerner, *J. Org. Chem.*, **37**, 470 (1972). Moist organic solutions were dried over anhydrous magnesium sulfate and evaporations were performed under reduced pressure at bath temperatures between 40 and 50°.

(24) In a preliminary experiment, Dr. Davaluri R. Rao prepared this compound during an attempted preparation of **5**.

(25) A sample of **7** was prepared by Dr. Ralph R. Rossi following the procedure in ref 7.

NaOH) 259 (15,400). Periodate consumption is reported in Table I.

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot C_2H_5OH$: C, 47.70; H, 6.47; N, 21.40. Found: C, 47.03; H, 6.10; N, 21.83.

A crystalline picrate, prepared by mixing several milligrams of **8** in water with a saturated aqueous solution of picric acid, had mp 207–209° dec.

Cyclonucleoside 10 from 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-β-L-glucofuranosyl)adenine (9).—A solution containing 50 mg of **9** in 3 ml of *N*,*N*-dimethylformamide was heated at reflux for 1 hr. The solvent was evaporated but the syrupy product failed to crystallize: λ_{max}^{MeOH} 272 mμ; ir (film, NaCl) 1010 and 681 cm^{-1} (tosylate anion). The syrup was also soluble in cold water. Tlc[26] in 5:1 chloroform–methanol gave R_f 0.05; **9** had R_f 0.54.

Anomers of 6-Deoxy-1,2,3,4-tetra-*O*-acetyl-L-glucopyranose (11 and 12).—Compound **6** (35 g) was treated with 735 ml of acetic acid, 73.5 ml of acetic anhydride, and 41 ml of concentrated sulfuric acid as described for the preparation of **8**. The syrup (25.4 g) which was obtained was dissolved in 280 ml of methanol, treated with 20 ml of 1 *N* methanolic sodium methoxide, and allowed to stand at room temperature for 40 min. The solution was brought to neutrality with Dowex 50 (H^+) resin, the resin was removed by filtration and washed thoroughly with methanol, and the methanol was evaporated. A thin syrup remained which formed a hard gum (13.3 g) upon evaporation (three times) with acetone. The entire gum was dissolved in 100 ml of dry pyridine (heat required) and chilled in an ice bath, and 110 ml of cold acetic anhydride was added in small portions over a period of 20 min. After 1 hr at 0°, the solution was kept at room temperature for 23 hr. The mixture was chilled in ice again and 120 ml of ice-cold ethanol was added. The solution was stirred for 30 min and then for 1 hr at room temperature, whereupon it was evaporated to a thin yellow syrup. This was dissolved in 150 ml of chloroform and washed with cold 10% aqueous sulfuric acid (100 ml), cold water (200 ml), saturated sodium bicarbonate (150 ml), and again with water (200 ml). After being dried, the chloroform was evaporated and the syrup was dissolved in warm ethanol. Large prismatic rods were slowly deposited over 3 days to afford 5.85 g of 6-deoxy-1,2,3,4-tetra-*O*-acetyl-β-L-glucopyranose (**11**), mp 148–149°. One recrystallization from ethanol raised the melting point to 149–149.5°, $[\alpha]^{23}D$ −21.6° (*c* 1.15, $CHCl_3$) [reported[18] for the D form, mp 146°, $[\alpha]D$ +21.5° (*c* 1, $CHCl_3$)].

Anal. Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.51; H, 6.07.

The mother liquor was concentrated somewhat by boiling and stored at room temperature. Large needles were deposited which closely resembled **11**, 0.71 g, mp 110–122°. 6-Deoxy-1,2,3,4-tetra-*O*-acetyl-α-L-glucopyranose (**12**) was isolated in pure form by recrystallization from ethanol to yield 334 mg, mp 122–124.5°, $[\alpha]^{23}D$ −104° (*c* 1.01, $CHCl_3$) [reported[19] for the D form, mp 117°, $[\alpha]D$ +122° (*c* 1.3, $CHCl_3$)].

Anal. Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.69; H, 6.05.

Additional concentration of the mother liquor by boiling yielded 4.1 g of crystals, mp 97–103°. Careful recrystallization from ethanol using seeds of **11** or **12** could effect a partial separation of the anomers. One recrystallization of the bulk product gave clumps of crystals melting at 110–120° and other clumps melting at 137–142°. No further crops of crystals of **11** and **12** could be isolated. Presumably the remaining 12 g of syrup, $[\alpha]^{25}D$ −50° (*c* 1.35, $CHCl_3$), was an anomeric mixture of peracetylated 6-deoxy-L-mannopyranose.

6-Deoxy-L-glucose (13).—In 19 ml of warm methanol was dissolved 1 g of **11**, the solution was chilled in an ice bath, and 1 ml of 1 *N* methanolic sodium methoxide was added. The solution was kept at room temperature for 1.5 hr and neutralized with Dowex 50 (H^+) resin, the resin was removed by filtration, and the methanolic solution was concentrated by evaporation to approximately 15 ml. The solution was treated with activated charcoal and the methanol was evaporated. A small amount of warm acetone was added and the clear, colorless syrup was rubbed with a glass rod until crystallization occurred. After standing for several hours, the crystals (166 mg) were filtered off and two more crops (139 mg) were obtained (305 mg, 62%), mp 142–143°, $[\alpha]^{22}D$ −29.8° (3 hr, final; *c* 2.01, H_2O) [lit.[27] mp 142–144°, $[\alpha]^{20}D$ −29.9 (3 hr, final; *c* 2, H_2O)].

6-Deoxy-2,3,4-tri-*O*-acetyl-α-L-glucopyranosyl Bromide (14). From 11.—To 3 g of **11** was added 14 ml of a 30–32% solution of hydrogen bromide in acetic acid (Eastman). The flask was stoppered and shaken for 15 min, by which time the compound had dissolved. Almost immediately a mass of white crystals began to form. After 1 hr, 20 ml of chloroform was added which dissolved the crystals. The solution was diluted further with 80 ml of chloroform, washed with ice–water (three 150-ml portions), and dried. The chloroform was evaporated, leaving a white solid which was recrystallized from benzene in three crops as large, colorless needles, 2.49 g (78%), mp 151–153° $[\alpha]^{24}D$ −255° (*c* 1.12, $CHCl_3$) [reported[20] for the D form mp 150–152°, $[\alpha]D$ +247° (*c* 3.89, $CHCl_3$)]. Preparations of the bromide were unstable even in a desiccator in the freezer and would decompose within 48 hr. The analysis was, therefore, quite poor.

From 12.—A mixture of 334 mg of **12** and 2.5 ml of hydrogen bromide in acetic acid (30–32%, Eastman) was allowed to react and worked up as described above. A yield of 168 mg of **14** was obtained which was identical in all respects with the compound prepared from **11**.

9-(6-Deoxy-β-L-glucopyranosyl)adenine (15). From 14.—A mixture of 2.7 g (5.7 mmol) of 6-benzamidochloromercuripurine, 2.7 g of Celite-545, and 200 ml of dry xylene was prepared and 30 ml of the solvent was distilled to remove traces of moisture. To this hot solution was added 2.0 g (5.7 mmol) of freshly prepared **14** and the mixture was heated at reflux for 3 hr.[21] The mixture was filtered while still hot and the filter cake was washed with 100 ml of warm chloroform. The solvents were evaporated, the residue was dissolved in 100 ml of chloroform, and the solution was filtered. The chloroform solution was washed with 30% aqueous potassium iodide (two 100-ml portions) and water (100 ml), and dried. Evaporation gave 4.4 g of a light orange oil, which was dissolved in 100 ml of methanol, and 9.5 ml of 1 *N* methanolic sodium methoxide was added. The solution was heated at reflux for 1 hr, the methanol was evaporated, and the residue was dissolved in 100 ml of water. Acetic acid was used to adjust to neutral pH, and the solution was washed with chloroform (three 25-ml portions) and evaporated to dryness. The residue was dissolved in 18 ml of methanol, and 50 ml of 10% methanolic picric acid was added. The flask was chilled in an ice bath for 1 hr and the picrate (2.03 g) was isolated by filtration and washed with cold methanol and ethyl ether.

The entire amount of picrate was dissolved in 300 ml of hot water, the yellow color was discharged with Bio-Rad AG1-X8 (CO_3^{2-}) resin, and stirring was continued for 1 hr.[7] The filtered solution was evaporated, whereupon crystallization occurred. The flask was chilled until crystallization appeared to be complete, affording 0.89 g (55%). Recrystallization from aqueous ethanol gave clusters of rosettes on the walls of the flask. **15** (0.72 g) was deposited in two crops: mp 290–294° dec; $[\alpha]^{23}D$ +21° (c 1.26, H_2O); uv max (0.1 *N* HCl) 257 mμ (ε 14,640), (H_2O) 259 (14,940), (0.1 *N* NaOH) 259 (15,250). The nucleoside consumed 1.81 mol of periodate per mol of nucleoside in less than 24 hr.

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.38; N, 24.90. Found: C, 46.89; H, 5.46; N, 24.98.

From 11 and 12.—From 13.7 g of **6** was prepared 13.4 g of a thick syrup containing **11** and **12** as described above. A portion of this (8.3 g) was treated with 14.2 g of 6-benzamidochloromercuripurine, 14.2 g of Celite-545, 3.3 ml of titanium tetrachloride, and 1200 ml of 1,2-dichloroethane as described for the preparation of **8**. A brown gum weighing 10.4 g was isolated which was dissolved in 150 ml of methanol and treated with 20 ml of 1 *N* methanolic sodium methoxide. After 45 min at reflux, the solution was evaporated, and the residue was dissolved in 100 ml of water and neutralized with acetic acid. The solution was washed with chloroform and the water was evaporated. A picrate (4.14 g) was prepared as described above, this was treated with the carbonate resin in 600 ml of hot water, and the water was evaporated. The product would not crystallize at this stage and so it was chromatographed on a column (40 × 2 cm) of Bio-Rad AG1-X2 (OH, 200–400 mesh) resin[9] which was packed with water. The product was eluted with 30% aqueous methanol, giving 1.29 g of slightly off-white crystals from ethanol, mp 287–291° dec. Recrystallization from aque-

(26) Tlc was performed on Brinkman F_{254} plates of 0.25-mm thickness.

(27) E. Zissis, N. K. Richtmyer, and C. S. Hudson, *J. Amer. Chem. Soc.*, **73**, 4714 (1951).

ous ethanol gave clusters of rosettes, mp 291–293° dec, identical with **15** prepared above.

Periodate Uptake.—Periodate uptake was determined spectrophotometrically at 300 mμ by the procedure developed for nucleosides by Rammler and Rabinowitz.[28]

Polarimetric Studies.—The procedure used here was similar to that used previously for the determination of anomeric configuration of a number of hexopyranosyl nucleosides,[29] except that the rotations of the dialdehydes and the dialcohols were determined in separate experiments.

Dialdehydes.—Between 10 and 13 mg of each nucleoside was weighed into a 2-ml volumetric flask and dissolved in 0.75 ml of water (heated, if necessary), and 0.5 ml of 0.25 *M* sodium metaperiodate was added at room temperature. The reaction was allowed to proceed in the dark for 3 days, the volume was adjusted to 2 ml with water, and the rotations were determined. The results are shown in Table III.

Dialcohols.—The exact same procedure was used here as described above except that after the 3 days, 60 mg of sodium borohydride was added, and the reaction was allowed to proceed for 45 min. The excess borohydride was destroyed by careful addition of 0.4 ml of 20% acetic acid. When effervescence ceased (1–2 hr), the volume was adjusted to 2 ml and the rotation was determined.

(28) D. H. Rammler and J. C. Rabinowitz, *Anal. Biochem.*, **4**, 116 (1962).
(29) L. M. Lerner and P. Kohn, *J. Med. Chem.*, **7**, 655 (1964).

Registry No.—**7**, 36807-77-9; **8**, 36807-78-0; **8** picrate, 36807-79-1; **9**, 36807-80-4; **11**, 36807-81-5; **12**, 36807-82-6; **13**, 35867-45-9; **14**, 36807-84-8; **15**, 36807-85-9.

Branched-Chain Glycosyl α-Amino Acids. I. Stereospecific Synthesis of 2-L-(3-Deoxy-1,2-*O*-isopropylidene-α-D-allofuranos-3-yl)glycine, an Analog of the Polyoxin Sugar Moiety

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Stereospecific hydroxylation of the hitherto described 3-*C*-*trans*-(methoxycarbonylmethylene)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2**) with osmium tetroxide or potassium permanganate in pyridine yielded 3-*C*-[*S*-hydroxy(methoxycarbonyl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) in high yield. Selective acetylation of **6** using acetic anhydride and pyridine gave 3-*C*-[*S*-acetoxy(methoxycarbonyl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**) in 73% yield which was stereoselectively dehydrated with thionyl chloride in pyridine to afford 3-*C*-*trans*-1′-*O*-acetyl-1′-methoxycarbonylmethylene-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-ribofuranose (**8**). Stereospecific catalytic reduction of **8** afforded 3-*C*-[*R*-acetoxy(methoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**10**). Tosylation of deacetylated **10** yielded the tosylate **12**, which was then transformed into an azide. Reduction of the latter compound afforded methyl 2-L-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)glycinate (**13**). Basic hydrolysis of **13** yielded 2-L-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)glycine (**15**). Selective hydrolysis of **15** afforded 2-L-(3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranos-3-yl)glycine (**16**). The ORD spectra of the branched-chain α-amino and α-hydroxy acid sugars are described.

The structurally novel amino acid sugar 5-amino-5-deoxy-D-allofuranuronic acid is a component of the polyoxin complex of antifungal agents.[1] The elucidation of structures of the polyoxins has been recently described.[1] Subsequently, the sugar component[2] and the nucleoside moiety of the polyoxins have been synthesized.[3,4] The sugar moiety of the polyoxins might be regarded as being composed of a two-carbon α-L-amino acid moiety attached to C-4 of the sugar. We report herein a stereospecific synthesis of an analog of the sugar moiety of the polyoxins in which the two-carbon α-L-amino acid moiety is attached to C-3 of a hexofuranose having essentially the same stereochemistry as the sugar of the polyoxin. In essence, the objective of the research described herein was to replace stereospecifically with inversion the C-3 hydroxyl of D-glucofuranose by a two-carbon α-L (*S*)[5] amino acid to yield a branched-chain sugar having the allo configuration. Such a sugar could then be readily degraded by periodate oxidation followed by sodium borohydride reduction to afford a branched-chain sugar possessing the D-ribo constitution.

The key intermediate in the synthesis of the branched-chain sugar was 3-*C*-*trans*-(methoxycarbonylmethylene)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2**), previously described[6] but not obtained in crystalline form. Compound **2** was prepared from the readily available 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**).[7] When the condensation of the ketose **1** and phosphonoacetic acid trimethyl ester in the presence of potassium *tert*-butoxide was allowed to take place at room temperature, the major component of the reaction products was a mixture of trans- and cis-unsaturated ribo sugars **2** and **3**. A minor component (about 6%) consisted of a mixture of trans- and cis-unsaturated sugars **4** which was tentatively believed to have the xylo configuration. The ribo-unsaturated sugars **2** and **3** were readily separated from the epimeric mixture of unsaturated sugars **4** by column chromatography on silica gel. Fractional crystallization of the mixture of trans- and cis-unsaturated sugars **2** and **3** from hexane afforded pure crystalline ribo trans-unsaturated sugar **2** in about 40% yield. Although the mixture of xylo

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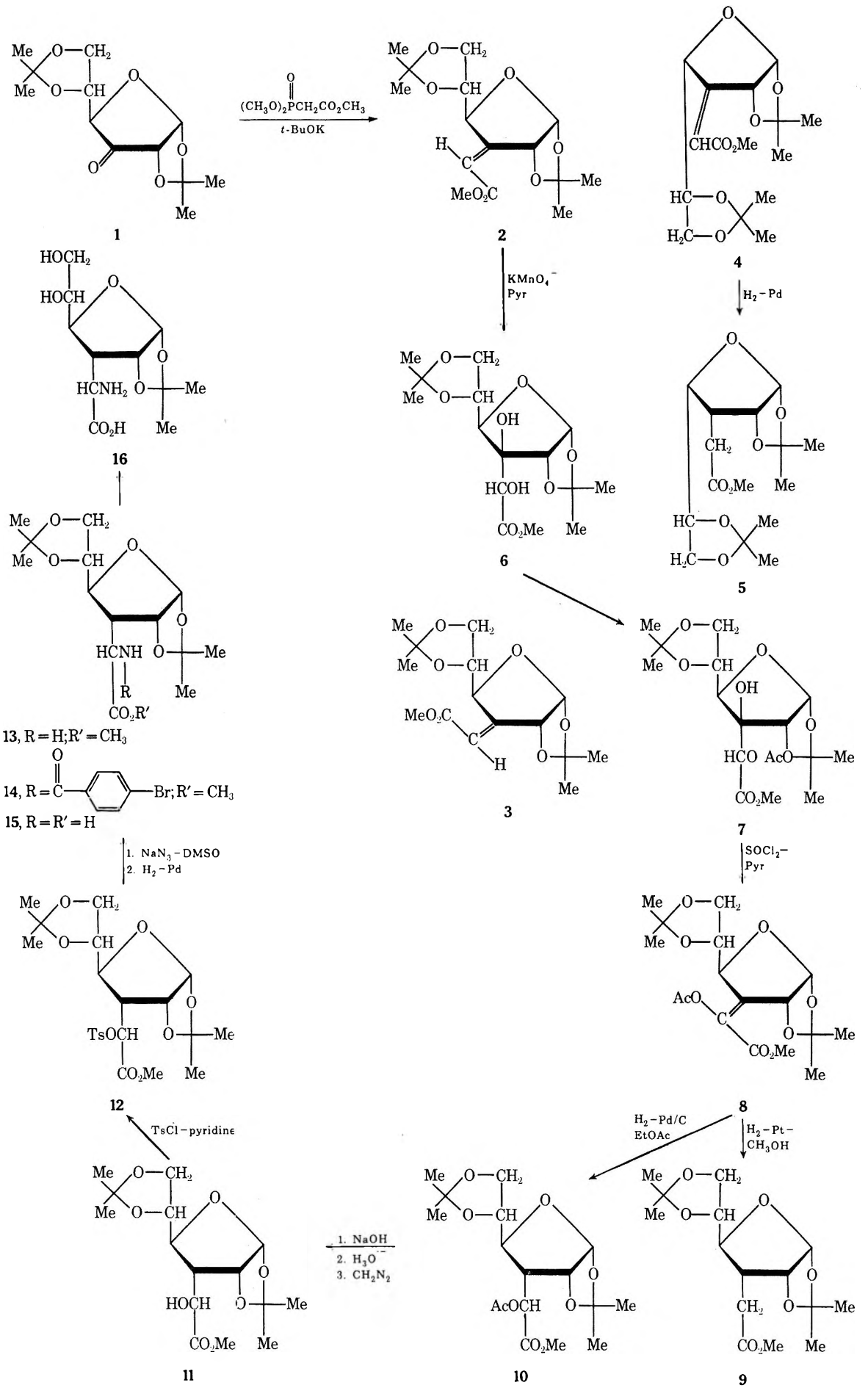
(2) T. Naka, T. Hashizumo, and M. Nishimura, *Tetrahedron Lett.*, 95 (1971).
(3) N. P. Damodaran, G. H. Jones, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **93**, 3812 (1971).
(4) H. Ohrui, H. Kuzuhara, and S. Emoto, *Tetrahedron Lett.*, 4267 (1971).
(5) R. S. Cahn and C. K. Ingold, *J. Chem. Soc.*, 612 (1951); R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962.
(6) A. Rosenthal and L. Nguyen, *J. Org. Chem.*, **34**, 1029 (1969).
(7) (a) P. J. Beynon, P. M. Collins, and W. G. Overend, *Proc. Chem. Soc.*, 342 (1964); (b) K. Onodera, S. Hirano, and N. Kashimura, *J. Amer. Chem. Soc.*, **87**, 4651 (1965); (c) K. Onodera, S. Hirano, and N. Kashimura, *Carbohyd. Res.*, **6**, 276 (1968).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KMnO4
Pyr
H2-Pd
1. NaN3-DMSO
2. H2-Pd
SOCl2-
Pyr
TsCl-pyridine
1. NaOH
2. H3O+
3. CH2N2
H2-Pd/C
EtOAc
H2-Pt-
CH3OH
13, R = H; R' = CH3
14, R = C(=O)-C6H4-Br; R' = CH3
15, R = R' = H
1
2
3
4
5
6
7
8
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10
11
12
16

trans- and cis-unsaturated sugars **4** could not be separated by preparative tlc, hydrogenation of this mixture in the presence of palladium on charcoal gave a new homogeneous crystalline branched-chain sugar **5**. The configuration of C-3 of **5** was readily ascertained from its nmr spectrum. The H-2 signal of **5** appears as a triplet at τ 5.27, showing that H-2 is coupled to H-3 and to H-1. On the other hand, in the glucofuranose series[8] there is no coupling between H-2 and H-3, thus leading to a doublet for H-2. Therefore H-1, H-2, and H-3 of **5** are all in the cis orientation. Because of overlapping signals an analysis of H-4 of **5** could not be made and therefore the configuration of C-4 of **5** is not known. Probably C-4 of **1** was epimerized under the basic conditions of the Wittig reaction and compound **4** might be expected to have the xylo configuration. Reduction of **4** might then give the gulo branched-chain sugar **5**.

Hydroxylation of the trans-unsaturated sugar **2** with osmium tetroxide in pyridine gave essentially pure *cis*-diol **6** in almost quantitative yield. When a combination of osmium tetroxide and 30% hydrogen peroxide was used as oxidant, the reaction on a macro scale proved hard to control, leading to side reactions. Conversion of **2** into **6** was most efficiently carried out (70% yield) by use of potassium permanganate in pyridine as oxidant. Although the yield of diol **6** was considerably lower in the latter hydroxylation reaction, the mixture of products was readily separated by silica gel column chromatography. Reaction conditions must be carefully controlled to reduce the side reactions.

The stereochemical assignment of structure of the diol **6** was based upon the well-known fact that hindered olefins are attacked from the less hindered face of the molecule to afford stereospecifically the *cis*-diol.[9] Thus, it was surmised that **6** was probably 3-*C*-[*S*-hydroxy(methoxycarbonyl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Confirmation of the structural assignment to **6** was provided by the fact that its optical rotatory dispersion (ORD) spectrum (see **6**, Figure 1) was similar to that of L-lactic acid.[10]

Selective acetylation of the diol **6** with acetic anhydride in pyridine afforded the monoacetate **7** in 73% yield. Stereoselective dehydration of the tertiary alcohol **7** was achieved using thionyl chloride in pyridine to afford, after silica gel column chromatography, the enol acetate **8** in over 60% yield. Because dehydrations of carbocyclic systems containing a tertiary hydroxyl group are known to proceed stereoselectively *via* a trans elimination of hydrogen and the hydroxyl group,[11] it was surmised that the enol acetate **8** must be the trans isomer. Although catalytic hydrogenation of the latter in ethyl acetate over palladium on charcoal proceeded stereoselectively to

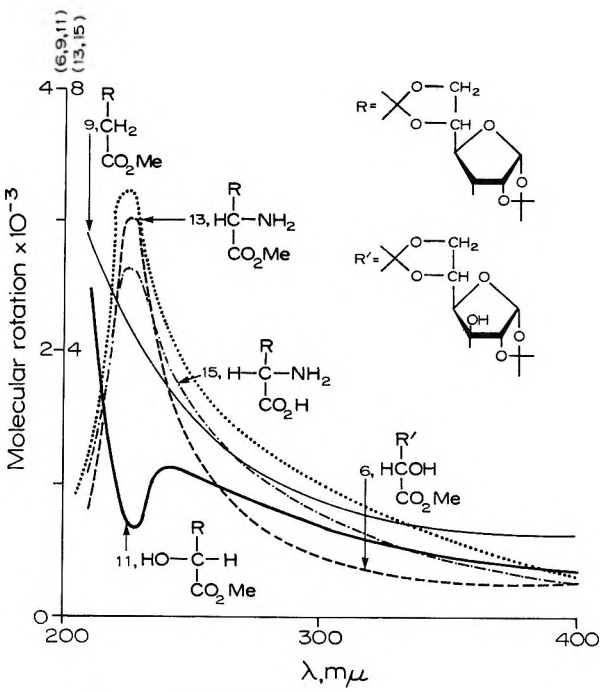

Figure 1.—Rotatory dispersion curves of branched-chain sugar **9**, branched-chain α-hydroxy ester sugars **6** and **11**, and L-(3-deoxyglycos-3-yl)amino acid ester **13** and amino acid **15**.

afford after column chromatography 3-*C*-[*R*-acetoxy(methoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**10**) in 65% yield, the product was contaminated with a minor product **9** in which the acetate group had undergone hydrogenolysis. Utilization of methanol as solvent led to an increase of the yield of the by-product **9**. Compound **9** was identical with the product obtained by direct reduction of either the trans- or cis-unsaturated sugar **2** or **3** and is therefore 3-*C*-methoxycarbonylmethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose.[6] Treatment of the α-acetate ester **10** with aqueous methanolic sodium hydroxide deacetylated and deesterified the product to afford an α-hydroxy acid which was immediately reesterified with diazomethane to yield after column chromatography the α-hydroxy ester **11** in an overall yield of 74% based on **10**. Compound **11** exhibited a negative Cotton effect in contrast to the positive Cotton effect exhibited by **6** (see **6** and **11**, Figure 1), thus establishing that an inversion of configuration of the asymmetric carbon in the branched chain of **6** had occurred during the dehydration and reduction steps to afford 3-*C*-[*R*-hydroxy(methoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**11**). Tosylation of the latter compound with *p*-toluenesulfonyl chloride in pyridine yielded the tosylate **12** in 78% yield. Conversion of the latter compound into an α-amino acid ester **13** was achieved by treatment of **12** with sodium azide in dimethyl sulfoxide at 55–60° for 40 hr followed by immediate hydrogenation of the azide over palladium on charcoal. The α-amino ester **13**, isolated after chromatography in 34% yield based on **12**, exhibited a positive Cotton effect (see **13** in Figure 1), which indicated, as expected, that a second inversion of configuration of the branched-chain asymmetric carbon had taken place when the tosylate was displaced by the azide group. The α-amino ester **13** gave

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a positive ninhydrin test and was characterized as its crystalline *p*-bromobenzamido derivative **14**. Treatment of the α-amino ester **13** with aqueous methanolic sodium hydroxide afforded the crystalline glycosyl α-amino acid **15** in 89% yield. Because compounds **13** and **15** exhibited positive ORD spectra (see curves **13** and **15** in Figure 1) which were similar to that of L-alanine,[12] compound **15** is therefore 2-L-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)-glycine. Selective hydrolysis of the 5,6-*O*-isopropylidene group of compound **15** with 50% aqueous acetic acid afforded, in 69% yield, the crystalline glycosyl amino acid 2-L-(3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranos-3-yl)glycine (**16**), which also exhibited a positive Cotton effect.

Experimental Section

General Considerations.—Pmr spectra were obtained in deuteriochloroform solution (unless otherwise stated) with tetramethylsilane as the internal standard (set at τ 10) using a Varian A-60 or Varian HA-100 spectrometer. The ORD measurements were performed on a JASCO Model ORD/UV-5 spectropolarimeter at room temperature. The infrared spectra were performed on a Perkin-Elmer Model 337 spectrometer. For column chromatography, silica gel "Davison" grade (60–200 mesh), and, for tlc, silica gel G (Mondray) were used. Optical rotations were measured at room temperature (22°) with a Perkin-Elmer automatic polarimeter Model 141. All melting points (micro hot stage) are corrected. Elemental analyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

Wittig Reaction of 1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (1) to Yield 3-*C*-*trans*- and -*cis*-methoxycarbonylmethylene-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (2 and 3) and 3-*C*-*trans*- and -*cis*-methoxycarbonyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-furanose (4).—An amount of 7.5 g of anhydrous ketose 1 was allowed to react with phosphonoacetic acid trimethyl ester according to a procedure already published[6] except that the temperature was kept at about 20°. The product (6.5 g), worked up as described previously, showed by tlc on silica gel using 4:1 benzene–ethyl acetate as developer two spots having R_f's of 0.45 and 0.40. The faster moving zone consisted of a mixture of trans- and cis-unsaturated branched-chain sugars **2** and **3** identical with the compounds described previously and a mixture of two new unsaturated compounds **4**. Gradient elution chromatography on silica gel (60 × 7.5 cm) of the product mixture using 6:1 chloroform–ethyl acetate followed by 3:1 chloroform–ethyl acetate as developer yielded one main fraction (faster mobility) and a slower moving zone. The faster moving zone was recrystallized from hexane to afford crystalline trans-unsaturated sugar **2** (3.3 g, 36.5%): mp 68–69°; $[\alpha]^{22}D$ +119° (*c* 2, chloroform); τ^{CDCl_3} 3.65 (q, H-1′), 4.15 (d, $J_{1,2}$ = 4.0 Hz, H-1), 4.23 (m, H-2), 5.32 (m, H-4), 6.0 (m, H-6 and H-5), 6.30 (s, $COCH_3$).

Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.09; H, 6.83.

The mother liquor from the recrystallization of compound **2** was evaporated to dryness to yield 1.1 g (12%) of an almost equal mixture of the trans- and cis-unsaturated sugars **2** and **3** (as evidenced by nmr). The slower moving zone (1.2 g, 13%) obtained from the column chromatography was purified by preparative tlc to afford about 0.6 g of a mixture of **2** and **3** and a new pair of unsaturated sugars **4** (about 0.6 g, 6%): τ^{CDCl_3} of **4**, 3.82–4.0 (m, C-1′ H), 4.20 (t, possibly H-1), 4.38 (two doublets), 4.60 (two doublets), 5.18 (d, J = 4 Hz), 5.1–5.75 (m), 6.26 and 6.28 (s, $COCH_3$).

Reduction of 2 and 4 to Yield 3-*C*-(Methoxycarbonylmethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (9) and 3-*C*-(Methoxycarbonylmethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (5).—Compound **2** was hydrogenated in the presence of 10% palladium on charcoal according to a previous procedure[6] to yield pure **9**: mp 57–59°; ORD (*c* 0.09, ethanol) $[\Phi]_{220}$ + 2400°, $[\Phi]_{225}$ + 2140°, $[\Phi]_{250}$ + 1565°.

Reduction of the trans and cis mixture of unsaturated sugars **4** gave in quantitative yield pure **5** (as evidenced by tlc). Compound **5** was sublimed under high vacuum to afford crystalline 3-*C*-(methoxycarbonylmethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose: mp 109–110°; $[\alpha]^{22}D$ −6° (*c* 1.6, chloroform); τ^{CDCl_3} 4.18 (d, $J_{1,2}$ = 4 Hz, H-1), 5.27 (t, $J_{1,2}$ = 4, $J_{2,3}$ = 4 Hz, H-2), 5.38–6.1 (overlapping signals), 6.35 (s, CO_2CH_3), 6.42–6.70 (m), 7.2–7.7 (overlapping peaks, H-3, H-1′), 8.45, 8.6, 8.65, 8.7 (four s, CH_3).

Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.85; H, 7.73.

Hydroxylation of 2 to Yield 3-*C*-[*S*-Hydroxy(methoxycarbonyl)-methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (6). A. Using Osmium Tetroxide.—To a solution of the unsaturated trans sugar **2** (0.105 g) in 3 ml of anhydrous pyridine was added osmium tetroxide (0.098 g) and the mixture was allowed to stand at room temperature for 3 hr. After addition of 4 ml of 3% aqueous sodium hydrogen sulfite the mixture was shaken for 10 min and then extracted twice with methylene chloride. The combined methylene chloride extracts were washed with water, dried over sodium sulfate, filtered, and evaporated to yield 0.120 g of an oil which was homogeneous by tlc.

B. Using Osmium Tetroxide and Hydrogen Peroxide.—To the unsaturated sugar **2** (0.100 g) in 2 ml of pyridine was added osmium tetroxide (0.005 g) followed by dropwise addition of 30% hydrogen peroxide (1.0 ml) over a period of 30 min. The reaction mixture was let stand at room temperature for an additional 0.5 hr. After addition of water the reaction mixture was extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to yield 0.120 g of oil which was darker in appearance than that obtained by procedure A above. The product was mainly **6**. Repetition of the reaction on a larger scale gave a mixture of products, possibly owing to poor control of the temperature during the addition of hydrogen peroxide.

C. Using Potassium Permanganate in Pyridine.—To a cold solution (kept at −10°) of the unsaturated sugar **2** (1.66 g) in 10 ml of water and 20 ml of pyridine was added dropwise with vigorous stirring a solution of potassium permanganate (0.90 g) in 20 ml of water over a period of 10 min. The reaction was very rapid. After addition of 50 ml of water and a few milliliters of alcohol (to prevent emulsification) the reaction mixture was extracted with chloroform (3 × 100 ml). The combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated to yield an oil (1.4 g, 76%) having a purity greater than 95% (evidenced by tlc and nmr). An analytical sample of **6** was prepared by preparative tlc on silica gel using 3:1 benzene–ethyl acetate as developer: $[\alpha]^{22}D$ +54° (*c* 1.5, chloroform); ORD (*c* 0.07, ethanol) $[\Phi]_{215}$ +1930°, $[\Phi]_{220}$ +2710°, $[\Phi]_{225}$ +3055°, $[\Phi]_{250}$ +1578°; τ^{CDCl_3} 4.15 (d, $J_{1,2}$ = 3.8 Hz, H-1), 5.42 (s, H-1′), 5.55 (d, $J_{2,1}$ = 3.8 Hz, H-2), 5.62–5.95 (overlapping peaks), 6.08 (s, OH, disappears on addition of D_2O), 6.20 (s, CO_2CH_3).

Anal. Calcd for $C_{15}H_{24}O_9$: C, 51.72; H, 6.94. Found: C, 51.57; H, 7.12.

Similar oxidation of **2** (8.1 g) but on a larger scale gave the diol **6** (68% yield) and a minor by-product (0.25 g). These substances were separated by silica gel column chromatography using 1:2 ethyl acetate–benzene as developer.

3-*C*-[*S*-Acetoxy(methoxycarbonyl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (7).—The diol **6** (0.110 g) was acetylated with a mixture of 1 ml of acetic anhydride and 2 ml of pyridine at room temperature for 3 hr. After removal of the acetylating mixture by evaporation under vacuum the monoacetate **7** was purified by preparative tlc on silica gel using 1:3 ethyl acetate–benzene as developer to yield 0.100 g (73%) of an oil which was distilled at 110° (0.1 mm): $[\alpha]^{22}D$ +35° (*c* 1.5, chloroform); τ^{CDCl_3} 4.10 (d, $J_{1,2}$ = 3.0 Hz, H-1), 4.26 (s, H-1′), 6.74 (OH), 7.81 (OAc).

Anal. Calcd for $C_{17}H_{26}O_{10}$: C, 52.30; H, 6.71. Found: C, 52.43; H, 6.71.

Dehydration of 7 to Yield 3-*C*-*trans*-1′-*O*-Acetyl-1′-methoxycarbonylmethylene-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (8).—To the monoacetate **7** (0.800 g) in anhydrous pyridine (10 ml) kept at 0° was added freshly distilled thionyl chloride (3 ml). After the mixture was allowed to stand at room temperature for 20 hr in the dark, ice was added. The reaction mixture was then extracted with dichloromethane (3 × 200 ml). The combined dichloromethane extracts were washed with water, dried over sodium sulfate, and evaporated under reduced pressure to yield a dark brown oil. This oil was chromatographed on 70 ml of silica using 3:1 benzene–ethyl acetate as developer to

(12) J. C. Craig and S. K. Roy, *Tetrahedron*, **21**, 391 (1965).

afford 0.476 g (62%) of enol acetate **8** and 0.084 g (11%) of impure sample. An analytical sample of **8** was prepared by preparative tlc using 3:1 benzene–ethyl acetate as developer followed by molecular distillation of the product at 110° (0.1 mm). The product was unstable at room temperature and had $[\alpha]^{22}D$ +57° (c 0.8, chloroform); τ^{CDCl_3} 4.12 (d, $J_{1,2}$ = 4 Hz, H-1), 4.38 (two d, $J_{2,1}$ = 4, J = 2 Hz), 5.0 (two d, $J_{4,5}$ = 5, J = 2 Hz), 5.78–6.3 (m), 6.24 (s, CO_2CH_3), 7.88 (OAc).

Anal. Calcd for $C_{17}H_{24}O_9$: C, 54.83; H, 6.50. Found: C, 55.03; H, 6.70.

Reduction of 8 to Yield 3-*C*-[*R*-Acetoxy(methoxycarbonyl)-methyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (10).—The enol acetate **8** (0.600 g) in 60 ml of purified ethyl acetate was hydrogenated at room temperature under 1 atm pressure in the presence of 5% palladium on carbon (0.300 g). The product was separated by silica gel column chromatography using 1:3 ethyl acetate–benzene as developer to afford 0.360 g (65%) of the acetate **10** and a mixture of the ester **9** and **10** (0.070 g, 13%). An analytical sample of **10** was prepared by preparative tlc followed by molecular distillation at 110° (0.1 mm) to yield an oil: $[\alpha]^{22}D$ +69° (c 0.4, chloroform); τ^{CDCl_3} 4.2 (d, $J_{1,2}$ = 4 Hz, H-1), 4.50 (d, $J_{1',3}$ = 7.5 Hz, H-1'), 5.3 (q, $J_{1,2}$ = 4, $J_{2,3}$ = 5 Hz, H-2), 5.7–6.1 (m), 6.20 (s, $COCH_3$), 7.35–7.7 (m, $J_{1',3}$ = 7.5, $J_{3,4}$ = 9.0, $J_{2,3}$ = 5 Hz, H-3), 7.90 (s, OAc), 8.48, 8.66, 8.70 (s, four CH_3).

Anal. Calcd for $C_{17}H_{26}O_9$: C, 54.54; H, 7.00. Found: C, 54.49; H, 7.07.

When the enol acetate **8** was reduced in the presence of platinum, palladium, or rhodium in methanol the ester **9** was produced as a major compound. The ester **9** had the same nmr and ir as the product obtained by catalytic hydrogenation of **2** or **3**.[6]

3-*C*-[*R*-Hydroxy(methoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (11).—The acetate **10** (0.360 g) was deacetylated at room temperature for 3 hr using 5 ml of methanol and 5 ml of 10% aqueous sodium hydroxide. The solution was then neutralized with hydrochloric acid with external cooling. The slightly acidic solution was saturated with sodium chloride and extracted with ethyl acetate (5 × 10 ml). The combined ethyl acetate extracts were dried over sodium sulfate and then evaporated to yield 0.293 g (96%) of an oil which was esterified in methanol with an ether solution of diazomethane. After evaporation of the solvent the hydroxy ester **11** was purified by silica gel column chromatography using 1:3 ethyl acetate–benzene as developer to afford 0.235 g (74%) of **11**. An analytical sample was prepared by preparative tlc followed by molecular distillation at 115° (0.1 mm) to yield an oil: $[\alpha]^{22}D$ +57° (c 3.8, chloroform); ORD (c 0.09, ethanol) $[\Phi]_{220}$ +1110°, $[\Phi]_{235}$ +658° (trough), $[\Phi]_{240}$ +1110°, $[\Phi]_{250}$ +1073°; τ^{CDCl_3} 4.25 (d, $J_{1,2}$ = 4 Hz, H-1), 5.22 (d, $J_{2,1}$ = 4 Hz, H-2), 5.25–5.9 (overlapping peaks), 5.92 (d, 2 hydrogens, J = 2.5 Hz), 6.2 (s, CO_2CH_3), 7.42–7.75 (m, H-3), 8.45, 8.53, 8.68, 8.72 (4 s, CH_3).

Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 54.60; H, 7.58.

3-*C*-[(*R*)-*p*-Toluenesulfonyloxy(methoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12).—The hydroxy ester **11** (0.050 g) in 2 ml of anhydrous pyridine was tosylated with *p*-toluenesulfonyl chloride (0.100 g) (all reagents must be pure and anhydrous) in the usual way to afford 0.055 g (78%) of the tosylate **12**, which was distilled at 125° (0.1 mm): $[\alpha]^{22}D$ +79° (c 1, chloroform); τ^{CDCl_3} 2.15 and 2.65 (two d, C_6H_4), 4.27 (d, $J_{1,2}$ = 4 Hz, H-1), 4.90 (d, $J_{1,3}$ = 9.0 Hz, H-1'), 5.40 (t, $J_{1,2}$ = 4, $J_{2,3}$ = 4 Hz, H-2), 5.85–6.2 (m), 6.30 (s, CO_2CH_3), 7.58 (s, CH_3), 7.5 (m, H-3), 8.62, 8.66, 8.73, 8.82 (four s, CH_3). Irradiation at τ 7.5 changed the doublet at τ 4.90 to a singlet and the triplet at τ 5.40 to a doublet.

Anal. Calcd for $C_{22}H_{30}O_{10}S$: C, 54.32; H, 6.13. Found: C, 54.35; H, 6.28.

Methyl 2-L-(3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)glycinate (13).—The tosylate **12** (0.200 g) and sodium azide (0.200 g) were heated for 40 hr at 55–60° in anhydrous dimethyl sulfoxide (3 ml). After the solvent was removed under high vaccuum at 50°, water (1 ml) and the dichloromethane (5 ml) were added. The organic extract was evaporated and the crude residue was dissolved in methanol (50 ml) and immediately hydrogenated over palladium on charcoal (0.100 g) at 1 atm pressure for 3 hr. The catalyst was then removed by filtration and the filtrate was evaporated under reduced pressure. The residue was extracted with dichloromethane and the solution was then evaporated to dryness to yield 0.120 g of a syrup which was purified by multiple ascending preparative tlc (nine plates of 20 × 20 cm) using ethyl acetate as developer. The principal zone (R_f 0.1), detected with iodine or ninhydrin, was extracted with 3:1 ethyl acetate–methanol. This extract was washed with aqueous sodium thiosulfate. Evaporation of the solvent afforded **13**, yield 0.050 g (34% based on the tosylate). A minor very diffuse zone of ninhydrin-positive material was not extracted. The crude sugar azide could not be purified by preparative tlc on silica gel.

The α-amino ester **13** was twice distilled at 90° (0.1 mm) to give a substance homogeneous by tlc: $[\alpha]^{22}D$ +60° (c 0.6, chloroform); ORD (c 0.12, ethanol $[\Phi]_{220}$ +5960°, $[\Phi]_{225}$ +6450° (peak), $[\Phi]_{250}$ +3970°; ir (film) 1735, (CO_2CH_3), 3350 cm^{-1} (NH); τ^{CDCl_3} 4.22 (d, $J_{1,2}$ = 4 Hz, H-1), 5.23 (t, $J_{1,2}$ = $J_{2,3}$ = 4 Hz), 5.6–6.14 (overlapping peaks), 6.26 (s, CO_2CH_3), 7.52–7.76 (m, H-1', clearly visible after addition of D_2O), 7.7–8.1 (NH_2, disappears on addition of D_2O), 8.62–8.78 (four s, CH_3).

Anal. Calcd for $C_{15}H_{25}O_7N$: C, 54.37; H, 7.60; N, 4.23. Found: C, 54.06; H, 7.37; N, 4.01.

Methyl 2-L-(3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)-*N*-*p*-bromobenzoylglycinate (14).—The amino ester **13** (0.005 g) was dissolved in dry pyridine (0.1 ml), and *p*-bromobenzoyl chloride (0.020 g) was added. After standing at room temperature for 3 hr water was added and the product was extracted with dichloromethane. The extracted solid product was purified by tlc on silica gel using 1:3 ethyl acetate–benzene as developer to remove *p*-bromobenzoic acid. The benzamido derivative **14** was recrystallized from ethanol–hexane: mp 108–109°; $[\alpha]^{22}D$ +46° (c 0.2, chloroform); τ^{CDCl_3} 2.55 (NH), 4.21 (d, $J_{1,2}$ = 4 Hz, H-1), 4.80 (t, J = 6.5 Hz, H-1'), 5.24 (t, $J_{1,2}$ = $J_{2,3}$ = 4 Hz, H-2), 7.3 (m, H-3). Irradiation of the signal at τ 2.55 collapsed the triplet at τ 4.8 to a doublet, $J_{1',3}$ = 6.5 Hz. Irradiation at τ 7.3 collapsed the triplet at τ 5.24 to a doublet having $J_{1,2}$ = 4 Hz.

Anal. Calcd for $C_{22}H_{28}NO_8Br$: C, 51.37; H, 5.49; N, 2.72. Found: C, 51.79; H, 5.65; N, 2.30.

2-L-(3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)-glycine (15).—The amino ester **13** (0.045 g) in 2.5% aqueous methanolic sodium hydroxide (2.5 ml of 1:1 solution) was kept at room temperature for 1 hr. The solution was then passed through 10 ml of Rexyn RG 51(H) (polystyrene carboxylic acid type resin) which was prewashed with 1% acetic acid and then water. Fractions which gave a positive ninhydrin test were collected and evaporated under reduced pressure to give 0.039 g (89%) of crystalline amino acid sugar **15**. This compound was recrystallized from methanol and water: mp 180–181°; R_f 0.35 on Whatman 20.1 paper using 5:2:1:1 ethyl acetate–*tert*-butyl alcohol–water–pyridine as developer: $[\alpha]^{22}D$ +25° (c 0.5, water); ORD (c 0.05, 0.5 *N* HCl in 95% ethanol) $[\Phi]_{220}$ +4560°, $[\Phi]_{225}$ +5200° (peak), $[\Phi]_{250}$ +3040° [the ORD was taken within 10 min (about 5% hydrolysis of the 5,6-*O*-isopropylidene group took place during a period of 30 min)]; τ^{D_2O} (external TMS) 4.06 (d, $J_{1,2}$ = 4 Hz, H-1), 5.01 (t, $J_{1,2}$ = $J_{2,3}$ = 4 Hz, H-2), 7.50 (m, H-3).

Anal. Calcd for $C_{14}H_{23}NO_7 \cdot {}^1/_2H_2O$: C, 51.53; H, 6.41; N, 4.29. Found: C, 51.64; H, 6.33; N, 4.07.

2-L-(3-Deoxy-1,2-*O*-isopropylidene-α-D-allofuranos-3-yl)glycine (16).—Compound **15** (0.030 g) in 50% aqueous acetic acid (2 ml) was kept at room temperature for 80 hr (the reaction was monitored by paper chromatography using the same solvent as in the identification of compound **15**). After the solvent was evaporated the amino acid **16** was crystallized from ethanol–water: yield 0.018 g (69%); mp 213–215°; $[\alpha]^{22}D$ +60° (c 0.5, water); R_f 0.15; ORD (c 0.045, 0.5 *N* HCl in 95% ethanol) $[\Phi]_{220}$ +5720°, $[\Phi]_{225}$ +6280° (peak), $[\Phi]_{250}$ +3690°; τ^{D_2O} (external TMS) 4.07 (d, J = 4 Hz, H-1), 5.0 (t, $J_{1,2}$ = $J_{2,3}$ = 4 Hz, H-2), 5.9 (d, J = 6 Hz, H-1'), 7.4 (m, H-3), 8.4 and 8.6 (two CH_3).

Anal. Calcd for $C_{11}H_{19}O_7N$: C, 47.65; H, 6.91; N, 5.05. Found: C, 47.79; H, 7.09; N, 4.70.

Registry No.—**2**, 18427-17-3; **5**, 36807-87-1; **6**, 36807-88-2; **7**, 36807-89-3; **8**, 36807-90-6; **9**, 18427-18-4; **10**, 36807-92-8; **11**, 36807-93-9; **12**, 36870-63-0; **13**, 36807-94-0; **14**, 36807-95-1; **15**, 36807-96-2; **16**, 36807-97-3.

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Amino Phosphonic Acids. II. Aminoalkylphosphonic Acids[1]

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Nine amino phosphonic acids have been synthesized from phosphonoalkanoate esters by the Curtius reaction. Five are new: 1-aminobutylphosphonic acid, 1-amino-2-methylpropylphosphonic acid, 1-aminopentylphosphonic acid, 1-aminoheptylphosphonic acid, and 1-aminohendecylphosphonic acid. Improvements in the synthesis and isolation of the amino phosphonic acids are described and the approximate pK values for seven of them are given.

The synthesis of amino phosphonic acids by the Curtius reaction[4] has been extended to the following compounds.

$$RR'C(CH_2)_xCO_2Et + P(OEt)_3 \longrightarrow RR'C(CH_2)_xCO_2Et \quad (1)$$
$$\quad Br \qquad\qquad\qquad\qquad\quad PO(OEt)_2$$
$$\quad 1 \qquad\qquad\qquad\qquad\quad 2$$

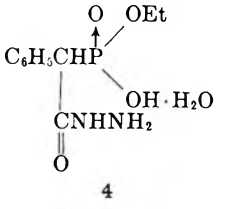
$$2 \xrightarrow[\text{reaction}]{\text{Curtius}} RR'C(CH_2)_xPO(OH)_2 \quad (2)$$
$$\qquad\qquad\qquad\qquad\quad NH_2$$
$$\qquad\qquad\qquad\qquad\quad 3$$

Compd	R	R′	x
a	C_2H_5	H	0
b	n-C_3H_7	H	0
c	i-C_3H_7	H	0
d	n-C_4H_9	H	0
e	n-C_6H_{13}	H	0
f	n-$C_{10}H_{21}$	H	0
g	H	H	2
h	CH_3	CH_3	0
i	C_6H_5	H	0

Attempts to prepare triethyl 2-methyl-2-phosphonopropionate (**2h**) by the methylation of triethyl phosphonoacetate[5] gave a mixture of the original ester and the monomethyl and the dimethyl derivatives, which could not be separated by fractional distillation; repeated methylation of triethyl 2-phosphonopropionate gave pure **2h**.

The Curtius reaction was carried out under a variety of conditions and ratios of reactants; the most satisfactory procedure is given in the Experimental Section.

Triethyl 2-phenyl-2-phosphonoacetate (**2i**) not only gave an easily crystallized hydrazide but the remainder of the Curtius reaction was surprising. Two crystalline intermediates were isolated and were found to correspond to structures **4** and **5**.



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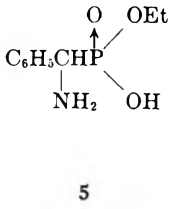

5

Experimental Section[6]

Ethyl 2-Bromoalkanoates (1).—These were prepared by a modified Schwenk and Papa[7] procedure. To 1 mol of the organic acid, held at 30°, 1.1–1.2 mol of thionyl chloride was added dropwise and the mixture was stirred at 60–80° until the gas evolution essentially stopped. At 80° 1.05 mol of Br_2 was added dropwise at approximately the rate that the Br_2 was consumed. Stirring was continued for several hours until the evolution of HBr nearly stopped. Absolute ethanol (100 ml) was added slowly to the crude acid chloride at 20–30°. After standing overnight, the mixture was washed with 100 ml of water, dilute $NaHSO_3$, and water. The organic layer was dried over anhydrous $MgSO_4$ and the dried ester was distilled slowly through a 24-in. Vigreux column to give the products in Table I.

Ethyl 4-Bromobutyrate (1g).—A mixture of 500 ml of absolute ethanol, 81 g of dry HBr, and 42 g of 4-butyrolactone was heated under reflux for 7 hr.[8] Distillation give 57.0 g (58%) of ethyl 4-bromobutyrate, bp 104–107° (33 mm), $n^{25}D$ 1.4537 [lit.[8] bp 76–78° (7 mm)].

Triethyl Phosphonoalkanoates (2).[9]—The reaction flask was equipped with a stirrer, thermometer, dropping funnel and a steam-jacketed condenser, causing ethyl bromide to pass through while the higher boiling reaction components condensed. The bromo ester 1 (1 mol) was heated to 160° and 1.2 mol of triethyl phosphite was added dropwise over a period of 2 hr. The reaction temperature was increased to 190° and held there until the evolution of ethyl bromide ceased. The mixture was distilled rapidly the first time below 3 mm, primarily to remove some nonvolatile residue that often seemed to catalyze the decomposition of 2. The second distillation was carried out with a 24-in. Fenske or spinning band column. Lower boiling fractions were unchanged triethyl phosphite and a small amount of diethyl ethylphosphonate. The relatively unreactive ethyl 2-bromo-3-methylbutyrate (2c) gave the best results when equal quantities of triethyl phosphite were added once an hour at 160° over a period of 60 hr. Ester 2c was also prepared by condensing the K derivative of triethyl phosphonoacetate with isopropyl bromide;[5] the esters prepared by the two routes were identical in all respects.

Triethyl 2-methyl-2-phosphonopropionate (2h) was prepared by methylating triethyl 2-phosphonopropionate (1 mol) as the K derivative in 1040 ml of toluene with 1.1 mol of methyl iodide.[5] To avoid the problem of separating a mixture of methylated products, the product from 3.5 mol of triethyl 2-phosphonopropionate was added to a slurry of 0.884 g-atom of K in 750 ml of toluene. The K dissolved slowly over a period of 2 hr. Methyl iodide (1 mol) was added and this second methylation reaction was carried out at 80° for 2 hr and at 100–112° for 8 hr. Solids were removed by filtering and the filtrate was distilled. Some

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(2) Taken in part from the Ph.D. dissertation submitted by J. P. B. to Texas A & M University, May 1963.

(3) Summer NSF Research Institute Participant (1961), Riverside City College, Riverside, Calif.

(4) J. R. Chambers and A. F. Isbell, *J. Org. Chem.*, **29**, 832 (1964). Credit for the synthesis of 2-amino-4-phosphonobutyric acid (glutamic acid analog), as described earlier by P. Masterlerz, *Acta Biochim. Pol.*, **4**, 19 (1957), was inadvertently omitted.

(5) G. M. Kosolapoff and J. S. Powell, *J. Amer. Chem. Soc.*, **72**, 4198 (1950).

(6) All melting points were determined with a Hershberg apparatus and with a thermometer, calibrated with a set of thermometers having Bureau of Standards calibrations; boiling points are uncorrected. Triethyl phosphite was redistilled after kindly being supplied by the Hooker Chemical Co. Anhydrous hydrazine (95+%) was obtained from Matheson Coleman and Bell. Dowex 50W-X8 and Dowex 21K resins and propylene oxide were kindly supplied by the Dow Chemical Co. All other reagents were the best grade available and were used without further purification. Index of refraction measurements were taken with a Bausch and Lomb Abbe 3-L refractometer and the potentiometric titrations were carried out with a Sargent Model D recording titrator. Benzoyl derivatives were prepared with a Labline "Stir-O-Vac" high-speed stirrer. Analyses were made by Galbraith Laboratories, Knoxville, Tenn.

(7) E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **70**, 3626 (1948).

(8) W. A. Reckhow and D. S. Tarbell, *ibid.*, **74**, 4960 (1952).

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TABLE I
BROMO ESTERS

Ester	Bp, °C (mm)	$n^{25}D$	Yield, %
Ethyl 2-bromobutyrate (1a)	67–69 (12)[a]		85
Ethyl 2-bromovalerate (1b)	93–96 (26)[b]	1.4462	86
Ethyl 2-bromoisovalerate (1c)	49–49.5 (1.6)[c]	1.4480	82
Ethyl 2-bromocaproate (1d)	53 (1)[d]	1.4488[d]	87
Ethyl 2-bromocaprylate (1e)	72–74 (0.7)[e]	1.4514	81
Ethyl 2-bromolaurate (1f)	119–121 (0.2)[f]	1.4550[f]	69
Ethyl 4-bromobutyrate (1g)	104–107 (33)[g]	1.4537[g]	58
Ethyl 2-bromo-2-phenylacetate (1i)	103–105 (1.4)[h]	1.5374	81

[a] Reference 9 gave bp 65° (10 mm). [b] N. A. Preobrazhenskii, M. E. Maurit, G. I. Bazilevskaya, G. V. Smiranova, M. M. El'manovich, A. I. Valakhanovich, and E. Persiyanova, *Zh. Obshch. Khim.*, **30**, 2250 (1960), gave bp 84–85° (10 mm). [c] B. Schleicher, *Justus Liebigs Ann. Chem.*, **267**, 114 (1892), gave bp 110–115° (40 mm). [d] Reference 9 gave bp 75° (4 mm), $n^{30}D$ 1.4456. [e] K. Bernhard and H. Lincke, *Helv. Chim. Acta*, **29**, 1457 (1946), gave bp 137–140° (25 mm). [f] Reference 9 gave bp 101° (0.1 mm), $n^{30}D$ 1.4531. [g] E. A. Prill and S. M. McElvain, *J. Amer. Chem. Soc.*, **55**, 1233 (1933), gave bp 104–105° (28 mm), $n^{25}D$ 1.4539. [h] H. Alexander, *Justus Liebigs Ann. Chem.*, **258**, 67 (1890), gave bp 143–145° (10 mm).

TABLE II
PHOSPHONOALKANOATE ESTERS

R	R′	x	Bp, °C (mm)	$n^{25}D$	d^{25}_4	Yield, %
C_2H_5	H	0	117–118 (0.6)[a]	1.4310[a]		87
n-C_3H_7[b]	H	0	98–100 (2.5)	1.4327	1.0579	70
i-C_3H_7[c]	H	0	85–85.5 (0.1)	1.4344	1.0543	67
n-C_4H_9	H	0	117.5–118 (0.85)[d]	1.4337[d]	1.0346[d]	87
n-C_6H_{13}	H	0	136–137 (0.75)[e]	1.4365	1.0178	72
n-$C_{10}H_{21}$	H	0	168–172 (0.25–0.35)[f]	1.4424[f]		58
H	H	2	120–122 (0.45)[g]	1.4355[g]		82
CH_3	CH_3	0	76–80 (0.25)[h]	1.4298[h]		53
C_6H_5	H	0	152–162 (1.0)[i]	1.4914[i]		75

[a] B. Fiszer and J. Michalski, *Rocz. Chem.*, **28**, 185 (1954), gave bp 152–154° (14 mm), $n^{20}D$ 1.4296. [b] *Anal.* Calcd for $C_{11}H_{23}O_5P$: C, 49.62; H, 8.71; P, 11.63. Found: C, 49.58, 49.64; H, 8.73, 8.82; P, 11.64, 11.60. [c] *Anal.* Calcd for $C_{11}H_{23}O_5P$: C, 49.62; H, 8.71; P, 11.63. Found: C, 49.51, 49.80; H, 8.65, 8.94; P, 11.60, 11.83. [d] Reference 9 gave bp 141° (4 mm), $n^{30}D$ 1.4300, d^{30}_4 1.0337. [e] V. Chavane, *Ann. Chim. (Paris)*, **4**, 352 (1949), gave bp 155–157° (1.5 mm). [f] Reference 9 gave bp 153–156° (0.1 mm), $n^{30}D$ 1.4398. [g] R. L. McConnell and H. W. Coover, Jr., *J. Amer. Chem. Soc.*, **78**, 4453 (1956), gave bp 127–129° (2.3 mm), $n^{20}D$ 1.4334. [h] Also $n^{30}D$ 1.4278. B. A. Arbuzov and V. S. Vinogradova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 54 (1957), gave bp 103–103.5° (1 mm), $n^{20}D$ 1.4310, and ref 7 gave bp 74° (0.2 mm), $n^{30}D$ 1.4286. [i] V. S. Abramov and S. Pall, *Tr. Kazansk. Khim. Tekhnol. Inst.*, **23**, 105 (1957), gave bp 180–181° (3 mm), $n^{20}D$ 1.4952.

additional solid separated during the distillation and an additional quantity was left as a residue (hygroscopic). Data for phosphonoalkanoate esters are given in Table II.

$$RR'C(CH_2)_xCO_2Et$$
$$|$$
$$PO(OEt)_2$$

Amino Phosphonic Acids (3).—The Curtius reaction was carried out similarly to what has been described earlier.[4] In the production of the C hydrazides, the best reaction temperature seemed to be 25–40° with 100% excess hydrazine; no advantage was found in using a greater excess. The only esters that reacted exothermically with hydrazine under these conditions were triethyl 2-phenyl-2-phosphonoacetate (2i) and triethyl 4-phosphonobutyrate (2g). The remaining esters were not immediately miscible with hydrazine and were much less reactive, 2c and 2h being the slowest to react. These slower reacting esters were added to the hydrazine at 25° at a rate which maintained a homogeneous reaction mixture. After all of the 2 was added, the homogeneous solution was allowed to stand for 16 hr. Longer reaction times caused the yields to decrease, probably because the hydrazine seems to react slowly with the phosphonate ester group to give N-alkylated hydrazine salts of the phosphonic acids. Most of the crude hydrazides were viscous oils, but some (from 2i, 2e, and 2f) crystallized after standing for several days or after stirring with ether. The excess hydrazine was removed by heating the crude hydrazide to 45° at 1 mm for a few minutes.

Varying amounts of hydrochloric acid and sodium nitrite in the acyl azide forming step were also investigated, indicating that more than 2 mol of these per mole of hydrazide offered no advantages. Usually the crude acyl azide was extracted in the ether layer at about − 10° and was added to absolute ethanol (200 ml/mol of starting 2). This solution was allowed to stand overnight at 25° to decompose the acyl azide.

After the ether and ethanol were removed, the crude urethane was hydrolyzed by heating under reflux with 100% excess HCl, HBr, or HI. (Each mole of urethane theoretically requires 3 mol of acid.) Constant-boiling HCl required 48-hr hydrolysis for maximum yield and HBr and HI caused complete hydrolysis in about 8 hr. The dark solution was evaporated to dryness under vacuum, the residue was dissolved in 1 l. of water/mol of 2, and the solution was decolorized with Norit A.

The propylene oxide procedure[4] gave the amino acid in fair purity but the following procedure gave a higher yield of amino acid and the purity was excellent. The decolorized solution was passed through a column of Dowex 50W-X8 (H^+) resin (having at least 1 equivalent weight capacity/mol of 2) and the column was washed with deionized water. The first eluate was strongly acidic but ninhydrin negative and was discarded. Continued washing with water eluted the amino acid as a slightly acidic, ninhydrin-positive solution. (The best ninhydrin reagent was prepared by dissolving 200 mg of ninhydrin in 80 ml of ethyl alcohol, 15 ml of glacial acetic acid, and 5 ml of collidine. This solution keeps well in a closed bottle in a refrigerator.) All of the amino acids except 1-amino-1-methylethylphosphonic acid (3h) gave deep violet colors with this reagent. No color was produced with 3h but, if this compound was added to a mixture of 1–2 drops of 0.2 M $CuSO_4$ and 1–2 drops of saturated aqueous $NaHCO_3$ in 1 ml of water, a clear, deep blue solution resulted. Another excellent continuous detecting scheme involved monitoring the eluate with a Nester-Faust refractive index monitor. Evaporating the amino acid eluate to dryness left a white solid that was recrystallized from water–ethyl alcohol.

The low solubility of 1-aminoheptylphosphonic acid (3e) in water necessitated the utilization of large volumes of water to elute 3e from Dowex 50 resin and to recrystallize it. Even this procedure failed with 1-aminohendecylphosphonic acid (3f). It was recovered by evaporating the urethane hydrolysate on a steam bath under an air jet. (Evaporation under vacuum resulted in violent foaming.) Purification of 3f was accomplished by digesting it with hot ethyl alcohol and with boiling water. The amino acid remained undissolved and is insoluble in all

TABLE III
AMINO PHOSPHONIC ACIDS

Registry no.	R	R′	z	Mp, °C, dec	Yield, %	Neut equiv Calcd	Neut equiv Found	pK1	pK2	pK3	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
14047-23-5	C_2H_5	H	0	285–286[a]	16–63	139	141	1.95	5.75	10.28	25.90	7.25	22.27	26.16	7.18	22.14
														25.98	7.17	22.44
13138-36-8	n-C_3H_7	H	0	298–299	13–46	153	154	1.95	5.83	10.32	31.37	7.90	20.23	31.13	7.85	20.36
														31.18	7.79	20.11
18108-24-2	iso-C_3H_7	H	0	280–281	6.5–14	153	155	2.04	6.00	10.45	31.37	7.90	20.23	30.91	7.75	20.58
														31.12	7.69	20.48
13138-37-9	n-C_4H_9	H	0	284–285	46–52	167	169	1.83	5.82	10.35	35.93	8.44	18.53	35.99	8.29	18.89
														36.16	8.38	18.92
35045-86-4	n-C_6H_{13}	H	0	289–290	16–62	*b*	*b*	*b*	*b*	*b*	43.07	9.29	15.87	43.17	9.23	15.89
														42.98	9.15	16.09
14581 07-8	n-$C_{10}H_{21}$	H	0	286–287	36–72	*b*	*b*	*b*	*b*	*b*	52.57	10.43	12.33	52.23	10.35	12.44
														52.19	10.28	12.28
13138-33-5	H	H	2	294–296[c]	36–49	139	140	2.11	6.97	11.01	25.90	7.25	22.27	25.71	7.15	22.66
														25.81	7.29	22.48
5035-79-0	CH_3	CH_3	0	274–275[d]	7–41	157[e]	157	2.09	6.05	10.43	22.93[e]	7.64[e]	19.72[e]	22.71	7.88	20.09
														22.65	7.63	19.92
18108-22-0	C_6H_5	H	0	299.5[f]	43[g]	187	189	1.80	5.60	9.50						

[a] M. E. Chalmers and G. M. Kosolapoff, *J. Amer. Chem. Soc.*, 75, 5278 (1953), gave mp >350°. [b] Not sufficiently soluble in water to make accurate measurements. [c] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, 69, 2112 (1947), gave mp 274°; N. Kreutzkamp and H. Schindler, *Arch. Pharm. (Weinheim)*, 295, 28 (1962), gave mp 274°. [d] T. Ya. Medved and M. I. Kabachnik, *Dokl. Akad. Nauk SSSR*, 84, 717 (1952), reported mp 258° for the monohydrate. [e] Values for the monohydrate. Heating the compound to 120° (30–40 mm) for 24 hr caused no loss of weight. [f] Reference *a* gave mp 271–273° and M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 868 (1953), gave mp 272–273°. [g] The result of only one run.

TABLE IV
N-BENZOYL DERIVATIVES

Registry no.	R	R′	z	Mp, °C	Yield, %	Neut equiv Calcd	Neut equiv Found	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
35045-90-0	C_2H_5	H	0	183–185	60	243	243	49.39	5.80	12.74	49.37	5.83	12.63
											49.34	5.84	12.50
35045-91-1	n-C_3H_7	H	0	186–187	75	257	256	51.36	6.27	12.04	51.28	6.37	12.17
											51.49	6.37	12.06
35045-92-2	i-C_3H_7	H	0	153–154	40	257	256	51.36	6.27	12.04	51.29	6.38	12.25
											51.40	6.43	12.07
35045-93-3	n-C_4H_9	H	0	106–107	51	289[a]	288	49.82[a]	6.97[a]	10.71[a]	49.86	7.05	10.78
											49.54	6.90	10.63
35045-94-4	n-C_6H_{13}	H	0	130–131	58	299	297	56.18	7.41	10.35	55.90	7.48	10.35
											55.83	7.35	10.43
35045-95-5	n-$C_{10}H_{21}$	H	0	83–85	45	355	355	60.83	8.50	8.72	61.09	8.57	8.92
											60.97	8.52	8.77
35045-96-6	H	H	2	145–147	50	243	241	49.39	5.80	12.74	49.36	5.90	12.65
											49.35	5.92	12.87
35045-97-7	CH_3	CH_3	0	207–208	43	243	241	49.39	5.80	12.74	49.21	5.71	12.83
											49.04	5.75	13.01
35045-98-8	C_6H_5	H	0	103.5[b]–129[c]	72	291[c]	295[c]						

[a] For the monohydrate. [b] The monohydrate; neut equiv 309 (calcd, 309), mp 103.5–105.5° from water. T. Ya. Medved and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1043 (1955), gave mp 105–107° for the monohydrate. [c] Anhydrous compound produced by heating the hydrate at 90° (30 mm). When the anhydrous compound was exposed to the air of the laboratory for 1 hr, the melting point changed to 103.5–105.5°.

common organic solvents and in dilute HCl. Significant amounts will dissolve in concentrated HCl and in dilute base, producing solutions that foam copiously. Data on the various amino acids are found in Table III.

$$RR'C(CH_2)_xPO(OH)_2$$
$$|$$
$$NH_2$$

A special case was the Curtius reaction of triethyl 1-phenyl-1-phosphonoacetate (**2i**). When this ester and hydrazine were condensed in a 1:2 molar ratio, the solution deposited crystals of the hydrazide after 2 days. The solid hydrazide (106.0 g) was slurried with ether and treated with HCl and $NaNO_2$ by the usual procedure. However, the two-phase mixture contained 10.0 g of a solid, which was removed and found to be slightly soluble in hot water (slightly acidic solution) but essentially insoluble in the common organic solvents. However, if this solid was suspended in boiling ethyl alcohol and a few drops of acetone were added, the solid dissolved completely. Cooling caused the separation of white needles, mp 187.5–189.5° dec. All of the properties of this compound were consistent with structure **4**.

Anal. Calcd for $C_{10}H_{17}N_2O_5P$: C, 43.48; H, 6.20; N, 10.14; P, 11.21. Found: C, 43.61, 43,83; H, 6.16, 6.06; N, 10.02, 9.95; P, 11.49, 11.52.

When the ether–alcohol solution of the acyl azide from **2i** was allowed to decompose overnight, a solid product (9.5 g) separated from solution. This solid had mp 248° dec, was soluble in cold water (neutral solution), and was insoluble in all common organic solvents. Hydrolysis of 1.0 g of this solid with 20% HCl allowed the recovery of 0.83 g of 1-amino-1-phenylmethylphosphonic acid (**3i**). Since no satisfactory recrystallization solvent was found, the unknown solid was washed thoroughly with ethyl alcohol, dried in a vacuum desiccator, and analyzed. All of the properties of the solid (mp 248°) were consistent with structure **5**.

Anal. Calcd for $C_9H_{14}NO_3P$: C, 50.23; H, 6.56; N, 6.51; P, 14.39. Found: C, 50.40, 50.47; H, 6.44, 6.57; N, 6.55, 6.68; P, 14.44, 14.48.

Approximate p*K* Values and Neutralization Equivalents.—Weighed quantities of the amino acids were dissolved in standardized HCl in a volumetric flask, and aliquots were taken and titrated with standardized NaOH with a Sargent Model D recording titrator. From at least three such plots, the approximate p*K* values and neutralization equivalents were read.

Preparation of Benzoyl Derivatives.—The amino acid (6–7 g) was dissolved in 25 ml of water and enough 3 *M* NaOH to give pH 10. The solution was cooled to 5° and 100% excess benzoyl chloride was added. While a temperature of 5° was maintained and while 3 *M* NaOH was added at a rate to maintain pH 10, the mixture was stirred with a high-speed stirrer. When there was no further reaction, concentrated HCl was added to pH 2 and the product was recovered as described earlier.[4] The derivatives were recrystallized usually from acetonitrile; see Table IV.

$$RR'C(CH_2)_xPO(OH)_2$$
$$|$$
$$NHCOC_6H_5$$

Highly purified samples of amino acids were obtained by the hydrolysis of the purified benzoyl derivatives and recovery of the amino acid by ion exchange chromatography.

Registry No.—**2b**, 35051-49-1; **2c**, 35051-50-4; **4**, 35045-80-8; **5**, 35045-81-9.

Amino Phosphonic Acids. III. The Synthesis and Properties of 2-Aminoethylphosphonic and 3-Aminopropylphosphonic Acids[1]

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2-Aminoethylphosphonic acid (2-AEP, **2**) is the first compound having a C–P bond to be isolated from biological materials. Because of its wide distribution in the animal kingdom, 2-AEP appears to be an important new biological compound. This paper reports our findings concerning the polymorphism of **2**, some of its other physical and chemical properties, and two new syntheses. The behavior of 3-aminopropylphosphonic acid is compared with that of **2**.

In 1959, Horiguchi and Kandatsu[3] first described the isolation of **2** from ciliate protozoa. Since then, **2** has been found in numerous other organisms and a new area of biochemistry has grown up around this compound. A review covering developments through March 1964 is available.[4] Although man has modest quantities of **2** available in his food, it has not been determined whether or not he makes any use of this compound.

2-Aminoethylphosphonic acid (**2**) was first synthesized by Finkelstein[5] by the use of the Hofmann reaction.

$$\underset{\mathbf{1}}{EtO_2CCH_2CH_2PO(OEt)_2} \xrightarrow{NH_3} H_2NOCCH_2CH_2PO(OEt)_2 \xrightarrow[\text{conc HBr}]{NaOBr} \underset{\mathbf{2}}{H_2NCH_2CH_2PO(OH)_2}$$

Finkelstein added that "the corresponding hydrazide was also prepared from the ester but would not undergo the Curtius rearrangement." In 1947 both Kosolapoff[6] and Chavane[7] reported an alternate synthesis of **2**.

In contrast to Finkelstein's findings, we have been able to synthesize **2** by the Curtius synthesis in yields as high as 83%. 2-Aminoethylphosphonic acid may also be prepared by the catalytic reduction of readily available diethyl cyanomethylphosphonate.

2-Aminoethylphosphonic acid (**2**) gives the characteristic color with ninhydrin reagent but the color yield is only about 3% of the color produced by 1-aminoethylphosphonic acid and the color yield varies with the nature of the ninhydrin reagent.

Horiguchi and Kandatsu[8] first found that samples of **2** from different sources occasionally give different ir spectra when the spectra are run on Nujol mulls or on KBr disks. They correctly interpreted this as the result of polymorphism. We have also studied this be-

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(3) M. Horiguchi and M. Kandatsu, *Nature (London)*, **184**, 901 (1959); *Bull. Agr. Chem. Soc. Jap.*, **24**, 565 (1960).

(4) L. D. Quin, "Topics in Phosphorus Chemistry," Vol. 4, M. Grayson and E. J. Griffith, Ed., Interscience, New York, N. Y., 1966, p 23.

(5) J. Finkelstein, *J. Amer. Chem. Soc.*, **68**, 2397 (1946).

(6) G. M. Kosolapoff, *ibid.*, **69**, 2112 (1947).

(7) V. Chavane, *C. R. Acad. Sci.*, **224**, 406 (1947); *Ann. Chim. (Paris)*, **4**, 352 (1949).

(8) M. Horiguchi and M. Kandatsu, *Agr. Biol. Chem. (Tokyo)*, **28**, 408 (1964).

havior of 2 and, although we agree with the main conclusions of Horiguchi and Kandatsu, some of our results differ significantly.

Whereas there is evidence that 2 forms a hydrochloride salt in solution, we were unable to prepare a dry salt with a satisfactory amine:HCl ratio; prolonged drying under vacuum produced a hygroscopic solid with an amine:HCl ratio of 1:0.9.

3-Aminopropylphosphonic acid behaved like 2 on cation and anion exchange resins, gave a weak color with ninhydrin reagent, but failed to give a dark blue, water-soluble cupric chelate. When added to a suspension of basic cupric carbonate, 2 produced a deep blue solution but with about half the color intensity produced by 1-aminoethylphosphonic acid.

Experimental Section[9]

Triethyl 3-Phosphonopropionate (1).—Sodium (2 g) was dissolved in 304 g (2.2 mol) of freshly distilled diethyl phosphonate, and an equal volume of dry benzene was added, followed by 200 g (2.0 mol) of ethyl acrylate, added dropwise to maintain a temperature of 60°. After the solution cooled to room temperature, a slight excess of acetic acid was added, the mixture was filtered, and the filtrate was distilled, giving 400.8 g (84%) of 1, bp 109–110° (0.6 mm), n^{25}D 1.4308 [lit.[10] bp 156–158° (12 mm), n^{20}D 1.4338].

Diethyl 2-Cyanoethylphosphonate.—This preparation was similar to the method used to prepare 1, using 159 g (3 mol) of acrylonitrile, 455.4 g (3.3 mol) of diethyl phosphonate, 6.9 g of Na, and 200 ml of benzene at a reaction temperature of 40–45°. The product weighed 444.7 g (77.5%), bp 111–112° (0.4 mm), n^{25}D 1.4386 [lit.[11] bp 127–128° (2 mm), n^{20}D 1.4380].

Diethyl Cyanomethylphosphonate.—A mixture of 365.2 g (2 mol) of triethyl phosphite and 151.0 g (2 mol) of chloroacetonitrile was heated to boiling under reflux. The boiling temperature slowly increased from 138° to 175° (EtCl evolution). More triethyl phosphite (33.2 g) was added and the heating was continued again to 175°. Distillation produced 323.5 g (91.5%) of liquid, bp 95° (0.3 mm), n^{25}D 1.4315 [lit.[12] bp 126–127° (2.0 mm), n^{20}D 1.4310].

2-Aminoethylphosphonic Acid (2) *via* the Curtius Reaction.—Triethyl 3-phosphonopropionate (0.1 mol) was added to hydrazine (0.2 mol) or to hydrazine hydrate at a rate to maintain a temperature of 30° and the clear solution was allowed to stand for an additional 1 hr to complete the hydrazide formation. The remainder of the reaction was run as has been described[13] with 16.5 ml of concentrated HCl, 0.2 mol of $NaNO_2$ in 20 ml of water, a total of 200 ml of ether, and 100 ml of absolute ethanol; the crude urethane was hydrolyzed for 48 hr with 50 ml of water and 100 ml of concentrated HCl.

After excess HCl was removed and the solution was decolorized (Norit A), 2 was recovered by absorbing it on Dowex 50 (H^+), washing with water to remove acidic impurities, and eluting 2 with 0.1–0.5 *M* NH_4OH. After this eluate was evaporated to dryness, the residue was dissolved in a small volume of water and passed through Dowex 21K (OH^-) to remove the NH_4^+. Then 2 was eluted with 0.1–0.5 *M* acetic acid, the eluate was evaporated to dryness, and the solid residue was dissolved in a minimum of hot water. Ethyl alcohol (95%) was added until solid began to separate and the mixture was chilled. The recovered 2 had mp 289–290° dec. Potentiometric titration gave neut equiv 127 (calcd 125), and the following pK values were obtained from the titration curve: pK_1 = 2.13, pK_2 = 6.45, pK_3 = 11.05. (Literature melting points have varied from 250°[7] to 296–299°;[3] lit.[7] pK_1 = 2.45, pK_2 = 7.00, pK_3 = 10.8.)

The *N*-benzoyl derivative of 2 was prepared,[14] mp 191–192°.

Anal. Calcd for $C_9H_{12}NO_4P$: C, 47.17; H, 5.28; P, 13.52; neut equiv, 229. Found: C, 47.22, 47.23; H, 5.20, 5.30; P, 13.52, 13.38; neut equiv, 230.

2-Aminoethylphosphonic Acid (2) *via* Diethyl Cyanomethylphosphonate.—Approximately 37 ml of wet Raney Ni was washed by pressure filtration with glacial acetic acid and then with acetic anhydride. This catalyst was quickly placed in a Parr hydrogenator bottle (250 ml) with 70.8 g (0.4 mol) of diethyl cyanomethylphosphonate, 12.0 g of anhydrous sodium acetate, and 120 ml of acetic anhydride. This mixture was shaken under hydrogen (60 psi) until absorption ceased (70% of the H_2 was absorbed in 1 hr but reaction was continued overnight). The mixture was filtered, the catalyst was washed with ethanol (95%), and the combined filtrates were evaporated to dryness under vacuum, leaving 127.8 g of crude yellow oil. This oil was heated under reflux with 100 ml of water, and three successive 100-ml portions of concentrated HCl were added during the 40-hr heating. From here on 2 was recovered by ion exchange chromatography as described above, except that as much as 1.2 equiv capacity of Dowex 50 resin was required to hold the Na^+ and to allow good separation of the fractions. When 2 was eluted from Dowex 21K (OH^-) with 0.5 *M* acetic acid, care was taken to avoid excessive heating of the resin by too rapid flow of the acid. The yield of 2 was 43.0 g (86.1%).

A somewhat different procedure involved combining 50 ml of absolue ethanol, saturated with NH_3, 17.7 g (0.1 mol) of diethyl cyanomethylphosphonate, and 1 ml of W-4 Raney Ni[15] in a hydrogenation bottle and shaking the mixture with an initial pressure of 60 psi of H_2. When the calculated amount of H_2 had been absorbed, the mixture was filtered, the filtrate was evaporated to dryness under vacuum, and the residue was dissolved in 50 ml of 50% ethanol. This solution was saturated with H_2S, the precipitated NiS was removed by filtration, the filtrate was heated under reflux for 48 hr with 25 ml of concentrated HCl, and 2 was recovered as above. There resulted 5.8 g (47%) of 2. The Ni may also be removed after the hydrolysis when the crude 2 is chromatographed on Dowex 50 resin; when 2 is eluted with 0.5 *M* NH_4OH, the Ni remains on the resin.

A further modification involved reducing 17.7 g (0.1 mol) of diethyl cyanomethylphosphonate in 70 ml of 95% ethanol and 40 ml of 10% HCl over 1 g of 10% Pd/C at 60 psi H_2 for 26 hr (calculated amount of H_2 absorbed). After removal of the catalyst, the filtrate was neutralized with $NaHCO_3$, the solution was evaporated to dryness under vacuum, the residue was extracted with two 50-ml portions of absolute ethanol, and the clear extract was distilled. There was recovered 11.4 g (63%) of diethyl 2-aminoethylphosphonate, a colorless liquid, bp 54–56° (0.025 mm), n^{25}D 1.4426 [lit.[16] bp 93–95° (4.0 mm), n^{20}D 1.4270].

Reaction of 2 with Ninhydrin.—Ninhydrin reagent prepared in various ways, as reported in the literature, gave varying color productions with 2; in some instances, no color at all resulted. The ninhydrin solution recommended in an earlier paper[14] was not suitable for 2; instead, a freshly prepared solution of 100 mg of ninhydrin in 100 ml of pH 7.0 buffer gave reliable results.

Polymorphism of 2.—In numerous ways, we have attempted to prepare samples of the metastable α form[8] of 2, without success. The α form has been described as heavy rhombic plates and the more stable β form as needles.[8] In one instance, a drop of a hot, saturated, aqueous solution of 2 was placed in the depression of a microscope slide, covered with a cover glass, and watched through a microscope as crystals formed. Perfect, heavy rhombic plates separated. To be certain that these were the desired α form, their ir spectrum (Nujol mull) was determined. These

(9) All melting points were determined with a Hershberg apparatus and with a thermometer which had been calibrated with a set of thermometers having Bureau of Standards calibrations; boiling points were uncorrected. Triethyl phosphite was kindly supplied by the Hooker Chemical Corp. and was redistilled before being used. Anhydrous hydrazine (95+%) was obtained from Matheson Coleman and Bell. Raney Ni, grade #28, was obtained from the Grace Co. Dowex 50W-X8 and Dowex 21K resins were kindly supplied by the Dow Chemical Co. All other reagents were the best grade available and were used without further purification. Infrared spectra were produced with a Beckman IR-8 spectrometer and titrations were carried out with a Sargent Model D recording titrator. A Nestor-Faust refractive index monitor was used to detect changes of composition of the ion exchange column eluates. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(10) N. Kreutzkamp and W. Mengel, *Chem. Ber.*, **100**, 709 (1967).

(11) B. A. Arbuzov and B. P. Lugovkin, *Zh. Obshch. Khim.*, **21**, 99 (1951).

(12) A. N. Pudovik and N. M. Lebedeva, *ibid.*, **25**, 2235 (1955).

(13) J. R. Chambers and A. F. Isbell, *J. Org. Chem.*, **29**, 832 (1964).

(14) J. P. Berry, A. F. Isbell, and G. E. Hunt, *ibid.*, **37**, 4396 (1972).

(15) A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.*, **68**, 1471 (1946).

(16) A. M. Pudovik and G. M. Denisova, *Zh. Obshch. Khim.*, **23**, 263 (1953).

rhombic crystals gave the spectrum normally given by needles—in other words, by the β form! From 30 samples of **2** prepared at different times, three samples gave the spectrum corresponding to the α form. All attempts to recrystallize these samples of the α form have invariably given the β form. We have normally been unable to determine which form we have either by observation of the solid with the unaided eye or with a microscope.

Registry No.—**2**, 2041-14-7; **2** (*N*-benzoyl), 35045-99-9.

The Stereochemistry of Aziridine Ring Expansion Reactions with Sulfur Nucleophiles to Give Thiazolidines and 2-Amino-2-thiazolines

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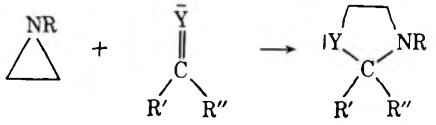
Received May 11, 1972

The ring enlargement reactions of aziridines with thiocyanic acid and acetone plus hydrogen sulfide to 2-amino-2-thiazolines **2** and 2,2-dimethylthiazolidines **9** proceed 100% stereospecifically with Walden inversion; for example *cis*- and *trans*-2,3-dimethylaziridine, **11** and **12**, with thiocyanic acid gave exclusively *trans*- and *cis*-2-amino-4,5-dimethyl-2-thiazoline, **13** and **14**, respectively. For the 2-amino-2-thiazolines **2** it was shown by means of ir and nmr spectra, that the tautomeric equilibrium between the forms with exocyclic and endocyclic double bond (eq 5) lies completely toward the 2-amino form **19a** with endocyclic double bond.

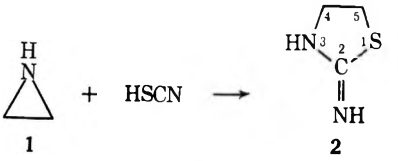
Aziridines can be ring expanded with suitable reagents according to the following general scheme (eq 1).[1]



(1)

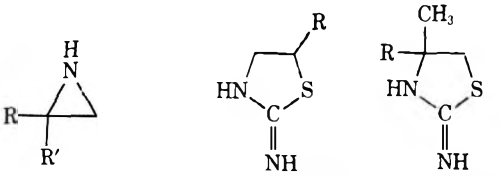
The reagent attacking the aziridine must have a multiple bond attached to an atom Y possessing a free electron pair. Only reactions in which the aziridine reacts under carbon–nitrogen cleavage (rather than carbon–carbon cleavage) are considered here. The ring expansion of aziridines with aldehydes,[2] aldehydes and ketones in the presence of H_2S,[2b,3-6] carbon disulfide,[1,7-10] xanthates,[1] isocyanates,[1] alkali thiocyanate or thiocyanic acid,[8,10,11] organic isothiocyanates,[1] thioacetamide,[1] and nitriles[1] have been reported. Many of these reactions proceed under acid catalysis which facilitates the opening of the aziridine ring.

Additions of Thiocyanic Acid to Give 2-Iminothiazolidines.—Gabriel and Colman discovered the reaction of aziridines (**1**) with thiocyanic acid to give 2-iminothiazolidines[8] according to eq 2. From phenylaziridine (**3a**)



(2)

in the presence of HCl they obtained 2-imino-5-phenylthiazolidine (**4a**). Earley, *et al.*, investigated in detail

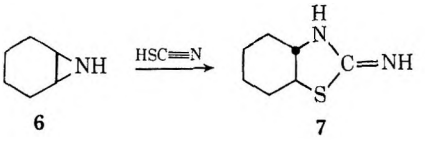


3a, R = C_6H_5; R′ = H
b, R = C_2H_5; R′ = H
c, R = CH_3; R′ = CH_3
d, R = CH_3; R′ = H

4a, R = C_6H_5
b, R = CH_3

5a, R = H
b, R = CH_3

the mechanism and kinetics of the addition of potassium thiocyanate to four aziridines, aziridine (**1**) itself, 2-ethylaziridine (**3b**), 2,2-dimethylaziridine (**3c**), and *N*-(*n*-butyl)aziridine and obtained in all cases the corresponding 2-iminothiazolidines.[11] From 2,2-dimethylaziridine (**3c**) they obtained 2-imino-4,4-dimethylthiazolidine (**5b**) by attack of the thiocyanate ion at the primary carbon atom of the aziridine ring. Finally, Mousseron, *et al.*, reported the addition of thiocyanic acid to *cis*-cyclohexenimine (**6**) to give the trans-fused thiazolidine **7** (eq 3).[10] The latter is



(3)

the only example where the stereochemistry of the reaction has been mentioned at all.

Additions of Aldehydes and Ketones in the Presence of Hydrogen Sulfide to Give 2-Alkyl- and 2,2-Dialkylthiazolidines.—Bestian[3] has shown that aziridine (**1**) treated with hydrogen sulfide in the presence of an aldehyde or ketone **8** gives a thiazolidine **9** according to eq 4; for example, the addition of hydrogen sulfide to

(1) P. E. Fanta in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part 1, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, pp 524–575. H. Bestian in "Methoden der Organischen Chemie," Vol. 11/2, Houben-Weyl, George Thieme Verlag, Stuttgart, 1958, p 223 ff; O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y., 1969, Chapter 3; J. McCormick, R. I. Kaplan, and B. J. Stormer, *Can. J. Chem.*, **49**, 699 (1971).

(2) (a) J. B. Doughty, C. L. Lazzell, and A. R. Collett, *J. Amer. Chem. Soc.*, **72**, 2866 (1950). (b) See, however, R. Tondeur, R. Sion, and E. Doray, *Bull. Soc. Chim. Fr.*, 2493 (1964).

(3) (a) H. Bestian, *Justus Liebigs Ann. Chem.*, **566**, 210 (1950); (b) H. Bestian (I. G. Farbenindusttie A.-G.), German Patent 747,733 (1939) [*Chem. Zentralbl.*, **I**, 952 (1945)].

(4) G. Drehfahl and M. Huebner, *J. Prakt. Chem.*, (4) **23**, 149 (1964); R. G. Kostyanovskii, *Dokl. Akad. Nauk SSSR*, **135**, 853 (1960) [*Chem. Abstr.*, **55**, 12380 (1961)]; F. Asinger, *Monatsh. Chem.*, **99**, 2090 (1968).

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(6) J.-L. Larice, J. Roggero, and J. Metzger, *ibid.*, 3637 (1967).

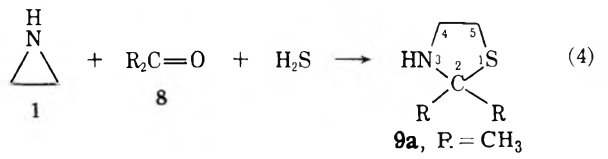
(7) S. Gabriel and H. Ohle, *Chem. Ber.*, **50**, 804 (1917).

(8) S. Gabriel and J. Colman, *ibid.*, **47**, 1866 (1914).

(9) T. A. Foglia, L. M. Gregory, G. Maerker, and S. F. Osman, *J. Org. Chem.*, **36**, 1068 (1971), and references cited therein.

(10) M. Mousseron, F. Winternitz, and R. Dennilauer, *C. R. Acad. Sci.*, **239**, 278 (1954); F. Winternitz, M. Mousseron, and R. Dennilauer, *Bull. Soc. Chim. Fr.*, **382**, 1228 (1956).

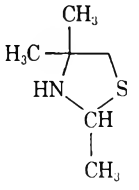
(11) J. E. Earley, O. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Amer. Chem. Soc.*, **80**, 3458 (1958).



(4)

1 8 9a, R = CH_3

aziridine (1) in the presence of acetone gives 2,2-dimethylthiazolidine (9a). Larice, Roggero, and Metzger investigated the similar reaction of 2,2-dimethylaziridine (3c) with acetaldehyde in the presence of hydrogen sulfide and found the product to be 2,4,4-trimethylthiazolidine (10), *i.e.*, attack of the



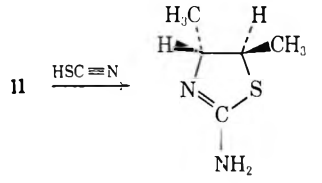
10

nucleophile took place exclusively at the less substituted primary carbon atom.[6]

Although numerous other authors and patents have used this reaction, no investigation of the stereochemistry of the reaction has been reported.

Results

Addition of Thiocyanic Acid.—When *cis*-2,3-dimethylaziridine (11) was treated with thiocyanic acid, *trans*-2-



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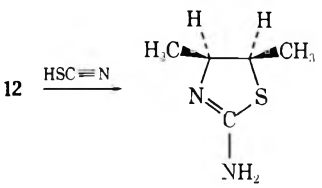


14

amino-4,5-dimethyl-2-thiazoline (13) was the only thiazoline isomer formed. Similarly, when *trans*-2,3-dimethylaziridine (12) was treated with thiocyanic acid, *cis*-2-amino-4,5-dimethyl-2-thiazoline (14) was the exclusive isomer formed. (The 2-amino-2-thiazoline structure is tautomeric with the 2-iminothiazolidine structure considered before, as will be discussed below, eq 5.) All preparative results are summarized in Table I.

Both the trans and cis isomers 13 and 14 were not previously reported in the literature. The stereospecificities of these two reactions was most easily determined by examination of the nmr spectra of the crude reaction products, especially in the region of the 4,5 methine protons (see Table II). The absence of any bands in the range of 4.10–4.30 ppm in the spectrum of the reaction product of the trans isomer 13 indicated the absence of the cis isomer 14. Similarly, the absence of bands between 3.30 and 3.50 ppm in the

TABLE I

PRODUCTS OF RING EXPANSION REACTIONS OF AZIRIDINES WITH SULFUR NUCLEOPHILES

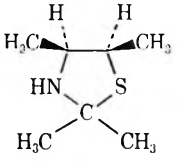
Aziridine	Nucleophile	Thiazolidine	% yield	Derivatives, mp, °C
11	Thiocyanic acid	13	73[a]	Picrate salt, 202–203
12	Thiocyanic acid	14	76[a]	Picrate salt, 201–202
3d	Thiocyanic acid	5a	79[a]	Oxalate salt, 227–230 Picrate salt, 236–239[c]
12	Hydrogen sulfide with acetone	15	15[b]	
3d	Hydrogen sulfide with acetone	16	24.2[b]	

[a] Crude weight yield of product. [b] Yield after one distillation. [c] Lit.[7] 230–244°, also depending on rate of heating.

spectrum of the reaction product of the cis isomer 14 showed the absence of the trans isomer 13.

2-Methylaziridine (3d) after treatment with thiocyanic acid gave only one of the two possible constitutional 2-thiazoline isomers as indicated by the single methyl doublet appearing in the nmr spectrum of the raw reaction product. This isomer was identified as being 2-amino-4-methyl-2-thiazoline (5a) from the melting point of the picrate salt reported in literature by Gabriel and Ohle.[7,12] These authors had obtained the compound from the reaction of 2-amino-1-bromopropane with thiocyanic acid.

Addition of Acetone in the Presence of Hydrogen Sulfide.—Acetone was added in the presence of hydrogen sulfide to *trans*-2,3-dimethylaziridine (12). The nmr spectrum of the crude reaction product indicated that *cis*-2,2,4,5-tetramethylthiazolidine (15) was the exclusive thiazolidine formed.



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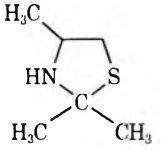


16

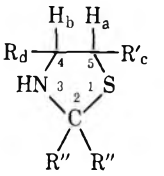
The addition of hydrogen sulfide to 2-methylaziridine (3d) in the presence of acetone gave a raw product in the nmr spectrum of which a single methyl doublet was observed, signifying that only one isomeric form was produced. On the base of the chemical shift of the 4- or 5-methyl group, the structure 2,2,4-trimethylthiazolidine (16) must be assigned to this product. This is in agreement with all other additions of sulfur nucleophiles to 2-alkylaziridines, specifically the addition of hydrogen sulfide in the presence of acetaldehyde to 2,2-dimethylaziridine (3c) to give solely 2,4,4-trimethylthiazolidine (10);[6] *i.e.*, nucleophilic attack takes place at the less substituted primary carbon atom. Compound 16 has been reported previously in the patent literature erroneously as 2,2,5-trimethylthiazolidine without proof of structure.[3b]

Nmr Spectra.—The nmr data of all thiazolidine deriv-

(12) The melting point of the picrate of the 4 isomer, 2-amino-4-methyl-2-thiazoline (5a), is 236–238°. (See Table I or Experimental Section for further comments.) The melting point of the picrate of the 5 isomer, 2-amino-5-methyl-2-thiazoline (4b), is 199–200°: P. Hirsch, *Chem. Ber.*, 23, 965 (1890); also ref 7.

TABLE II

NMR DATA OF THIAZOLIDINES[a]



Compd	H_a (at C-5)	H_b (at C-4)	H_c (at C-5)	H_d (at C-4)	At C-2
14	3.86[b] (qu, J_{ac} = 6.5)	4.13[b,c] (qu, J_{bd} = 6.8)	1.24[b] (d, J_{ca} = 6.5)	1.30[b] (d, J_{db} = 6.8)	NH_2, 6.19 (s)
13	3.64[b] (qu, J_{ac} = 6.3)	3.73[b,c] (qu, J_{bd} = 6.0)	1.25 (d, J_{ca} = 6.3)	1.40 (d, J_{db} = 6.0)	NH_2, 6.02 (s)
5a (R′ = H cis to R)	3.43 (q, J_{ac} = 10.1, J_{ab} = 7.0)	4.25 (q,[c] J_{ba} = 7.0, J_{bc} = 7.8, J_{bd} = 6.5)	2.94 (q, J_{ca} = 10.1, J_{cb} = 7.8)	1.28 (d, J_{db} = 6.5)	NH_2, 4.81 (s)
15	4.49[b] (m)	4.60[b,c] (m)	1.09[b] (d, J_{ca} = 6.9)	1.16[b] (d, J_{db} = 5.7)	*cis*-CH_3, 1.53 (s)
					trans-CH_3, 1.67 (s)
16		3.05–3.75 (m, J_{bd} = 5.7)		1.35 (d, J_{db} = 5.7)	*cis*-CH_3, 1.55 (s)
					trans-CH_3, 1.66 (s)

[a] All spectra were determined in $CDCl_3$ solution; chemical shifts are in δ (ppm) (J in hertz) downfield from internal tetramethylsilane; s = singlet, d = doublet, q = quartet, qu = quintet, m = multiplet. [b] Overlapping peaks. [c] Predominant pattern in actually higher multiplet.

atives investigated are summarized in Table II. The 4- and 5-methyl groups and methine protons of the 4,5-dimethylthiazolidine derivatives were analyzed as A_3XYB_3 systems with $J_{AY} = J_{BX} = 0$. In all compounds studied, the 4-methine proton appears at lower field than the 5-methine proton by about 0.1–0.4 ppm. The differences are generally smaller for the 4- and 5-methyl groups although the 4-methyl group still appears at lower field than the 5-methyl group. This is in agreement with the general behavior of protons neighboring a saturated nitrogen atom[13,14] *vs.* a sulfur atom[15] and also with the assignment of thiazolidine derivatives given by all other authors.[9,16] The assignment is also supported, as will be discussed, by the coupling between the 4-methine proton and the neighboring N–H proton.

In practically all 4,5-dimethylthiazolidine derivatives examined the vicinal coupling constant between the 4- and 5-methine proton is very nearly of the same magnitude as the coupling constant between the methine protons and the corresponding geminal methyl groups. For this reason the 4- and 5-methine protons appear essentially as two quintets which frequently overlap partially.

Assignment of the Cis- or Trans Configuration.—The assignment of the cis or trans configuration with respect to the 4,5-methyl groups is based mainly on the comparison between the chemical shifts at the 4 and 5 positions. The 4- and 5-methyl groups in all compounds examined absorb at ~0.1 ppm higher field in the cis compounds than in the corresponding trans isomers. On the other hand, the 4- and 5-methine protons absorb at ~0.5 ppm lower field in the *cis*-thiazolidines than in the trans isomers. This effect can be attributed mainly to the diamagnetic anisotropy of the *C*-methyl bond and is found in many cis–trans isomer pairs of planar three- to five-membered-ring compounds.[17] A methyl group has the tendency to shield a neighboring substituent in the cis position and to deshield a neighboring substituent in trans orientation. Thus, two *trans*-4,5-methyl groups will mutually deshield each other so as to shift both methyl bands to lower field. At the same time the 4 and 5 protons will be shielded by the neighboring methyl groups and therefore shift upfield.[17]

Likewise, two *cis*-4,5-methyl groups will mutually shield each other causing the methyl bands to appear at higher field. The 4,5 protons will now be deshielded and therefore move to lower field.

The same effect results from the two protons. The diamagnetic anisotropy of carbon–hydrogen bond presently is assumed to be ~0.75 that of a carbon–carbon bond. This means that the effect of the carbon–hydrogen bonds opposes that of the methyl group, but cannot completely cancel it out.[18]

A more accurate treatment has to take into account the three C–H bonds of the methyl group as well as the rotation of the methyl group. This does not substantially change, however, the above conclusions.[19] A criterion frequently used for the assignment of the cis or trans configuration is based on the 4-H,5-H coupling constant. In three- to five-membered rings, which cannot deviate appreciably from planarity, cis proton coupling is generally larger than trans proton coupling, as expected from the Karplus rule.[14,20] Unfortunately this criterion is difficult to apply in the present case since in most compounds examined the multiplet pattern of the 4- and 5-methine protons is so complex that an accurate evaluation of the corresponding coupling constant is difficult. Probably the difference between the cis and trans vicinal coupling constant is much smaller in thiazolidine derivatives than in the 2-thiazoline or 2-oxazoline derivatives owing to the increased flexibility of the five-membered ring in the former.

The nmr spectrum of *cis*-2,2,4,5-tetramethylthiazolidine (**15**) clearly showed two distinct bands for the two methyl groups at carbon position two. The peak

(13) Protons neighboring an unsaturated nitrogen atom would be shifted downfield still further.

(14) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969.

(15) Reference 14, p 163.

(16) M. Chanon and J. Metzger, *Bull. Soc. Chim. Fr.*, 2855 (1968).

(17) Reference 14, p 234 ff.

(18) Reference 14, p 78 ff.

(19) J. Elguero and A. Fruchier, *Bull. Soc. Chim. Fr.*, 496 (1970).

(20) S. Sternhell, *Quart. Rev. Chem. Soc.*, **23**, 236 (1969); ref 14, p 286 ff.

TABLE III

IR DATA[a] FOR 2-AMINO-2-THIAZOLINES (CH_2Cl_2)

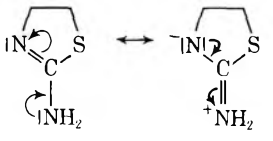
Compd	C=N[b]	C—N[c]	ν_a(N—H)	ν_s(N—H)	Other
5a	1645 (s)	1310 (m)	3510 (m)	3415	3110 (m), 2933 (m), 1595 (m), 1022 (m), 921 (S)
13	1639 (s)	1314 (m)	3509 (m)	3410	3100 (m), 2941 (m), 1595 (m), 1434 (m), 1019 (m), 1003 (m), 993 (m), 915 (m)
14	1647 (s)	1321 (m)	3520 (m)	3420 (m)	3110 (m), 2959 (m), 1595 (m), 1495 (m), 1443 (m), 1380 (m), 1063 (m), 1010 (m), 914 (m)

[a] In cm^{-1}. [b] Amidine I band. [c] Amidine III band.

at high field can be assigned to the group cis to the methyl groups at atoms 4 and 5, on the base of the shielding between *cis*-methyl groups discussed above, which applies to methyl groups in 1,3 position as well.[21]

Infrared Data of 2-Amino-2-thiazolines.—The important ir data of the 2-amino-2-thiazolines are summarized in Table III. All 2-amino-2-thiazolines show the C=N stretch (amide or amidine I band)[22] as a very strong band at 1640 cm^{-1} which is in the usual region of 1600–1640 cm^{-1} for 2-thiazoline and 2-amino-2-thiazoline derivatives.[23,24]

A medium to strong band around 1315 cm^{-1} may be assigned as mainly due to the C—N stretch (amidine III band). The band under consideration closely corresponds to the amide III band, which appears around 1290 cm^{-1}.[22] The higher frequency than that found for a typical C—N stretch (1220–1020 cm^{-1}) is, as in the amide III band, due to the resonance between forms **17** and **18**. Sharp and medium bands at

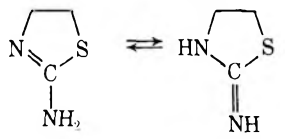


17 **18**

~3510 and 3420 cm^{-1} must be assigned to the asymmetric and symmetric N—H stretch of the amino group at C-2.[25,26] The medium to weak band around 3350 cm^{-1} is probably due to associated N—H.

Other medium to strong bands common in all 2-amino-2-thiazolines examined appear at ~3100, 1590, 1020, and 915 cm^{-1}. The band at ~3100 cm^{-1} has long been the subject of controversy in amides. The usual explanation for the band in amides is as a combination band between the N—H in-plane bending and the C=O stretching.[27] Bellamy has pointed out that this band persists in thiolactams with five- and six-membered rings although the explanation just mentioned is impossible.[28] The band at ~1590 cm^{-1} is usually assigned to the amino deformation $\delta(NH_2)$.[29]

2-Amino-2-thiazolines are basically capable of existing in two tautomeric forms (eq 5). The 2-amino-2-



(5)

19a **19b**

thiazoline form, **19a**, has an endocyclic double bond, whereas the other tautomer, the 2-iminothiazolidine, **19b**, possesses an exocyclic double bond.

The above ir data clearly show that the 2-amino-2-thiazoline tautomer **19a** with endocyclic double bond is the predominant, if not exclusive, form present. This is in agreement with the generalization that amino tautomers are always more stable than their imino tautomers[30] as well as with the behavior of the very similar equilibrium of 2-amino-2-oxazolines where also the endocyclic form has been found to be the predominant tautomer.[26] The exocyclic tautomer **19b** should not be present in the tautomeric equilibrium (eq 5) in a significant percentage, since all bands expected for this tautomer are absent in the ir spectrum. Thus no ν(C=N) band due to the exocyclic tautomer **19b** and no amide II band between 1500 and 1575 cm^{-1}, which the exocyclic tautomer **19b** as a secondary amide (amidine) should show, can be detected in the ir spectrum.

Discussion

Although all of the ring expansions of aziridines examined proceed identically with Walden inversion, the detailed mechanisms for the two reactions are different and so will be discussed in turn.

Formation of 2-Amino-2-thiazolines.—Mechanism 6, illustrated by the reaction of the *cis*-aziridine **11** to give the *trans*-2-thiazoline **13**, seems to account best for the observed results of the additions of thiocyanic acid to aziridines to give 2-amino-2-thiazolines.

Thus the reaction involves one inversion on opening of the protonated aziridine ring **20** by the thiocyanate ion to give the corresponding 2-aminothiocyanate **21** (threo depicted in mechanism 6). This is followed

(21) M. Anteunis and F. Alderweireldt, *Bull. Soc. Chim. Belg.*, **73**, 889, 903 (1964).

(22) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1954; L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen, London, 1968.

(23) T. Nishiguchi, H. Tochio, A. Nabeya, and Y. Iwakura, *J. Amer. Chem. Soc.*, **91**, 5835, 5841 (1969).

(24) W. Otting and F. Drawert, *Chem. Ber.*, **88**, 1469 (1955); A. I. Myers, *J. Org. Chem.*, **24**, 1233 (1959); A. R. Katritzky and A. P. Ambler in "Physical Methods in Heterocyclic Chemistry," Vol. 2, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, p 161 ff.

(25) J. Pitha, J. Jonás, J. Kovár, and K. Bláha, *Collect. Czech. Chem. Commun.*, **26**, 834 (1961).

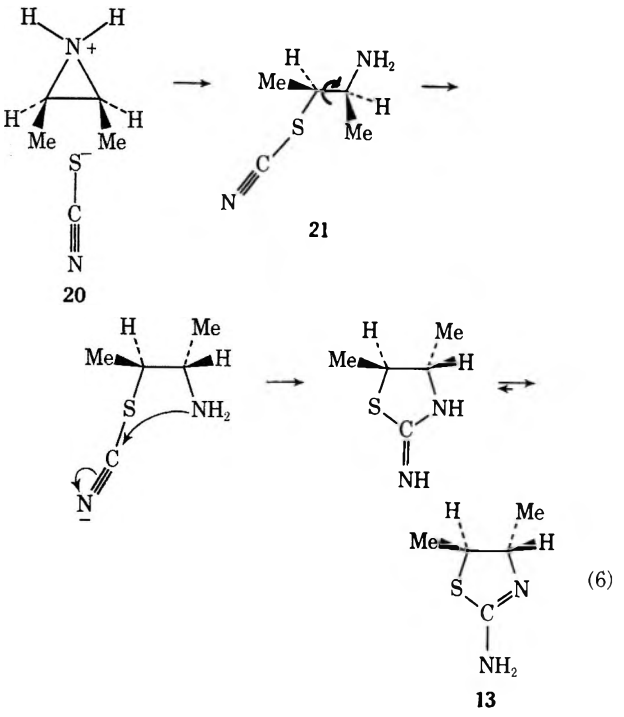
(26) J. R. Carson, G. I. Poos, and H. R. Almond, Jr., *J. Org. Chem.*, **30**, 2225 (1965).

(27) T. Miyazawa, *J. Mol. Spectry.*, **4**, 155, 168 (1960).

(28) Reference 22b, p 286.

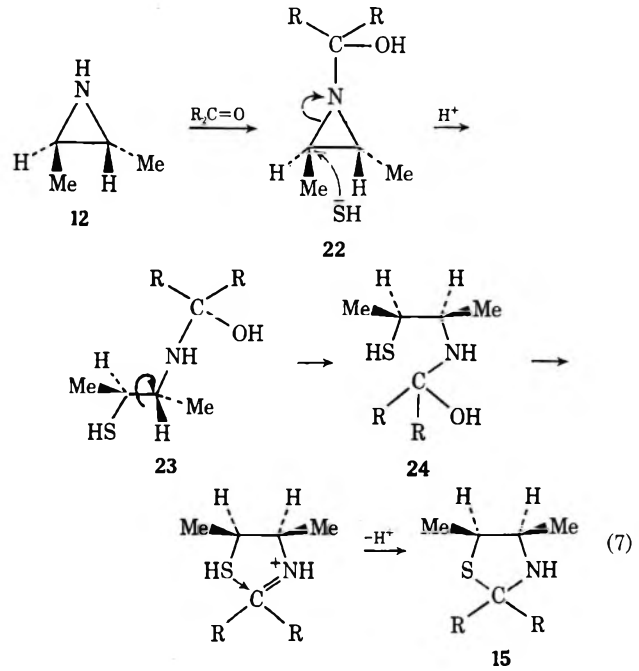
(29) B. Schrader, W. Meier, K. Gottlieb, H. Agatha, H. Barentzen, and P. Bleckmann, *Ber. Bunsenges.*, **75**, 1263 (1971); P. Bleckmann, B. Schrader, W. Meier, and K. Takahachi, *ibid.*, **75**, 1279 (1971); G. B. Aitken, J. L. Duncan, and G. P. McQuillan, *J. Chem. Soc. A*, 2695 (1971).

(30) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **2**, 66 (1963).



by rotation around the C—C bond of the former aziridine ring and ring closure to give, after several tautomerization steps, the 2-amino-2-thiazoline (**13** depicted in mechanism 6).

Formation of 2,2-Dialkylthiazolidines.—For the formation of thiazolidines by the ring expansion of N-unsubstituted aziridines with hydrogen sulfide in the presence of aldehydes and ketones, mechanism 7, illus-



trating the reaction of *trans*-2,3-dimethyaziridine (**12**) to give *cis*-2,2,4,5-tetramethylthiazolidine (**15**), seems to account best for the observed results. It has been well established that N-unsubstituted aziridines form hemiaminals of the type **22** with aldehydes and ketones.[2b,5,6] The mechanism then again involves one inversion on opening of this hemiaminal **22** to give the 2-aminothiol derivative **23** (erythro illustrated), followed by rotation around the C—C bond of the former aziridine ring and ring closure to give the final thiazolidine (*cis*-**15**, illustrated). It is known that the reaction under consideration also proceeds with N-substituted aziridines. Here the formation of the hemiaminal **22** is prevented, and the reaction is likely to proceed by the aziridine ring opening with SH^- to give the corresponding 2-aminothiol, which with acetone in turn then can form the hemiaminal **24** (with NR in place of NH).

The reactions of 2-methylaziridine (**3d**) with all sulfur nucleophiles led exclusively to the corresponding 4-methylthiazolidine derivatives, indicating that the attack at the primary carbon atom is favored over attack at the secondary carbon atom. This is, of course, in agreement for the S_N2 mechanism postulated for all reactions.

Experimental Section

General Procedures.—All ir spectra were taken on Perkin-Elmer Model 137 and Perkin-Elmer Model 225 spectrophotometers. Nmr spectra were taken on a Varian A-60 nmr spectrometer. Deuterated chloroform was used as a solvent if not specified otherwise, with tetramethylsilane as an internal standard. Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Boiling points are not corrected.

The microanalyses were performed by the Hoffmann-La Roche Corp., Nutley, N. J., to whom we would like to extend our thanks.

cis- and *trans*-**dimethylaziridines, 11 and 12,** were synthesized according to the method given by Dickey and coworkers from the corresponding epoxybutanes.[31] On the base of nmr and ir spectra, both isomers were >99% stereochemically pure.

The epoxybutanes, *cis*- and *trans*-2,3-epoxybutane, were made by a method described by Winstein and Lucas, by the addition of HOBr to *trans*- and *cis*-2-butene, respectively, and elimination of HBr with aqueous NaOH.[32] *N*-Bromosuccinimide was used, however, in place of *N*-bromoacetamide.

2-Amino-4-methyl-2-thiazoline (**5a**).—2-Methylaziridine (**3d**, 0.20 g, 3.5 mmol) dissolved in 2 ml of ether was slowly added to an ether solution containing an excess of thiocyanic acid at 0°. Upon addition, the raw product settled out as an oil. After the mixture stood at room temperature for 24 hr, the ether was distilled off and the oil was taken up in chloroform and dried with potassium carbonate. After evaporation of the solvent, the crude product remained as a viscous liquid yielding 0.32 g (79%) of **19**, picrate mp 236–239° (lit.[7] mp 230–244°, also dependent on rate of heating), oxalate mp 227–230°.

Anal. Calcd for $C_{10}H_{11}N_5O_7S$: C, 34.79; H, 3.21; N, 20.28; S, 9.28. Found: C, 34.87; H, 3.18; N, 20.31; S, 9.13.

trans-**2-Amino-4,5-dimethyl-2-thiazoline** (**13**) was prepared from *cis*-2,3-dimethylaziridine (**11**) in 73% crude yield, using the same method as was used for compound **5a**, picrate mp 202–203°.

Anal. Calcd for $C_{11}H_{13}N_5O_7S$: C, 36.77; H, 3.65; N, 19.49; S, 8.92. Found: C, 36.51; H, 3.39; N, 19.48; S, 8.63.

cis-**2-Amino-4,5-dimethyl-2-thiazoline** (**14**) was prepared from *trans*-2,3-dimethylaziridine (**12**) in 76% crude yield using the same procedure as was used for compound **5a**, picrate mp 201–202°.

Anal. Calcd for $C_{11}H_{13}H_5O_7S$: C, 36.77; H, 3.65; N, 19.49; S, 8.92. Found: C, 36.98; H, 3.73; N, 19.55; S, 8.77.

cis-**2,2,4,5-Tetramethylthiazolidine** (**15**) was prepared from 0.467 g of *trans*-2,3-dimethylaziridine (**12**) in 2 ml of acetone through which hydrogen sulfide was bubbled in excess for 2 hr; then for an additional half hour hydrogen sulfide was added under slight overpressure. The solution was heated for 2 hr at 40°, then at 60° for 2 additional hr. After heating, any remaining solvent was removed at reduced pressure. Distillation of the raw product gave a 0.137-g (15%) yield: ir (CH_2Cl_2) 3340 (br), 2915 (m), 1453 (m), 1379 (m), 1361 (m), 1142 (m), 1116 (m), 812 cm^{-1} (s).

2,2,4-Trimethylthiazolidine (**16**) was prepared from 0.57 (10

(31) F. H. Dickey, W. Fickett, and H. J. Lucas, *J. Amer. Chem. Soc.*, **74**, 944 (1952).

(32) S. Winstein and H. J. Lucas, *ibid.*, **61**, 1576 (1939).

mmol) of 2-methylaziridine (3d) using the procedure given for 15. Distillation at reduced pressure gave 0.316 g (24.2% yield): bp 59° (18 mm) [lit.[3b] bp 55° (13 mm)]; ir (CH_2Cl_2) 3350 (br), 2915 (m), 1458 (m), 1379 (m), 1364 (m), 1125 (s), 802 cm^{-1} (s).

Registry No.—5a, 35740-21-7; 5a oxalate, 35740-22-8; 13, 35740-69-3; 13 picrate, 35740-70-6; 14, 35740-71-7; 14 picrate, 35740-72-8; 15, 35740-73-9; 16, 35740-23-9.

Acknowledgments.—We wish to thank the National Science Foundation (NSF Grant GY-6070) and the Rutgers Research Council for financial support.

The Reaction of Thiophene-3,4-dicarbonyl Chloride with Aluminum Chloride and Benzene

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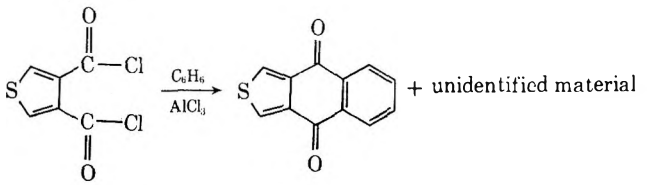
The reaction of thiophene-3,4-dicarbonyl chloride (1) with aluminum chloride and benzene has been shown to afford 4,9-dihydronaphtho[2,3-*c*]thiophene-4,9-dione (2), 1,1-diphenyl-1*H*,3*H*-thieno[3,4-*c*]furan-3-one (14), 3,4-dibenzoylthiophene (15), and 4-benzoylthiophene-3-carboxylic acid (16), depending upon the reaction conditions. These results contrast with literature reports of analogous reactions involving furan and pyrrole derivatives (10 and 11). A further example of a lactone derivative similar to 14 is seen in the treatment of 4-(α-hydroxybenzyl)-3-thiophenecarboxylic acid (26) with phosphorus pentachloride to give 1-phenyl-1*H*,3*H*-thieno[3,4-*c*]furan-3-one (28).

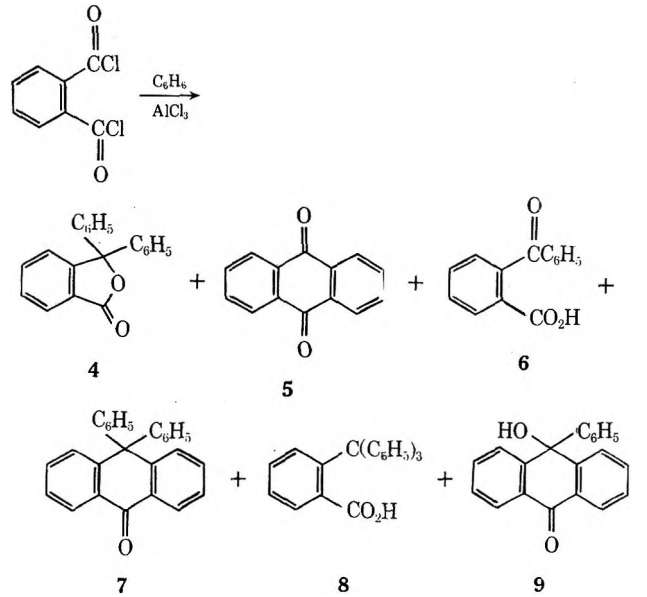
In an earlier report[1] concerning the synthesis of 4,9-dihydronaphtho[2,3-*c*]thiophene-4,9-dione (2), *via* the reaction of thiophene-3,4-dicarbonyl chloride (1) with



1 2

benzene and aluminum chloride, there was also isolated a second reaction product whose structure was not determined at that time.

The reaction of phthaloyl chloride (3) with benzene and aluminum chloride has been studied by several workers and shown to lead to the formation of as many

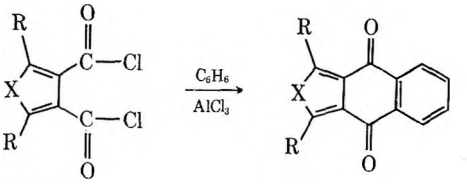


4 5 6

7 8 9

as six different products, 4–9,[2] depending upon the reaction conditions.

There are a few reports in the literature concerning the acylation reactions of the heterocyclic analogs of phthaloyl chloride.[3] Nightingale and coworkers have studied the acylation reactions of the pyrrole derivative 10[3b] and the analogous furan derivatives 11 with benzene.[3a,c] The only products isolated in each case



10, R = CH_3; X = *n*-C_4H_9N **12**, R = CH_3; X = *n*-C_4H_9N
11, R = CH_3, C_6H_5; X = O **13**, R = CH_3, C_6H_5; X = O

were cyclic diketones 12 and 13. Attempts to acylate toluene with pyridine-2,3- and -3,4-dicarbonyl chlorides resulted in the formation of dark, intractable oils.[3c]

The unexpected isolation of a second product from the reaction of 1 with benzene and aluminum chloride motivated further study of this reaction. An investigation of this reaction involving the variation of quantities of reactants and reaction conditions was undertaken.

This study led not only to the isolation of 2, but also to the isolation and characterization of 1,1-diphenyl-1*H*,3*H*-thieno[3,4-*c*]furan-3-one (14), 3,4-dibenzoylthiophene (15), and 4-benzoylthiophene-3-carboxylic acid (16). This appears to be the first report of the isolation of a heterocyclic analog of 3,3-diphenylphthalide (4) in an acylation reaction. The results of this investigation are summarized in Table I.

The 1:1 ratio of dicarbonyl chloride 1 to benzene (runs 1–3) appeared to favor the exclusive formation of the cyclic diketone 2. Similar observations[2] had

(1) D. W. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.*, **37**, 1712 (1972).

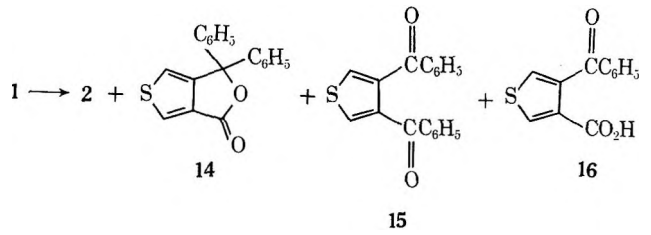
(2) M. Copisarow, *J. Chem. Soc.*, **111**, 10 (1917).

(3) (a) D. V. Nightingale and B. Sukornick, *J. Org. Chem.*, **24**, 497 (1959); (b) D. V. Nightingale and J. A. Gallagher, *ibid.*, **24**, 501 (1959); (c) D. V. Nightingale and H. L. Needles, *J. Heterocycl. Chem.*, **1**, 74 (1964).

TABLE I

Run	Moles of C_6H_6[e]	Solvent	Temp, °C	Yield,[g] % 2	14	15	16
1[a]	0.02	$(CH_2Cl)_2$	0	52.8			
2[b]	0.02	$(CH_2Cl)_2$	0–25	57.0			
3[c]	0.02	$(CH_2Cl)_2$	25	58.5	1–2		
4[c]	0.04	$(CH_2Cl)_2$	25	39.7	1–2		
5[d]	0.04	$(CH_2Cl)_2$	25	38.8	1–2	6.8	
6	0.5	C_6H_6	10	6.1	21.8	6.0	6.3
7	0.5	C_6H_6	25	4.4	26.2	10.8	8.0
8	0.5	C_6H_6	50	8.9	28.2	2.7	
9[f]	0.5	C_6H_6	50	7.7	29.8	11.0	

[a] 1 and C_6H_6 added at 0°. [b] 1 added at 0°; C_6H_6 added at 25°. [c] 1 and C_6H_6 added at 25°. [d] Same as *c*, but C_6H_6 added rapidly. [e] Dried over sodium. [f] Undried benzene was used. [g] Recrystallized material calculated on average of at least three runs.



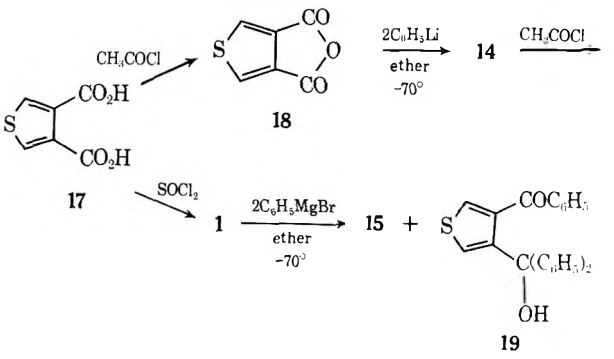
been made for the formation of anthraquinone (**5**). As the temperature was increased, the amount of **2** increased accompanied by the formation of a small amount of phthalide-type compound **14** (run 3). Higher reaction temperatures have also been shown to favor the formation of 3,3-diphenylphthalide (**4**) during the acylation of benzene with phthaloyl chloride.[2]

A 1:2 ratio of dicarbonyl chloride **1** to benzene (runs 4 and 5) showed decreased amounts of **2** and small amounts of **14** and 3,4-dibenzoylthiophene (**15**). The increased rate of addition of benzene (run 5) apparently favored the formation of **15** over **14**, possibly indicating that ring closure to a phthalide-type structure is a slower process than intermolecular acylation. This is in agreement with the observation that rapid addition of thiophene to **1** results in the formation of 3,4-bis(2-thenoyl)thiophene.[1]

Substantial changes in product distribution were observed when benzene was used as the solvent (runs 6–9). Under these conditions the yields of cyclic diketone **2** were greatly reduced (6–9%) while the yields of phthalide-type compound **14** were greatly increased (22–30%). The keto acid **16** appeared to be formed only at lower temperatures (runs 6 and 7). It has been shown that lower reaction temperatures also seem to favor the formation of *o*-benzoylbenzoic acid (**6**) during the acylation of benzene with phthaloyl chloride.[2] When undried benzene was used (run 9) in an attempt to determine the effect of traces of water on the formation of the keto acid **16**, no significant change was observed in the product distribution. The amounts of isolated diketone **15** varied slightly (3–11%) in these runs.

The formation of *o*-dibenzoylbenzene in the phthaloyl chloride acylation of benzene has not been reported.[4] Nightingale and coworkers[3a,b] did not report the formation of either the 3,4-dibenzoylpyrrole or the 3,4-dibenzoylfurans in the acylation of benzene with the corresponding dicarbonyl chlorides **10** and **11**. However, earlier work[1] has demonstrated the formation of 3,4-bis(2-thenoyl)thiophene in the acylation of thiophene with thiophene-3,4-dicarbonyl chloride (**1**). Thus, it appears at this time that the formation of the diaroyl ketones in this type of acylation reaction is unique for the thiophene nucleus.

SCHEME I



The identities of 1,1-diphenyl-1*H*,3*H*-thieno[3,4-*c*]furan-3-one (**14**) and 3,4-dibenzoylthiophene (**15**) were determined by spectroscopic methods as well as by independent synthesis. The preparation of **14** by the method of Nightingale[3a] and **15** by the method of Jensen[5] are shown in Scheme I. Thiophene-3,4-dicarboxylic acid (**17**) was the starting compound in the syntheses of both **14** and **15**. Treatment of **17** with acetyl chloride[6] gave thiophene-3,4-dicarboxylic acid anhydride (**18**) in 73% yield. Addition of 2 equiv of phenyllithium at −70° to **18** afforded a sample of **14** in 6% yield, identical in all respects with **14** previously obtained from the acylation reaction. Addition of 2 equiv of phenylmagnesium bromide to **1** gave the expected diketone **15** in 17% yield. This product was also identical in all respects with the sample of 3,4-dibenzoylthiophene (**15**) obtained during the acylation reaction. A small amount (5%) of another white, crystalline solid was also isolated from the latter reaction. Spectral and analytical data are consistent with the assigned structure for α,α-diphenyl-4-benzoyl-3-thiophenemethanol (**19**).

Several different reaction pathways can be proposed for the acylation of benzene with thiophene-3,4-dicarbonyl chloride (**1**) analogous to those proposed by Elderfield[7] for the acylation of benzene with phthaloyl chloride (**3**). The different possible pathways are summarized in Scheme II. The four pathways are designated A, B, C, and D.

Intramolecular acylation, path A, is favored when there is a 1:1 ratio of **1** to benzene. When a twofold excess of benzene is used, paths B and C become important, but path A still predominates. Finally, when a large excess of benzene is used, path A becomes less important, as would be expected on statistical grounds, and path B appears to be most favorable. However, intermolecular acylation, path C, does not appear to be as favored as might be expected. This lower percentage of intermolecular acylation product may be due to steric interaction of the adjacent benzoyl groups. Path D appears to become important at lower reaction temperatures.

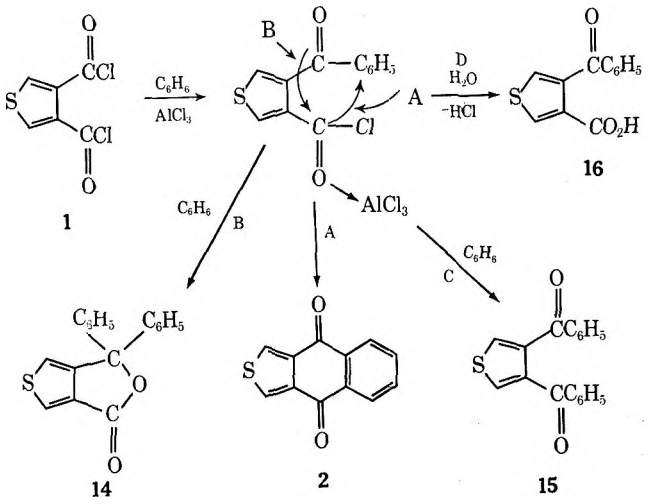
(4) A. G. Peto in "Friedel-Crafts and Related Reactions," Vol. III, Part I, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, Chapter XXXIV.

(5) F. Jensen, *J. Org. Chem.*, **25**, 269 (1960).

(6) J. Sice, *ibid.*, **19**, 70 (1954).

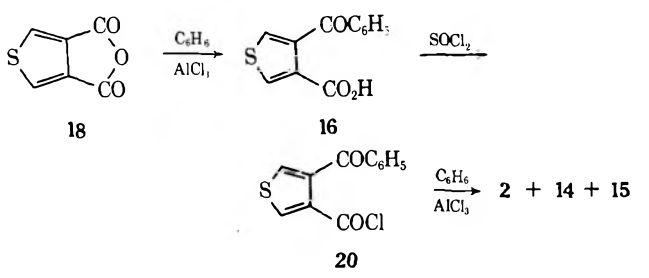
(7) R. C. Elderfield, "Heterocyclic Compounds," Vol. II, Wiley, New York, N. Y., 1951, p 101.

Scheme II

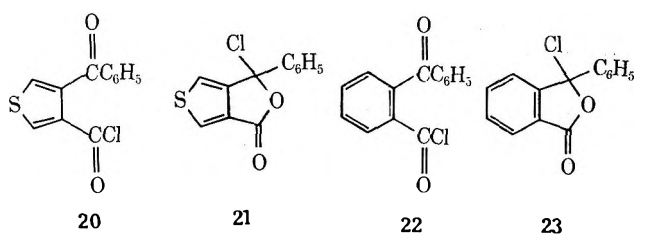


In order to determine whether 4-benzoylthiophene-3-carbonyl chloride (**20**) could act as an intermediate, **20** was synthesized and allowed to react with benzene and aluminum chloride as shown in Scheme III.

Scheme III



The acylation of benzene with the anhydride **18** resulted in the formation of the keto acid **16** in 63% yield.[8] The keto acid chloride **20** was formed in the usual manner and allowed to react with benzene and aluminum chloride.[9] Three reaction products were isolated: 1,1-diphenyl-1*H*,3*H*-thieno[3,4-*c*]furan-3-one (**14**), 3,4-dibenzoylthiophene (**15**), and 4,9-dihydronaphtho[2,3-*c*]thiophene-4,9-dione (**2**) in 30, 16, and 6% yields, respectively. The ir spectrum of crude **20** exhibits the distinct carbonyl frequencies at 1650 (ketone C=O) and 1750 cm^{-1} (acid chloride C=O), consistent with the normal keto acid chloride structure **20**. However, the possibility of the existence of a mixture of normal **20** and pseudo keto acid chloride **21** cannot be excluded, since the acid chloride carbonyl absorption occurs in the region of the lactone carbonyl absorption, 1760 cm^{-1}. In the case of *o*-benzoylbenzoyl chloride (**22**), it has been shown that



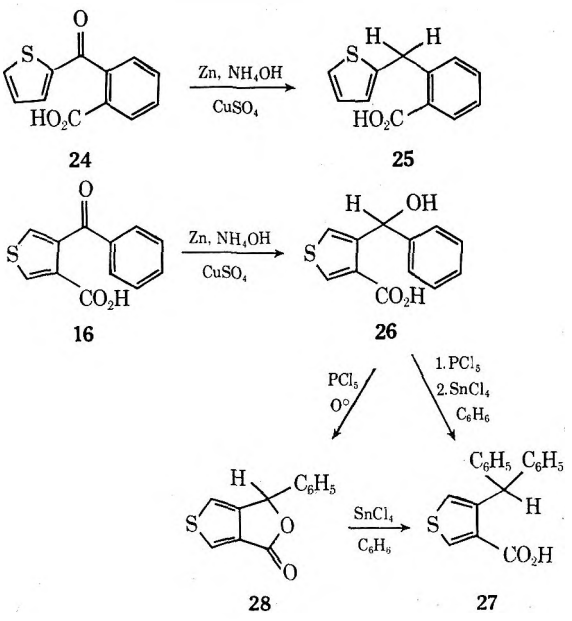
(8) P. Pirson, A. Schonne, and L. Christiaens, *Bull. Soc. Chim. Belg.*, **79**, 575 (1970).

(9) A. Haller and A. Guyot, *Bull. Soc. Chim. Fr.*, **25**, 49 (1901).

both the normal and pseudo[10] isomer, **22** and **23**, respectively, exist, and that *both* **22** and **23** produce 3,3-diphenylphthalide (**4**) upon reaction with benzene and aluminum chloride.[11]

Another example of the formation of a phthalide-type derivative came to light in the course of some work paralleling the above study. Whereas reduction of *o*-(2-thenoyl)benzoic acid (**24**) with zinc and ammonium hydroxide afforded the methylene compound **25**,[12] similar reduction of the analogous 4-benzoylthiophene-3-carboxylic acid (**16**) gave the corresponding hydroxy acid **26** (Scheme IV). This acid could be converted

Scheme IV



directly to 3-benzhydrylthiophene-3-carboxylic acid (**27**) by treatment with phosphorus pentachloride followed by reaction with benzene in the presence of stannic chloride. A closer examination of this transformation showed that it proceeded *via* the lactone **28**, which could be isolated in 36% yield from the hydroxy acid **26**, by treatment at 0° with phosphorus pentachloride. The lactone **28** could be converted to the acid **27** by means of benzene and stannic chloride at 0°.

Experimental Section[13]

The Reaction of Thiophene-3,4-dicarbonyl Chloride with Aluminum Chloride and Benzene.—A suspension of thiophene-3,4-dicarboxylic acid[1] (**17**) (3.44 g, 0.02 mol) in thionyl chloride (10 ml) was heated to reflux for 1 hr. The excess thionyl chloride was removed by codistillation with benzene. The resulting dicarbonyl chloride was dried *in vacuo* and used immediately.

A. 1,2-Dichloroethane as Solvent (Runs 1–5, Table I).—To a stirred suspension of aluminum chloride (5.85 g, 0.044 mol) in 1,2-dichloroethane (25 ml) was added dropwise a solution of the dicarbonyl chloride (0.02 mol) in 1,2-dichloroethane (35 ml). A solution of dry benzene (0.02–0.04 mol) in 1,2-dichloroethane was added dropwise over 15 min and the resulting brown reaction mixture was stirred for 12 hr The dark reaction mixture was poured

(10) H. Meyer, *Monatsh.*, **25**, 475, 1177 (1904).

(11) A. Guyot and J. Catel, *Bull. Soc. Chim. Fr.*, **35**, 1135 (1906).

(12) H. E. Schroeder and V. Weinmayr, *J. Amer. Chem. Soc.*, **74**, 4357 (1952).

(13) All temperatures are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. Nuclear magnetic resonance spectra were recorded on Varian HA-60 and Varian T-60 spectrometers using tetramethylsilane as an internal standard (τ 10) and solvents as specified.

onto ice and dilute hydrochloric acid. The organic extracts were washed with saturated sodium bicarbonate solution and water and dried ($MgSO_4$). Evaporation yielded a sticky yellow solid which was dissolved in hot benzene and placed onto a column of alumina. Elution with benzene followed by evaporation left a pale yellow solid material. This yellow solid was recrystallized from glacial acetic acid, giving pale yellow needles of 4,9-dihydronaphtho-[2,3-*c*]thiophene-4,9-dione (**2**) (39–59%), mp 276–277°. The mother liquor was diluted with water and extracted with benzene. The benzene extracts were washed with saturated sodium bicarbonate solution and water and dried ($MgSO_4$). Evaporation yielded a pale yellow solid, whose ir spectrum indicated the presence of either lactone **14** and/or 3,4-dibenzoylthiophene (**15**).

The basic extract of the reaction mixture was acidified and extracted with chloroform. Evaporation yielded traces of brown crusty solid which could not be purified by chromatography over silica gel or recrystallization from the usual organic solvents.

B. Benzene as Solvent (Runs 6–9, Table I).—To a solution of the crude dicarbonyl chloride in dry benzene (50 ml) was added *via* Gooch tubing, in small portions, aluminum chloride (5.85 g, 0.044 mol). The resulting red suspension was stirred at room temperature for 12 hr. The reaction mixture was worked up in the manner described above. The yellow solid obtained was dissolved in hot benzene and allowed to cool slowly to give 4,9-dihydronaphtho[2,3-*c*]thiophene-4,9-dione (**2**) in 4–9% yields. The mother liquor was concentrated and the hot solution was diluted with hexane (1:1) and allowed to cool slowly; lactone **14** in 22–29% yields was obtained as a white crystalline solid, mp 156–159°. Further concentration and dilution with hexane (3:1 hexane–benzene) gave tiny white clusters of 3,4-dibenzoylthiophene (**15**) in 3–11% yields, mp 95–96°.

An analytical sample of 1,1-diphenyl-1*H*,3*H*-thieno[3,4-*c*]furan-3-one (**14**) was obtained by recrystallization from hexane–benzene (1:1): mp 159–161°; ir (KBr) 1760 cm^{-1} (lactone C=O); nmr (acetone-d_6) τ 1.76 (d, 1 H, $J_{2,5}$ = 2 Hz, thiophene), 2.12 (d, 1 H, $J_{2,5}$ = 2 Hz), 2.39–2.77 (m, 10 H, benzene).

Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.94: H, 4.13; S, 10.96. Found: C, 73.74; H, 4.10; S, 10.80.

Analytical sample of 3,4-dibenzoylthiophene (**15**) was obtained by recrystallization from hexane–benzene (3:1): mp 98–99°; ir (KBr) 1670, 1630 cm^{-1} (C=O); nmr (CS_2) τ 2.37–2.50 (m, 6 H, aromatic), 2.53–2.78 (m, 6 H, aromatic); *m/e* 292.

Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.94; H, 4.13; S, 10.96. Found: C, 74.11; H, 4.07; S, 10.99.

The basic extract was acidfied and extracted with benzene and dried ($MgSO_4$). Evaporation left 6–8% yields (runs 6 and 7) of 4-benzoylthiophene-3-carboxylic acid (**16**), mp 125–130° (lit.[8] mp 132°).

Addition of Phenyllithium to Anhydride 18.—To an ethereal solution of the anhydride **18**[6] (2.80 g, 0.018 mol) at −70° was added dropwise ethereal phenyllithium (0.036 mol) over a period of 20 min. After the addition was complete, the brick red solution was stirred at −70° for 3 hr and allowed to stir overnight at room temperature. The reaction mixture was poured into 150 ml of water, and the aqueous layer was extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and water and dried ($MgSO_4$). Evaporation gave a white, crystalline material (0.31 g, 5.8%), mp 154–156°. A mixture melting point with pure **14** obtained in the acylation experiment showed no depression.

Addition of Phenylmagnesium Bromide to Dicarbonyl Chloride 1.—Ethereal phenylmagnesium bromide prepared from bromobenzene (9.1 g, 0.058 mol) was added dropwise under nitrogen to a solution of the dicarbonyl chloride **1** (5.0 g, 0.029 mol) in ether (125 ml) maintained at −70°. The reaction mixture was poured onto ice and dilute hydrochloric acid. The ether extract was washed with saturated sodium bicarbonate solution and water and dried ($MgSO_4$). Evaporation followed by fractional crystallization (hexane–benzene) gave a white solid (0.58 g, 5.4%), mp 176–177°. The spectral and analytical data of this compound are consistent with the structure of α,α-diphenyl-4-benzoyl-3-thiophenemethanol (**19**): ir (KBr) 3300 (OH), 1625 cm^{-1} (C=O); nmr (polysol-*d*) τ 2.0–2.2 (d, 1, H, J = 3.0 Hz, thiophene), 3.4–3.6 (d, 1 H, J = 3.0 Hz, thiophene), 2.2–2.9 (m, 16 H, aromatic, alcohol).

Anal. Calcd for $C_{24}H_{18}O_2S$: C, 77.81; H, 4.90; S, 8.66. Found: C, 78.01; H, 5.03; S, 8.74.

A second crop of crystals consisted of 3,4-dibenzoylthiophene (**15**) (1.46 g, 17.3%), mp 94–96°. A mixture melting point with pure **15** obtained in acylation experiments showed no depression.

4-Benzoylthiophene-3-carbonyl Chloride (20).—A mixture of 4-benzoylthiophene-3-carboxylic acid (2.32 g, 0.01 mol) and thionyl chloride (9 ml) was stirred at room temperature overnight. The excess thionyl chloride was removed by codistillation with benzene, leaving a dark oil, ir (neat) 1650 (ketone C=O), 1750 cm^{-1} (acid chloride C=O), which was used immediately.

Reaction of 4-Benzoylthiophene-3-carbonyl Chloride (20) with Aluminum Chloride and Benzene.—The procedure for the acylation reaction and isolation of products was the same as that used in the acylation of benzene with the dicarbonyl chloride **1**.

From the acylation of dry benzene (50 ml) with **20** (2.5 g, 0.01 mol) and aluminum chloride (2.66 g, 0.02 mol) at 25° was obtained lactone **14** (0.87 g, 30%), cyclic diketone **2** (0.12 g, 5.6%), and 3,4-dibenzoylthiophene (**15**) (0.47 g, 16%). There was no evidence of keto acid **16** formation.

4-(α-Hydroxybenzyl)-3-thiophenecarboxylic Acid (26).—Into a 3-l. flask fitted with a reflux condenser and stirring bar were placed 28% ammonium hydroxide (1000 ml), copper(II) sulfate (0.5 g), 4-benzoylthiophene-3-carboxylic acid (**16**) (17.25 g, 0.074 mol), and zinc dust (50 g, 0.77 mol). The mixture was heated to reflux for 32 hr. Fresh portions (250 ml) of ammonium hydroxide were added every 3 hr.

The hot solution was then filtered and acidified with 6 *M* HCl, cooled, and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporation yielded a gummy residue which could not be recrystallized. The sodium salt of the acid was heated with Norit, filtered, and acidified to give **26** as a white solid (17.3 g, 79.8%) which was recrystallized from benzene–hexane, mp 123–124°.

An analytical sample of **26** was obtained by further recrystallization from benzene–hexane: mp 124–124.5°; ir (KBr) 3300 (OH), 3100–2500 (acid OH), 1670 cm^{-1} (C=O), nmr (acetone-d_6) τ 1.70 (d, 1 H, J = 3.5 Hz, thiophene), 2.40–2.80 (m, 6 H, C_6H_5 and thiophene), 3.70 (s, 1 H, methine), 4.03 (br, s, 1 H, OH).

Anal. Calcd for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30; S, 13.69. Found: C, 61.31; H, 4.29; S, 13.91.

4-Benzhydrylthiophene-3-carboxylic Acid (27).—Into a 25-ml flask were placed the hydroxy acid **26** (1.17 g, 0.005 mol) and dry benzene (15 ml). Phosphorus pentachloride (10.4 g, 0.005 mol) was added to the cooled solution in small portions. After addition was complete, the reaction mixture was heated on a steam bath for 10 min and then cooled.

To the cooled reaction mixture was added dropwise a solution of tin(IV) chloride (1.76 g, 0.8 ml, 0.007 mol) in dry benzene (15 ml). After the addition was complete, the reaction mixture was stirred at 0° for 1 hr, allowed to reach room temperature, and then heated to reflux. It was then poured onto ice and 2 *M* HCl and extracted with ether. The ether extracts were washed with sodium bicarbonate solution and water and dried ($MgSO_4$). The basic extract was acidified, extracted with ether, and dried ($MgSO_4$). The basic extract was acidified, extracted with ether, and dried ($MgSO_4$). Evaporation yielded 0.18 g of crude acid **27**. The organic extract was evaporated and 1.15 g of reddish solid was obtained. The solid was dissolved in a minimum amount of benzene and placed onto a silica gel column. Elution with benzene gave an additional 0.42 g of acid **27**, mp 170°. The total yield of acid **27** obtained was 0.60 g (41%).

Recrystallization of **27** from benzene–hexane gave a white solid: mp 170°; ir (KBr) 3150–2600 cm^{-1} (acid OH), 1680 (C=O); nmr (DMSO-d_6) τ −2.3 (br, s, 1 H, COOH), 1.80 (d, 1 H, J = 3.5 Hz, H_5), 2.60–3.10 (m, 10 H, C_6H_5), 3.33 (d, 1 H, J = 3.5 Hz, H_2), 3.80 (s, 1 H, methine).

Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79; S, 10.89. Found: C, 73.56; H, 4.79; S, 11.06.

1-Phenyl-1*H*,3*H*-thieno[3,4-*c*]furan-3-one (28).—Into a 25-ml flask were placed the hydroxy acid **26** (1.2 g, 0.005 mol) and dry benzene (10 ml). To the cooled, stirred suspension was added phosphorus pentachloride (1.0 g, 0.005 mol) in small portions. After the addition was complete, the reaction mixture was allowed to reach room temperature and then heated to reflux. The pale yellow solution was poured onto water and extracted with ether. The ether extracts were washed with saturated sodium bicarbonate solution and water and dried ($MgSO_4$). The basic extract was acidified and yielded 0.2 g of starting material. The organic layer was evaporated and the resulting oil was dissolved in benzene and placed onto a silica gel column. Elution with chloroform yielded a white solid (0.33 g, 36%), mp 98–99°.

An analytical sample of **28** was recrystallized from benzene–hexane: mp 99–100°; ir (KBr) 1760 cm^{-1} (lactone C=O);

nmr ($CDCl_3$) τ 2.05 (d, 1 H, J = 2.5 Hz, thiophene), 2.63 (s, 5 H, C_6H_5), 2.88 (q, 1 H, thiophene), 3.67 (d, 1 H, J = 1.0 Hz, methine).

Anal. Calcd for $C_{12}H_8O_2S$: C, 66.64; H, 3.73; S, 14.83. Found: C, 66.87; H, 3.55; S, 14.79.

Registry No.—**1**, 33527-26-3; **2**, 33527-20-7; **14**, 36540-46-2; **15**, 36540-47-3; **19**, 36540-48-4; **20**, 36540-49-5; **26**, 36540-50-8; **27**, 36540-51-9; **28**, 36540-52-0; aluminum chloride, 7446-70-0; benzene, 71-43-2.

1,2,4-Triazoles. XXXII. Syntheses and Correlation of Proton Magnetic Resonance Spectral Characteristics with Molecular Orbital Parameters of Derivatives of the *s*-Triazolo[4,3-*a*]quinoline and *s*-Triazolo[3,4-*a*]isoquinoline Ring Systems[1]

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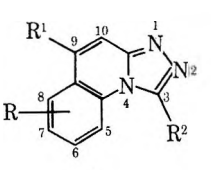
The syntheses and proton magnetic resonance (pmr) spectral data at 60 MHz for several members of the title ring systems are described. Confirmation of the spectral assignments was obtained by examination of several of the products at 100 MHz. Of particular interest are correlations observed between chemical shifts and electron densities calculated by the FEHT method. Ultraviolet absorption data for these ring systems are also described.

In a continuation of our interests in the chemistry of the *s*-triazole ring system, we have extended our study of the *s*-triazolo[4,3-*a*]pyridine and *s*-triazolo[1,5-*a*]pyridine systems[2] to include two benzo-fused derivatives, the *s*-triazolo[4,3-*a*]quinoline (**1**) and the *s*-triazolo[3,4-*a*]isoquinoline (**2**) ring systems. The influence of the fused benzene ring on the spectral and chemical properties of these ring systems is of interest as is the nature of the electron delocalization throughout these systems. The empirical correlation between chemical shifts and calculated π-electron densities in the benzenoid series[3] suggested the study of the ring systems from these viewpoints. The presence of heteroatoms in these nonalternant heterocycles requires the use of SCF[3-6] methods for the calculation of the electron densities. This method, in contrast to the simple Hückel approach, has been shown[3] to provide useful correlations of the above type. To aid in the interpretation of the pmr spectra, suitable methyl-substituted products were synthesized by the procedures described below.



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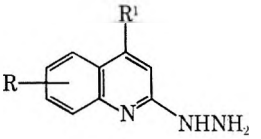

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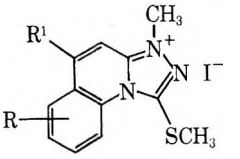

4

Synthetic Procedures.—Reports of the synthesis of *s*-triazolo[4,3-*a*]quinoline[7] and of 9-methyl-*s*-triazolo[4,3-*a*]quinoline-3-thiol[8] appeared as early as 1900. Oxidative ring closure of various aromatic aldehyde 2-quinolyl hydrazones with ferric chloride or nitrobenzene was shown[9a] to be an effective route to 3-substituted derivatives, and the introduction of substituents into the 3 position analogous to those reported for the *s*-triazolo[4,3-*a*]pyridine system[10] was also described.[9b]

Standard procedures developed for other ring systems[10] were used for the synthesis of the *s*-triazolo[4,3-*a*]quinoline derivatives described in Table I. The intermediate 2-quinolylhydrazines used in the cyclization reactions were prepared in good yields from the appropriate methyl-substituted quinoline *via* the 1-methyl-2-quinolones and 2-chloroquinolines.[11] These hydrazines, with or without substituents in either the benzene or the pyridine rings, readily cyclized with aliphatic acids to the desired products except as described below. Cyanogen bromide and carbon disulfide were found to be quite effective in forming the 3-amino (**1**, $R^2 = NH_2$) and 3-mercapto (**1**, $R^2 = SH$) derivatives. 8-Methyl-2-quinolylhydrazine was found to be extremely resistant to cyclization with either formic acid or acetic acid, the *N*-formyl and *N*-acetyl

(1) Support of this work by Public Health Service Research Grant CA 08495-01, National Cancer Institute, and by the University of Kentucky Computing Center, is gratefully acknowledged.

(2) K. T. Potts, H. R. Burton, T. H. Crawford, and S. W. Thomas, *J. Org. Chem.*, **31**, 3522 (1966), and references cited therein.

(3) G. G. Hall, A. Hardisson, and L. M. Jackman, *Tetrahedron, Suppl. 2*, **19**, 101 (1963), and references cited therein.

(4) A. Streitwieser, Jr., "Molecular Orbital Calculations for Organic Chemistry," Wiley, New York, N. Y., 1962, Chapter 16, and references cited therein.

(5) M. J. S. Dewar and G. J. Gleicher, *J. Chem. Phys.*, **44**, 759 (1966).

(6) C. A. Girard and S. L. Smith, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, ORGN 188; C. A. Girard, "Some Empirical Investigations on a Fock Modified Extended Hückel Molecular Orbital Method," Ph.D. Dissertation, M. I. King Library, University of Kentucky, Lexington, Ky., 1972.

(7) W. Marckwald and E. Meyer, *Ber.*, **33**, 1885 (1900).

(8) W. Marckwald and M. Chain, *ibid.*, **33**, 1895 (1900).

(9) (a) S. Naqui and V. R. Srinivasan, *Indian J. Chem.*, **3**, 162 (1965); (b) G. S. Sidhu, S. Naqui, and D. S. Iyengar, *J. Heterocycl. Chem.*, **3**, 158 (1966); (c) see also H. Reimlinger, J. J. M. Vandewalle, and W. R. F. Lingier, *Chem. Ber.*, **103**, 1960 (1970).

(10) K. T. Potts and H. R. Burton, *J. Org. Chem.*, **31**, 251 (1966); K. T. Potts, H. R. Burton, and S. K. Roy, *ibid.*, **31**, 256 (1966).

(11) W. H. Perkins and R. Robinson, *J. Chem. Soc.*, 1978 (1913).

Table I[e]

Some *s*-Triazolo[4,3-*a*]quinolines (1)[e]

Registry no.	R	R[1]	R[2]	Mp, °C	Uv data (CH_3OH), λ_{max} (log ϵ)
235-06-3	H	H	H	170–171[a]	245[b] (3.72), 278 (3.71), 297 (3.71), 307 (3.93), 318 (3.98)
35359-22-9	H	H	CH_3	168–169	203 (4.63), 211 (4.65), 215 (4.64), 228[b] (4.46), 238[b] (4.31), 290 (4.11), 301 (3.92), 314 (3.87)
35359-23-0	H	H	SH	274	276 (3.99), 312[b] (4.07), 322 (4.05)
35359-24-1	H	H	SCH_3	117–119[c]	248 (3.74), 258 (3.78), 303 (4.09), 316 (4.08)
35359-25-2	H	CH_3	H	227–228	210[b] (4.39), 230 (4.61), 243[b] (4.06), 267 (3.82), 274[b] (3.73), 313[b] (3.73), 325 (3.87), 338 (3.66)
35359-26-3	H	CH_3	CH_3	195	212 (4.53), 216 (4.53), 225[b] (4.38), 231[b] (4.36), 243 (4.14), 253 (3.99), 281[b] (3.93), 292 (3.82), 302 (3.93), 316 (3.82)
35359-27-4	H	CH_3	SH	280[d]	212 (5.05), 270[b] (4.59), 278 (4.72), 321 (4.25).
35359-28-5	7-CH_3	H	H	192–193	216 (4.43), 230[b] (4.50), 235 (4.53), 250 (4.04), 280 (4.02), 291 (4.02), 308 (3.71), 325 (3.68)
35359-29-6	7-CH_3	H	CH_3	160–161	213 (4.56), 217 (4.57), 227 (4.53), 233 (4.53), 251[b] (4.06), 263 (3.73), 269[b] (3.82), 283 (4.03), 293 (4.03), 306[b] (3.82), 320 (3.68)
35359-30-9	7-CH_3	H	NH_2	245 dec	215 (4.60), 251 (4.15), 260[b] (4.04), 297[b] (3.90), 328 (4.04)
35359-31-0	7-CH_3	H	SH	294–296 dec	211 (4.62), 220 (4.67), 273[b] (4.30), 282 (4.47), 305 (3.85), 318 (3.85)
35359-32-1	6-CH_3	H	H	190–191	211–215 (4.45), 226 (4.35), 231[b] (4.33), 280[b] (4.00), 288 (4.04), 313[b] (3.40)
440-54-0	H			119–120	235 (4.30), 238 (4.30), 262 (3.84), 271[b] (3.48), 304 (3.35), 317 (3.30)
7639-56-7	CH_3			168	240 (4.59), 247 (4.59), 265 (3.77), 275[b] (3.70), 306 (3.26), 320 (3.14)
27210-14-6	NH_2			268–270 dec	209 (4.70), 250[b] (4.58), 259 (4.69), 304 (3.66)

[a] Lit.[6] mp 175°. [b] Shoulder. [c] We thank Dr. S. Naqui for the preparation of this compound. [d] Lit.[7] mp 280°. [e] Satisfactory analytical values (±0.4% for C, H, N) were reported for all new compounds in table: Ed.

compounds, respectively, being obtained. The *N*-formyl compound was readily cyclized to the desired 5-methyl-*s*-triazolo[4,3-*a*]quinoline by heating about its melting point for 6 hr; however, the *N*-acetyl compound (ν_{CO} 1665 cm^{-1}) did not cyclize under similar conditions. This is most likely due to the large steric interaction of the methyl groups at positions 3 and 5 of the fused ring system, which is clearly shown by suitable models. A similar steric interaction was observed in the formation of 3,5-disubstituted *s*-triazolo[4,3-*a*]pyridines,[10] but in the present case the overlap of the two methyl groups is so great that ring closure is prevented.

The *s*-triazolo[4,3-*a*]quinoline-3-thiols, when treated with methyl iodide and base, readily formed the anticipated 3-methylthio compounds; with excess methyl iodide the corresponding 1-methyl-3-methylthio-*s*-triazolo[4,3-*a*]quinolinium iodides (4) were obtained. That further reaction of the 3-methylthio compounds with methyl iodide occurred so readily is understandable on comparison of the π-electron densities at N-1 for this ring system with those of *s*-triazolo[4,3-*a*]-pyridine.[10] The alternative route to these 1-substituted products was also successful in this system. Thus 1-methyl-1-(4-methyl-2-quinolyl)hydrazine, prepared from 2-chloro-4-methylquinoline and methyl hydrazine, when treated with cyanogen bromide gave 1,9-dimethyl-3-amino-*s*-triazolo[4,3-*a*]quinolinium bromide.

In the *s*-triazolo[3,4-*a*]isoquinoline system (2) only the 3-phenyl derivative had been prepared previously.[9a,c] Our present work shows that cyclization of 1-isoquinolylhydrazine with aliphatic acids is a convenient route to the 3-alkyl derivatives and that the 3-amino compound is also readily available by cyclization with cyanogen bromide. The limitation to the synthesis of derivatives of this ring system lies in the involved processes needed to obtain the appropriate 1-isoquinolylhydrazines.

Proton Magnetic Resonance Spectra.—Observed chemical shifts and coupling constants for the compounds described above are listed in Table II. In general, the spectra of the *s*-triazolo[4,3-*a*]quinolines consist of an isolated signal near 9.20 ppm and a complex aggregation of peaks between 7.40 and 8.20 ppm relative to internal TMS. The isolated signal near 9.20 ppm can be unambiguously assigned to H_3, since it disappears upon substitution at that position. The remaining complex pattern arises from five or six (depending on the degree of substitution) closely spaced, strongly coupled protons and cannot be readily analyzed on a first-order basis. Examination of the spectra

TABLE II

Substituents R	R¹	R²	Chemical shifts[a] of protons at positions 3	5	6	7	8	9	10	Coupling constants, Hz
Pmr Parameters for Some *s*-Triazolo[4,3-*a*]quinolines (1)										
H	H	H	9.25 ± 0.01	8.02 ± 0.03	7.69 ± 0.05	7.53 ± 0.05	7.80 ± 0.03	7.60 ± 0.03	7.68 ± 0.03	$J_{5,6}$ = 7.8; $J_{6,7}$ = 7.5; $J_{7,8}$ = 7.5; $J_{5,7}$ = 1.3; $J_{6,8}$ = 1.8; $J_{9,10}$ = 9.5; $J_{3,10}$ = 1.2
H	H	CH_3[b]	*3.15 ± 0.01*	8.22 ± 0.03	7.65 ± 0.05	7.55 ± 0.05	7.80 ± 0.03	7.48 ± 0.03	7.60 ± 0.03	
H	CH_3	H	9.16 ± 0.01	7.95 ± 0.05	7.62 ± 0.05	7.53 ± 0.05	7.78 ± 0.05	*2.59 ± 0.01*	7.45 ± 0.03	$J_{5,6}$ = 7.9; $J_{6,8}$ = 1.6; $J_{9,10}$ = 9.1; $J_{3,10}$ = 1.2
7-CH_3	H	H	9.20 ± 0.01	7.86 ± 0.03	7.48 ± 0.05	*2.53 ± 0.01*	7.57 ± 0.03	7.53 ± 0.03	7.64 ± 0.03	
H	CH_3	CH_3	*3.04 ± 0.01*	8.13 ± 0.05	7.65 ± 0.05	7.55 ± 0.05	7.85 ± 0.05	*2.59 ± 0.01*	7.44 ± 0.01	$J_{9,10}$ = 9.2
5-CH_3	H	H	9.54 ± 0.01	*2.96 ± 0.01*	7.46 ± 0.08	7.46 ± 0.08	7.46 ± 0.08	7.57 ± 0.05	7.70 ± 0.01	
Pmr Parameters for Some *s*-Triazolo[3,4-*a*]isoquinolines (2)										
H	H	H	8.75 ± 0.01	7.88 ± 0.01	7.11 ± 0.01	7.63 ± 0.10	7.63 ± 0.10	7.63 ± 0.10	8.70 ± 0.03	$J_{5,6}$ = 7.0
H	H	CH_3	*2.75 ± 0.01*	7.64 ± 0.03	7.07 ± 0.01	7.55 ± 0.10	7.55 ± 0.10	7.55 ± 0.10	8.67 ± 0.03	$J_{5,6}$ = 7.1; $J_{6,10}$ = 0.5

[a] Chemical shifts (extrapolated to infinite dilution) are given in parts per million downfield from internal TMS. [b] Methyl proton absorptions italicized.

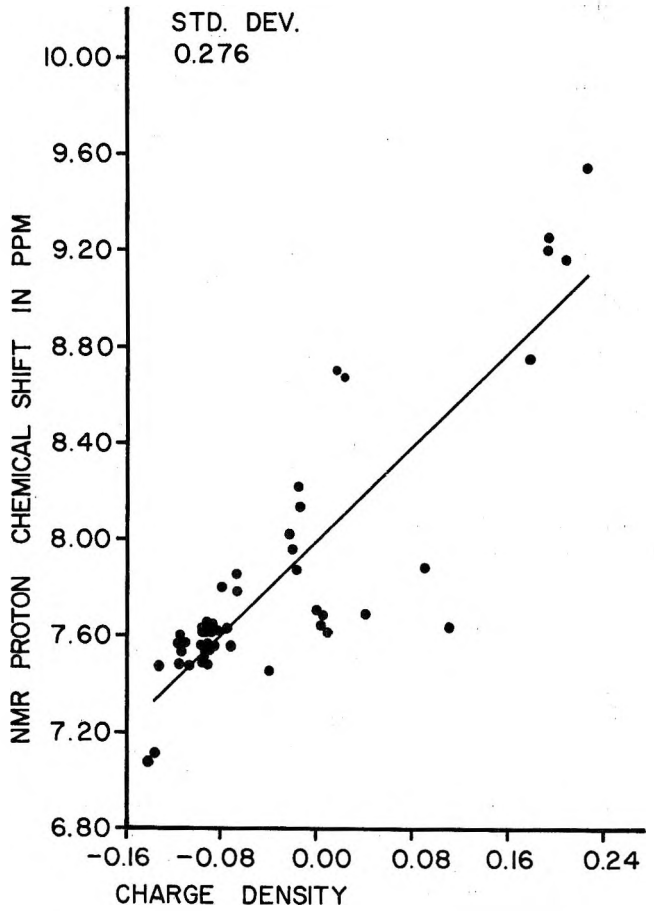

Figure 1.—Plot of proton chemical shift (extrapolated to infinite dilution) *vs.* proton environmental charge density.

from various methyl-substituted compounds and utilization of spin decoupling techniques lead to a satisfactory analysis of these spectra and provided chemical shift data sufficiently accurate for the purposes of this investigation. Assignments were confirmed by examination of the 100-MHz spectra of *s*-triazolo[4,3-*a*]quinoline and its 7-methyl and 3,9-dimethyl derivatives.

The spectra of two *s*-triazolo[3,4-*a*]isoquinolines were analyzed in a similar manner.

Chemical shifts of the methyl groups and ring protons are in accord with expectations[2] with one exception, the unusually low-field signal (8.70 ppm) for H_{10} in the isoquinoline series. Position 10 does have a low charge density (*vide infra*), but this is not low enough to explain the observed shift. Chloroform is known to hydrogen bond strongly to N_1, but specific solvent effects do not provide a suitable rationalization, since the dilution shift of H_{10} is quite similar to that of other protons in the molecule. (In the concentration range investigated, all dilution shifts were 5 Hz or less.) Ring current effects do not appear to be important, since an analogous shift is not observed for H_5 in the quinoline series where it has a similar geometrical relationship to the *s*-triazole ring. Possibly, the unusual downfield shift of H_{10} in the isoquinolines reflects the local anisotropy of the N_1–N_2 bond. Alternatively, the nonbonding electron pair on N_1 might repel the bonding electrons in C–H bond at position 10, thus producing the requisite deshielding of H_{10}.

TABLE III
ASSUMED BOND LENGTHS AND BOND ANGLES USED IN THE CALCULATIONS

Bond	Bond length, Å	Bond angles
C_{10a}–N_1 (I)	1.360	Five-membered rings, 108°
C_{10b}–N_1 (II)	1.360	Six-membered rings, 120°
N_1–N_2	1.270	
N_2–C_3	1.360	
C_3–N_4	1.390	
All other bonds	1.397	

Theoretical.—Fock-EHT (FEHT) self-consistent field (SCF) calculations were carried out according to procedures described elsewhere.[6] All input parameters were identical with those used previously for a variety of nitrogen heterocycles, including *s*-triazolo[4,3-*a*]pyridines. The specific bond lengths and bond angles used in the calculations are shown in Table III.

Results

In Figure 1 the proton environmental charge (equal to the sum of the charge densities on the hydrogen concerned and the σ and π densities on the adjacent carbon[12]) are plotted against the experimentally deter-

(12) Tables of calculated charge densities will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-4410. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

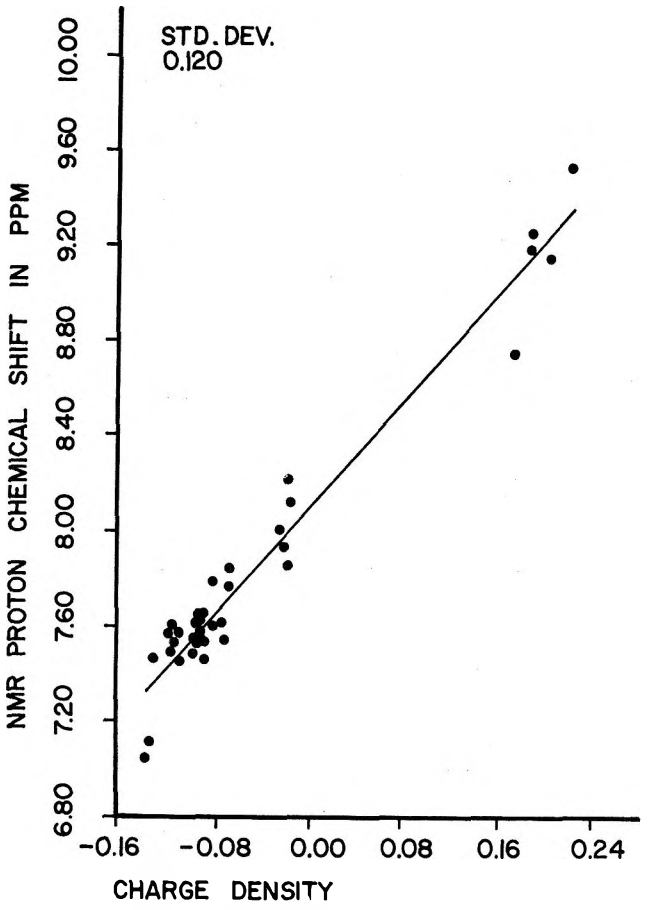

Figure 2.—Plot of proton chemical shift (at infinite dilution) *vs.* proton environmental charge density for protons in the benzenoid portions of the triazoloquinolines (S.D. = 0.120 ppm).

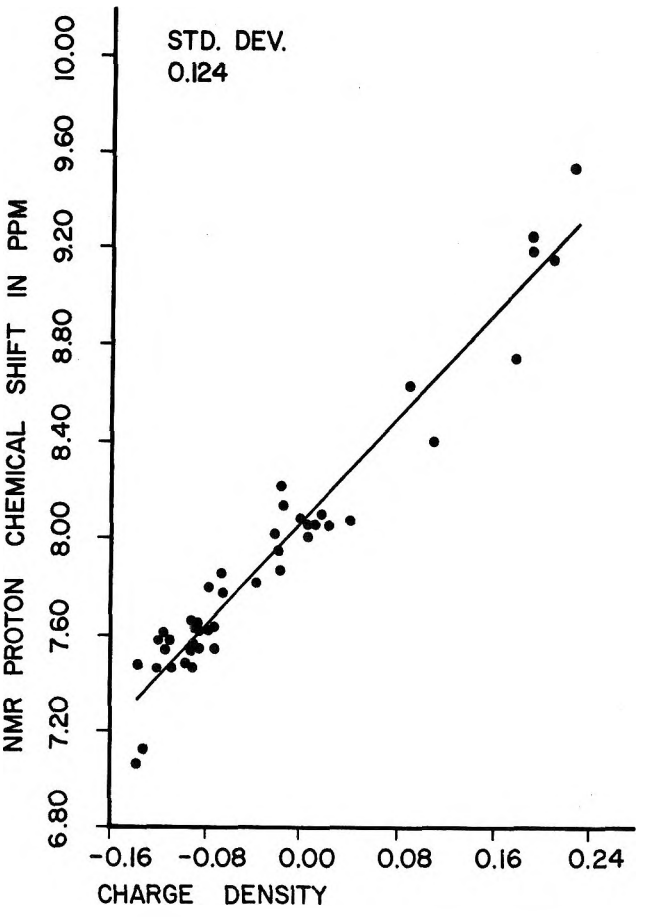

Figure 3.—Plot of corrected proton chemical shifts (at infinite dilution) *vs.* proton environmental charge density (S.D. = 0.124 ppm).

mined chemical shifts (S.D. = 0.276 ppm). The result is noticeably better than plots *vs.* proton, carbon σ, or carbon π densities alone. The empirical correlation between proton environmental charge density (PECD) and chemical shifts in the benzenoid portions of the molecules is excellent, as shown in Figure 2 (S.D. = 0.120 ppm). Application of corrections for anisotropy effects to H_{10} in all compounds and to H_5 in the iso series of 0.375 and 0.75 ppm, respectively, results in excellent empirical agreement (Figure 3, S.D. = 0.124). The resulting slope of 5.40 ppm/electron observed for these results is appreciably smaller than those observed previously (7–10 ppm/electron), but in excellent agreement with the values predicted theoretically (4–7 ppm/electron).[13,14]

The improved correlation resulting from the use of environmental charge density rather than simple π density probably is due to the polarizing effect of heteroatoms on the σ electron system in heterocycles, which is likely to produce significantly different σ densities at various sites, particularly near the heteroatoms. This is, of course, in contrast to carbocyclic systems where the carbon σ densities vary little if at all, and the variations in π density are the controlling factor.

Conclusions

The calculated results presented here are subject to all the uncertainties and criticisms inherent in any empirical or semiempirical MO treatment. Within the empirical framework the data support two significant conclusions. First, the chemical shift of a proton attached to an aromatic system, particularly complex heteroaromatics, usefully reflects the ground state σ and π electron density at the adjacent carbon. Second, the inclusion of the carbon σ electron density changes is desirable when considering the ground state charge distribution and resulting character of heteroaromatic compounds. Finally, it is noteworthy that the charge densities calculated by the FEHT method for these compounds yield proton chemical shift correlations which fit the same empirical expressions as do correlations for olefins, carbocyclic aromatics, and simple heterocyclic aromatics using a single set of input parameters and the appropriate geometry.[15]

Experimental Section[16]

The reaction conditions described below were found to be the most satisfactory for the preparation of the various chloroquinolines. 2-Chloro-6-methylquinoline[17] and 1-chloroisoquinoline[18]

(13) A. H. Gawer and B. P. Dailey, *J. Chem. Phys.*, **42**, 2658 (1965), and references cited therein.

(14) G. Fraenkel, R. E. Carter, A. McLachlan, and J. H. Richards, *J. Amer. Chem. Soc.*, **84**, 4623 (1960).

(15) C. A. Girard and S. L. Smith, unpublished observations.

(16) All evaporations were done under reduced pressure using a Rotavap apparatus. Melting points were determined in capillaries and infrared spectra were measured on a Perkin-Elmer Model 421 infrared spectrophotometer. The ultraviolet absorption data were obtained using a Beckman DK2 spectrophotometer and microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

(17) F. H. Hamer, *J. Chem. Soc.*, 209 (1928).

(18) B. Elpern and C. S. Hamilton, *J. Amer. Chem. Soc.*, **68**, 1436 (1946).

have been described previously and 2-chloro-4-methylquinoline was obtained commercially.

1,8-Dimethyl-2-quinoline.—Dimethyl sulfate (126.0 g) was added dropwise to 8-methylquinoline (143.0 g) with constant stirring. The reaction mixture solidified and was then heated on a steam bath for 0.5 hr. The methosulfate was dissolved in water (200 ml) and cooled to 0°, and solutions of sodium hydroxide (200 g) in water (300 ml) and potassium ferricyanide (700 g) in water (1300 ml) were added simultaneously, keeping the temperature of the mixture below 7°. The product was left overnight at room temperature and then extracted with chloroform. The chloroform extract was washed, dried (Na_2SO_4), and distilled, yielding a dark solid that, on distillation under reduced pressure, gave a light-colored oil, bp 210–215° (25 mm), that soon crystallized. It was recrystallized from benzene, forming colorless needles, yield 104.0 g, mp 96–97°.

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.3; H, 6.35; N, 8.1. Found: C, 76.4; H, 6.6; N, 8.1.

2-Chloro-8-methylquinoline.—1,8-Dimethyl-2-quinolone (40.0 g) was heated under reflux with phosphorus oxychloride (40.0 g) and phosphorus pentachloride (75.0 g) for 5 hr. The excess oxychloride was removed under reduced pressure and the residue was poured into ice water. The reaction mixture was basified with potassium hydroxide solution (pH 9–10) and then thoroughly extracted with benzene. The organic layer was washed, dried (Na_2SO_4), and concentrated; the dark residue distilled under reduced pressure, bp 210–220° (20–30 mm), yielding a solid that crystallized from benzene as short, colorless needles, yield 8.0 g, mp 55–56°.

Anal. Calcd for $C_{10}H_8ClN$: C, 67.6; H, 4.5; N, 7.9. Found: C, 67.5; H, 4.7; N, 8.2.

The picrate crystallized from alcohol as yellow needles, mp 133–135°.

Anal. Calcd for $C_{16}H_{11}ClN_4O_7$: N, 13.8. Found: N, 13.85.

The procedure found most satisfactory for the preparation of the hydrazines is illustrated below. 1-Hydrazinoisoquinoline has been described previously.[19]

2-Hydrazino-6-methylquinoline.—2-Chloro-7-methylquinoline (20.0 g) was refluxed with 95% hydrazine hydrate (50 ml) in ethanol (100 ml) for 2 hr. The excess hydrazine and alcohol were removed under reduced pressure and the residue was treated with cold water, basified with sodium hydroxide solution, and extracted with ether. The ethereal extract was washed, dried (Na_2SO_4), and distilled, giving a solid residue that crystallized from benzene (charcoal) as colorless needles, yield 15.0 g (75%), mp 151° dec.

Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.4; H, 6.35; N, 24.3. Found: C, 69.6; H, 6.4; N, 24.15.

In a similar fashion, 2-hydrazino-4-methylquinoline crystallized from benzene as colorless needles, yield 90%, mp 144–145°.

Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.4; H, 6.35; N, 24.3. Found: C, 69.4; H, 6.5; N, 24.3.

2-Hydrazino-8-methylquinoline formed colorless needles (75%) from benzene, mp 122°.

Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.4; H, 6.35; N, 24.3. Found: C, 69.7; H, 6.4; N, 24.3.

***s*-Triazolo[4,3-*a*]quinolines and *s*-Triazolo[3,4-*a*]isoquinolines.**—The general procedures used for the preparation of the compounds described in Table I are illustrated below.

7-Methyl-*s*-triazolo[4,3-*a*]quinoline.—2-Hydrazino-6-methylquinoline (2.0 g) was heated under reflux with 98% formic acid (5 ml) for 1 hr. The excess formic acid was then removed under reduced pressure and the residue was treated with ice-cold water (50 ml). Basification with sodium hydroxide, followed by extraction with chloroform, yielded a solid that, when recrystallized from benzene, separated as colorless needles, yield 2.0 g (95%), mp 192–193°.

3-Amino-7-methyl-*s*-triazolo[4,3-*a*]quinoline.—2-Hydrazino-6-methylquinoline (2.12 g) was dissolved in methanol (125 ml), and cyanogen bromide (1.3 g) was added carefully in the cold. After 3 hr of reflux, the excess methanol was removed under reduced pressure and the residue was treated with water and basified. The solid that separated was collected and washed with water. It crystallized from ethanol as fine, colorless needles, yield 2.0 g (87%), mp 245° dec.

7-Methyl-*s*-triazolo[4,3-*a*]quinoline-3-thiol.—2-Hydrazino-6-methylquinoline (5.2 g) in chloroform (150 ml) was refluxed with carbon disulfide (7.0 g) for 8 hr. Chloroform was then distilled off and the resulting product was recrystallized from methanol (charcoal) from which it separated as golden yellow needles, yield 4.5 g (70%), mp 294–296° dec.

1,7-Dimethyl-3-methylthio-*s*-triazolo[4,3-*a*]quinolinium Iodide.—7-Methyl-*s*-triazolo[4,3-*a*]quinoline-3-thiol (0.5 g) was dissolved in 10% sodium hydroxide solution (10 ml) and methyl iodide (1 ml) was added to it with vigorous shaking. The mixture was then left standing overnight when a solid separated. This was filtered, washed with water, and recrystallized from ethanol, from which it separated as colorless needles: yield 0.5 g; mp 247–248° dec; $\lambda_{max}^{CH_3OH}$ 222 nm (log 4.51), 244 sh (3.86), 252 (4.39), 296 sh (3.85), 310 (3.98), 326 (3.92), 338 sh (3.85).

Anal. Calcd for $C_{13}H_{14}IN_3S$: C, 42.0; H, 3.8; N, 11.3. Found: C, 42.1; H, 3.8; N, 11.1.

Similarly 1,9-dimethyl-3-methylthio-*s*-triazolo[4,3-*a*]quinolinium iodide was prepared from 9-methyl-*s*-triazolo[4,3-*a*]quinoline-3-thiol. It crystallized from alcohol, forming fine, colorless needles: yield 75%; mp 299–300° dec; $\lambda_{max}^{CH_3OH}$ 218 nm (log 4.78), 215 (4.41), 219 sh (4.03), 302 (4.16), 332 (4.20).

Anal. Calcd for $C_{13}H_{14}IN_3S$: C, 42.0; H, 3.8; N, 11.2. Found: C, 41.5; H, 4.3; N, 10.9.

1-Methyl-1-(4-methyl-2-quinolyl) Hydrazine.—2-Chloro-4-methylquinoline (8.0 g) was dissolved in methanol (100 ml), and methyl hydrazine (6.0 g) was added to it slowly in the cold. The mixture was then refluxed for 1 hr. The excess reagents were removed under reduced pressure and the residue (5.0 g) was poured into water. The precipitate was filtered, washed, and recrystallized from benzene–petroleum ether (bp 30–60°) from which the product separated as colorless needles, mp 53–54°. It was characterized as the picrate, which formed yellow needles from ethanol, mp 170° dec.

Anal. Calcd for $C_{17}H_{16}N_6O_7$: C, 49.0; H, 3.9. Found: C, 49.5; H, 4.2.

3-Amino-1,9-dimethyl-*s*-triazolo[4,3-*a*]quinolinium Bromide.—1-Methyl-1-(4-methyl-2-quinolyl) hydrazine (1.9 g) in methanol (20 ml) was treated with cyanogen bromide (1.1 g) in the cold and the resulting mixture was refluxed for 3 hr. Methanol was then removed under reduced pressure and the residue was recrystallized several times from alcohol, forming fine, colorless needles: mp 299–300° dec; $\lambda_{max}^{CH_3OH}$ 214 nm (log ϵ 4.47), 242 (4.13), 291 sh (3.80), 303 (3.90), 328 (3.98).

Anal. Calcd for $C_{12}H_{13}BrN_4$: C, 49.1; H, 4.4; N, 19.1. Found: C, 48.9; H, 4.6; N, 18.9.

Reaction of 8-Methyl-2-quinolylhydrazine with Acetic Acid.—The above hydrazine (3.5 g) was refluxed with acetic acid (6 ml) for 5 hr. After evaporation to dryness, water was added and the reaction mixture was neutralized. The product that separated crystallized from methanol–benzene as white flakes: mp 203–204°; ir (Nujol) main bands 3268, 1653, 1613, 1342, 1267, 1006, 848, 800, 763 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 67.0; H, 6.0; N, 19.5. Found: C, 67.2; H, 6.0; N, 19.3.

Pmr Spectra.—Samples were prepared at several concentrations in deuteriochloroform containing TMS, degassed by the freeze–thaw technique, and sealed under vacuum. Spectra were determined on a Varian HA-60-IL spectrometer operating in the frequency sweep mode (probe temperature ~25°) and were calibrated by counting peak positions directly. Reported chemical shifts were obtained by extrapolation to infinite dilution. Computer analyses of portions of the spectra were accomplished using NMRIT, NMREN,[20] and LAOCOON III.[21] Spin-decoupling experiments were performed with Hewlett-Packard audio oscillators (Models 200CD and 201CD). Calculations were carried out as described previously[6] using IBM 7040 and 360/50 computers.

Registry No.—1,8-Dimethyl-2-quinolone, 35359-35-4; 2-chloro-8-methylquinoline, 4225-85-8; 2-chloro-8-methylquinoline picrate, 35359-37-6; 2-hydrazino-6-methylquinoline, 35359-38-7; 2-hydrazino-4-methylquinoline, 21703-52-6; 2-hydrazino-8-methylquinoline, 35359-40-1; 1,7-dimethyl-3-methylthio-*s*-triazolo[4,3-*a*]-quinolinium iodide, 35359-41-2; 1,9-dimethyl-3-methylthio-*s*-triazolo[4,3-*a*]quinolinium iodide, 35356-62-8; 1-methyl-1-(4-methyl-2-quinolyl) hydrazine, 35356-63-9;

(19) CIBA Ltd., British Patent 710,047 (June 2, 1954); *Chem. Abstr.*, **49**, 7606 (1955).

(20) J. D. Swalen and C. A. Reilly, *J. Chem. Phys.*, **37**, 21 (1962).

(21) LAOCOON III is an improved version of LAOCOON II: S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).

1-methyl-1-(4-methyl-2-quinolyl) hydrazine picrate, 35356-64-0; 3-amino-1,9-dimethyl-*s*-triazolo[4,3-*a*]-quinolinium bromide, 35356-65-1; compound of mp 203–204°, 35427-27-1.

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The Mechanism of the Benzidine Rearrangement. II.[1,2] The Rearrangement of *N*-Acetylhydrazobenzene

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In concentrated perchloric acid–sodium perchlorate solutions, *N*-acetylhydrazobenzene undergoes an intramolecular rearrangement to *N*-acetylbenzidine. The rate of rearrangement has a first-order dependency on the Hammett acidity, H_0, and is subject to a small solvent isotope effect, $k_{H_2O}/k_{D_2O} = 1.27$. A small but reproducible substrate isotope effect is observed on the rate of rearrangement of the ring perdeuterated material, $k_H/k_D = 1.07$. On the basis of these observations it is concluded that the rearrangement is clearly a manifestation of the benzidine rearrangement, that the mechanism of rearrangement involves a single proton transfer in an equilibrium established prior to the rate-limiting process, and that both the solvent deuterium isotope effect and the substrate deuterium isotope are secondary isotope effects. Arguments are given in favor of a pathway involving a rate-limiting heterolysis of the nitrogen–nitrogen σ bond following the preequilibrium proton transfer. The electron-withdrawing, inductive effect of the *N*-acetyl substituent is envisaged to usurp the catalytic role of the second proton in the acid-catalyzed rearrangement of hydrazobenzene. The driving force for bond heterolysis and rearrangement is a cumulation of the repulsion between the *N*-acetyl group and the protonated *N'*-amino nitrogen, and incipient bonding of a π-complex type. The reaction of *N*-acetylhydrazobenzene to give benzidine (and presumably diphenyline) in dilute acid solutions probably proceeds *via* slow hydrolysis to hydrazobenzene, followed by rapid rearrangement to the observed product(s).

The research described in this series on the mechanism of the benzidine rearrangement was incepted with the intention of investigating the nature of the transient bonding forces responsible for imparting *intra*molecularity to the transformation. Accordingly, structural analogs of hydrazobenzene have been prepared and investigated with the expectation that the mode of rearrangement of these compounds will provide evidence which will aid in defining the energetics of the rate-limiting and the product-forming stages of the reactions.

The first paper in this series[1] reports evidence for the formation of *N*-acetyl-*O*,*N*-diphenylhydroxylamine as a transient intermediate in the reaction of *N*-acetyl-*N*-phenylhydroxylamine with diphenyliodonium hydroxide. The *N*-acetyl-*O*,*N*-diphenylhydroxylamine thus produced was found to undergo a spontaneous, intramolecular rearrangement to 4'-hydroxy-4-acetamidobiphenyl and traces of 2'-hydroxy-4-acetamidobiphenyl. The spontaneity of this benzidine-like rearrangement in the absence of acid catalysis was rationalized as resulting from the combination of the electron-withdrawing effect of the *N*-acetyl substituent with the greater electronegativity of the *O*-phenyl oxygen as compared to nitrogen, which together simulate the electronic characteristics of the diprotonated hydrazobenzene cation.

In this paper there is described a mechanistic study of the acid-catalyzed rearrangement of *N*-acetylhydrazobenzene which was carried out with the intention of examining the possibility that the *N*-acetyl function can act as an internal general acid catalyst in such processes generally.

Experimental Section

Melting and boiling points are uncorrected. Pmr spectra were recorded with a Varian A-60 spectrometer and ir spectra with a Perkin-Elmer 21 spectrometer.

Instrumentation.—All kinetic measurements were performed with a Zeiss PMQ-II spectrophotometer equipped with a thermostated cell compartment and cell holder. The mass spectrometer analyses were carried out on an Atlas CH-4 mass spectrometer, by recording the cracking pattern and the detail in the molecular weight region at low ionization potentials.

Materials.—The concentrated perchloric acid (70–72%) and sodium perchlorate (analytical grade) used were the commercially available materials, as were deuterium oxide, sulfuric acid-d_2 (99.6 atom % D), and benzene-d_6 (99.5 atom % D). Perchloric acid-d_1 and nitric acid-d_1 were prepared from the corresponding anhydrous sodium salts according to the procedures described for the isotopically normal materials.[4]

N-Acetylhydrazobenzene was prepared after the method of Goldschmidt and Euler. The crude product was recrystallized from chloroform, mp 162–163° (reported[5] mp 159°).

2,3,4,5,6,2',3',4',5',6'-Decadeuterio-*N*-acetylhydrazobenzene was prepared by the nitration of benzene-d_6 with nitric acid-d_1 and sulfuric acid-d_2 followed by reduction of the resulting nitrobenzene-d_5 (99.5 atom % deuterium content by nmr) with zinc dust in alcoholic sodium hydroxide and acylation with acetic anhydride.[5] Each step was carried out according to the usual procedures employed for the isotopically normal materials. The resulting ring perdeuterio-*N*-acetylhydrazobenzene, mp 162–163°, gave pmr and ir spectra which indicated a high degree of ring deuterium content.

The Acid-Catalyzed Reaction of *N*-Acetylhydrazobenzene in Ethanol–Water Solution.—*N*-Acetylhydrazobenzene, 1.00 g (4.43 mmol), dissolved in 75 ml of ethanol and 10 ml of concentrated hydrochloric acid, gave, after standing at room temperature for 24 hr, a white, crystalline precipitate. This material was collected by vacuum filtration, redissolved in water, and neu-

(1) This work was done in partial fulfillment of the requirements for the Ph.D. degree by Michael F. Dunn. First paper in this series: J. R. Cox, Jr., and M. F. Dunn, *Tetrahedron Lett.*, 985 (1963).

(2) The authors gratefully acknowledge the support of this work by the National Science Foundation under Grant GP-1576.

(3) To whom inquiries should be addressed at the University of Houston.

(4) G. Brauer, Ed., "Handbook of Preparative Inorganic Chemistry," 2nd ed, Academic Press, New York, N. Y., 1963, pp 318, 491.

(5) S. Goldschmidt and K. Euler, *Chem. Ber.*, **55**, 616 (1922).

tralized to *ca.* pH 8 by the addition of dilute sodium hydroxide. The soft, white solid which separated was extracted into ether. Evaporation of the extract yielded 0.55 g (62% of theory) of a glistening, almost white solid, mp 123–124°, which exhibited an infrared spectrum superimposable upon that of authentic benzidine. Kinetic studies on the rate of hydrolysis of *N*-acetylbenzidine indicate that only a small amount of the benzidine produced could have resulted from the hydrolysis of *N*-acetylbenzidine.

The Rearrangement of *N*-Acetylhydrazobenzene in Concentrated Mineral Acid.—Treatment of *N*-acetylhydrazobenzene, 1.00 g (4.43 mmol), with 10 ml of 60% perchloric acid yielded immediately a dark, greenish-brown solution. Dissolution was accompanied by the evolution of considerable heat. This solution was cooled in ice and neutralized by the careful addition of sodium hydroxide. The tan solid which separated was recrystallized from hot ethanol, yielding an almost white, crystalline material, mp 202–203° dec, shown to be identical with authentic *N*-acetylbenzidine (reported[6] mp 199° dec) by mixture decomposition point, which was undepressed, and by comparison of ir spectra, which were superimposable: yield 0.83 g (83% of theory). Ether extraction of the aqueous filtrate followed by evaporation gave approximately 0.1 g of an oily, brown residue which was not identified.

The Mixed Rearrangement of Perdeuterio- and Isotopically Normal *N*-Acetylhydrazobenzene.—*N*-Acetylhydrazobenzene, 0.1000 g (0.443 mmol), and perdeuterio-*N*-acetylhydrazobenzene, 0.1394 g (0.591 mmol), were ground to fine powders and thoroughly mixed. The mixture was added to a 50-ml flask containing 25 ml of 6.01 formal (*F*) perchloric acid. Solution was brought about by placing the mixture on the surface of the ground glass joint of the flask and mulling with perchloric acid by grinding a stopper in the joint. The resulting mull was then washed into the flask with more acid. This method for effecting solution was employed to avoid the marked tendency of the material to form cakes which do not dissolve readily in the acid medium. Addition was completed in 15 min. The resulting mixture was stirred for 80 min, during which time a precipitate of insoluble *N*-acetylbenzidinium perchlorate formed. The collected precipitate was dispersed in 25 ml of distilled water and neutralized with anhydrous sodium carbonate. The resulting precipitate of *N*-acetylbenzidine was recovered after vacuum drying in a yield of 0.1840 g (77% of theory). This material was recrystallized from methanol and sublimed, 160–170° (0.05 mm), yielding white crystals (as star clusters), mp 205.4–206.4°. The analysis of the mass spectrum of this mixture is given in Table II.

Ring perdeuterio-*N*-acetylhydrazobenzene, by itself, was rearranged under the same conditions. On work-up, the crude rearranged material was obtained in a yield of 91.5% of theory. Analysis of the mass spectrum of this material indicated at least 98.8% ring deuterium content; see Table II.

Kinetic Studies.—The conversion of *N*-acetylhydrazobenzene to benzidine in 30% methanol–water was studied in solutions of perchloric acid maintained at a constant ionic strength of 1.08 with added sodium perchlorate. Rate measurements were made by following the change in optical density at 235 mμ (the absorption maximum for *N*-acetylhydrazobenzene) and at 280 mμ (the absorption maximum for benzidine) of neutralized aliquots withdrawn at various time intervals from a solution thermostated at 30 ± 0.1 or 60.0 ± 0.1°, depending on the particular experiment. Rearrangement of hydrazobenzene under the same conditions gave a product mixture having a uv spectrum identical with that of the product mixture obtained from *N*-acetylhydrazobenzene by the procedure described above.

Rate studies of the rearrangement of *N*-acetylhydrazobenzene to *N*-acetylbenzidine were carried out in concentrated perchloric acid–sodium perchlorate solutions 6.0 in total ionic strength. Stock solutions were prepared by the dilution of the appropriate amounts of sodium perchlorate and standardized concentrated perchloric acid to the desired concentrations, according to Harbottle.[7] Individual kinetic runs were then performed by adding an appropriate amount of *N*-acetylhydrazobenzene to a 5-ml aliquot of the stock solution. Solution was effected by vigorously shaking for about 20 sec. The quartz cuvette then was filled from a capillary eye dropper to avoid including any undissolved particles. Changes in optical density corresponding to the appearance of *N*-acetylbenzidinium ion (λ_{max} 268 mμ, ϵ_{max} 1.84×10^4) were measured as a function of time. The absorbance of the solution at 236.6 mμ was found to be invariant during the course of a kinetic run. No spectrophotometric evidence could be found for the formation of products other than *N*-acetylbenzidine during the period of time required for completion of a kinetic run. However, prolonged observations at 268 mμ indicate that the product undergoes a slow hydrolysis.

Results

Under preparative conditions (see Experimental Section), benzidine was isolated in 62% of theory from *N*-acetylhydrazobenzene in ethanol–dilute hydrochloric acid. In methanol–water solutions of dilute perchloric acid (Table I) *N*-acetylhydrazobenzene affords a product mixture with uv spectrum identical with that obtained from the rearrangement of hydrazobenzene under the same conditions. Thus, benzidine (and presumably diphenyline) are the products of the reaction of *N*-acetylhydrazobenzene under conditions of dilute aqueous (or alcoholic) hydrochloric or perchloric acid catalysis, in good agreement with the findings of Vecera, *et al.*[8]

TABLE I

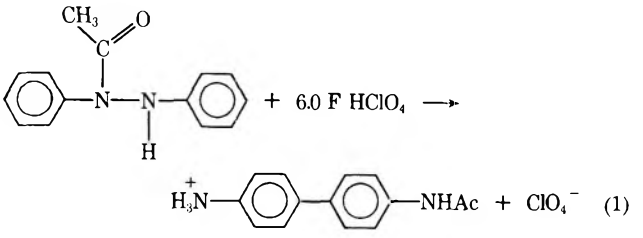
THE ACID-CATALYZED REACTION OF *N*-ACETYLHYDRAZOBENZENE TO BENZIDINE IN 30% METHANOL–WATER SOLUTIONS

Temp,[a] °C	$[H^+]$ $HClO_4$	$NaClO_4$	k_h,[b] hr^{-1}	$t_h^{1/2}$, hr	$k_h/[H^+]$	k_b,[b] hr^{-1}	$t_b^{1/2}$, hr	$k_b/[H^+]$
30.0	1.080	0.000	0.040	17	0.035	0.038	18	0.035
30.0	0.753	0.227	0.025	28	0.033	0.025	28	0.033
30.0	0.540	0.520	0.020	35	0.037	0.019	37	0.035
30.0	0.374	0.706	0.015	46	0.040	0.016	42	0.044
60.0	1.080	0.000	0.59	1.2	0.54	0.58	1.2	0.53

[a] The temperature was controlled within ±0.1°. [b] The rate constant k_h is the apparent rate of disappearance of *N*-acetylhydrazobenzene and k_b is the apparent rate of formation of benzidine.

The spectrophotometric kinetic studies summarized in Table I demonstrate that the rate of disappearance of *N*-acetylhydrazobenzene and the rate of appearance of benzidine are experimentally identical. The reaction is found to follow second-order kinetics (first order with respect to stoichiometric acidity and first order with respect to *N*-acetylhydrazobenzene). Comparison of the relative rates of this process at 30.0 and 60.0° allows estimation of the apparent energy of activation, 18 kcal mol^{-1}.

In contrast, the reaction of *N*-acetylhydrazobenzene under conditions of concentrated mineral acid catalysis gives the product *N*-acetylbenzidine in nearly quantitative yield (see Experimental Section) according to eq 1. This finding is in good agreement with the observations of Pongratz and Scholtis on the composition of the re-



(1)

(6) H. Schmidt and G. Schultz, *Chem. Ber.*, **12**, 489 (1879).

(7) G. Harbottle, *J. Amer. Chem. Soc.*, **73**, 4024 (1951).

(8) M. Vecera, J. Petranek, and J. Gasparic, *Collect. Czech. Chem. Commun.*, **22**, 1063 (1957).

TABLE II

THE MASS SPECTRA OF THE PRODUCTS FROM THE REARRANGEMENTS OF 2,3,4,5,6,2′,3′,4′,5′,6′-DECADEUTERIO-*N*-ACETYLHYDRAZOBENZENE AND *N*-ACETYLHYDRAZOBENZENE IN 6.01 *F* $HClO_4$

	Relative peak intensities		
Material	226	230	234
Isotopically normal	248	~2	~2
Authentic perdeuterio	8		675
Rearrangement mixture (42.1% protio and 57.9% perdeuterio)	348	~0.75	498

arrangement products in concentrated hydrochloric acid.[9]

The presumed *intra*molecularity of this process was tested by mass spectrometric analysis of the products resulting from rearrangement of an approximately equimolar mixture of ring perdeuterio- and isotopically normal *N*-acetylhydrazobenzene in 6 *F* perchloric acid. If rearrangement is intramolecular, then the mass spectrum of the products should exhibit only parent peaks corresponding to the isotopically normal and to the octadeuterio materials (*m/e* 226 and 234, respectively). The peak at *m/e* 230 (the mass corresponding to the parent peak of the cross product) is a direct measure of *inter*molecular recombination. Table II summarizes the results of this experiment. *These data clearly demonstrate that no more than 0.2% of the products can be accounted for via an intermolecular pathway.* Exchange of ring-substituted deuterium with solvent hydrogen under the same conditions of rearrangement was found not to be significant. Deuterium-labeled *N*-acetylbenzidine obtained *via* rearrangement of ring perdeuterated *N*-acetylhydrazobenzene in isotopically normal perchloric acid contained at least 98.8% ring-bound deuterium (measured as the *m/e* 234/233 ratio, Table II).

Kinetic investigation of the rearrangement was carried out in the aqueous perchloric acid–sodium perchlorate system of Harbottle.[7] This system, in which the total perchlorate ion concentration is maintained at 6.0 *F*, was chosen for the advantage it provides in the linearity of its Hammett acidity function (H_0) over the range 2–6 *F* perchloric acid. Additional advantages are derived from a low water activity and an acidity range that gives convenient rearrangement rates at easily accessible temperatures.

The kinetics of rearrangement were measured by following directly the uv spectral changes accompanying the appearance of *N*-acetylbenzidinium ion. The results of these measurements are presented in Table III. Apparent first-order kinetics were found over greater than 90% completion of reaction. *A plot of H_0 vs. log k_{app} (Figure 1) gives a linear correlation with a slope near unity (slope 0.833).* The corresponding plot of log [$HClO_4$] *vs.* log k_{app} gives a nonlinear correlation (Figure 2).

The solvent deuterium isotope effect upon the rate of rearrangement was determined by comparing rates in isotopically normal and deuterium oxide–perchloric acid-d_1 solutions, both 6.01 *F* in perchloric acid. The ratio of rates obtained, $k_{H_2O}/k_{D_2O} = 1.27$, reflects a 20% rate decrease for the deuterated solvent system.

(9) A. Pongratz and K. Scholtis, *Chem. Ber.*, **75**, 138 (1942); see also D. W. Davies and D. L. Hammick, *J. Chem. Soc.*, 475 (1954).

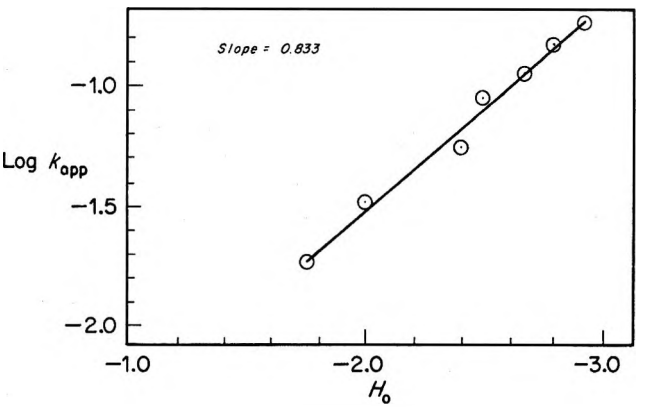


Figure 1.—H_0 *vs.* log k_{app} for the rearrangement of *N*-acetylhydrazobenzene in solutions of perchloric acid–sodium perchlorate 6 *F* in perchlorate ion.

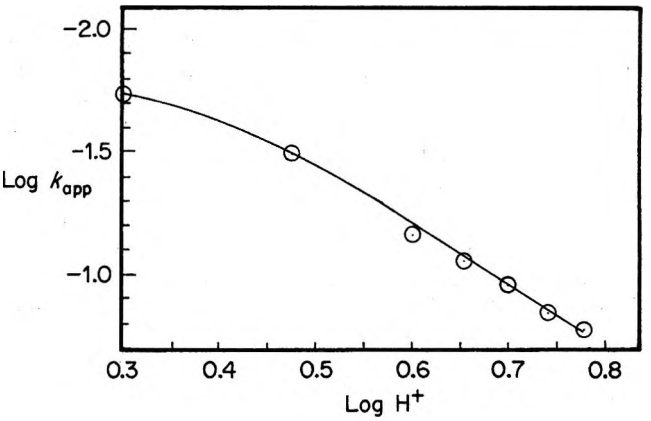


Figure 2.—Log H^+ *vs.* log k_{app} for the rearrangement of *N*-acetylhydrazobenzene in solutions of perchloric acid–sodium perchlorate 6 *F* in perchlorate ion.

TABLE III

THE ACID-CATALYZED REARRANGEMENT OF *N*-ACETYLHYDRAZOBENZENE TO *N*-ACETYLBENZIDINE IN CONCENTRATED PERCHLORIC ACID–SODIUM PERCHLORATE

Temp,[a] °C	[$HClO_4$], *F*	[$NaClO_4$], *F*	$-H_0$	h_0[b]	k_{app},[c] min^{-1}	$t_{1/2}$, min	k_{app}/h_0 × 10^4	$k_{app}/[H^+]$ × 10^2
30.0	6.01	0.00	2.92	832	0.175	3.96	2.10	2.92
30.0	5.50	0.50	2.78	605	0.143	4.84	2.36	2.60
30.0	5.00	1.00	2.64	437	0.110	6.30	2.51	2.20
30.0	4.50	1.50	2.49	302	0.0872	7.95	2.89	1.94
30.0	4.00	2.00	2.40	218	0.0548	11.9	2.68	1.46
30.0	3.00	3.00	2.00	108	0.0325	21.6	2.97	1.07
30.0	2.00	4.00	1.76	53	0.0184	37.1	3.47	0.92
20.0	6.01	0.00	2.92	832	0.0467	14.8		
20.0	5.00	1.00	2.64	437	0.0284	24.4		

[a] The temperature was controlled to ±0.1°. [b] These values were obtained from the relationship $H_0 = -\log h_0$. [c] The reproducibility of k_{app} was 0.005 min^{-1}.

This decrease is considerably greater than the experimental error (*ca.* 5%) involved in the rate determinations.

A small but reproducible substrate deuterium isotope effect ($k_H/k_D = 1.07$) on the rate of rearrangement of the ring perdeuterio *N*-acetylhydrazobenzene was observed. To ensure that this decrease in rate did not result from a systematic experimental error, alternate kinetic runs on the isotopically normal and perdeuterio materials were carried out using the same stock solution of acid. Kinetic runs carried out in this way consistently gave a larger rate constant for the isotopically normal material.

Discussion

We define the term "benzidine rearrangement" to mean the intramolecular transformations of hydrazoaromatic compounds and their isoelectronic analogs, including, but not limited to, those processes which occur under protonic and Lewis acid catalysis. The mass spectral studies presented herein unequivocally demonstrate the intramolecularity of the acid-catalyzed rearrangement of *N*-acetylhydrazobenzene, and it is, therefore, a manifestation of the benzidine rearrangement in the sense of our definition.

The finding that the rate of rearrangement has a first-order dependency on the Hammett acidity (H_0) of the concentrated perchloric acid–sodium perchlorate mixtures is good evidence for a mechanism involving *a single proton transfer prior to the rate-determining step.*[10]

A growing number of examples of the benzidine rearrangement exhibit either a first-order dependency on Hammett acidity or an apparent order which varies between one and two with increasing acidity. Examples in which the apparent order in H_0 varies with the acidity are found to behave according to the rate expression $v = k(\text{hydrazo})(H_0) + k'(\text{hydrazo})(H_0)$,[2] the expression derived for a mechanism involving two parallel pathways for rearrangement that differ only in the respective hydrogen ion dependencies.[12] Banthorpe and O'Sullivan, reasoning from the considerable body of evidence that the transition state of the benzidine rearrangement is highly polar, predicted[13] that either electron-releasing or electron-withdrawing substituents in hydrazobenzene might lower the kinetic order in protons of its rearrangement. Most of the examples encountered previously have been substituted with electron-releasing substituents, some being first order in protons[11,14-17] and some, transitional.[18-22] One previous example of transitional kinetics[23] and one of first-order proton dependence[24] in which electron-withdrawing substituents were present have been reported. As Banthorpe and O'Sullivan point out,[13,24] these substituents greatly reduce both the base strength of the hydrazobenzene molecule and the absolute rate of its rearrangement. *N*-Acetylhydrazobenzene provides the first example of confinement to a one-proton process in which the ring is not substituted. The *N*-acetyl substituent also decreases the basicity of the hydrazobenzene as well as the rate of rearrangement.

The absence of the equilibrium protonation isotope effect on the rate of rearrangement in D_2O solutions observed for other examples of the benzidine rearrangement[11] could not have been predicted. However, it has been found experimentally that D_0, the Hammett acidity function of sulfuric acid-d_2, is numerically the same as H_0 for solutions of the same acid concentration.[25] Hence, the deuterium-donating ability of concentrated sulfuric acid-d_2 is numerically the same as the proton-donating ability of isotopically normal sulfuric acid.

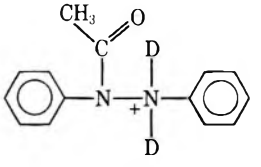
The observation that D_0 and H_0 are equivalent is rationalized in the following way. Equilibrium isotope effects arise from differences in the equilibrium constants, respectively, for protonation and deuteration according to eq 2 and 3, where B is a moderately weak base.

$$H_2SO_4 + B \overset{K_H}{\rightleftharpoons} BH^+ + HSO_4^- \quad (2)$$

$$D_2SO_4 + B \overset{K_D}{\rightleftharpoons} BD^+ + DSO_4^- \quad (3)$$

However, as the base strength of B decreases, the ratio K_H/K_D approaches unity[26] because the difference between the zero point vibrational energies of BH^+ and BD^+ becomes a smaller percentage of the total ground state energy difference (as measured by K_H or K_D) between B and its conjugate acid.

The decreased rate in perchloric acid-d_1 then becomes understandable as a secondary isotope effect if one assumes that (a) the ratio K_D/K_H for the formation of the conjugate acid of *N*-acetylhydrazobenzene is close to unity; (b) the rearranging species in D_2O–perchloric acid-d_1 is the conjugate acid of *N*-acetyl-*N*-deuteriohydrazobenzene (**1**); and (c) the rate-determining step of



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the rearrangement is N–N bond scission. Although no perfect analog of this system has been found by the authors in the literature, α-deuterium substitution at an aliphatic carbon regularly reduces the rate of solvolysis of halides by a degree of magnitude very similar to that measured in this work.[27,28]

Secondary isotope effects which arise from deuterium substitution at a site remote from the reaction center are well known.[29] The small but reproducible substrate isotope effects on the rate of rearrangement of ring perdeuterio-*N*-acetylhydrazobenzene clearly belong to the category of secondary isotope effects. This observation is the first report of a secondary isotope effect on the rate-limiting step of an acid-catalyzed benzidine rearrangement in which the effect arose from ring deuterium substitution. Since all available evidence pinpoints the N–N cleavage as rate limiting, the isotope effect therefore attaches to this process.

Various mechanisms have been suggested for the benzidine rearrangement. Of these, the two leading

(10) L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, pp 283–286. Also see ref 11.
(11) D. V. Banthorpe, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2386 (1962).
(12) D. A. Blackadder and C. Hinshelwood, *ibid.*, 2898 (1957).
(13) D. V. Banthorpe and M. O'Sullivan, *J. Chem. Soc. B*, 615 (1968).
(14) D. V. Banthorpe and E. D. Hughes, *J. Chem. Soc.*, 2502 (1962).
(15) W. N. White and E. E. Moore, *J. Amer. Chem. Soc.*, **90**, 526 (1968).
(16) D. V. Banthorpe and A. Cooper, *J. Chem. Soc. B*, 605 (1968).
(17) D. V. Banthorpe, A. Cooper, and C. K. Ingold, *ibid.*, 609 (1968).
(18) W. N. White and R. Preisman, *Chem. Ind. (London)*, 1752 (1961).
(19) D. V. Banthorpe, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2418 (1962).
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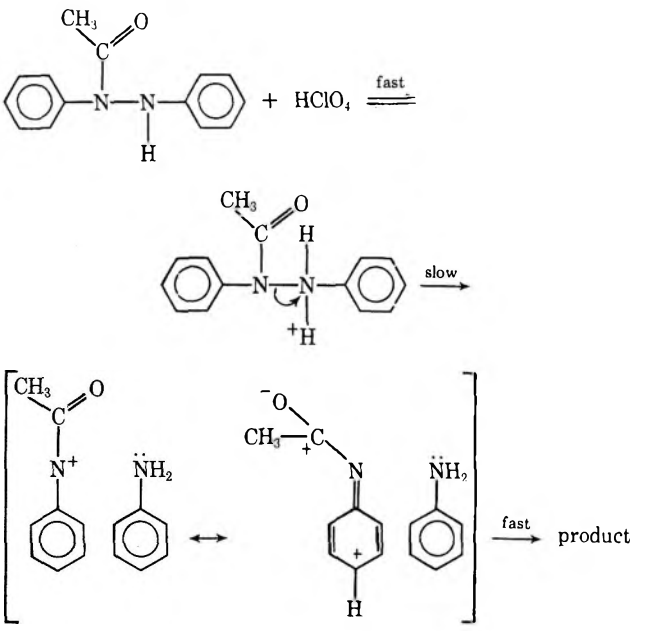
(22) D. V. Banthorpe, C. K. Ingold, and J. Roy, *J. Chem. Soc. B*, 64 (1968).
(23) D. V. Banthorpe, C. K. Ingold, and M. O'Sullivan, *ibid.*, 624 (1968).
(24) D. V. Banthorpe and M. O'Sullivan, *ibid.*, 627 (1968).
(25) E. Hogfelt and J. Bigeleisen *J. Amer. Chem. Soc.*, **82**, 15 (1960).
(26) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 187.
(27) E. A. Halevi, "Progress in Physical Organic Chemistry," Vol. 1, Interscience, New York, N. Y., 1963, pp 171–173.
(28) V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Amer. Chem. Soc.*, **90**, 418 (1968).
(29) Reference 27, pp 200–204.

contenders are the "polar transition state" mechanism[30,31] and the "π-complex intermediate" mechanism.[32] Shine has recently made a critical review of these and other suggestions.[33] Since the experimental evidence does not provide unambiguous criteria for defining all of the mechanistic features, the proposed pathways rely heavily on intuitive arguments which at times take on polemic overtones. These controversies have served to obscure the fundamentally important evidence that the rate-limiting process differs from the product-forming process. The rate-limiting step is strongly influenced by polar factors, suggesting substantial charge separation in the transition state. The structures of the various products formed suggest a geometry for the intermediate in which the rings are roughly parallel and are free to rotate relative to each other about an axis perpendicular to the planes of the rings. This orientation would not be required, in the transition state or in an intermediate, by ionic bonding. Hence, the transition state for the rate-limiting process leads to a metastable intermediate from which products are formed over a separate transition state.

The free energy of activation for the rate-limiting process may be lowered either by raising the free-energy content of the ground state or by lowering the free-energy content of the transition state, or by a combination of both. Proponents of the "polar transition state" theory have characteristically focused on the former,[13,30,31] while proponents of the "π-complex intermediate" have focused on considerations of bonding in the intermediate, since multicenter bonding, with or without a strong charge-transfer component, may readily be envisioned to play the major role in the stabilization of this structure, which is a π complex in Dewar's terminology.[32] The essence of the controversy seems to concern the degree to which bonding similar to that in the proposed intermediate lowers the energy of the transition state leading to the intermediate. That is, how much of the "driving force" for the rate-limiting step of the reaction is due to lowering of the free energy of the transition state by virtue of the stabilization of the presumed, intermediate π complex? Although at present no method has been made available, either experimental or theoretical, by which the intermediate can be characterized—a necessary step in the definition of the energy surface on which it resides—it is still instructive to consider energetic factors which arise from bond breaking.

Protonation of one or both nitrogens of an hydrazobenzene greatly facilitates its rearrangement. In most previous examples of hydrazobenzenes which rearrange at a detectable rate upon monoprotonation, at least one ring has been substituted so as to make it more effective than a phenyl ring in stabilizing a positive charge. Such substitution being absent, diprotonation is required, unless other factors contribute to N–N bond polarization.[13,24]

The observation reported herein that ring protons are not exchanged with solvent during the rearrangement, taken with the demonstrated equilibrium protonation process, clearly defines both protonation sites as the nitrogen atoms and not the unsubstituted carbon atoms of the rings. Relief in the transition state of the coulombic repulsion generated by the protonation clearly contributes significantly to the energetics of the process. Breslow and McNelis[34] observed that the repulsion between the dipole of the carbonyl group and the positively charged nitrogen atom of 2-acetylthiazolinium salts greatly facilitated nucleophilic addition to the carbonyl carbon, resulting in acyl–carbon bond cleavage. We believe that the carbonyl function of N′-protonated *N*-acetylhydrazobenzene similarly facilitates N–N bond cleavage. Since the rate of cleavage of the bond to nitrogen in an N-substituted anilide is sensitive to the ability of the leaving group to stabilize a negative charge,[35] we believe that the bond breaking is heterolytic in nature. We envision the sequence surrounding the rate-limiting step as follows.



The bracketed intermediate should certainly possess considerable stabilization from multicenter bonding, and in it the positive charges have been effectively delocalized. The balance of the repulsive and the bonding forces which operate in the transition state is undefined at present, but we believe both of them to contribute to lowering the free energy of activation. This model accommodates and explains the first-order dependency on H_0, in that the *N*-acetyl substituent usurps the catalytic role of the second proton in the usual benzidine rearrangement. It also is an isoelectronic analog of *N*-acetyl-*O*,*N*-diphenylhydroxylamine, which rearranges with great facility.[1] In highly symmetrical molecules such as hydrazobenzene itself, bonding in the transition state may have less of a charge-transfer component, and therefore less polarity, than in unsymmetrical systems such as ours. Description of the bonding in this series of metastable structures remains a fascinating challenge to the theoretical chemist.

(30) D. V. Banthorpe, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2864 (1964).

(31) D. V. Banthorpe, *Chem. Rev.*, **70**, 295 (1970).

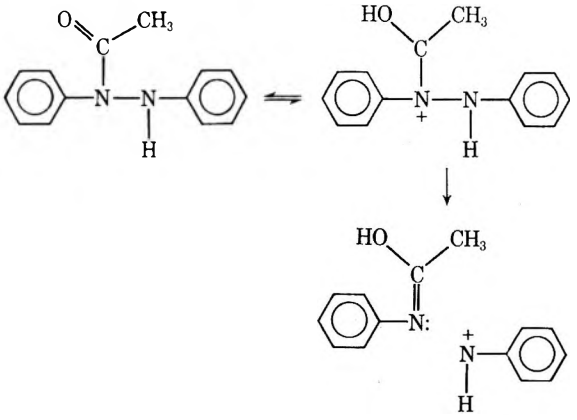
(32) M. J. S. Dewar and A. P. Marchand, "Annual Review of Physical Chemistry," Vol. 16, Annual Review, Inc., Palo Alto, Calif., 1965, pp 321–344.

(33) H. J. Shine in "Mechanisms of Molecular Migrations," Vol. 2, B. S. Thyagarajan, Ed., Wiley, New York, N. Y., 1969, p 191.

(34) R. Breslow and E. McNelis, *J. Amer. Chem. Soc.*, **82**, 2394 (1960).

(35) Rearrangement of *O*,*N*-diacyl-*N*-phenylhydroxylamines has been found to have a strong dependency on the leaving group: M. F. Dunn, Ph.D. Thesis, Georgia Institute of Technology, 1966. See also ref 1.

The alternate possibility that heterolytic scission of the N–N bond occurs in the opposite sense, that is,



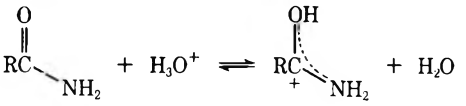
is not totally excluded by the work reported herein, but is inconsistent with the growing body of evidence that heterolysis of an electronegative substituent on nitrogen in a substituted anilide readily occurs to afford an *N*-acylnitrenium cationoid fragment.[1,35,36] This theme will be developed in subsequent papers.

The recent proposal[37] by Allan that the benzidine rearrangement occurs *via* a species protonated at C-1 and nitrogen of one ring of hydrazobenzene may be ruled out on several grounds. (1) Electronic considerations suggest that C-1 is a very weakly basic position. (2) Consideration of models shows that the stereochemical problem is not greatly diminished by this pathway. (3) Protonation of C-1 and the adjacent nitrogen offers little driving force for heterolytic N–N bond breaking; yet this factor is known to be prominent in the energetics of the process. (4) The model cannot successfully be extended to the work reported herein.

The detailed course of the rearrangement in dilute acid which is accompanied by hydrolysis is less clearly established. The H_0 of 1.080 *F* perchloric acid in 30% aqueous methanol has not been established, but it may be approximated from the data of Yates and Wai[38] to be about −0.4. It should be noted that addition of 5 *F* $NaClO_4$ to 1 *F* $HClO_4$ lowers the activity of water in the solution[39] and increases the Hammett acidity, thereby making the H_0 more negative by about one (logarithmic) unit.[7] Thus, although the rate of rearrangement in 2 *F* $HClO_4$–4 *F* $NaClO_4$ solution at first appears to have been abnormally accelerated over that in 1 *F* $HClO_4$, the acceleration is due in large measure to the increased acidity of the medium. Extrapolation of the rates measured in solutions 6 *F* in electrolyte to an H_0 of −0.4 suggests that the rate of rearrangement of acetylhydrazobenzene in 1 *F* $HClO_4$ *without* added salt should be about 1.3×10^{-3} min^{-1}. The measured rate of conversion of acetylhydrazobenzene to deacylated rearrangement products is about one-half this calculated rate, 6.6×10^{-4} min^{-1}. Although the extrapolation may be faulty, the possibility of rearrangement followed by deacylation is not grossly inconsistent with the predicted magnitudes of the rearrangement in dilute acid.

Other considerations favor slow deacylation followed by rearrangement, however. (1) *N*-Acetylbenzidine is deacylated under the reaction conditions only about as rapidly as the overall conversion occurs, and it should have been readily detectable in the solution if it had been formed as an intermediate. Although a search was made for it, none was found. In contrast, hydrazobenzene rearranges very rapidly in acid solutions of the concentrations used, and could not have been detected, if formed. (2) Although the rearrangement product in the presence of concentrated electrolytes was exclusively *N*-acetylbenzidine, in dilute solution products other than benzidine were formed. Hydrazobenzene is known to afford considerable diphenyline under these conditions. (3) The rate of the benzidine rearrangement is known[11] to have a large, positive salt effect. The extrapolation of the rate of rearrangement of *N*-acetylhydrazobenzene ignored any possible salt effect, and may have given much too high a predicted rate on that account.

If indeed the reaction in dilute acid proceeds *via* a rate-limiting deacylation, perhaps the most surprising feature of the work reported here is the relative response of the rates of amide hydrolysis and rearrangement to the acidity of the solutions. It has been known for many years that the rate of acid-catalyzed hydrolysis of amides passes through a maximum with increasing acid concentration and then falls as the concentration of acid is further increased.[40] The conjugate acid species of an ordinary amide which is favored at equilibrium is protonated on oxygen



and this species is almost certainly the intermediate in the acid-catalyzed hydrolysis of amides. Yates and Stevens[41] have compared literature data on amide hydrolysis from many sources with acidity functions developed for amides,[42] and have correlated the rate–acidity dependence of acid-catalyzed amide hydrolysis with the water activity of the reaction medium. Several treatments suggest that the transition state contains three molecules of water. The rate of hydrolysis is, therefore, reduced in concentrated solutions in which the water activity is low.

Since conjugate acids other than that which participates in the hydrolysis are present in equilibrium with that species at concentrations proportional to the acidity of the medium, the postulated change in mechanistic course appears consistent with competition of two pathways involving two conjugate acid species. This formulation requires, however, that the conjugate acid species which rearranges be that which is present at equilibrium in smaller amount than that which undergoes hydrolysis. *A priori* the unacylated nitrogen would seem to be the most basic site in *N*-acetylhydrazobenzene; yet the N-protonated conjugate acid is the species we believe to be responsible for rearrangement.

In summary, the weight of the evidence seems to us to point to a pathway in dilute acid of rate-limiting

(36) R. L. Nolen, Jr., Ph.D. Thesis, University of Houston, 1970.
(37) Z. J. Allan, *Tetrahedron Lett.*, 4225 (1971).
(38) K. Yates and H. Wai, *J. Amer. Chem. Soc.*, **86**, 5408 (1964).
(39) Yates and Wai[38] have shown that the H_0 of concentrated aqueous solutions of strong acids is a remarkably consistent function of water activity.
(40) V. K. Krieble and K. A. Holst, *J. Amer. Chem. Soc.*, **60**, 2973 (1938).
(41) K. Yates and J. B. Stevens, *Can. J. Chem.*, **43**, 529 (1965).
(42) K. Yates and J. C. Riordan, *ibid.*, **43**, 2328 (1965).

deacylation followed by rapid rearrangement. Verification of this hypothesis must await detailed kinetic and product studies in regions of intermediate acidity and salt concentrations.

Registry No.—*N*-Acetylhydrazobenzene, 22293-38-5; 2,3,4,5,6,2′,3′,4′,5′,6′-decadeuterio-*N*-acetylhydrazobenzene, 36358-15-3; *N*-acetylbenzidine, 3366-61-8; benzidine, 92-87-5.

Electron Impact Induced Stereospecific Hydrocarbon Fragmentations. Mass Spectrometric Determination of the Configuration at C-5 in Steroidal Hydrocarbons[1]

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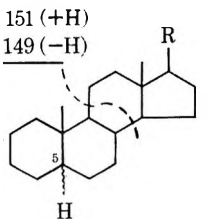
Received September 6, 1972

The mass spectra of C-17 side chain bearing steroidal hydrocarbons exhibit stereospecific fragmentation reactions which are diagnostic for the configuration at C-5. The resulting fragment ions are most probably derived from a D-seco molecular ion which is formed by the facile cleavage of the 13–17 bond in the presence of the C-17 side chain. Consequently, these stereospecific reactions are absent in the spectra of C-5 epimeric androstanes which lack the side chain. The cleavage patterns and fragmentation mechanisms of these reactions were studied with the aid of substituent and deuterium labeling techniques and metastable peak analysis. This study lead to the discovery of a site-specific hydrogen transfer from C-12 in association with the formation of the diagnostically important *m/e* 151 ion. The synthesis of the various labeled compounds is described.

Initial recognition of mass spectroscopy as an indispensable tool in structure elucidation originates from hydrocarbon chemistry. Its value in two-dimensional structure elucidation is well established, but generally in this field mass spectroscopy provides very little steric information. In a recent review of the stereoisomeric effect on the mass spectra of hydrocarbons, Meyerson and Weitkamp[2] concluded that the spectra of hydrocarbon stereoisomers, unlike those of many functional group containing species, show no clear evidence of stereospecific reactions. Similarly, careful analysis of the mass spectra of the various 1-methyl- and 2-methyldecalins by the same authors revealed only very modest differences between these stereoisomers.[3] Correlation does exist, for example, between the relative intensity of the $M^+ - CH_3$ fragment ions and the relative stability of the molecules, but these spectral variations are very sensitive to experimental conditions, and they are meaningful only in comparative studies.

Extraction of the maximum amount of structural information (including stereochemistry) from the mass spectrum of a compound is especially important in gc–mass spectroscopy, which can be used to analyze submilligram amounts of complex mixtures. The structure elucidation of the components in such mixtures depends largely on the interpretation of the fragmentation patterns. The importance of reliable interpretations is, therefore, obvious in fields such as natural product chemistry and biological research, where scarcity of the material, or complexity of the mixture, often preclude the application of other physical or chemical techniques.

During the course of earlier detailed examination of the fragmentation mechanisms of steroidal hydrocarbons,[4,5] it was noted that the C-5 epimeric preganes (III and IV) exhibit a significant difference in the relative intensities of the *m/e* 149 and 151 ions.[4] To test for the generality of this fragmentation as a diagnostic feature for the stereochemistry at the A/B ring junction, we examined the mass spectra of the three most important C-5 epimeric hydrocarbon pairs, androstanes (I and II, Figures 1 and 2), pregnanes (III and IV, Figures 3 and 4), and cholestanes (V and VI, Figures 5 and 6) under various experimental conditions. It was found that the characteristic features in the *m/e* 147–153 region of the spectrum provide unequivocal differentiation between the 5α and 5β epimers of C-17 side chain bearing hydrocarbons (see Figures 3–6). This mass range is dominated by an intense *m/e* 149 ion in the spectra of 5α steroids while two significant peaks (*m/e* 149 and 151) are characteristic for the 5β epimers. This difference, however, is not apparent in the mass spectra of 5α- and 5β-androstanes (I and II), which consist of the tetracyclic nucleus only without any side chain at C-17 (compare Figures 1 and 2).



I, 5α; R = H
II, 5β; R = H
III, 5α; R = C_2H_5
IV, 5β; R = C_2H_5
V, 5α; R = C_8H_{17}
VI, 5β; R = C_8H_{17}

The stereoisomeric effect on the fragmentations of these hydrocarbons is of considerable practical as well as theoretical interest. Its practical significance has been clearly demonstrated[6] by the recent studies of the constituents of Green River shale and California petro-

(1) Presented in part at the Pacific Conference on Chemistry and Spectroscopy, Anaheim, Calif., Oct 1971.

(2) S. Meyerson and A. W. Weitkamp, *Org. Mass Spectrom.*, **1**, 659 (1968).

(3) S. Meyerson and A. W. Weitkamp, *ibid.*, **2**, 603 (1969).

(4) L. Tökés, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968).

(5) L. Tökés and C. Djerassi, *ibid.*, **91**, 5017 (1969).

(6) (a) E. J. Gallegos, *Anal. Chem.*, **43**, 1151 (1971); (b) W. K. Seifert, E. J. Gallegos, and R. M. Teeter, *J. Amer. Chem. Soc.*, **94**, 5880 (1972).

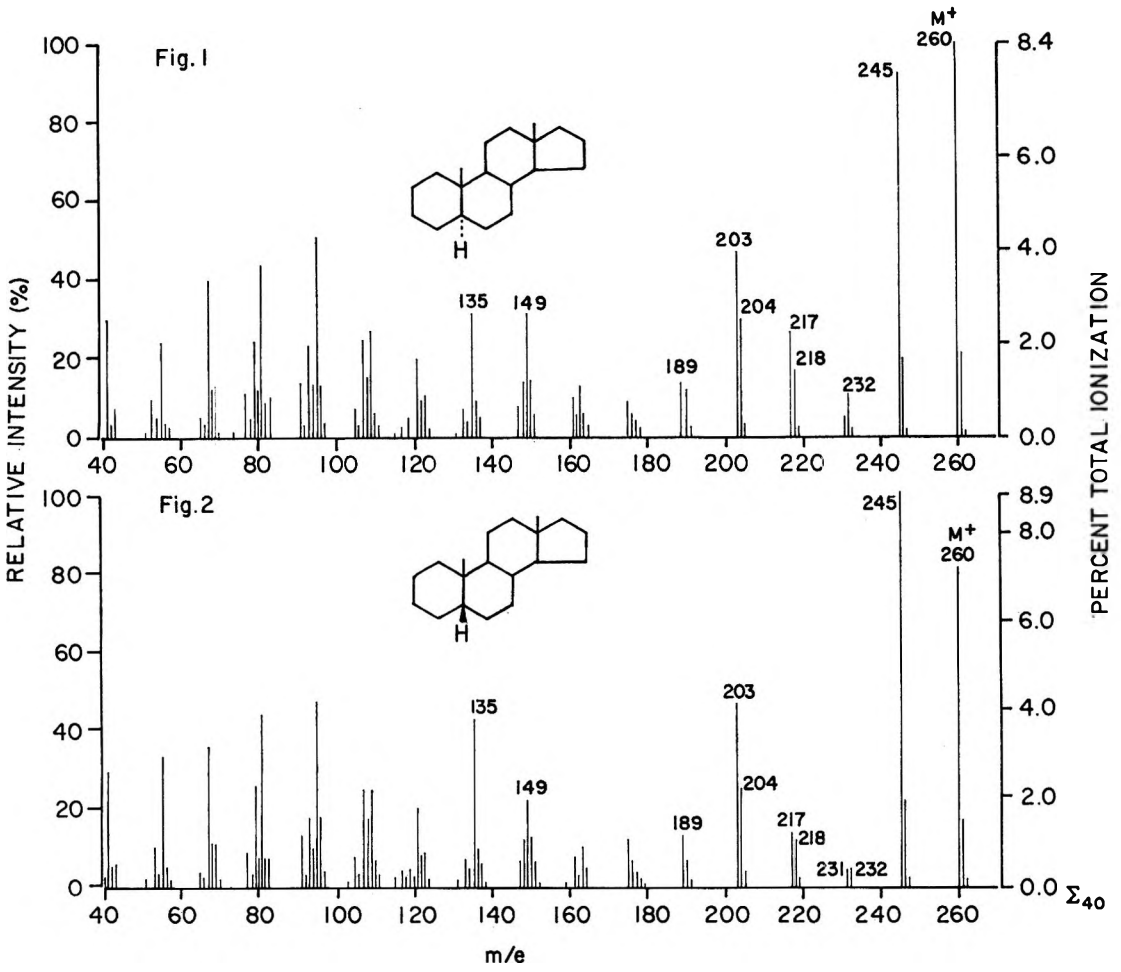


Figure 1.—Mass spectrum of 5α-androstane (I), measured at 70 eV.
Figure 2.—Mass spectrum of 5β-androstane (II), measured at 70 eV.

leum. The same characteristic differences were found in the spectra of C-5 epimeric cholestanes, cholanes, and bisnorcholanes and this observation was applied to the structure elucidation of a variety of steroidal hydrocarbon constituents. The generality of this stereoisomeric effect and its fragmentation mechanism, however, have not been established.

This mass spectrometric stereochemical information may also find an important application in the carbon-skeleton analysis[7] of steroidal compounds. This technique involves stripping of all functional groups and saturation of double and triple bonds by catalytic hydrogenation in less than a milligram of sample, followed by gas chromatographic separation and mass spectrometric analysis of the resulting hydrocarbons. If suitable catalytic systems can be developed to avoid epimerization of the asymmetric centers, the application of this technique could be extended to stereochemical studies in addition to skeletal size determination.

A priori it is reasonable to assume that the same cleavage is responsible for the formation of both *m/e* 149 and 151 ions and the mass difference is then due to different directions of the net hydrogen transfer. Precise understanding of the genesis of the *m/e* 151 ion is essential, however, to establish the criteria and limitations of the formation of this ion when its presence or absence is utilized for stereochemical assignment of unknown steroids.

The *m/e* 149 ion is a general feature of steroidal hydrocarbon spectra. Various mechanisms have been proposed[8] for the formation of this ion in the 5α series, but the true complexity of this cleavage was uncovered only as a result of extensive deuterium-labeling work.[4] In 5α-androstane this ion is generated by different cleavage patterns, yielding a complex mixture of fragments,[5] while in 5α-pregnane and 5α-cholestane about 90% of it originates from rings A and B, by the net ruptures of the 8–14 and 9–11 bonds[4] (see I–VI). This major cleavage pattern requires the loss of an extra hydrogen from the charge-retaining fragment. The labeling results, however, revealed three hydrogen transfers in association with this cleavage in relatively high degree of site specificity. Two of them (5α H and 8β H) originate from the charge-retaining side and one (14α H) from the expelled neutral fragment.[4] The lower and upper range of the transfer values, depending on the extent of deuterium loss or retention due to fragment ions (~10%) which do not originate from rings A and B, are summarized on VII.[9] The interpretation of these results is further complicated by the possible

(7) This technique has been recently reviewed by M. Beroza, *Accounts Chem. Res.*, **3**, 33 (1970).

(8) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, p 345; H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, Holden-Day, San Francisco, Calif., 1963, p 96.

(9) It should be noted that this cleavage pattern cannot be established unequivocally on the basis of deuterium-labeling evidence alone. The loss of a single deuterium from a tertiary position can be interpreted in terms of either deuterium transfer or as expulsion of that CD unit. The complex results indicated on VII could also be interpreted as shown below, although

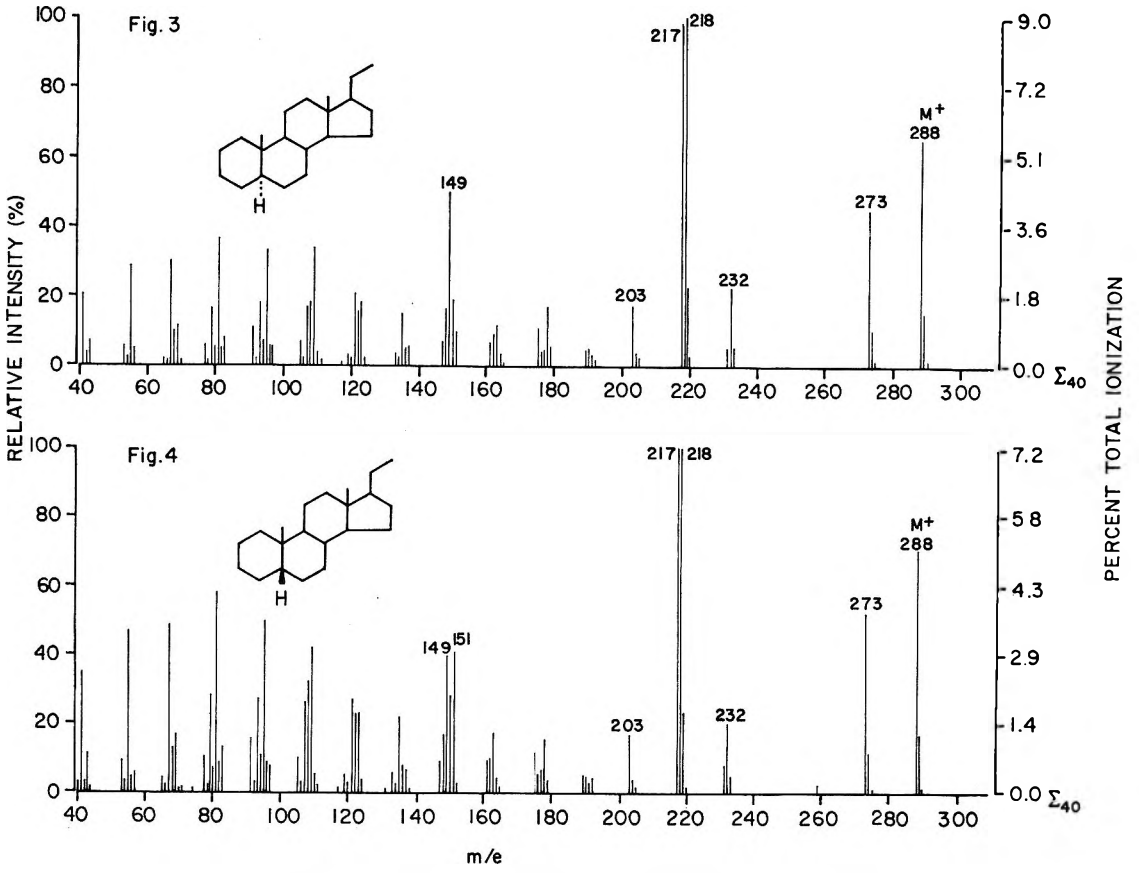
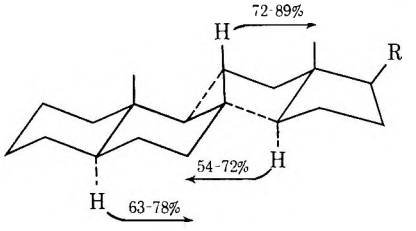


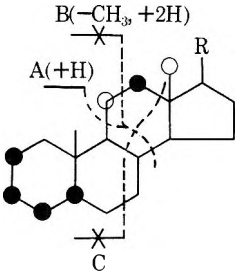
Figure 3.—Mass spectrum of 5α-pregnane (III), measured at 70 eV.
Figure 4.—Mass spectrum of 5β-pregnane (IV), measured at 70 eV.



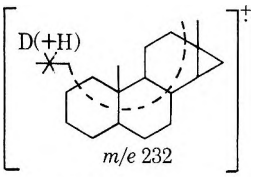
VII (*m/e* 149)

participation of different fragmentation reactions which can lead to similar *m/e* 149 fragment ions consisting of rings A and B, but are derived from parent ions other than the molecular ion. Refocused scanning for metastable peaks indicated the participation of six precursor ions in forming the *m/e* 149 ion,[10] but the extent of their participation is unknown.

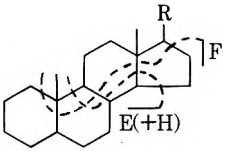
Examination of the mass spectra of some ring A deuterated 5β-cholestanes, which we had available from other studies, indicated that the lower intensity *m/e* 149 peak is due to more than one major fragment ions which originate from different parts of the molecule. The diagnostically important *m/e* 151 ion, on the other hand, appeared to be quite homogeneous, retaining carbon atoms 2, 3, and 4. Since this information and the loss of the side chain are compatible with several cracking patterns (see A–F in VIII–X) we decided to prepare additional deuterium and substituent labeled pregnanes and cholestanes to shed light on the genesis of this ion. The syntheses of these labeled compounds, the labeling results, and their interpretations are discussed below.



VIII (*m/e* 151)

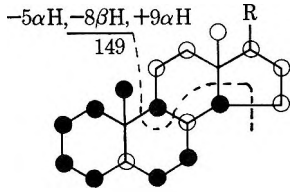


IX (*m/e* 151)



X (*m/e* 151)

this alternative is energetically much less likely. Rigorous differentiation between these two alternative would require carbon isotope labeling.



(10) C. C. Fenselau and F. P. Abramson, *Org. Mass Spectrom.*, **2**, 915 (1969).

Syntheses of Labeled Compounds[11]

The preparation of *2,2,3ξ,4,4-d*$_5$ and *2,2,3,3,4,4-d*$_6$ labeled 5β-cholestanes (XIV and XV) were carried out

(11) For a recent survey of the various deuterium-labeling techniques in the steroid field, see L. Tökés and L. Throop in "Organic Reactions in Steroid Chemistry," Vol. 1, J. Fried and J. A. Edwards, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1972, Chapter 4.

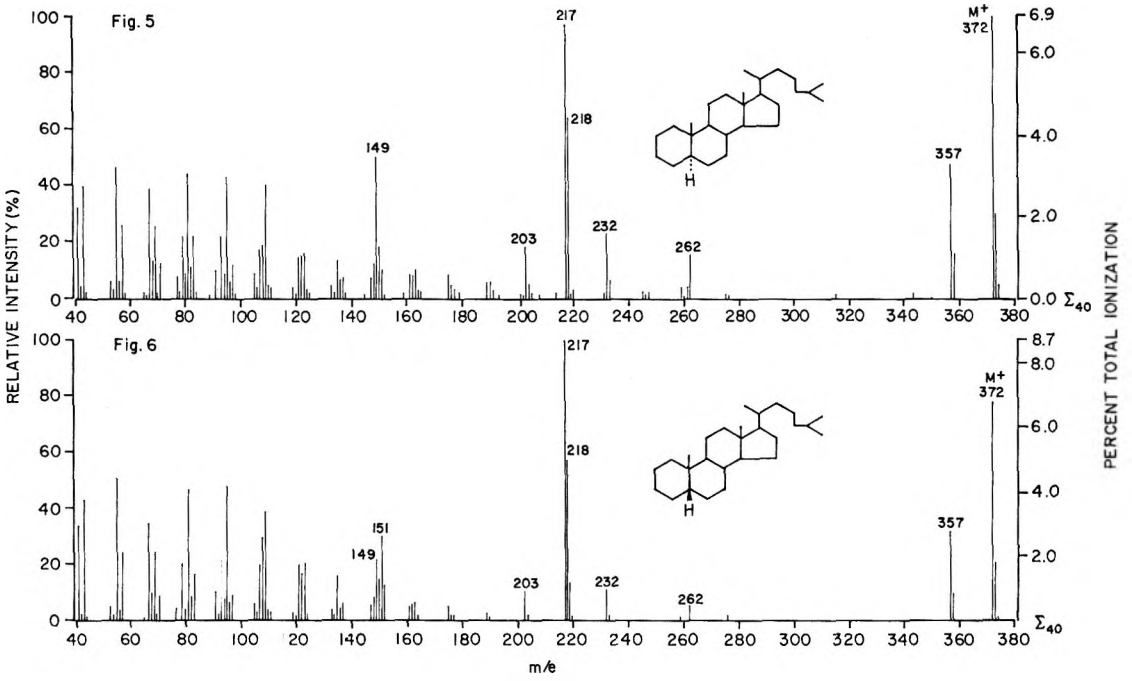
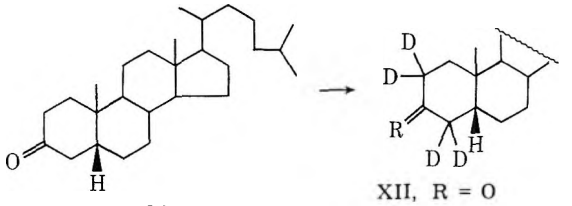
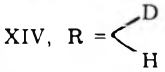


Figure 5.—Mass spectrum of 5α-cholestane (V), measured at 70 eV.
Figure 6.—Mass spectrum of 5β-cholestane (VI), measured at 70 eV.

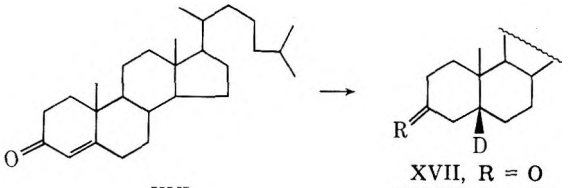
in connection with other studies, using 5β-cholestan-3-one-*2,2,4,4*-d_4 (XII) as a common intermediate in both syntheses. The pentadeuterio 5β-cholestane (XIV) was prepared by lithium aluminum deuteride treatment of the tosylhydrazone derivative (XIII) of XII followed by quenching of the reaction mixture with ethyl acetate and water. This reaction gave the expected[12] 5β-cholestane-*2,2,3ξ,4,4*-d_5 (XIV) in 73% isotopic purity. In the 5α series this reaction is known to give mainly the 3α-deuterio derivative (70%).[12] We made no attempt, however, to establish the configuration of the deuterium at C-3. Electrochemical reduction[13] of the tetradeuterio ketone XII in dioxane and deuteriosulfuric acid gave 5β-cholestane-*2,2,3,3,4,4*-d_6 (XV) in 85% isotopic purity.



XI

XII, R = O
XIII, R = NNHTs
XIV, R = 
XV, R = D_2

Deuteration of the 5β position was carried out to check if this site is involved in hydrogen transfer similar to that observed in the formation of the *m/e* 149 ion in the 5α series.[4] Catalytic deuteration of cholest-4-en-3-one followed by alkaline back-exchange of the deuterium from C-4, gave a mixture of 5α-d_1 and 5β-d_1 cholestan-3-ones which were separated by thin layer chromatography. Modified Huang-Minlon reduction of the pure 5β-d_1-cholestan-3-one (XVII) gave 5β-d_1-cholestane (XVIII) in 81% isotopic purity.



XVI

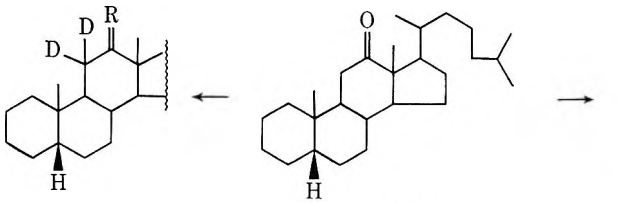
XVII, R = O
XVIII, R = H_2

The preparations of both *11,11*-d_2 and *12,12*-d_2 labeled 5β-cholestanes (XXII and XXIV) were carried out starting with 5β-cholestan-12-one[14] (XIX). Base-catalyzed deuterium exchange of XIX gave the *11,11*-d_2 ketone (XX) which was then converted into its tosylhydrazone derivative (XXI). Treatment of the tosylhydrazone with sodium borohydride, first in boiling methanol, then in boiling dioxane to speed up the reaction, consumed all the starting material and gave a mixture of less polar products. Thin layer chromatographies on silica gel, then on silver nitrate impregnated silica gel, gave pure 5β-cholestane-*11,11*-d_2 (XXII) in 21% yield, which was free of any olefin contaminants and exhibited 89% isotopic purity.

Deuteration of the C-12 position was carried out by lithium aluminum deuteride treatment of the tosylhydrazone derivative (XXIII) of XIX, followed by quenching of the reaction mixture with deuterium oxide. Owing to the very limited supply of the starting ketone (3 mg) and the low yield obtained from the reduction of this sterically hindered tosylhydrazone, the resulting 5β-cholestane-*12,12*-d_2 (XXIV) could be characterized only by thin layer chromatography and gc–mass spectrometric analysis.[15]

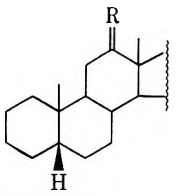
Availability of 18-methylpregn-4-ene-3,20-dione[16] (XXV) provided an attractive short route to a C-18 labeled derivative which is a key compound to test for

(12) M. Fischer, Z. Pelah, D. H. Williams, and C. Djerassi, *Chem. Ber.*, **98**, 3236 (1965).
(13) L. Throop and L. Tökés, *J. Amer. Chem. Soc.*, **89**, 4789 (1967).
(14) J. Gawronski and M. Kielczewski, *Rocz. Chem.*, **44**, 1175 (1970).
(15) It has been reported in ref 4 that under identical conditions lithium aluminum hydride treatment of *11,11*-d_2-5α-pregnane 12-tosylhydrazone yields *11,11*-d_2-5α-pregnane as the saturated hydrocarbon product.
(16) G. V. Baddeley, H. Carpio, and J. A. Edwards, *J. Org. Chem.*, **31**, 1026 (1966).



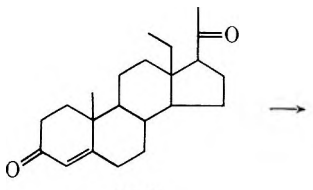
XX, R = O
XXI, R = NNHTs
XXII, R = H_2

XIX

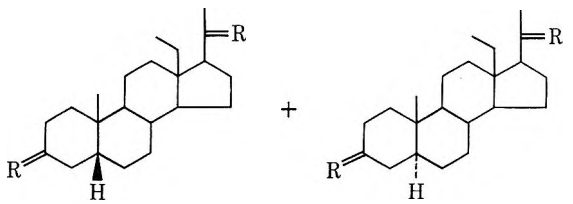


XXIII, R = NNHTs
XXIV, R = D_2

the possible participation of cleavage pattern D (see IX) in the formation of the *m/e* 151 ion. Catalytic hydrogenation of XXV gave a readily separable mixture of C-5 epimeric diones (XXVI and XXVII). As expected from the corresponding pregnane-3,20-diones, these epimers exhibited almost identical optical rotatory dispersion and circular dichroism curves as well as 19-H chemical shifts in the nmr in deuteriochloroform solution The very similar optical properties of the 3,20-diones, in spite of the opposite signs of the Cotton effects of C-5 epimeric 3 ketones, is due to the overwhelmingly strong positive Cotton effect of the 20-ketone function.[17] The stereochemical assignment of these epimers was based on the amplitude of the Cotton effects (the lower value being due to the negative contribution of the 3 ketone of the 5β skeleton) and on the 10-Hz chemical-shift difference of the 19-H resonances in hexadeuteriobenzene solution. The 5β configuration was assigned to the major product, which exhibited the less shielded 19-H resonance.[18]



XXV



XXVI, R = O
XXVIII, R = H_2

XXVII, R = O
XXIX, R = H_2

Modified Huang-Minlon reduction of these diones gave the desired 5β and 5α 18-methylpregnanes (XXVIII and XXIX) whose 19-H resonances were in good agreement with those of their pregnane analogs.[19]

(17) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, N. Y., 1960, p 55.

(18) The chemical shifts of the 19-H resonances of 5α- and 5β-cholestan-3-ones in hexadeuteriobenzene solution are 0.66 and 0.75 ppm, respectively.

(19) For the 19-H resonances of 5α- and 5β-pregnanes, see N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, Chapter 2.

This confirmed the stereochemical assignments of the diones. The mass spectral characteristics in the *m/e* 147–152 region were also very similar in the spectra of the labeled and unlabeled pregnanes in both 5α and 5β series, which indicates that the methyl group was indeed a legitimate substituent label at C-18.

The 18-methyl-5β-pregnane (XXVIII) did not crystallize owing to the presence of a very small isomeric contaminant. This isomer could be separated only by gas chromatography and exhibited virtually identical nmr and mass spectral characteristics with those of the major product XXVIII. This contaminant is apparently the 17α isomer of 18-methyl-5β-pregnane arising from C-17 epimerization prior to the hydrazone formation of the 20 ketone.[20] The equal relative intensities of the *m/e* 149 and 151 fragment ions of both 17α and 17β 18-methyl-5β-pregnanes indicate that the genesis of the diagnostically important *m/e* 151 ion is independent of the stereochemistry at C-17.

Discussion of Mass Spectral Results

The 70-eV spectra of 5α and 5β androstanes, pregnanes, and cholestanes are reproduced in Figures 1–6. The shift values of the *m/e* 149–152 ions in the spectra of the labeled compounds are listed in Table I and summarized on structure VIII (full dots, label retained; shaded dot, one of the two deuteriums retained; circle, label lost). The most noticeable difference between the two androstane spectra (Figures 1 and 2) is the higher intensity of the $M^+ - CH_3$ (*m/e* 245) and *m/e* 135 ions in the spectrum of 5β-androstane as compared to the molecular ion. These relative intensity differences, however, are sensitive to variations of the ion source temperature and other experimental parameters, and can be used to identify the androstane epimers only in a comparative manner.

It has been established that in 5α-androstane (I) the expelled methyl radicals originate exclusively from the C-18 and C-19 angular methyl groups in 3:2 ratio, respectively.[5] The more intense $M^+ - CH_3$ fragmentation in 5β-androstane (II) may be due to enhanced loss of the C-19 methyl group to relieve the increased strain of the A/B cis ring junction. Confirmation of this hypothesis will await deuterium labeling of this position.

With C-17 side chain bearing hydrocarbons (Figures 3–6) the pronounced difference in the relative intensities of the *m/e* 149 and 151 peaks provides a much more general and reliable differentiation between the C-5 epimers. In the 5α series this mass range is dominated by an intense peak at *m/e* 149, whereas two major peaks, at *m/e* 149 (of somewhat reduced intensity) and 151, are characteristic for the 5β hydrocarbons. The same difference prevails also at low ionization potentials (20 and 15 eV).[21] The formation of the diagnostic *m/e* 151 fragment ion from 5β steroids is unaffected by the size of the side chain, by the configuration at C-17 (as indicated by the spectrum of 18-

(20) Gc–mass spectral analysis of the crude reduction mixture revealed the presence of some 18-methyl-5β-pregnan-20-one together with smaller quantities of its 17α epimer. The structural assignments of these ketones were based on the known [L. Tökés, R. T. LaLonde, and C. Djerassi, *J. Org. Chem.*, **32**, 1020 (1967)] fragmentation patterns of both 17β and 17α epimeric pregnan-20-ones.

(21) For the 20-eV spectra of C-5 epimeric cholestanes, ergostanes, and stigmastanes, see ref 6a.

TABLE I

SHIFTS[a] OF MASS SPECTRAL PEAKS OF THE LABELED ANALOGS OF 5β-STEROIDAL HYDROCARBONS

5β-Cholestanes	Isotopic purity, %	m/e $C_{11}H_{17}^+$	$C_{11}H_{18}^+$	$C_{11}H_{19}^+$	$C_{11}H_{20}^+$
d_0 (VI)		149	150	151	152
2,2,3ξ,4,4-d_5 (XIV)	d_4, 24 d_5, 73 d_6, 3	149 (36%) 154 (64%)	150 (23%) 155 (77%)	151 (6%) 156 (94%)	152 (~90%)[b]
2,2,3,3,4,4-d_6 (XV)	d_4, 2 d_5, 13 d_6, 85	149 (32%) 155 (~60%)	150 (25%) 156 (75%)	151 (10%) 157 (90%)	152 (~90%)
5β-d_1 (XVIII)	d_0, 16 d_1, 81 d_2, 3	149 (52%) 150 (48%)	150 (36%) 151 (64%)	151 (7%) 152 (93%)	152 (92%) 153 (8%)
11,11-d_2 (XXII)	d_0, 2 d_1, 9 d_2, 89	149 (85%) 150 (15%)	150	151	152
12,12-d_2 (XXIV)	d_0, 6 d_1, 35 d_2, 57 d_3, 2	149	150	151 (52%) 152 (48%)	152
18-methyl[c] (XXVIII)		149[d]	150	151 165 (<5%)	

[a] The shift values are corrected for isotopic impurity as well as for ^{13}C contributions and are reliable to ±5%. [b] Owing to poor isotopic purity, the reliability of this shift is ±10%. [c] This sample is 18-methyl-5β-pregnane. [d] This ion is present in the expected relative intensity, but it cannot be determined with certainty how much of the m/e 135 and 149 ions is shifted by 14 mass units.

methyl-5β,17α-pregnane; see previous section), and by the presence of a methyl substituent at C-18 (see XXVIII in Table I). The ensuing discussion of the genesis of this fragment ion allows further predictions about the generality (or limitations) of its diagnostic value.

Examination of the spectra of the various model compounds and initially available ring A labeled 5β-cholestanes (XIV and XV) revealed the loss of the side chain and retention of carbon atoms 2, 3, and 4 in the m/e 151 ion and in about two-thirds of the m/e 149 ions. These ions, therefore, could be formed by a ring C cleavage which is analogous to the one leading to the majority of the m/e 149 ions in the 5α series[4] (see I–VI and cleavage A in VIII). There are other cleavage patterns, however, which can lead to the m/e 151 ions and are also compatible with these results (see patterns B–F on VIII–X), but most of them could be eliminated with the aid of subsequent labeling results (see Table I).

Complete loss of the two deuteriums from C-11 rules out the participation of the mechanistically quite reasonable B and C cleavages (see VIII). Pattern D, which would involve further fragmentation of the m/e 232 ion (see IX), is excluded by the loss of the C-18 methyl label. The remaining two fragmentation patterns E and F (see X) are compatible with all the currently available labeling results. They can be deemed unlikely, however, since both of them (especially E) would involve energetically very unfavorable fragmentation mechanisms. Deuterium labeling at positions 15, 16, or 19 could establish unequivocally the possible participation of path F, but carbon isotope labeling would be needed for the rigorous exclusion of pattern E (see footnote 9).

Retention of one of the two deuteriums from C-12 in the m/e 151 ion (see XXIV in Table I) provides further mechanistic support for cleavage pattern A. For a fragmentation mechanism to be consistent with our current knowledge of this ion, the requirement for the presence of a side chain at C-17 (independent of its configuration) and for the β configuration at C-5, as well as the labeling results shown in Table I, have to be taken into account. Such mechanisms are outlined in Scheme I.

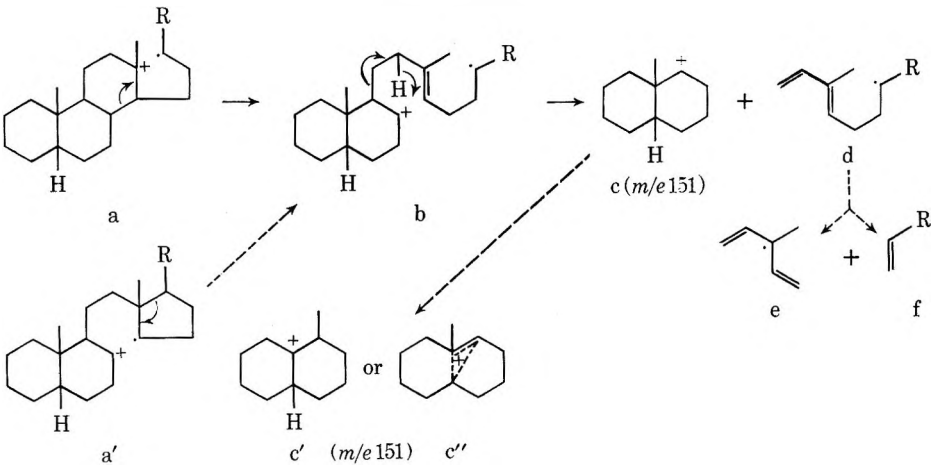
Rupture of the 13–17 bond in forming molecular ion a is the most important primary cleavage of C-17 side chain bearing steroidal hydrocarbons.[4,22] This molecular ion is known to undergo ring D cleavages and various hydrogen transfers, leading to most of the diagnostically important fragment ions in the high-mass range of the spectrum.[4] Alternatively, opening of ring C, *via* cleavage of the activated 8–14 bond, yields a homoallylically stabilized ion radical (b). The rupture of the 13–17 bond in the presence of a C-17 side chain in molecular ion a′ may be another possible fragmentation leading to ion b. Transfer of one of the allylic hydrogens from C-12 to C-8 in ion b triggers the fission of the 9–11 bond, forming the m/e 151 ion (c) and a diene radical (d). Both c and d may undergo further reactions to gain stabilization. Methyl migration[23] in the m/e 151 ion, for example, leads to a tertiary carbonium ion (c′) or cleavage of the activated 5–10 bond can yield a homoallylically stabilized ion (c″). Radical d can undergo fission to give a conjugated diene radical e and an olefin f.

These mechanisms are fully consistent with the labeling results shown in Table I. Molecular ions a or a′ account for the requirement for the presence of a side chain at C-17 (independent of its configuration), since the 13–17 bond cleavage is not very significant in 5α and 5β androstanes (I and II).[5,22] The C-5 stereochemistry may play an important role at the fragmentation of molecular ion b. Examination of the Dreiding models of the 5α and 5β epimers of ion b indicates that the C-17 radical site can reach easily to the 5α tertiary hydrogen, but it can not approach the 5β hydrogen to within rea-

(22) G. Eadon, S. Popov, and C. Djerassi, *J. Amer. Chem. Soc.*, **94**, 1282 (1972).

(23) For a recent review on electron impact induced rearrangements see R. G. Cooks, *Org. Mass Spectrom.*, **2**, 481 (1969).

SCHEME I

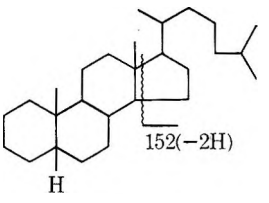


sonable bonding distance without encountering serious overlaps between various parts of the molecule. It is possible, therefore, that in the 5α series the transfer of the 5α hydrogen leads ultimately to the m/e 149 ion (70% deuterium loss has been found from this site[4]), while at this stage in the 5β series an alternate fragmentation path (b → c) is preferred which yields the m/e 151 ion. This is in good agreement with the reduced intensity of the m/e 149 ion in the 5β series, of which no more than 65–70% can originate from cleavage pattern A (see Table I).

Refocused measurement of metastable peaks[24] in the spectrum of 5β-cholestane (VI) confirmed that at least part of the m/e 149 and 151 ions is derived directly from the molecular ion. These measurements revealed a total of 14 possible parent ions for the m/e 149 ion and 10 for the m/e 151 ion, but these metastable peaks have no direct relevance to the relative significance of the participating cleavages. These results are in agreement with earlier findings[10] that the fragment ion which shows more complex deuterium-labeling results (m/e 149 in this case) is the one which exhibits the more numerous modes of formation.

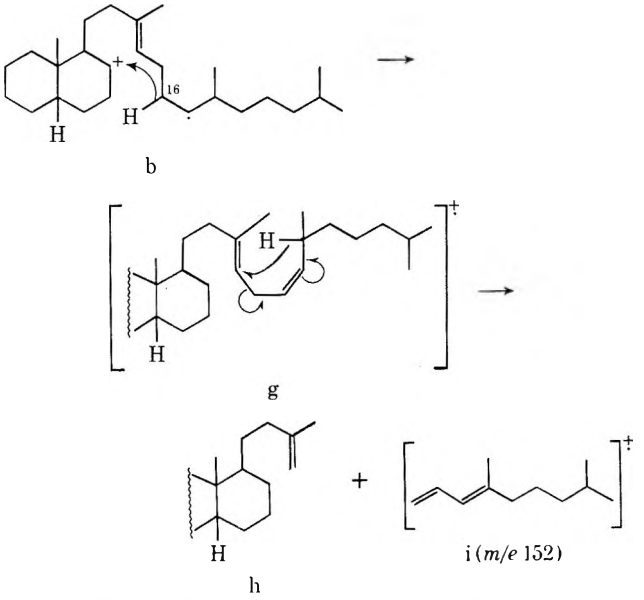
The m/e 152 ion in the spectrum of 5β-cholestane (Figure 6) is also a stereospecific fragmentation product. This ion is absent in Figures 1–5 and its presence only in the spectrum of 5β-cholestane can be explained by the retention of the side chain in it. This is further substantiated by the observed small peaks at m/e 166 and 180 in the spectra of methyl and ethyl homologs of 5β-cholestane, 5β-ergostane, and 5β-stigmastane, respectively, while these peaks are absent in the spectra of the corresponding 5α epimers.[25] The m/e 152 ion lost all ring A and ring C labels (see Table I). It is apparently due to a ring D fragmentation in which the charge is retained on the side chain bearing portion which loses two hydrogens to the neutral side (see XXX).

The stereochemical dependence of this fragmentation may be due to the same reason as proposed for the genesis of the m/e 151 ion (*vide supra*), namely,



XXX

hindered hydrogen transfer from the 5β position to the C-17 radical site in ion b. In discussing the various fragmentations of ion b it was shown above how transfer of the C-12 hydrogen leads to the m/e 151 fragment ion. Alternatively, hydrogen transfer in ion b may occur from C-16 just as well, since this position is also activated by the isolated radical site at C-17. This leads to an ionized diene g which can undergo a second hydrogen transfer from the tertiary and allylic C-20 position to C-13 in a six-membered transition state. This second hydrogen transfer then triggers the fission of the 14–15 bond to yield a neutral olefin and the ionized conjugated diene i (m/e 152). Confirmation of this fragmentation mechanism, however, will have to await further deuterium-labeling evidence.



Cracking pattern A, with or without a reciprocal hydrogen transfer, appears to be responsible for about 75% of the low-intensity m/e 150 ion. The remaining

(24) M. Barber and R. M. Elliot, ASTM E-14 Committee, 12th Annual Conference on Mass Spectrometry and Allied Topics, Montreal, Canada, 1964; J. H. Futrell, K. R. Ryan, and L. W. Sieck, *J. Chem. Phys.*, **43**, 1832 (1965); T. W. Shannon, T. E. Mead, C. G. Warner, and F. W. McLafferty, *Anal. Chem.*, **39**, 1748 (1967).

(25) Personal communications with Dr. E. J. Gallegos, Chevron Research Co., Richmond, Calif.

25% originates from other parts of the molecule. Owing to its low intensity this ion was not investigated in further detail.

In conclusion, C-17 side chain bearing steroidal hydrocarbons exhibit stereospecific fragmentation reactions which are diagnostic for the configuration at C-5 when the other asymmetric centers are in their "normal" (8β,9α,10β,13β) configuration. It has not been established as yet whether changing of one or more of the other asymmetric centers has any effect on these stereospecific fragmentations. It is known,[22] however, that in the spectrum of *D*-nor-5α-pregnane the diagnostic mass range is dominated by an intense peak at *m/e* 148 which may interfere with the interpretations. The mechanistic details uncovered in this study, including the site-specific hydrogen transfer from C-12 in the formation of the *m/e* 151 ion, are significant contributions to the understanding of the electron impact induced behavior of the steroidal hydrocarbon skeleton.

Diagnostically important stereospecific fragmentations, in the sense of the "presence or absence" of fragment ions rather than "relative intensity differences," usually involve bond forming as well as breaking steps. The stereospecificity of these fragmentations is primarily due to the specific requirements in the spatial relationship between the bond-forming species. Such a stereospecific fragmentation can be of practical diagnostic value only if it is the sole or at least the main contributor in the genesis of the fragment ion in consideration. This is the criterion which most hydrocarbon fragment ions fail to meet. It is not surprising, therefore, that polycyclic hydrocarbons, which are more likely to retain several asymmetric centers after the preferential cleavage of a strained bond, are more prone to exhibit stereospecific fragmentations than the bicyclic compounds used in earlier studies. The C-17 side chain on a tetracyclic steroidal skeleton behaves like a fragmentation-triggering "functional group" by promoting the rupture of the 13–17 bond. This dominant primary cleavage assures the formation of several reasonably homogeneous fragment ions which can facilitate the observation of stereospecific fragmentation reactions if the spatial significance of the isomeric center (C-5 in this case) is not destroyed by the primary cleavage.

Experimental Section[26]

5β-Cholestan-3-one-*2,2,4,4-d*$_4$ (XII).—A solution of 5β-cholestan-3-one (XI, 25 mg) in methanol-*O-d* (5 ml) was saturated with 10% sodium deuterioxide in deuterium oxide and then heated under reflux for 36 hr. After cooling, ether was added and the organic phase was quickly washed with ice-cold water. Drying (Na_2SO_4) and evaporation of the ether yielded 23 mg of 5β-cholestan-3-one-*2,2,4,4-d*$_4$ (XII, 91%) which exhibited 1% d_2, 12% d_3, and 87% d_4 isotope composition by mass spectrometric analysis.

5β-Cholestane-*2,2,3ξ,4,4-d*$_5$ (XIV).—The labeled ketone (XII, 10 mg) was dissolved in methanol-*O-d* (15 ml), *p*-toluenesulfonyl hydrazine (20 mg) and 1 drop of deuteriosulfuric acid were added, and the solution was heated under reflux for 4 hr. A few drops of water was added and the crystalline precipitate which formed upon refrigeration was collected, washed with aqueous methanol (1:1), then dried under vacuum at 50°. The resulting crystalline d_4-tosylhydrazone (XIII, 13 mg, 89%) was dissolved in dry monoglyme (20 ml), lithium aluminum deuteride (40 mg) was added, and the mixture was heated under reflux for 24 hr. The excess deuteride was decomposed by the addition of a few drops of ethyl acetate and water, then the heating was resumed for 10 min. Dilute hydrochloric acid was added and the resulting solution was diluted with water. Ether extraction, washing of the ether phase with dilute sodium bicarbonate solution and water, drying (Na_2SO_4), and evaporation of the solvent gave a glassy residue. Chromatography of the residue on silver nitrate impregnated silica gel plate in hexane and elution of the fraction which exhibited the same R_f value as authentic 5β-cholestane yielded 2.9 mg (34%) pure 5β-cholestane-*2,2,3ξ,4,4-d*$_5$ (XIV), mp 69–70° (MeOH). For isotope composition see Table I.

5β-Cholestane-*2,2,3,3,4,4-d*$_6$ (XV).—A solution of 5β-cholestan-3-one-*2,2,4,4-d*$_4$ (XII, 10 mg) in dry dioxane (5 ml) and 10% deuteriosulfuric acid in deuterium oxide (3 ml) was electrolyzed for 4 hr in the presence of a lead cathode at 200 mA current.[27] The reaction mixture was diluted with water and extracted with ether. Washing with dilute sodium bicarbonate solution and water, drying (Na_2SO_4), and evaporation of the ether gave a glassy residue. Chromatography on silver nitrate impregnated silica gel plate in hexane and elution of the hydrocarbon fraction gave 3 mg (31%) of pure 5β-cholestane-*2,2,3,3,4,4-d*$_6$ (XV), mp 68–69.5° (MeOH). For isotope composition see Table I.

5β-*d*$_1$-Cholestane (XVIII).—A solution of cholest-4-en-3-one (XVI, 100 mg) in 50 ml of methanol was deuterated at room temperature and atmospheric pressure in the presence of 10% palladium on charcoal catalyst. The deuterium uptake ceased in about 10 min. The catalyst was removed by filtration and the residue after the evaporation of the solvent was chromatographed on silica gel plates in 15% ethyl acetate in hexane. The more polar fraction, which had the same R_f value as authentic 5β-cholestan-3-one, gave 55 mg of the 4ξ,5β-d_2 product, which was dissolved in methanol, and the solution was saturated with 1 *N* sodium hydroxide solution. After heating under reflux for 5 hr, water was added and the mixture was extracted with ether. Washing with water, drying (Na_2SO_4), and evaporation of the ether gave 55 mg (54%) of 5β-d_1-cholestan-3-one (XVII), isotope composition 15% d_0, 79% d_1, and 6% d_2.

A solution of the 5β-d_1 ketone (XVII, 15 mg) in 2 ml of ethylene glycol, 1 ml of 1-butanol, and 0.5 ml of hydrazine hydrate was heated under reflux for 1 hr. After cooling to about 100°, potassium hydroxide (150 mg) was added and the reaction mixture was heated without a condenser until the temperature reached about 210°. The heating was then continued under an air-cooled condenser for 4 hr at 210–220°. After cooling, ether and water were added, the ether phase was washed and dried (Na_2SO_4), and the solvent was evaporated. The residue was filtered through a small silica gel column in hexane, yielding 12 mg (83%) of pure 5β-d_1-cholestane (XVIII), mp 69–70° (MeOH). For isotope composition see Table I.

5β-Cholestane-*11,11-d*$_2$ (XXII).—A solution of 5β-cholestan-12-one[14] (XIX, 7 mg) in methanol-*O-d* (5 ml) was saturated with 10% sodium deuterioxide in deuterium oxide and then heated under reflux for 2 days. After cooling ether was added and the organic phase was washed rapidly with ice-cold water. Drying (Na_2SO_4), evaporation of the ether, and thin layer chromatography of the residue gave crystalline 5β-cholestan-12-one-*11,11-d*$_2$ (XX, 5 mg, 72%) which exhibited 7% d_1 and 93% d_2 isotope composition by mass spectrometric analysis.

The labeled ketone (XX, 4.8 mg) was dissolved in methanol-*O-d* (4 ml), *p*-toluenesulfonylhydrazine (10 mg) and 1 drop of deuteriosulfuric acid were added, and the solution was heated under reflux for 4 hr. A few drops of water was added and the crystalline precipitate which formed upon refrigeration was collected, washed with aqueous methanol (1:1), then dried under vacuum at 50°. The resulting crystalline *11,11-d*$_2$-5β-cholestan-12-one tosylhydrazone (XXI, 5.8 mg), 84%, which contained only traces of starting material according to spot

(26) The mass spectra were measured on Atlas CH-4 (equipped with EFO-4B ion source) and CH-7 mass spectrometers at 70 eV ionizing potential unless otherwise stated. The refocused measurement of metastable peaks was carried out on an AEI-MS-9 mass spectrometer by Mr. R. Ross and Dr. D. M. Smith of Stanford University. The nmr spectra were measured on a Varian HA-100 spectrometer using tetramethylsilane as internal reference. The ir spectra were determined on a Perkin-Elmer Model 237 Infracord spectrometer, the ORD spectra on a JASCO-ORD/UV-5 spectrometer, and the CD curves were measured by Mrs. Ruth Records at Stanford University on a JASCO-ORD/CD spectrometer. The elemental analyses were determined by Miss L. Jaime on a Hewlett-Packard Model 185 CHN Analyzer.

(27) For detailed description of the electrolysis cell and reaction conditions see ref 11, pp 166–169.

chromatography, was heated with methanol (5 ml) for a few minutes and then 10 mg of sodium borohydride was added. After heating under reflux for 1 hr, an additional 10 mg of sodium borohydride was added and the heating was continued for 1 hr. Since a thin layer chromatographic spot test still showed the presence of some starting material, the methanol was distilled off under reduced pressure and the residue was treated again with fresh sodium borohydride (10 mg) in boiling dioxane (5 ml). After 5 hr of heating all starting material was consumed. Ether was added and the organic phase was washed with plenty of water. Drying (Na_2SO_4) and evaporation of the solvents gave an oily residue (5.2 mg) which was chromatographed on a silica gel plate in hexane. The fraction which showed identical R_f value with authentic 5β-cholestane, yielded 1.5 mg of semicrystalline product which according to gc–mass spectrometric analysis was contaminated with an olefin. Chromatography of this product on a silver nitrate impregnated silica gel plate in hexane gave pure 5β-cholestane-*11,11-d*$_2$ (XXII, 0.8 mg, 21%), mp 68–70° (MeOH), isotopic purity 89% (see Table I).

5β-Cholestane-*12,12-d*$_2$ (XXIV).—The tosylation of 5β-cholestan-12-one[14] (XIX, 3 mg) was carried out the same way as described above for the preparation of the *11,11-d*$_2$ tosylate (XXI) but using undeuterated methanol and sulfuric acid. The resulting crystalline tosylhydrazone (XXIII, 4.3 mg, 100%) was dissolved in dry dioxane (2.5 ml) and was heated under reflux with lithium aluminum deuteride (20 mg) for 20 hr. The excess deuteride was decomposed by the careful addition of a few drops of deuterium oxide and the heating was resumed for 10 min. Dilute hydrochloric acid and water were added. Ether extraction, washing of the ether phase with dilute sodium bicarbonate solution and water, drying (Na_2SO_4), and evaporation of the solvent gave a glassy residue (2.5 mg). Chromatography on silver nitrate impregnated silica gel plate in hexane and elution of the fraction which exhibited the same R_f value as authentic 5β-cholestane, gave pure 5β-cholestane-*12,12-d*$_2$ (XXIV, 0.5 mg, 17%); for isotope composition see Table I. The gc retention time and the mass spectrum of this sample were identical with those of authentic 5β-cholestane (VI) with the exception of the mass shifts of the deuterium-containing ions in its mass spectrum.

Hydrogenation of 18-Methylpregn-4-ene-3,20-dione (XXV).—18-Methylpregn-4-ene-3,20-dione[15] (XXV, 140 mg) in ethyl acetate (30 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium-on-charcoal catalyst. When the hydrogen uptake ceased the catalyst was removed by filtration and the residue after evaporation of the solvent was chromatographed on silica gel plates in ether–hexane (3:7, the plates were developed twice). Elution of the less polar fraction gave 18-methyl-5α-pregnane-3,20-dione (XXVII, 43 mg, 31%): mp 183–183.5° (aqueous MeOH); ir (KBr) 1695 and 1710 cm^{-1}; $[\alpha]_D$ +123.3 ± 4.2° (*c* 1.1, $CHCl_3$); ORD (*c* 0.12, MeOH) $[\alpha]_{308}$ 3438 (pk), $[\alpha]_{267}$ −4144 (tr); CD (*c* 0.044, MeOH) $[\theta]_{288}$ +18.562 (max); nmr ($CDCl_3$) 0.99 (19-H), 2.17 ppm (21-H); nmr (C_6D_6) 0.53 (19-H), 1.885 ppm (21-H); mass spectrum *m/e* 330 (M^+). *Anal.* Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.01; H, 10.43.

The more polar fraction consisted of 18-methyl-5β-pregnane-3,20-dione (XXVI, 76 mg, 54%): mp 112.5–114° (aqueous MeOH); ir (KBr) 1705 cm^{-1}; $[\alpha]_D$ 123.2 ± 2.7° (*c* 1.37, $CHCl_3$); ORD (*c* 0.10, MeOH) $[\alpha]_{309}$ 2937 (pk), $[\alpha]_{265}$ − 2649 (tr); CD (*c* 0.10, MeOH) $[\theta]_{288.6}$ +15.80 (max); nmr ($CDCl_3$) 1.00 (19-H), 2.17 ppm (21-H); nmr (C_6D_6) 0.64 (19-H), 1.92 ppm (21-H); mass spectrum *m/e* 330 (M^+). *Anal.* Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.83; H, 10.58.

18-Methyl-5β-pregnane (XXVIII).—A solution of 18-methyl-5β-pregnane-3,20-dione (XXVI, 20 mg) in ethylene glycol (2.5 ml), 1-butanol (1 ml), and hydrazine hydrate (95%, 1 ml) was heated under reflux for 1.5 hr. After cooling to about 100° potassium hydroxide (150 mg) was added and the heating was continued without a condenser until the temperature of the reaction mixture reached about 210°. After heating for 8 hr at 210–220° under an air-cooled condenser, the reaction mixture was cooled, diluted with water, and extracted with ether. The ether extract was washed with water and dried (Na_2SO_4) and the solvent was evaporated. The oily residue was chromatographed on a small (1 g) silica gel column. Elution with hexane (10 ml) gave noncrystalline 18-methyl-5β-pregnane (XXVIII, 9.5 mg, 52%) which exhibited a single tlc spot in a variety of solvent systems: nmr ($CDCl_3$) 0.895 ppm (19-H); mass spectrum *m/e* 302 (M^+). According to nmr and gc–mass spectral analysis this compound was contaminated with about 5% of an isomeric product, tentatively identified as 18-methyl-5β,17α-pregnane. This contaminant exhibited a virtually identical mass spectrum with that of the main component and a 19-H signal in the nmr ($CDCl_3$) at 0.90 ppm as a shoulder on the 19-H resonance (0.895 ppm) of XXVIII.

18-Methyl-5α-pregnane (XXIX).—18-Methyl-5α-pregnane-3,-20-dione (XXVII, 25 mg) was reduced under the same conditions as described above for the 5β isomer, except that the reaction mixture was heated at 210–220° for 5 hr only, yielding pure 18-methyl-5α-pregnane (XXIX, 4 mg, 17%): mp 88–89° (MeOH); nmr ($CDCl_3$) 0.76 ppm (19-H); mass spectrum *m/e* 302 (M^+). *Anal.* Calcd for $C_{22}H_{38}$: C, 87.34; H, 12.66. Found: C, 87.14; H, 12.70. This product was homogeneous according to gc–mass spectral analysis.

Registry No.—I, 438-22-2; II, 438-23-3; III, 641-85-0; IV, 481-26-5; V, 481-21-0; VI, 481-20-9; XIV, 36783-17-2; XV, 36783-18-3; XVIII, 36783-19-4; XXII, 36783-20-7; XXIV, 36783-21-8; XXVI, 36783-22-9; XXVII, 36783-23-0; XXVIII, 36783-24-1; XXIX, 36783-25-2.

Acknowledgment.—We wish to thank Dr. M. Kielczewski of the University of Poznan for the generous gift of 5β-cholestan-12-one, Dr. A. M. Duffield for his valuable comments on this manuscript, and Dr. D. M. Smith of Stanford University for the refocused measurement of metastable peaks.

Mercuration of α,β-Unsaturated Steroidal Ketones and Other Unsaturated Systems[1]

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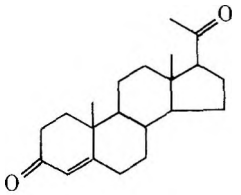
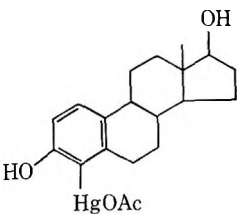
For the preparation of androgen and progesterone receptor inhibitors, the oxymercuration of α,β-unsaturated ketones was studied. In contrast to a number of model compounds, steroidal α,β-unsaturated ketones were unreactive when treated with mercuric acetate in methanol at room temperature. For those 3-keto steroids with a readily abstractable allylic proton, heating of the steroid with mercuric acetate in methanol and in acetic acid resulted in the formation of mercurous acetate, presumably due to oxidation of the steroid. For those 3-keto steroids without this structural feature and with a C-1 double bond, addition of acetoxymercuri ion occurs in acetic acid at the α side of the C-1 double bond. The proton at C-2 is abstracted, and the 2-acetoxymercuri-1-en-3-one is formed. The acetate ion was replaced with chloride ion, and 2-chloromercuri-5α-androst-1-ene-3,17-dione, 2-chloromercuri-1,4-androstadiene-3,17-dione, 2-chloromercuri-1,4,6-androstatriene-3,17-dione, 2-chloromercuri-1,4,6-androstatrien-17β-ol-3-one, 2-chloromercuri-17α-methyl-1,4,6-androstatrien-17β-ol-3-one, and 2-chloromercuri-1,4,6-pregnatriene-3,20-dione were isolated.

The isolation from the chick oviduct of a protein which binds progesterone (**1**) with great affinity ($k_d \simeq 8.3 \times 10^{-10}$ mol/l. in 0.3 *M* KCl at 1–4°) has been described by Sherman, Corvol, and O'Malley.[3] This protein may function as a progesterone target tissue receptor. The addition of sodium *p*-chloromercuribenzoate to the oviduct receptor eliminates the binding of progesterone, indicating the presence of sulfhydryl groups at or near the binding site. It is feasible that if a functionalized steroid could be synthesized which would bind irreversibly to a sulfhydryl group, progesterone binding to the oviduct receptor would be blocked.

Chin and Warren[4] have described the synthesis of 4-acetoxymercuriestradiol (**2**) and its use for the affinity



1



2

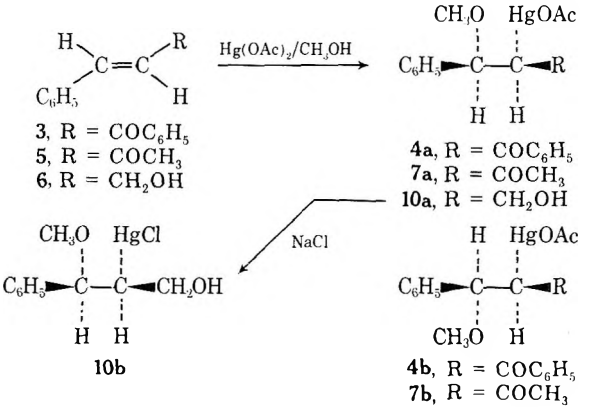
labeling of sulfhydryl groups. Muldoon and Warren[5] demonstrated that this mercurated steroid mimics estradiol in the production of certain biological responses and in the mode of its binding to uterine estradiol receptors. Further experiments[6] now indicate that 4-acetoxymercuriestradiol binds irreversibly to an estradiol receptor.

This work encouraged us to attempt the synthesis of mercurated steroids which would bind irreversibly to progesterone or androgen receptors. Our aim was to introduce mercury into the steroidal skeleton adjacent to the C-3 carbonyl group by the direct oxymercuration of α,β-unsaturated ketones.

Results and Discussion

Oxymercuration of α,β-Unsaturated Ketones and Alcohols.—Methoxymercuration of *trans*-benzalacetophenone (**3**) with mercuric acetate in methanol at room temperature gave α-acetoxymercuri-β-methoxy-β-phenylpropiophenone (**4**) (Scheme I).[7] On the assumption that the oxymercuration of an unstrained olefin such as **3** [as well as *trans*-benzalacetone (**5**) and cinnamyl alcohol (**6**) below] is preferably trans,[8] the nmr spectrum of the crude reaction product indicated that it contained 81% of the erythro (**4a**) and 19% of the threo (**4b**) isomer. Recrystallization of the crude product gave **4a** with the same sharp melting point as the compound described by Middleton.[7]

SCHEME I



Treatment of *trans*-benzalacetone (**5**) with mercuric acetate in methanol at room temperature gave 3-acetoxymercuri-4-methoxy-4-phenyl-2-butanone (**7**) (Scheme I). The nmr spectrum of the crude product indicated that the erythro (**7a**) and threo (**7b**) isomers are formed in the ratio of 85:15, respectively. The crude reaction product was further characterized by replacement of the acetoxymercuri group with bromine and with iodine.[9,10] *erythro*-3-Bromo- and -3-iodo-4-methoxy-4-phenyl-2-butanone (**8a** and **9a**) and the respective threo isomers (**8b** and **9b**) were formed, but

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(2) Supported by National Institutes of Health Grant HD-05797.

(3) M. R. Sherman, P. L. Corvol, and B. W. O'Malley, *J. Biol. Chem.*, **245**, 6085 (1970).

(4) C.-C. Chin and J. C. Warren, *ibid.*, **243**, 5056 (1968).

(5) T. G. Muldoon and J. C. Warren, *ibid.*, **244**, 5430 (1969).

(6) T. G. Muldoon, *Biochemistry*, **10**, 3780 (1971).

(7) E. B. Middleton, *J. Amer. Chem. Soc.*, **45**, 2763 (1923).

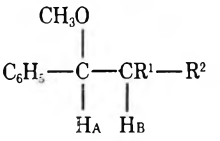
(8) W. Kitching, *Organometal. Chem. Rev.*, **3**, Part A, 61 (1968).

(9) F. R. Jensen and L. H. Gale, *J. Amer. Chem. Soc.*, **82**, 148 (1960).

(10) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N. Y., 1968, pp 77–86.

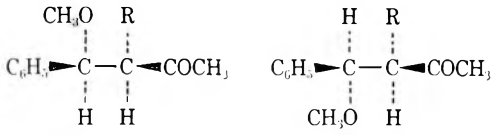
TABLE I

NMR DATA FOR OXYMERCURI AND OXYHALO COMPOUNDS IN DEUTERIOCHLOROFORM[a]



Compd	R¹	R²	Configuration	δ_{HA}[b]	δ_{HB}[b]	J_{AB}, Hz	δ_{OCH_3}[c]	R², δ_{CH}[c]
4a	HgOAc	COC_6H_5	Erythro	5.20	4.62	7.0	3.32	
4b	HgOAc	COC_6H_5	Threo	5.25	4.79	9.5	3.21	
7a	HgOAc	$COCH_3$	Erythro	4.93	3.83	6.5	3.25	2.04
7b	HgOAc	$COCH_3$	Threo	*d*	*d*	*d*	3.17	2.29
8a	Br	$COCH_3$	Erythro[e]	4.57	4.46	8.0	3.27	2.15
8b	Br	$COCH_3$	Threo[e]	4.55	4.27	9.5	3.13	2.33
9a	I	$COCH_3$	Erythro[e]	4.76	4.41	9.5	3.22	2.11
9b	I	$COCH_3$	Threo[e]	4.69	4.42	10.5	3.19	2.44
10b	HgCl	CH_2OH	Erythro	4.71	3.34[f]	7.5	3.26	
11[g]	HgBr	COC_6H_5	*h*	5.35	4.60	*i*	*i*	*i*
12[g]	HgBr	CO_2CH_3	*h*	5.00	3.65	*i*	*i*	*i*

[a] Chemical shift (δ) in parts per million downfield from TMS. Measured at 60 MHz at about 35°. [b] Doublet or as noted otherwise. [c] Singlet. [d] Too weak to observe. [e] Tentative assignment. [f] Center of multiplet, 3.21–3.50 ppm. [g] From ref 11. [h] Not assigned. [i] Not reported.



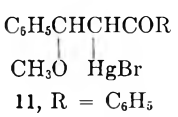
8a, R = Br
9a, R = I

8b, R = Br
9b, R = I

in each case, only one isomer was isolated and this is tentatively assigned the threo configuration (**8b** and **9b**).

Cinnamyl alcohol (**6**) was also methoxymercurated (Scheme I). The crude product was characterized as 2-chloromercuri-3-methoxy-3-phenyl-1-propanol (**10b**). Its nmr spectrum indicates that mainly the erythro isomer (**10a**) is formed in the reaction.

The structure of erythro-α-acetoxymercuri-β-methoxy-β-phenylpropiophenone (**4a**) was established directly by Middleton.[7] The assignment of the structures to the other mercuration (**4b**, **7**, and **10**) and halogenation (**8** and **9**) products are made by comparison of their respective nmr spectra with that of **4a** (Table I). The assigned chemical shifts for **4**, **7**, and **10** are in accord with those reported[11] for α-bromomercuri-β-methoxy-β-phenylpropiophenone (**11**) and methyl α-bromomercuri-β-methoxy-β-phenylpropionate (**12**) (Table I). The coupling between the chiral protons in **11** and **12** was not reported and the configurations of these two compounds were not assigned.[11]



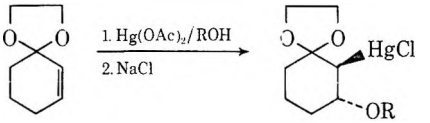
11, R = C_6H_5
12, R = OCH_3

The nmr spectra of the halogenation products of **7a** show a shift to lower field for the high-field chiral proton signal. This confirms our assignments of the low-field and high-field signals of **7a** (Table I). Since the preferred conformation of erythro and threo isomers of **8** and **9** could not be predicted,[12] comparisons of the chemical shifts and coupling constants of the chiral protons and the chemical shifts of the methyl protons in the spectra of *erythro*- and *threo*-**8** and -**9** with *erythro*- and *threo*-**7** were used to tentatively assign the configurations of the isomers of **8** and **9**.

Oxymercuration of 2-cyclohexenone in methanol and in tetrahydrofuran (THF)–water[13] was unsuccessful. In THF–water, 2-cyclohexenone apparently reacts, as evidenced by the typical precipitation and color changes reported for this type of reaction.[13] The product did not have the expected properties of an α-mercuri ketone and remains unidentified.

Methoxy- and hydroxymercuration of 2-cyclohexenone ethylene ketal (**13**) at room temperature gave *trans*-2-chloromercuri-3-methoxycyclohexanone ethylene ketal (**14**) and *trans*-2-chloromercuri-3-hydroxycyclohexanone ethylene ketal (**15**), respectively (Scheme II). Treatment of either ketal with aqueous acid

SCHEME II



13

14, R = CH_3
15, R = H

caused hydrolysis of the ketal blocking group, but returned only 2-cyclohexenone.

The structure and configuration of **14** and **15** were assigned on the basis of their nmr spectra. The constant for the coupling between the two chiral protons (10.5–12.0 Hz) shows them to be diaxial.[14] The signal for the C-2 proton in the nmr spectra of **14** and **15** is a doublet at 2.66 and 2.71 ppm, respectively. The multiplet due to the C-3 proton in each is at a substantially different chemical shift, 3.23–3.60 ppm for **14** and 3.78–4.36 ppm for **15**, and thus the structures of **14** and **15** are as assigned.

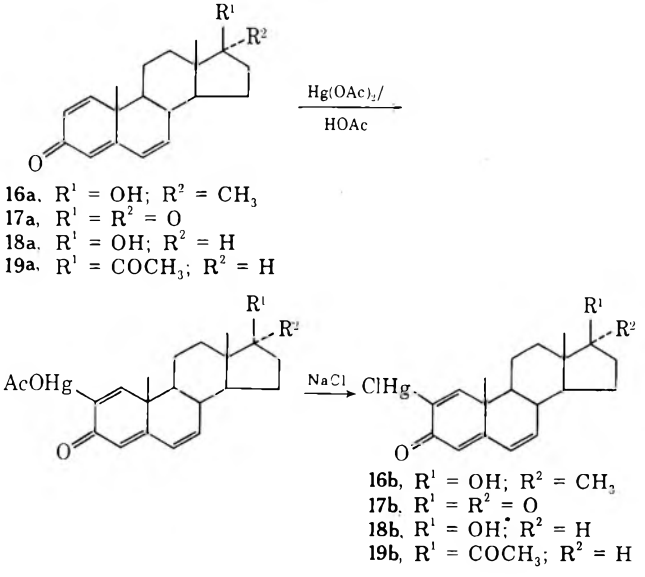
Oxymercuration of Steroids.—Using the same reactions as discussed above for methoxy- and hydroxy-

(11) A. J. Bloodworth and R. J. Bunce, *J. Chem. Soc. C*, 1453 (1971).
(12) C. A. Kingsbury and D. C. Best, *J. Org. Chem.*, **32**, 6 (1967).
(13) H. C. Brown and P. J. Geoghegan, Jr., *ibid.*, **35**, 1844 (1970).
(14) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963).

mercuration, progesterone (**1**) and its bis ethylene ketal were unreactive at room temperature even on the addition to the former reaction of a catalytic amount of perchloric acid. Similarly, 1,4-androstadien-17β-ol-3-one, 5α-androst-1-ene-3,17-dione, 5-pregnen-3β-ol-20-one, and 5-androstene-3β,17β-diol 17-benzoate were unreactive. Attempts to force reaction with progesterone (**1**) were unsuccessful in that heating a mixture of **1** and mercuric acetate in methanol and in methanol with added perchloric acid resulted in the precipitation of a large quantity of mercurous acetate, presumably owing to oxidation of progesterone by mercuric acetate. Precipitation of a large amount of mercurous acetate also occurs when 4-androstene-3,17-dione is boiled with mercuric acetate in acetic acid.

Substitution of Mercury at C-2 in the Steroid Nucleus.—The ready oxidation of progesterone (**1**) by mercuric acetate in boiling acetic acid is probably related to dehydrogenation reactions by mercuric acetate under similar conditions.[15] It may be assumed that, if an unsaturated steroidal ketone does not have an easily abstractable allylic hydrogen atom, the steroid would be resistant to oxidation on heating with mercuric acetate in acetic acid, and an oxymercury adduct, similar to **4** and **7**, might be obtained. This argument may be used to explain a reaction recently reported by Kocor and Gumulka.[16,17] In an attempt to oxidize 17α-methyl-1,4,6-androstatrien-17β-ol-3-one (**16a**), they obtained 2-chloromercuri-17α-methyl-1,4,6-androstatrien-17β-ol-3-one (**16b**) (Scheme III). The

SCHEME III



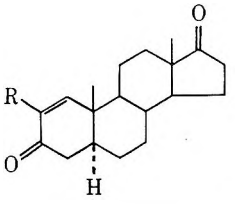
16a, R^1 = OH; R^2 = CH_3
17a, R^1 = R^2 = O
18a, R^1 = OH; R^2 = H
19a, R^1 = $COCH_3$; R^2 = H

16b, R^1 = OH; R^2 = CH_3
17b, R^1 = R^2 = O
18b, R^1 = OH; R^2 = H
19b, R^1 = $COCH_3$; R^2 = H

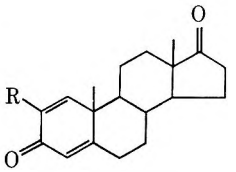
steroid **16a** is resistant to oxidation, since the allylic hydrogen at C-8 is not easily abstracted.[18]

As suggested by this reasoning, a series of steroids containing the 1,4,6-trien-3-one system (**17a**–**19a**) was mixed with mercuric acetate in boiling acetic acid. After reaction, the products were treated with sodium chloride, and 2-chloromercuri-1,4,6-androstatriene-3,17-dione (**17b**), 2-chloromercuri-1,4,6-androstatrien-17β-ol-3-one (**18b**), and 2-chloromercuri-1,4,6-pregnatriene-3,20-dione (**19b**) were obtained. Similarly, 2-chloromercuri-17α-methyl-1,4,6-androstatrien-17β-ol-3-one (**16b**) was also prepared from **16a**. In none of these reactions was mercurous acetate formed in any appreciable amount.

During the course of reaction of **16a**–**19a** with mercuric acetate, it is possible to follow the conversion of the steroidal substrate to the 2-acetoxymercuri derivative using nmr spectroscopy. In the substrate spectrum, the doublet at 7.1 ppm (J = 10.0 Hz) is assigned to the proton at C-1. On mercuration at C-2, this doublet collapses to a singlet and is shifted to a slightly lower field. Using this technique, it was found that, while **16a**–**18a** react very readily with an equivalent amount of mercuric acetate (50% conversion in 15 min at 118°), a comparable conversion of **19a** in 15 min requires a 4-equiv excess of mercuric acetate. The reactivity of 5α-androst-1-ene-3,17-dione (**20a**) is also less than that of **16a**–**18a** and a 50% conversion to 2-acetoxymercuri-5α-androst-1-ene-3,17-dione required a reaction time of 24 hr with a 4-equiv excess of mercuric acetate. 2-Chloromercuri-5α-androst-1-ene-3,17-dione (**20b**) was prepared using these reaction conditions.



20a, R = H
b, R = HgCl



21a, R = H
b, R = HgCl

The 1,4-dien-3-one and 4,6-dien-3-one systems are also resistant to oxidation by mercuric acetate in boiling acetic acid. Using a 4-equiv excess of mercuric acetate, 1,4-androstadiene-3,17-dione (**21a**) was converted to its 2-acetoxymercuri derivative and 2-chloromercuri-1,4-androstadiene-3,17-dione (**21b**) was isolated. A 50% conversion required a reaction time of 6 hr. Similar attempts to mercurate 1,4-androstadien-17β-ol-3-one, 1,4-pregnadiene-3,20-dione, and 4,6-pregnadiene-3,20-dione were unsuccessful. In none of these reactions was more than a trace of mercurous acetate produced.

The structure of each of the 2-chloromercuri steroids, **16b**–**21b**, was established by combustion analysis and a variety of spectral measurements. All show a strong absorption band at 1610–1640 cm^{-1}, shifted 15–35 cm^{-1} bathochromically from 1640–1665 cm^{-1} for the unmercurated steroid. Contrary to the report by Kocor and Gumulka[16,17] there is no absorption band in the ir spectra of **16b** in the region 1650–1750 cm^{-1}. The nmr spectra of the mercurated steroids showed predictable differences from those of the parent steroids. Finally, the mass spectrum of each of the 2-chloromercuri steroids showed molecular ions and daughter fragments of the expected mercury isotope pattern.[19] The interpretation of the fragmentations is simplified by this characteristic pattern and is in accord with the assigned structures.

(15) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 644–646.
(16) M. Kocor and M. Gumulka, *Tetrahedron Lett.*, 3067 (1969).
(17) M. Kocor and M. Gumulka, *Rocz. Chem.*, **45**, 1003 (1971).
(18) R. H. Shapiro and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 2825 (1964).
(19) "Handbook of Chemistry and Physics," 43rd ed, C. D. Hodgman, R. C. Weast, R. S. Shankland, and S. M. Selby, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1962, pp 493–494.

TABLE II

RATE OF REACTION OF STEROIDAL UNSATURATED KETONES WITH MERCURIC ACETATE IN ACETIC ACID-d_4 AT 87°[a]

Steroid substrate	Initial concentrations: Steroid, mol l.$^{-1}$	Mercuric acetate, mol l.$^{-1}$	Rate constant[b] $k \times 10^2$, l. mol^{-1} min^{-1}
1,4,6-Androstatriene-3,17-dione (**17a**)	0.50	0.50	1.50[c] ± 0.06[d]
	0.50	0.25	1.42[e] ± 0.01
	0.25	0.50	1.46 ± 0.002
	0.10	0.50	1.49 ± 0.01
	0.050	0.50	1.50 ± 0.007
1,4,6-Pregnatriene-3,20-dione (**19a**)	0.50	0.50	1.18[f] ± 0.001
	0.25	0.50	1.16[c] ± 0.000
	0.10	0.50	1.53 ± 0.000

[a] Temperature ±3°. [b] Unless noted otherwise, based on data up to 75% substrate conversion. [c] Based on data up to 50% substrate conversion. [d] Standard deviation from least squares fit. [e] Based on data up to 18% substrate conversion. [f] Based on data up to 25% substrate conversion.

Kinetics and Mechanism for Steroid Mercuration.—The rate of reaction of 1,4,6-androstatriene-3,17-dione (**17a**) and 1,4,6-pregnatriene-3,20-dione (**19a**) with mercuric acetate were studied quantitatively at 87° in a nmr spectrometer. The solvent was acetic acid-d_4. The chemical shifts of the C-1 proton signal in the spectrum of the substrate and of the product were used to follow the course of the reaction with time. Although it has been shown[20] that mercuric acetate reacts with acetic acid, the pseudo-first-order rate constant for this process (4.8×10^{-4} min^{-1} at 90.5° and 6.2×10^{-5} min^{-1} at 70.2°) precludes its interference with these present rate measurements. Since in none of the nmr spectra was there any evidence detected for polymercuration of the steroids, it is also assumed that the amount of mercuric acetate at any stage in the reaction can be calculated from its initial concentration and the amount of product formed.

The rate constants shown in Table II were calculated in the usual way.[21] As seen in Table II, the rate for reaction of **17a** is constant over a considerable concentration range of **17a**. When the initial concentration of **17a** is equal to or larger than the initial concentration of mercuric acetate, the rate constant decreases rapidly after some reaction has occurred (Figure 1). For calculation of these rate constants, data up to 50 and 18% substrate conversion, respectively, were used. When the initial concentration of **17a** was smaller than that of mercuric acetate, data up to 75% conversion of **17a** were used. The decrease in rate constant with reaction is even more pronounced in the case of 1,4,6-pregnatriene-3,20-dione (**19a**), and the kinetic data are not too compelling for a second-order reaction. However, it is considered that the reaction is approximately second order and is being complicated by a side reaction. For high initial concentrations of **19a**, the rate constant is somewhat low, but with a four molar excess of mercuric acetate it is essentially the same as that of **17a** (Table II and Figure 1).

The rate of reaction of 1,4-androstadiene-3,17-dione (**21a**) with mercuric acetate in acetic acid-d_4 at 87° is too slow to measure. Using 0.10 *M* **21a** and 0.50 *M* mercuric acetate, there was no detectable reaction after 180 min. With the same conditions, 73% of **17a** was converted to 2-acetoxymercuri-1,4,6-androstatriene-3,17-dione.

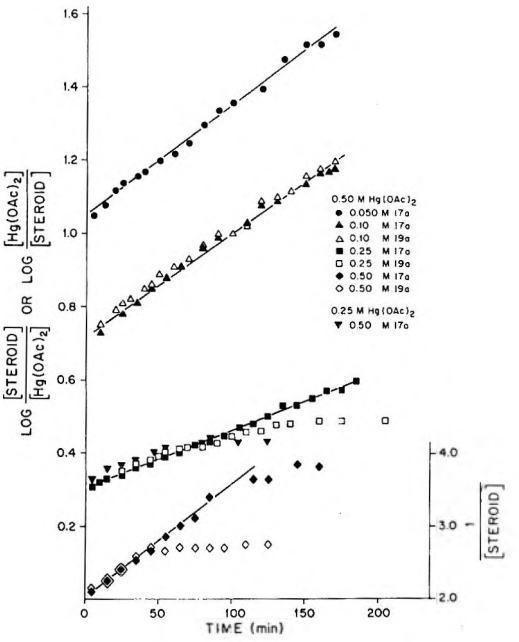
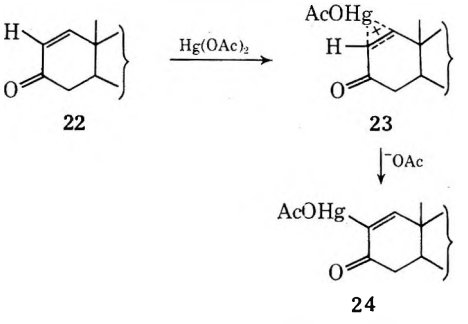


Figure 1.—Comparison of rate data for the mercuration of 1,4,6-androstatriene-3,17-dione (**17a**) and 1,4,6-pregnatriene-3,20-dione (**19a**) with mercuric acetate in acetic acid-d_4 at 87°. Lines are drawn through the data obtained for **17a** when its initial concentration (shown on the figure) is equal to or less than that of mercuric acetate.

All attempts to detect a mercuric acetate adduct, similar to **4** and **7**, were unsuccessful. When 1,4,6-androstatriene-3,17-dione (**17a**) was allowed to stand with mercuric acetate in acetic acid at room temperature for 70 hr, a 17% conversion to the 2-acetoxymercuri derivative resulted, but no trace of a mercuric acetate adduct could be observed. When methanol was the solvent no reaction occurred. After this latter mixture was boiled for 1 hr, only **17a** was isolated. When mercuric perchlorate in acetic acid[22] was used with **17a** at room temperature a 50% conversion to the 2-acetoxymercuri derivative was detected in 20 hr. Again no intermediate adduct was detected.

All of these results suggest that the reaction proceeds by the sequence shown in Scheme IV. Attack of the acetoxymercuri ion at the α side of the C-1 double bond of **22** gives **23**. The proton at C-2 is abstracted and **24** is formed. A similar course for the mercuration of

SCHEME IV



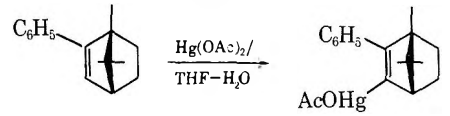
22 23 24

(20) H. C. Brown and C. W. McGary Jr., *J. Amer. Chem. Soc.*, **77**, 2306 (1955).

(21) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, pp 12–19.

(22) A. J. Kresge, M. Dubeck, and H. C. Brown, *J. Org. Chem.*, **32**, 745 (1967).

SCHEME V



other sterically hindered carbon–carbon double bonds has been reported,[23,24] an example of which is shown in Scheme V.

The order of reactivity 1,4,6-trien-3-one > 1,4-dien-3-one > 1-en-3-one and the accelerated rate using mercuric perchlorate in acetic acid does not distinguish between the formation of the intermediate **23** or the abstraction of the C-2 proton of **23** as the rate-limiting step.

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Optical rotations were measured using a visual polarimeter and 1-dm sample tubes. Ir spectra were obtained with a Beckman Model IR-10 spectrophotometer and were measured as potassium bromide pellets. Reported nmr spectra were obtained as solutions in deuteriochloroform with a Varian Model A-60 or Model XL-100-15 operating at 60 or 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield with tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are estimated to ± 0.5 Hz. Reaction rates were determined on the XL-100-15 nmr spectrometer by measurement and comparison of the relative intensities of the signals for the C-1 proton of the substrate and product. Acetic acid-d_4 was used as solvent in these determinations and the deuterium lock mode of the spectrometer was locked to the CD_3 peak of the solvent. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Molecular weights were determined with an LKB Type 9000 mass spectrometer using an ionizing voltage of 70 eV. As indicated, the reported molecular ions (M^+) are those corresponding to the most abundant isotope of mercury (^{202}Hg).[19]

Preparation of 2-Chloromercuri Steroids.—A solution of the steroid in boiling glacial acetic acid was mixed with a solution of mercuric acetate also in boiling glacial acetic acid. In each case, after reaction, the cooled mixture was diluted with excess saturated aqueous sodium chloride. The mercurated steroids were extremely difficult to purify since even after purification they tended to form gums. They also appeared to have a high affinity for solvents, as indicated by the nmr spectra of purified compounds which showed additional protons characteristic of the solvent used. It is for these reasons that, although conversion to the mercurated steroid was high, the isolated yield of pure mercurated compound in some cases was low. Repeated recrystallizations or precipitations were performed at the expense of yield in order to achieve high purity.

α-Acetoxymercuri-β-methoxy-β-phenylpropiophenone (4).—A solution of *trans*-benzalacetophenone (**3**) (5.00 g, 24.0 mmol) and mercuric acetate (7.60 g, 23.8 mmol) in methanol (80 ml) was allowed to stand at room temperature for 2 days. Complete evaporation of the solvent gave a mixture of 81% *erythro*-**4** (**4a**) and 19% *threo*-**4** (**4b**): nmr see Table I and δ 7.2–8.0 ppm (m, 10, aromatic H). Recrystallization of the solid mixture from methanol gave **4a** (8.9 g, 74%) as white needles: mp 115–116° (lit.[7] mp 115°); nmr see Table I and δ 7.2–8.0 ppm (m, 10, aromatic H).

3-Acetoxymercuri-4-methoxy-4-phenyl-2-butanone (7).—A solution of *trans*-benzalacetone (**5**) (25.0 g, 0.171 mol) and mercuric acetate (54.5 g, 0.171 mol) in methanol (250 ml) was allowed to stand at room temperature for 17 days, during which a solid precipitated (49.3 g, 66%). This solid was a mixture of 85% *erythro*-**7** (**7a**) and 15% *threo*-**7** (**7b**): mp 112–115°; nmr Table I and δ 7.34 ppm (s, 5, aromatic H).

3-Bromo-4-methoxy-4-phenyl-2-butanone (8).—Bromine (7.4 g, 0.046 mol) was added to a stirred suspension of 3-acetoxymercuri-4-methoxy-4-methyl-2-butanone, 85% erythro (**7a**) and 15% threo (**7b**) isomer (20.0 g, 0.0458 mol) in methanol (500 ml). After 1 hr the solution was clear, and the solvent was evaporated. The residue was dissolved in ether, and the solution was washed with aqueous sodium bromide and then with water. After drying, the ether solution was evaporated, and distillation of the residue gave a mixture of *erythro*-**8** (**8a**) and *threo*-**8** (**8b**) (9.0 g, 77%) as an oil, bp 84–99° (0.35 mm). A portion of this oil (5.24 g) was chromatographed on silica gel (175 g). Elution with heptane–carbon tetrachloride gave pure **8b** (1.88 g, 28%), recrystallized from petroleum ether (bp 30–60°): mp 68–69°; nmr see Table I and δ 7.38 ppm (s, 5, aromatic H).

Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.09; Br, 31.08. Found: C, 51.12; H, 5.15; Br, 31.35.

The later fractions were mixtures of **8a** and **8b**. That containing 83% **8a** afforded its nmr spectrum, Table I and 7.33 ppm (s, 5, aromatic H).

3-Iodo-4-methoxy-4-phenyl-2-butanone (9).—Iodine (6.0 g, 0.024 mol) was added to a stirred suspension of 3-acetoxymercuri-4-methoxy-4-methyl-2-butanone, 85% erythro (**7a**) and 15% threo (**7b**) isomer (10.0 g, 0.0229 mol). After 20 min, the solvent was evaporated and the residue was dissolved in ether. The ethereal solution was washed successively with 10% aqueous sodium bisulfite, aqueous potassium iodide, and water. After drying, evaporation of the ether gave a mixture of 40% *erythro*-**9** (**9a**) and 60% *threo*-**9** (**9b**) as an oil, nmr Table I and δ 7.31 and 7.36 ppm (two s, total 5 protons, aromatic H for **9a** and **9b**, respectively). Crystallization from petroleum ether gave **9b** (1.78 g, 26%) as white needles: mp 80–81°; nmr Table I and δ 7.36 ppm (s, 5, aromatic H).

Anal. Calcd for $C_{10}H_{13}IO_2$: C, 43.45; H, 4.31; I, 41.72. Found: C, 43.21; H, 4.28; I, 41.63.

***erythro*-2-Chloromercuri-3-methoxy-3-phenyl-1-propanol (10b).**—A solution of cinnamyl alcohol (5.00 g, 37.3 mmol) and mercuric acetate (12.0 g, 37.7 mmol) in methanol (100 ml) was allowed to stand at room temperature for 36 hr, after which the sodium hydroxide test for mercuric ion was negative. The solution was filtered and its volume was reduced to 50 ml by evaporation. Addition of saturated aqueous sodium chloride (50 ml) caused the precipitation of a white solid (14.6 g), mp 115–120°. Recrystallization of this solid from methanol–water and then chloroform gave **10b** (9.9 g, 66%) as white plates: mp 121–122°; nmr Table I and δ 2.5 (s, 1, OH), 3.84–3.98 (m, 2, CH_2OH), and 7.42 ppm (s, 5, aromatic H).

Anal. Calcd for $C_{10}H_{13}ClHgO_2$: C, 29.93; H, 3.27; Hg, 49.99. Found: C, 29.83; H, 3.35; Hg, 50.19.

***trans*-2-Chloromercuri-3-methoxycyclohexanone Ethylene Ketal (14).**—2-Cyclohexenone ethylene ketal[25] (**13**), bp 87–90° (25 mm) [lit.[25] bp 86.5–88.5° (23 mm)] (0.650 g, 4.64 mmol), was added to a stirred slurry of mercuric acetate (1.48 g, 4.64 mmol) in methanol (5 ml). After stirring for 5 min, the mixture was diluted with saturated aqueous sodium chloride, causing precipitation of **14** as a white solid (1.47 g, 78%), mp 115–120°. Recrystallization of this solid from methanol containing a trace of triethylamine gave **14** (0.750 g, 40%) as white needles: mp 117–118°; nmr δ 2.66 (d, 1, J = 12.0 Hz, ClHgCH), 3.40 (s, 3, $COCH_3$), 3.23–3.60 (m, 1, CH_3OCH), and 4.04 ppm (s, 4, OCH_2-CH_2O).

Anal. Calcd for $C_9H_{15}ClHgO_3$: C, 26.54; H, 3.71; Cl, 8.71; Hg, 49.25. Found: C, 26.47; H, 3.68; Cl, 8.53; Hg, 49.05.

***trans*-2-Chloromercuri-3-hydroxycyclohexanone Ethylene Ketal (15).**—2-Cyclohexenone ethylene ketal[25] (**13**) (7.00 g, 49.9 mmol) was added to a solution of mercuric acetate (18.0 g, 56.5 mmol) in tetrahydrofuran (70 ml) and water (70 ml). The yellow color of the solution disappeared after 37 sec, and after 7 min, saturated aqueous sodium chloride (25 ml) was added. The oil which separated was extracted into chloroform. This solution was dried, and the chloroform was evaporated. Crystallization of the residue from benzene gave **15** (12.2 g, 62%) as white needles: mp 137–138°; nmr δ 2.71 (d, 1, J = 10.5 Hz, ClHgCH), 3.06 (s, 1, OH, disappeared on addition of D_2O), 4.05 (s, 4, OCH_2CH_2O), and 3.68–4.36 ppm (m, 1, HOCH).

Anal. Calcd for $C_8H_{13}ClHgO_3$: C, 24.43; H, 3.33; Cl, 9.02; Hg, 51.01. Found: C, 24.38; H, 3.13; Cl, 8.99; Hg, 51.19.

2-Chloromercuri-17α-methyl-1,4,6-androstatrien-17β-ol-3-one (16b).—17α-Methyl-1,4,6-androstatrien-17β-ol-3-one (**16a**), mp

(23) J. M. Coxon, M. P. Hartshorn and A. J. Lewis, *Tetrahedron Lett.*, 3521 (1969).

(24) V. I. Sokolov, V. V. Bashilov, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **188**, 127 (1969); *Chem. Abstr.*, **72**, 3549n (1970).

(25) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965).

136–138° (lit.[26] mp 139–140°), nmr δ 1.00 (s, 3, C-18 H), 1.23 (s, 6, C-17 CH_3 and C-19 H), 2.30 (b s, 1, OH, disappeared on addition of D_2O), 5.92–6.36 (m, 4, C-2, C-4, C-6, and C-7 H), and 7.08 ppm (d, 1, J = 10.0 Hz, C-1 H), prepared from 17α-methyl-5-androstene-3β,17β-diol[27] by dehydrogenation[28] (0.813 g, 2.72 mmol), and mercuric acetate (4.00 g, 12.6 mmol) in acetic acid (20 ml) were heated for 15 min. Dilution of the reaction mixture with saturated aqueous sodium chloride (250 ml) precipitated a yellow solid. The solid was thoroughly washed with water, and crystallization from 95% ethanol gave a yellow microcrystalline first crop (0.574 g, 40%), mp 193–195° dec, and a white, powdery second crop (0.090 g, 6%), mp 183–185° dec. Two recrystallizations of the combined crops from 95% ethanol gave **16b** (0.370 g, 25%) as pale yellow microcrystals: mp 180–181° dec (lit.[16] mp 155–162°); ir 1585 (C=C) and 1612 cm^{-1} (C=O); nmr δ 1.00 (s, 3, C-18 H), 1.06 and 1.11 (two s, 3 and 3, C-17 CH_3 and C-19 H), 2.97 (s, 1, OH, disappeared on addition of D_2O), 6.0–6.3 (m, 3, C-4, C-6, and C-7 H), and 7.29 ppm (s, 1, C-1 H).

Anal. Calcd for $C_{20}H_{25}ClHgO_2$: C, 45.03; H, 4.72; Cl, 6.65; Hg, 37.60; mol wt ($C_{20}H_{25}Cl^{202}HgO_2$), 534. Found: C, 44.95; H, 5.18; Cl, 6.65; Hg, 38.07; mol wt, 534 (M^+).

2-Chloromercuri-1,4,6-androstatriene-3,17-dione (17b).—1,4,6-Androstatriene-3,17-dione[27] (**17a**) (5.00 g, 17.7 mmol) and mercuric acetate (13.00 g, 40.8 mmol) in acetic acid were heated for 30 min. Dilution of the reaction mixture with water (250 ml) containing sodium chloride (15 g) precipitated a solid which was washed with water. Trituration of the solid with acetone (50 ml) left a white powder (5.00 g), mp 230–240° dec. On standing the acetone solution deposited crystals of **17b** (0.329 g, 3.6%), mp 280–285° dec. The residue from the trituration was extracted with hot acetone (400 ml) and the hot acetone solution was combined with the acetone mother liquors obtained earlier. This solution was evaporated to one-sixth (75 ml) its original volume. Dilution with *n*-hexane (100 ml) caused the precipitation of a white powder (3.80 g), mp 180–240° dec. Crystallization of this solid from acetone gave **17b** (0.867 g, 9.5%) as white needles: mp 280–285° dec; $[\alpha]^{25}D$ +27° (*c* 0.84, $CHCl_3$); ir 1615 (conjugated C=O) and 1715 cm^{-1} (C=O); nmr δ 1.03 (s, 3, C-18 H), 1.30 (s, 3, C-19 H), 6.05–6.45 (m, 3, C-4, C-6, C-7 H), 7.28 (s, 1, C-1 H), and 7.28 ppm (d, ~0.2, J = 280 Hz, C-1 H coupled to ^{199}Hg).

Anal. Calcd for $C_{19}H_{21}ClHgO_2$: C, 44.10; H, 4.09; Cl, 6.85; Hg, 38.77; mol wt ($C_{19}H_{21}Cl^{202}HgO_2$), 518. Found: C, 43.80; H, 4.26; Cl, 6.87; Hg, 38.81; mol wt, 518 (M^+).

2-Chloromercuri-1,4,6-androstatrien-17β-ol-3-one (18b).—1,4,6-Androstatrien-17β-ol-3-one[27] (**18a**) (1.00 g, 3.52 mmol) and mercuric acetate (5.00 g, 15.7 mmol) in acetic acid (20 ml) were heated for 10 min. Dilution with saturated aqueous sodium chloride (100 ml) precipitated a solid (1.64 g) which was 70% pure **18b** (nmr). Crystallization of this solid followed by four recrystallizations from chloroform–ether gave **18b** (0.032 g, 1.7%) as pale yellow microcrystals: mp 189–192° dec; ir 1620 (C=O) and 3440 cm^{-1} (OH); nmr δ 0.90 (s, 3, C-18 H), 1.27 (s, 3, C-19 H), 2.70 (s, 1, OH), 3.64 (m, 1, HOCH), 5.87–6.34 (m, 3, C-4, C-6, and C-7 H), and 7.27 ppm (s, 1, C-1 H).

Anal. Calcd for $C_{19}H_{23}ClHgO_2 \cdot 1.2CHCl_3$:[29] C, 36.61; H, 3.68; mol wt ($C_{19}H_{23}Cl^{202}HgO_2$), 520. Found: C, 36.27; H, 3.62; mol wt, 520 (M^+).

2-Chloromercuri-1,4,6-pregnatriene-3,20-dione (19b).—1,4,6-Pregnatriene-3,20-dione (**19a**), mp 148–149 (lit.[30] mp 150–152°), nmr δ 0.76 (s, 3, C-18 H), 1.22 (s, 3, C-19 H), 2.16 (s, 3, C-21 H), 5.91–6.37 (m, 4, C-2, C-4, C-6, and C-7 H), and 7.08 ppm (d, 1, J = 10.0 Hz, C-1 H), prepared from 5-pregnen-3β-ol-20-one[27] by dehydrogenation[28] (4.40 g, 14.2 mmol), and mercuric acetate (22.0 g, 69.0 mmol) in acetic acid (40 ml) were heated for 30 min. Dilution with saturated aqueous sodium chloride precipitated a solid. The solid was washed with water and then extracted into chloroform. The chloroform solution was washed with saturated aqueous sodium chloride and dried. Evaporation of the chloroform left a yellow gum (4.40 g) which was at least 80% **19b** (nmr). The gum was dissolved in acetone and then poured into saturated aqueous sodium chloride. The precipitated oil was extracted into chloroform and this solution was dried. Evaporation of chloroform left a gum which on heating in 95% ethanol gave **19b** (2.5 g, 32%), mp (135° softens) 150° dec. This was difficult to crystallize and readily formed a gum on warming in a solvent. An analytical sample was obtained by heating a suspension of the solid in ethanol for a few minutes, allowing the mixture to cool to 50°, decantation of the ethanolic solution from any gummy residue, and then allowing crystallization to proceed at 0° for 24 hr. Two repetitions of this procedure gave **19b** (0.51 g, 6.6%) as off-white microcrystals: mp (shrinks 137°) 145–150° dec; $[\alpha]^{25}D$ +58° (*c* 1.0, $CHCl_3$); ir 1620 (conjugated C=O), 1680 cm^{-1} (C=O); nmr δ 0.77 (s, 3, C-18 H), 1.27 (s, 3, C-19 H), 2.18 (s, 3, C-21 H), 5.94–6.36 (m, 3, C-4, C-6, and C-7 H), and 7.28 ppm (s, 1, C-1 H).

Anal. Calcd for $C_{21}H_{25}ClHgO_2$: C, 46.24; H, 4.62; Cl, 6.50; Hg, 36.78; mol wt ($C_{21}H_{25}Cl^{202}HgO_2$), 546. Found: C, 46.02; H, 4.88; Cl, 6.66; Hg, 36.53; mol wt, 546 (M^+).

2-Chloromercuri-5α-androst-1-ene-3,17-dione (20b).—5α-Androst-1-ene-3,17-dione[31] (**20a**) (0.200 g, 0.698 mmol) and mercuric acetate (1.00 g, 3.14 mmol) in acetic acid (5.0 ml) were heated for 24 hr. Dilution of the reaction mixture with saturated aqueous sodium chloride (50 ml) precipitated a gummy solid, which was extracted into chloroform. This solution was washed with water until the wash water was neutral. Evaporation of the dried chloroform solution left a gum which on trituration with ether gave a white solid (0.100 g), over 90% pure **20b** (nmr). Crystallization of this solid from chloroform–ether followed by three recrystallizations from the same solvents gave **20b** (0.040 g, 12%) as white microcrystals but containing chloroform:[29] mp 180° dec; ir 1640 (conjugated C=O) and 1730 cm^{-1} (C=O); nmr δ 0.92 (s, 3, C-18 H), 1.08 (s, 3, C-19 H), and 7.25 ppm (s, 1, C-1 H).

Anal. Calcd for $C_{19}H_{25}ClHgO_2 \cdot CHCl_3$:[29] C, 37.48; H, 4.09; mol wt ($C_{19}H_{25}Cl^{202}HgO_2$), 522. Found: C, 37.80; H, 3.97; mol wt, 522 (M^+).

2-Chloromercuri-1,4-androstadiene-3,17-dione (21b).—1,4-Androstadiene-3,17-dione[27] (**21a**) (2.00 g, 7.03 mmol) and mercuric acetate (10.0 g, 31.4 mmol) in acetic acid (125 ml) were heated for 6 hr. Dilution with saturated aqueous sodium chloride gave a yellow precipitate (0.440 g). This solid was a 1:1 mixture of **21a** and **21b** (nmr). The aqueous filtrate was thoroughly extracted with chloroform, and the chloroform solution was washed with water until neutral. Evaporation of the dried solution left a yellow oil (1.80 g) with a nmr spectrum identical with that of **21a**. The solid (0.440 g) was dissolved in chloroform and **21b** was precipitated by the careful addition of *n*-hexane. Reprecipitation on cooling from hot 95% ethanol gave **21b** (0.16 g, 44%) as a white, amorphous solid: mp 282–283° dec; ir 1640 (conjugated C=O) and 1725 cm^{-1} (C=O); nmr δ 0.94 (s, 3, C-18 H), 1.31 (s, 3, C-19 H), 6.20 (s, 1, C-4 H), and 7.17 ppm (s, 1, C-1 H).

Anal. Calcd for $C_{19}H_{23}ClHgO_2$: C, 43.93; H, 4.46; Cl, 6.83; Hg, 38.92; mol wt ($C_{19}H_{23}Cl^{202}HgO_2$), 520. Found: C, 43.72; H, 4.16; Cl, 6.52; Hg, 38.90; mol wt, 520 (M^+).

Registry No.—**4a**, 36794-15-7; **4b**, 36794-16-8; **7a**, 36794-17-9; **7b**, 36794-18-0; **8a**, 36794-19-1; **8b**, 36794-20-4; **9a**, 36794-21-5; **9b**, 36794-22-6; **10b**, 36794-23-7; **14**, 36794-24-8; **15**, 36794-25-9; **16a**, 28816-02-6; **16b**, 24272-44-4; **17a**, 633-35-2; **17b**, 36794-29-3; **18b**, 36794-30-6; **19a**, 4192-93-2; **19b**, 36794-32-8; **20b**, 36794-33-9; **21a**, 897-06-3; **21b**, 36794-35-1.

(26) G. O. Weston, D. Burn, D. N. Kirk, and V. Petrow, British Patent 854,343 (1960); *Chem. Abstr.*, **55**, 18813f (1961).

(27) Purchased from Searle Chemicals, Inc., Chicago, Ill., and used without further purification.

(28) A. B. Turner, *Chem. Commun.*, 845 (1966).

(29) Inclusion of chloroform was indicated by enhancement of the chloroform signal in the nmr spectrum of this sample in deuteriochloroform.

(30) S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964).

(31) Purchased from Steroloids, Inc., Pauling, N. Y., and used without further purification.

Spectral Studies on Cyclic Enamino Ketones[1a]

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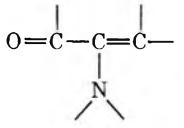
Vinyl proton chemical shifts in 3-amino-2-cycloalkenones parallel those of cyclic enamines in being inversely ordered relative to the following apparent order of increasing nitrogen lone-pair-electron delocalization: morpholino < dimethylamino < pyrrolidino and 1-cyclohexenylamines < 1-cyclopentenylamines. Similar effects are apparent in 2-amino-2-cycloalkenones, but the actual order of vinyl proton chemical shifts is reversed because of greater electron withdrawal from β positions in 2-cyclopentenones than from those in 2-cyclohexenone systems. Greater nitrogen lone-pair-electron delocalization into five- than six-membered rings is demonstrated by variable temperature nmr data which indicates ~2–3 kcal/mol larger $\Delta G^{\pm}$ for rotation about the C—N bond of the enamino ketone system in five- than in six-membered-ring 3-dimethylamino-2-cycloalkenones.

Monoenamines derived from 1,2- and 1,3-dicarbonyl compounds represent superimpositions of two important structural moieties: vinyl amines (enamines) and α,β-unsaturated carbonyl systems. 2-Amino-2-alkenones, **1** (derived from 1,2-dicarbonyl compounds), and 3-amino-2-alkenones, *2* (derived from 1,3-dicarbonyl compounds), may be viewed as either (a) α,β-unsaturated carbonyl systems with amino substituents at α and β positions, respectively, or (b) vinyl amines conjugated with carbonyl groups so as to place the carbonyl group α or β, respectively, to the amino substituent. Such a view suggests interesting possibilities regarding the distribution of electron density in these



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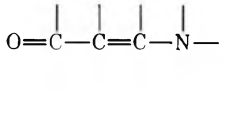

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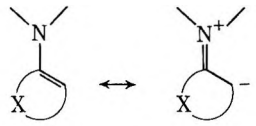
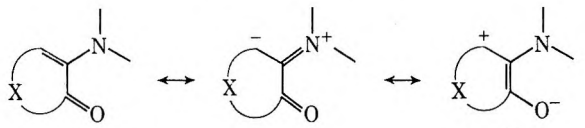
systems, especially in regard to sites of nucleophilic activity. Several reports related to alkylation, protonation, and other nucleophilic reactions of enamino ketones have appeared in the literature.[2-8] In considering the possibilities for electron density distribution in enamino ketones derived from cyclic 1,2 and 1,3 diketones it is helpful to note that the familiar cannonical structures illustrating electron delocalization in α,β-unsaturated cyclic ketones, **3** and **4**, and enamines of cyclic ketones, **5** and **6**, may be combined to represent the principal contributing structures for resonance hybrids of 2-amino-2-cycloalkenones, **7–9**, and 3-amino-2-cycloalkenones, **10–13**.

An interest in using monoenamines derived from diketones as synthetic intermediates led us to compare spectral data on a number of cyclic enamino ketones, related enamines, and α,β-unsaturated ketones. A summary of vinyl proton chemical shifts for these compounds is given in Table I. Ir and uv data for selected compounds also are included.

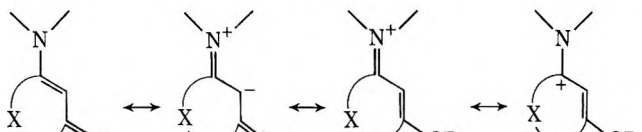
3 4



5 6



7 8 9



10 11 12 13

Chemical shifts of vinyl protons have been interpreted previously as evidence for steric and electronic effects of delocalization of the nitrogen lone-pair electrons in simple enamines.[9,10] Increases of electron density at the carbon terminus of the enamine provide greater shielding of the vinyl proton and result in upfield shifts in the nmr absorptions of the vinyl proton. Inspection of the data for simple enamines, **14–21**, reveals several interesting facts regarding ring-size effects. The vinyl proton chemical shifts of five-membered-ring enamines are consistently smaller than those of the analogous six-membered-ring systems (**14** > **15**, **16** > **17**, **18** > **19**, **20** > **21**). This trend indicates that the nitrogen lone-pair electrons are more extensively delocalized into five- than six-membered rings, an observation consistent with previous reports.[9,10] The dependence of the vinyl proton shift on the structure of the amino group also is apparent. The pyrrolidino enamines, in which nitrogen is incorporated in a five-membered ring, provide greater shielding of the vinyl proton than either morpholino or piperidino enamines in which nitrogen is part of a six-membered ring. The dimethylamino derivatives exhibit intermediate levels of shielding for vinyl protons. The order of chemical

(1) (a) This work was supported in part by Grant 634 of the University Research Committee of the University of Alabama to R. H. Garner and U. S. Public Health Service Grant 1 RO1 ES00464-01 from the National Institute of Environmental Health Sciences to A. W. Hayes. (b) NDEA Fellow, 1967–1970.

(2) (a) G. H. Alt in "Enamines," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, p 115; (b) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 794 (1964); (c) *ibid.*, **29**, 798 (1964); (d) *ibid.*, **30**, 1407 (1965).

(3) S. Danishefsky and R. Cavanaugh, *Chem. Ind. (London)*, 2171 (1967).

(4) J. Goerdeler and U. Keuser, *Ber.*, **97**, 2209 (1964).

(5) C. A. Grob and H. J. Wilkens, *Helv. Chim. Acta*, **50**, 725 (1957).

(6) S. Hunig, E. Benzing, and E. Lucke, *Ber.*, **90**, 2833 (1957).

(7) N. J. Leonard and J. A. Adamick, *J. Amer. Chem. Soc.*, **81**, 595 (1959).

(8) A. I. Meyers, A. H. Reine, and R. Gault, *J. Org. Chem.*, **34**, 698 (1968).

(9) W. D. Gurowitz and M. A. Joseph, *ibid.*, **32**, 3289 (1967).

(10) K. Nagarajan and S. Rajappa, *Tetrahedron Lett.*, 2293 (1969).

shifts with respect to the amino group is as follows: morpholino > piperidino > dimethylamino pyrrolidino (*e.g.*, **16** > **20** > **18** > **14** and **17** > **21** > **19** > **15**).

Enamino ketones may be considered as α,β-unsaturated ketones with an amino substituent at either the α or β position. The amino and keto groups, respectively electron releasing and electron withdrawing, exert opposing effects on the electron shielding of the enamine vinyl proton in both types of enamino ketones. Hence, the vinyl proton signals in the enamino ketones are observed at lower field than those of the simple enamines and at higher field than those of the corresponding α or β protons in the conjugated ketones. Structures **3** and **4** demonstrate that the conjugative electron withdrawal of the keto group is greater at the β position than the α position. The vinyl proton signals of the 2-amino-2-cycloalkenones, **24**–**27**, appear at lower field than those of the 3-amino-2-cycloalkenones, **28**–**34**, a comparison that is qualitatively similar to the relative chemical shifts of α and β protons in 2-cycloalkenones **22** and **23**. A greater electron density is indicated at the enamine carbon termini for the 3-amino-2-cycloalkenones than is the case for the 2-amino-2-cycloalkenones.

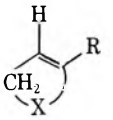
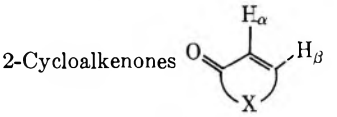
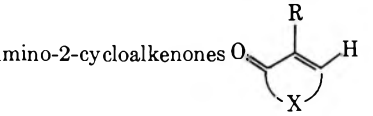
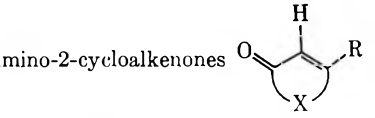
In the 3-amino-2-cycloalkenone systems the vinyl proton chemical shifts are smaller for five- than six-membered-ring derivatives (**30** < **28**, **32** < **31**, **34** < **33**), an indication that the generalization of greater nitrogen lone-pair-electron delocalization to the enamine carbon termini in five- *vs* six-membered rings observed in simple enamines also appears to apply to the 3-amino-2-cycloalkenones. However, the ir data indicate that the 3-pyrrolidino group is more effective in lowering the carbonyl stretching frequency in six- than in five-membered rings ($\Delta\nu$ for **28** *vs.* **22** = 96 cm^{-1} compared to $\Delta\nu$ for **30** *vs.* **23** = 74 cm^{-1}). The pyrrolidino group also produces a larger bathochromic shift in the uv for six- than for five-membered-ring derivatives ($\Delta\lambda$ for **28** *vs.* **22** = 77 nm compared to $\Delta\lambda$ for **29** *vs.* **23** = 62 nm). These observations suggest that in the 3-amino-2-cycloalkenone system electron density at carbon may be greater in five-membered-ring derivatives (structure **11** important) and electron density at oxygen may be greater in six-membered-ring derivatives (structure **12** important).

In the case of the 2-amino-2-cycloalkenones the larger shifts of vinyl protons in **25** and **27** compared to **24** and **26** appear to contradict the generalization that nitrogen lone-pair delocalization is greater into five- than six-membered rings. This point is clarified by the fact that the β proton in **23** is markedly less shielded than the β proton in **22** ($\Delta\nu$ = 0.76 ppm), an indication that a ring-size effect allows greater electron withdrawal from the β proton of α,β-unsaturated ketones in five- than in six-membered rings. It should be noted that the difference between the chemical shifts for the vinyl proton of **25** and the β proton of **23** (1.93 ppm) is greater than that between **24** and the β proton of **22** (1.45 ppm). Thus, greater delocalization of nitrogen lone-pair electrons into five- than six-membered rings also applies to the 2-amino-2-cycloalkenone systems, but the trend toward smaller chemical shifts for the five-membered-ring derivatives is reversed by the greater electron-withdrawal effect of the keto group in five- than in six-membered ring. Consequently, both structures **8** and **9** are more important in five- than in six-membered rings.

Since the 3-amino-2-cycloalkenones may be considered to be vinylogous amides, it was apparent that the

TABLE I

NMR CHEMICAL SHIFTS OF VINYL PROTONS AND OTHER SPECTRAL DATA OF ENAMINES AND ENAMINO KETONES

Compd[a]	Chemical shift of vinyl proton ppm	Ir (C=O, C=C), cm^{-1}	Uv, λ_{max} (log ϵ), nm
Enamines 			
14 [R = Py; X = $(CH_2)_3$]	4.27		
15 [R = Py; X = $(CH_2)_2$]	4.00		
16[b] [R = Mp; X = $(CH_2)_3$]	4.57		
17 [R = Mp; X = $(CH_2)_2$]	4.37		
18 [R = Dm; X = $(CH_2)_3$]	4.46		
19 [R = Dm; X = $(CH_2)_2$]	4.16		
20[b] [R = Pp; X = $(CH_2)_3$]	4.53		
21[b] [R = Pp; X = $(CH_2)_2$]	4.25		
2-Cycloalkenones 			
22[c] [X = $(CH_2)_3$]	5.93 (H_α)	1691	225 (4.14)
	6.99 (H_β)	1621	
23[c] X = $(CH_2)_2$]	6.10 (H_α)	1720	217 (4.06)
	7.75 (H_β)	1593	
2-Amino-2-cycloalkenones 			
24 [R = Py; X = $(CH_2)_3$]	5.54	1674	217 (3.68)
25 [R = Py; X = $(CH_2)_2$]	5.82	1699 1606	
26 [R = Py; X = $CH(CH_3)CH_2$]	5.72	1700 1610	214 (3.78) 314 (3.48)
27 [R = Mp; X = $(CH_2)_2$]	6.32		
3-Amino-2-cycloalkenones 			
28 [R = Py; X = $(CH_2)_3$]	5.06	1595 1546	302 (4.54)
29 [R = Py; X = $CH_2C(CH_3)_2CH_2$]	5.04	1598 1548	303 (4.53)
30 [R = Py; X = $(CH_2)_2$]	4.87	1646 1543	279 (4.40)
31 [R = Mp; X = $(CH_2)_3$]	5.24		
32 [R = Mp; X = $(CH_2)_2$]	5.05	1650 1550	281 (4.70)
33 [R = Dm; X = $CH_2C(CH_3)_2CH_2$]	5.14		305 (4.41)
34 [R = Dm; X = $(CH_2)_2$]	4.92	1635 1575	278 (4.12)

[a] Py = pyrrolidino, Mp = morpholino, Dm = dimethylamino, Pp = piperidino. [b] Data taken from ref 10. [c] E. S. Waight and H. N. A. Al-Jallo, *J. Chem. Soc.* (*B*), 73 (1966).

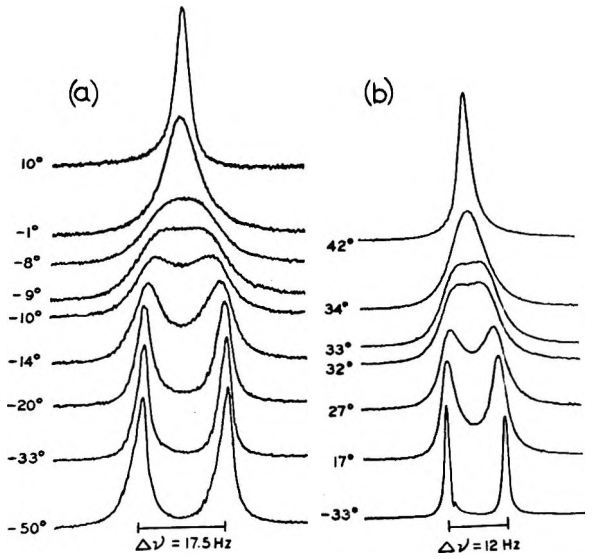
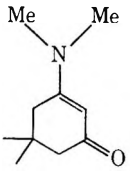


Figure 1.—The 100-MHz nmr spectra of methyl signals of (a) **33** and (b) **34** in $DCCl_3$ solution at various temperatures.

dnmr method of determining differences in rotational barriers about the C–N bond could be used for evaluating differences in the extent of nitrogen lone-pair-electron delocalization in these systems. An analogous nmr study of the C—N bond rotational barrier in the noncyclic vinylogous amide 3-dimethylaminoacrolein, $(CH_3)_2NCH{=}CHCHO$, reports the activation free energy for rotation at the coalescence temperature to be 15.8 kcal/mol.[11] In the present case the dimethylamino derivatives **33** and **34** were chosen for study be-



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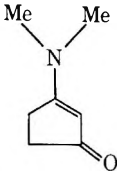


34

cause of the simplicity of the analysis. The nmr spectra for the *N*,*N*-dimethyl singlets of **33** and **34** over a temperature range including the coalescence point are shown in Figure 1. In the case of **33** the methyl signals are separated by a frequency difference of 17.5 Hz and coalesce at −9°. The separation of methyl signals in **34** is 12 Hz and coalescence occurs at 33°.

Activation free energies for rotations were calculated by use of the Eyring equation[12] employing rotational rate constants calculated at coalescence temperatures.[13] The data and results of the calculations are summarized in Table II. Although the approximate methods employed may introduce considerable uncertainty regarding the absolute accuracy of the results,[14] comparison of the two results obtained by this method should be meaningful. The 2.4-kcal/mol greater activation free energy for **34** is a significant indication of a higher rotational barrier for the C—N bond in the five-membered-ring derivative compared to that in the six-membered analog. The higher rotational barrier in **34** indicates greater nitrogen lone-pair-electron delocalization in this system, a conclusion in agreement with previously presented data.

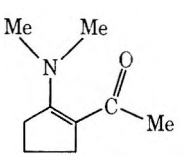
TABLE II

ACTIVATION FREE ENERGIES FOR ROTATION ABOUT THE C—N BOND IN ENAMINO KETONES

Compd	T_c, C°	$\Delta\nu$	ΔG^*, kcal/mol	$\Delta\Delta G^*$
33	−9	17.5	13.5	
				2.4
34	33	12.0	15.9	

The qualitative observation was made that in the ambident temperature spectra of **29** and **30** the signals for the CH_2N protons of **30** were partially resolved into a set of triplets. The analogous signals for **29** were unresolved, indicating a lower coalescence temperature and probably a lower free energy of activation for the six-membered-ring derivative **29**.

To determine the effect on rotational barriers of fixed trans *vs.* cis geometry of the enamine double bond, an attempt was made to obtain comparative data on the *cis*-enamino ketones **35** and **36**. The syntheses of **35**



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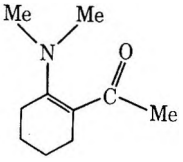

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and **36** involved acetylation of the 1-dimethylaminocyclopentene and 1-dimethylaminocyclohexene, respectively. Inspection of the nmr spectra of the distilled products of these reactions indicated that both **35** and **36** were present in ~1:1 ratio with the corresponding unconjugated double-bond isomers, an observation similar to other reported cases of acetylation of enamines.[15] No convenient separation of these isomeric product mixtures was devised, but the nmr spectra of both product mixtures containing **35** and **36** were examined at various temperatures. No significant changes were noted in either spectra at temperatures as low as −60°, an indication that the coalescence temperatures and rotational barriers for **35** and **36** are relatively low compared to those of **33** and **34**.

Experimental Section

Nmr spectra were obtained on a Varian HA-100 spectrometer using solutions in deuterated chloroform. Chemical shifts are reported in parts per million downfield from tetramethylsilane used as an internal standard. Mass spectra were obtained using a CEC 21-104 spectrometer. Ir spectra were taken on a Perkin-Elmer Model 337 spectrophotometer. Uv spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer. Melting and boiling points are uncorrected.

General Procedures for Preparation of Morpholino and Pyrrolidino Enamines and Enamino Ketones.—Enamines **14**, **15**, and **17** were prepared by the method of Stork, *et. al.*[16] The same procedure was used for the preparation of enamino ketones **24**–**26** using 1.75:1.00 molar ratios of pyrrolidine and the appropriate diketones in refluxing benzene. Enamines **18** and **19** were prepared by the method of Blanchard.[17] Enamino ketones **27**–**32**

(11) (a) H. E. A. Kramer and R. Gompper, *Z. Phys. Chem. (Frankfurt am Main)*, **43**, 292 (1964); (b) H. E. A. Kramer, *Justus Liebigs Ann. Chem.*, **696**, 28 (1966).

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(16) G. Stork, A. Brizzolara, H. Landesman, J. Szmusovisz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 345 (1963).

(17) E. P. Blanchard, *J. Org. Chem.*, **28**, 1397 (1963).

TABLE III

PHYSICAL DATA FOR ENAMINES AND ENAMINO KETONES

Compd	Bp (mm) or mp, °C	Lit. bp (mm) or mp, °C	Nmr, δ[a] (J, Hz)	Mass spectrum (70 eV) M$^+$ (rel intensities)
14	108–109 (20)	105–107 (13)[b]		
15	93–94 (18)	88–92 (13)[b]		
17	111–115 (19)	104–106 (12)[b]		
18	80–85 (35)	81 (35)[c]		
19	72–84 (95)	85–86 (104)[c]		
24	68–70 (0.1)	70–71 (0.2)[d]		165 (87), 150 (31), 137 (38), 136 (100), 109 (35), 108 (39), 81 (45), 70 (58)
25	83–84 (0.5)		5.82 (t, J = 3, 1 H, =CH) 3.1–3.4 (t, J = 7, 4 H, CH_2) 2.25–2.55 (m, 4 H, CH_2CH_2CO) 1.65–2.0 (m, 4 H, CH_2)	
26	69–70 (1.0)	85–90 (0.4)[e]	5.72 (apparent t, J = 3.5, 1 H, =CH) 3.1–3.5 (m, 4 H, CH_2N) 2.05–2.7 (m, 3 H CH_2CH) 1.9 (m, 4 H, CH_2CH_2) 1.1 (d, J = 7, 3 H, CH_3)	
27		59–60	6.32 (apparent t, J = 3, 1 H, O=CH) 3.74 (m, 4 H, OCH_2) 3.07 (m, 4 H, NCH_2) 2.44 (m, 4 H, $=CCH_2CH_2CO$)	
28	86–88	84–88[f]		
29	134–135	131–133[g]		
30[b]	104–105		4.87 (s, 1 H, =CH) 3.10–3.55 (2 t, J = 6, 4 H, CH_2N) 2.25–2.70 (2 t, J = 4, 4 H, CH_2CH_2CO) 1.90–2.20 (m, 4 H, CH_2)	151 (77), 123 (24), 122 (100), 108 (38), 95 (67), 44 (32), 81 (16), 70 (27)
31[b]	93–95		5.24 (s, 1 H, =CH) 3.67 (m, 4 H, OCH_2) 3.25 (m, 4 H, NCH_2) 1.80–2.45 (m, 6 H, $=CCH_2CH_2CH_2CO$)	
32[b]	106–107		5.05 (s, 1 H, =CH) 3.7–3.8 (t, J = 6, 4 H, OCH_2) 3.35–3.45 (t, J = 6, 4 H, NCH_2) 2.3–2.7 (2 t, J = 7, 4 H, CH_2CH_2CO)	167 (100), 137 (4), 110 (29), 109 (26), 108 (29), 85 (38), 81 (48), 55 (70)

[a] s, singlet; d, doublet; t, triplet; 2 t, two triplets partially resolved; m, multiplet. [b] Reference 16. [c] Reference 17. [d] R. A. Jerussi, *J. Org. Chem.*, **34**, 3648 (1969). [e] R. T. Dahill, Jr., *ibid.*, **31**, 2694 (1966). [f] Reference 18. [g] Reference 7.

were prepared using the procedure reported by Panouse and Sannie[18] for the preparation of **28**. Physical data on these compounds are recorded in Table III. In the case of compounds previously reported comparative literature physical constants are recorded. Mass spectral and nmr data are included for compounds not previously reported in the literature. Difficulties in purification prevented satisfactory characterization of these compounds by elemental analysis. However, in all cases spectral evidence supports the assigned structures.

General Procedure for Preparation of Dimethylamino Enamino Ketones.—A pressure bottle was charged with ~0.03 mol of the appropriate diketone in 100 ml of either anhydrous ether or *p*-dioxane and an excess of either anhydrous calcium chloride or sodium carbonate and cooled in an ice bath. After the addition of a fourfold excess of dimethylamine, the bottle was sealed and heated at ~80° in an oil bath overnight. After cooling the bottle was opened and the reaction mixture filtered. The residue was washed sparingly with chloroform and the organic phases were combined. After removal of the solvent, the residual oil or solid was crystallized (ether for **33**, 1:5:10 methylene chloride–ether–pentane for **34**) to yield 60–70% of the dimethamino enamino ketone containing a small amount of the starting diketone. Physical data on these compounds are included in Table III.

Registry No.—**24**, 18543-93-6; **25**, 36287-24-8; **26**, 4933-43-1; **27**, 24454-33-9; **28**, 19805-73-3; **29**, 3357-16-2; **30**, 36287-28-2; **31**, 16179-67-2; **32**, 36287-30-6; **33**, 31039-88-0; **34**, 36287-32-8.

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Electrochemical and Spectroscopic Studies of Cation Radicals. I. Coupling Rates of 4-Substituted Triphenylaminium Ions

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Data are presented on the electrochemically determined coupling rates of 21 mono-para-substituted triphenylaminium cation radicals in acetonitrile at platinum. There is a definite trend in coupling rate as a function of substituent; *i.e.*, there appears to be a Hammett-type relationship. Most substituent effects can be adequately described by σ^+ values from carbonium ion reactions with the exception of strong electron-donating functional groups. These substituents lend enhanced stabilization to cation radicals above that in carbonium ions. These data are intended to serve as a basis for further electrochemical and spectroscopic studies into the effects of substituents on cation radical stabilities.

Cation radicals as acknowledged entities are relative newcomers to the field of organic chemistry. In the past few years, their presence has been confirmed in an ever-increasing number of electroorganic oxidations. In fact, data are accumulating at such a rate that the future may see the cation radical cited as the primary intermediate in organic electrooxidations. Due to their present and projected importance, it would seem desirable to acquire data that would characterize the behavior of these species as a whole. Of primary importance is the effect of substituents upon cation radical stabilities; substituent effects in unoxidized molecules have been extensively, if not completely, characterized. However, the paucity of data for cation radicals is striking but understandable due to their relatively short chemical history. This communication is the first of a series that is intended to help alleviate this information gap.

In studying substituent effects on cation radical properties, one might anticipate Hammett-type behavior, *i.e.*, a linear relationship between various radical properties and substituent reactivity constants assigned to the various functional groups. Initially, one would attempt to correlate radical properties with σ^+ values, reactivity parameters pertinent to carbonium ion reactions. Hopefully, the existing σ^+ values might apply within the limits of experimental error to the cation radical systems. If this were not the case, then a new series of substituent reactivity constants would have to be obtained from empirical data to fit the properties of cation radicals.

The assumption of Hammett-type behavior, even in a qualitative sense, for cation radicals is at present questionable. In fact, Walter has proposed non-Hammett behavior for a series of triarylaminium cation radicals based on epr and visible absorption spectra,[2] with an LCAO–MO treatment to back up the experimental data. However, contradictory spectral data have been presented on both triarylaminium cation radicals[3] and para-substituted *N,N*-dimethylanilinium radicals[4] which indicate that the behavior of arylaminium cation radicals may obey the Hammett relationship at least in a qualitative sense. In view of this controversy over the available spectral data, it was felt that electrochemical studies would be more reliable as a starting point; once a firm basis were established difficulties with spectral data could, hopefully, be resolved. Certainly, a truly reliable set of substituent parameters should apply to spectral as well as electrochemical data.

In the electrochemical oxidation of triphenylamines in acetonitrile, it has been proposed that the initial step is the formation of the cation radical; two of these then couple in solution to form a substituted tetraphenylbenzidine (TPB).[5,6] Quantitative data have been obtained for several 4-substituted triphenylamines in the form of second-order coupling rate constants, and it was generally found that electron-donating substituents tended to stabilize the cation radicals while electron-withdrawing groups had the opposite effect.[7-9] Even based on the behavior of the relatively few derivatives for which quantitative data were obtained it was obvious that the substituents were exerting a large effect on the rate constant in a predictable fashion; hence, it was hoped that these systems would serve as a sensitive probe for studying substituent effects upon cation radical properties.

Experimental Section

The coupling rate constants were determined using either chronoamperometry or rotating disk voltammetry, the former for systems with relatively slow coupling rates and the latter for those with rapid decomposition of the cation radicals. These two techniques complement one another nicely, since chronoamperometry is useful in the second-order rate constant range of 10^{-1} to 10^{3} mol^{-1} sec^{-1} and rotating disk is usable over the range of 10^{3} to 10^{8}. The instrumentation for chronoamperometric studies was standard; that for rotating disk voltammetry employed "rotoamperometry" for rapid data acquisition.[10]

In the triphenylamine systems, the kinetic behavior does not strictly fit any of the extreme cases for which digital simulation working curves are available.[8,9] However, the $K = 0/0$ case best approximates these systems; so it was chosen. In this case one is assuming that there are no ECC complications (*i.e.*, amine cation radical oxidizing the benzidine parent) competing with the purely electrochemical steps. Since the E°'s for the amine and benzidine couples are always fairly close, this seems a reasonable assumption. Also, since all the working curves nearly coincide over a fairly wide range of N_{app}, selection of a particular working curve is not critical if one works on this coincidental portion.

In Table I, the digital output of the chronoamperometric

(1) Correspondence should be addressed to the University of Idaho.
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TABLE I

DIGITAL FORM OF THE CHRONOAMPEROMETRIC WORKING CURVE FOR THE MECHANISM

$$A \overset{1e^-}{\rightleftharpoons} B;\ 2B \xrightarrow{k} C;\ C \overset{2e^-}{\rightleftharpoons} D$$

N_{app}[a]	Log ktC_A[b]	N_{app}	Log ktC_A
1.028	−1.699	1.720	0.301
1.036	−1.599	1.753	0.401
1.044	−1.499	1.782	0.501
1.055	−1.399	1.806	0.601
1.068	−1.299	1.826	0.701
1.084	−1.199	1.844	0.801
1.104	−1.099	1.858	0.901
1.128	−0.999	1.871	1.001
1.156	−0.899	1.882	1.101
1.189	−0.799	1.891	1.201
1.227	−0.699	1.900	1.301
1.270	−0.599	1.908	1.401
1.317	−0.499	1.915	1.501
1.369	−0.399	1.921	1.601
1.423	−0.299	1.927	1.701
1.479	−0.199	1.932	1.799
1.534	−0.099	1.937	1.899
1.587	0.001	1.942	1.998
1.636	0.101	1.946	2.098
1.680	0.201	1.950	2.198
		1.954	2.298

[a] N_{app} = apparent number of electrons per molecule at any time during the electrochemical process, or $(it^{1/2}/C_A)_{kinetic}/(it^{1/2}/C_A)_{one\text{-}eletron}$. [b] t = electrolysis time for the corresponding value of N_{app}; C_A = initial concentration of parent amine.

working curve used is presented for convenience. The same type of data for other working curves is available upon request.

A more serious consideration is that the slopes of the working curves become very small at the extremes so that a slight error in determining N_{app} is magnified tremendously in calculating the rate constant. In practice, it appears that the chronoamperometric working curves are only quite reliable between N_{app} values of 1.15–1.60, where the slope is relatively large. Therefore, it was necessary to juggle concentration of the amine and the measurement time gate to get within this region on the working curve.

Another thorny experimental problem was estimation of one-electron values for the various derivatives. This was not difficult for the systems with slow radical decomposition rates since the first electrochemical step could be readily monitored at low amine concentrations and short time gates. For the other systems, one-electron values had to be estimated from calculated diffusion coefficients[9] and from long time gate experiments and high amine concentrations (where the ECE process proceeds essentially to completion) for chronoamperometric studies; for rotating disk work, one-electron values could be readily obtained for all the compounds investigated.

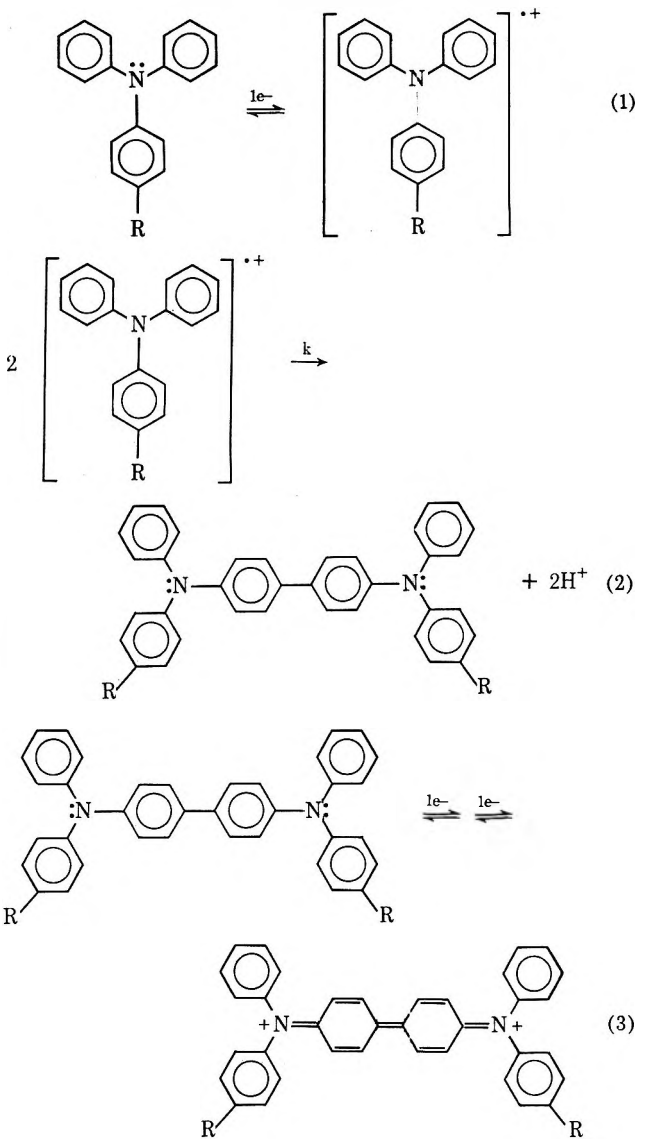
In acetonitrile–0.1 F tetraethylammonium perchlorate (TEAP), the solvent system used for this work, the maximum time allowable for running current–time curves was found to be about 8 sec. After this time convection usually sets in, thus distorting the curves. At short times (0.1–0.6 sec) large background corrections were necessary on low-concentration runs, making work in this range difficult at best. Background corrections were often not necessary, but they were carried out for all runs.

The values listed for the second-order coupling rate constants are averages of from 6 to 12 runs on each compound; the uncertainties listed are the extreme variations from the average values. Runs were carried out over at least a tenfold variation in concentration for each compound to detect a concentration-dependent variation of k; none was found. Although there were variations in the rate constants with concentration, they were generally random. As mentioned, it was found that the best results were obtained when operating on the linear portions of the working curves, that is between N_{app} values of 1.15 to 1.60. A good deal of the deviation in the measurements accrued from working outside this region.

In all these systems, benzidines are formed from the triphenylamines by intermolecular coupling (*vide infra*). In some cases,

SCHEME I

ANODIC OXIDATION PATHWAY FOR 4-SUBSTITUTED TRIPHENYLAMINES



the benzidines formed have been previously characterized;[7] for a number of other amines generation of the corresponding benzidines was verified by electrochemical and spectroscopic methods, as well as by chemical isolation. For all systems controlled-potential electrolyses were carried out, and the presence of the corresponding benzidines was confirmed both electrochemically and spectroscopically in solution; in all cases the amount of benzidine formed was at least 90% of the anticipated amount, with the exception of the methylthio derivative (*vide infra*).

Based on these experiments, it is felt with reasonable certainty that no extraneous chemical complications are affecting the processes shown in Scheme I during the time scales involved in the chronoamperometric and rotating disk experiments (8–30 sec).

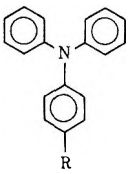
All measurements were conducted at 22 ± 1° in a one-compartment cell. Platinum button electrodes were employed for both rotating disk and chronoamperometry studies with a platinum wire auxiliary and sce reference. The $E_{1/2}$ values were obtained from rotating disk voltammograms at rotation rates where the chemical follow-up reaction would be completely outstripped. This was possible in all cases in the rotation range of 2000–8000 rpm. These values, then, are *true* $E_{1/2}$'s not shifted by associated chemical reactions.

Compound preparation was straightforward in all cases. Triphenylamine itself was Eastman White Label and was recrystallized from methanol.

In many cases, the substituted triphenylamines were prepared by Ullmann reactions using either 1 mol of para-substituted

TABLE II

PREPARATIVE DATA ON 4-SUBSTITUTED TRIPHENYLAMINES



R	Registry no.	Method of preparation	Recryst medium	Mp, °C	Lit mp, °C (ref)
OCH_3	4316-51-2	Ullmann reaction	Hexane	104–105	104 (15)
OC_2H_5	4316-52-3	Ullmann reaction	Ethanol–hexane	89–90[a]	
OC_6H_5	36809-17-3	Ullmann reaction	Benzene–hexane	107–108[a]	
SCH_3	36809-18-4	Ullmann reaction	Hexane	83–84[a]	
$NHCOCH_3$	4316-77-2	Ullmann reaction	Methanol–water	199–201	195 (16)
C_6H_5	4432-94-4	Ullmann reaction	Methanol	109–110	110 (17)
CH_3	4316-53-4	Ullmann reaction	Methanol	68–69	68–69 (18)
C_2H_5	36809-22-0	Ullmann reaction	Ethanol–hexane	53–54[a]	
t-C_4H_9	36809-23-1	Ullmann reaction	Heptane	52–53[a]	
H	603-34-9	Commercial product	Methanol	126–127	
F	437-25-2	Ullmann reaction	Ethanol–hexane	101–102	98–98.5 (19)
Cl	4316-56-7	Ullmann reaction	Hexane	108–109	106–107 (20)
Br	36809-26-4	Bromination of triphenylamine	Heptane	112–114	94–96 (11)
$COOCH_3$	25069-30-1	Ullmann reaction	Acetonitrile	86–87	88 (23)
CHO	4181-05-9	Formylation of triphenylamine	Ethanol	132–134	132–133.5 (13)
$COCH_3$	1756-32-7	Ullmann reaction	Benzene–ethanol	138–140	142–143 (21)
COC_6H_5	16911-33-4	Ullmann reaction	Benzene–hexane	126–127	127–128 (22)
$SO_2N(C_2H_5)_2$	36809-31-1	Ullmann reaction	Benzene–ethanol	91–93	
CF_3	36809-32-2	Ullmann reaction	Benzene–heptane	104–105	
CN	20441-00-3	Ullmann reaction	Ethanol	126–127	126–127 (7)
NO_2	4316-57-8	Nitration of triphenylamine	Methanol	140–142	139–142 (14)

[a] New compound. Analytical data show C, H, and N analyses within ±0.4% of theoretical values: Ed.

aniline and 2 mol of iodobenzene or mole-per-mole amounts of diphenylamine and the appropriate para-substituted iodobenzene. The reactions were run at about 200° for 12–18 hr; potassium carbonate was added to take up the HI liberated, and copper powder was used as a catalyst. No solvent was used in most cases; when the reaction mass would solidify, a few milliliters of xylene was added. It was found that the elimination of solvent from the reaction increased the yields considerably over earlier syntheses. Yields of 40–80% were routinely achieved using the above conditions.

The hot reaction mixtures were extracted with hexane whenever possible, benzene being used in alternate cases; the extraction liquids were then chromatographed on Woelm neutral alumina with hexane or benzene using a column with a diameter of 20 mm and a length of 300–400 mm. Recrystallizations were effected from various media; these data, along with uncorrected melting points, are presented in Table II. Completion of the Ullmann reactions and formation of the desired products were verified by electrochemical behavior and infrared spectra (absence of N–H peak), as well as by CHN analyses.

Three of the amines were prepared by direct substitution reactions. Bromination with *N*-bromosuccinimide in dry benzene yielded 4-bromotriphenylamine,[11,12] and triphenylamine-4-aldehyde was prepared by formylation of triphenylamine with *N*,*N*-dimethylformamide and phosphoryl chloride.[13] 4-Nitrotriphenylamine was prepared by nitrating triphenylamine with a nitric acid–acetic acid mixture using the procedure of Herz.[14] The product was chromatographed on Woelm neutral alumina with benzene–ether and recrystallized from methanol. Physical data were available for a number of other derivatives;[15-23] for those compounds not previously reported CHN analyses were run, and the precentages agreed with calculated values to within ±0.4%.

Hückel molecular orbital calculations employed parameters used previously.[7]

σ^+ values were used for all substituents for which values were available; these data were taken from the compilation of Brown and Okamoto.[24] Where σ^+ constants were not available, σ values were used; these were extracted from a standard source.[25]

The σ^+ values chosen are for para-substituted derivatives. In the case of these coupling reactions, where the coupling site is far removed from the substituents, this choice is open to question. However, the open para positions are, in fact, in conjugation with the substituents through the amine nitrogen and, as evidenced by the large variation in the coupling rate constant with substituent, the extent of conjugation is considerable.

Results and Discussion

The anodic oxidations of 4-substituted triphenylamines have been proposed to go by the pathway shown in Scheme I. The only aspect of the mechanism that is

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TABLE III

ELECTROCHEMICAL DATA ON 4-SUBSTITUTED TRIPHENYLAMINES

No.	Substituent	$E_{1/2}$[a]	n value[b]	σ^+ (σ)[c]	k, mol^{-1} sec^{-1}
1	OCH_3	0.79	1.98	−0.78	$6 \pm 2 \times 10^{-1}$
2	OC_2H_5	0.80	2.01	−0.78	$8 \pm 3 \times 10^{-1}$
3	$NHCOCH_3$	0.82	2.02	−0.6	1.5 ± 0.4
4	OPh	0.87	2.02	−0.5	4.0 ± 1.0
5	SCH_3	0.82	0.97		
6	CH_3	0.90	1.99	−0.31	$9.0 \pm 1.0 \times 10^1$
7	C_2H_5	0.89	2.03	−0.30	$1.0 \pm 0.1 \times 10^2$
8	t-C_4H_9	0.91	2.06	−0.26	$1.0 \pm 0.1 \times 10^2$
9	C_6H_5	0.92	2.10	−0.18	$6.0 \pm 0.6 \times 10^1$
10	F	1.04	2.03	−0.07	$5.0 \pm 0.8 \times 10^2$
11	H	1.00	2.02	0.00	$1.2 \pm 0.4 \times 10^3$
12	Cl	1.05	1.94	0.11	$6.5 \pm 1.3 \times 10^2$
13	Br	1.05	1.96	0.15	$1.4 \pm 0.3 \times 10^3$
14	$COCH_3$	1.16	2.01	(0.50)	$2.6 \pm 0.7 \times 10^3$
15	COC_6H_5	1.16	2.03	(0.50)	$3.0 \pm 0.9 \times 10^3$
16	$COOCH_3$	1.15	2.00	0.48	$3.3 \pm 1.0 \times 10^3$
17	CHO	1.18	2.04	(0.22)	$4.7 \pm 1.5 \times 10^3$
18	CF_3	1.17	2.07	(0.54)	$6.4 \pm 2.0 \times 10^3$
19	$SO_2N(C_2H_5)_2$	1.17	2.06	(0.57)	$7.2 \pm 2.3 \times 10^3$
20	CN	1.22	2.05	(0.66)	$1.0 \pm 0.3 \times 10^4$
21	NO_2	1.25	2.02	(0.79)	$1.4 \pm 0.4 \times 10^4$

[a] Values taken from rotating disk voltammograms. [b] These data were obtained by controlled-potential coulometry of roughly millimolar solutions. [c] Numbers in parentheses are σ values; others are σ^+.

open to serious question is whether the coupling step occurs *via* a radical–radical or radical–parent pathway. The experimental data available suggest very strongly that it is indeed a radical–radical coupling reaction.[9]

This being the case, then, the variation in the coupling rate constant as a function of the substituent in the 4 position should yield definitive information regarding the effects of functional groups on cation radical stabilities. The coupling rates are presented in Table III along with some standard electrochemical data. In all cases, n values of 2.0 ± 0.1 were obtained; this is what one would anticipate if the amines were being quantitatively transformed to the corresponding benzidines with no further chemical complications present. The only exception to this was the methylthio derivative, which does not form the corresponding benzidine upon oxidation. The product formed has not been identified, but it is significant to note that the decomposition rate for the cation radical of this species is quite slow, about that of the alkoxy derivatives. Thus, one can say that, qualitatively, the methylthio group tends to lend considerable stabilization to the triphenylamine cation radical. This marked stabilization for cation radical species by the methylthio group has been noted in other systems;[26,27] so it appears to be a general phenomenon.

In Figure 1, the data are plotted as log k *vs.* σ^+ or σ. The only alteration from the values given in Table III is for triphenylamine itself to correct for the fact that there are more coupling sites available for this molecule than for the others having a single para substituent. Thus, for two 4-substituted triphenylaminium cation radicals there are four possible coupling site combinations while for the triphenylaminium radical itself there are nine. Because of this, the k value for triphenylamine in Table III was multiplied by $^4/_9$ for plotting in Figure 1. The numbers in the diagram correspond to the various substituents as listed in Table III, as are the uncertainty limits.

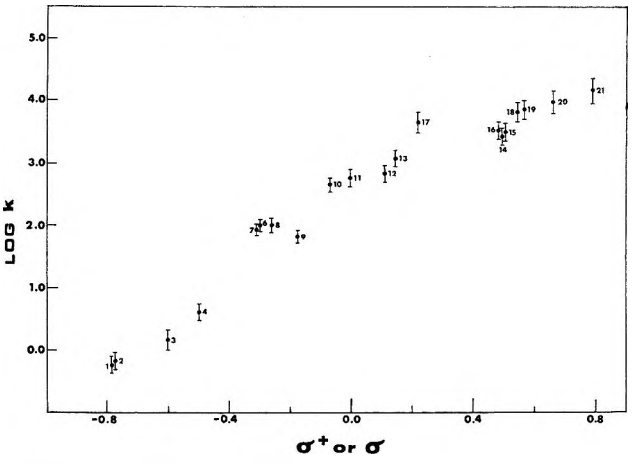


Figure 1.—Plot of second-order coupling rate constants *vs.* Hammett substituent constants. Numbered points correspond to those in Table III. Points 1 and 2 are slightly offset to avoid confusion in the presentation of error limits.

A straight line is not included in Figure 1 because of the scatter in several of the points. A hypothetical line with little scatter could be drawn through points 6–8, 10–16, and 18–21. Using these points, a plot of log k_x/k_0 *vs.* σ^+ yields a ρ value of 2.0. This substantial value reflects the marked effect of substituent on the coupling rate. A plot using only σ values showed a great deal more scatter than the data in Figure 1 and in particular compounds 1–4 were a good deal to the right of their positions in Figure 1. The better agreement with σ^+ than with σ values for the electron-donating substituents is indicative of a polar transition state (the cation radical) which is stabilized by strong electron-donating substituents.

It is noteworthy that points for compounds 1–4, all containing strong electron-donating functional groups, lie below the hypothetical line. This infers that the

(26) A. K. Carpenter and R. F. Nelson, unpublished data.
(27) A. Zweig and J. E. Lehnsen, *J. Amer. Chem. Soc.*, **87**, 2647 (1965).

σ^+ values available for carbonium ion reactions are not sufficiently negative to account for the stabilization of cation radicals by these substituents. It has been shown that methoxy groups do indeed stabilize carbonium ions by resonance stabilization due to charge localization on the substituent;[28] in free radicals, however, it has recently been demonstrated that methoxy group stabilization is small.[29] In cation radicals, it appears that the stability of the radical depends on keeping the unpaired electron density at the potential reaction site minimal. Therefore, resonance forms where the unpaired electron is localized at other positions will contribute to enhanced stability.

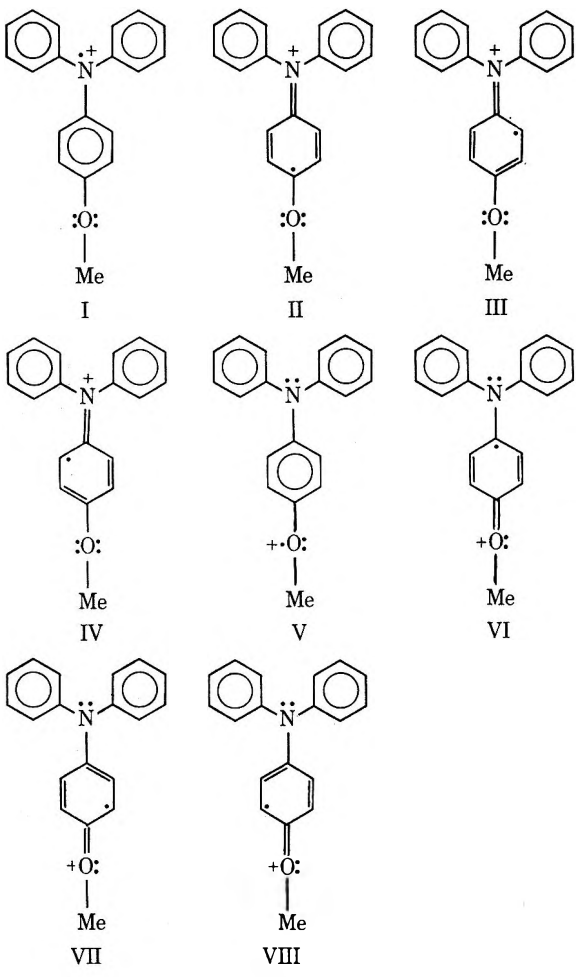
Two points need to be rationalized, namely, the facts that strong electron donors lend stabilization to the cation radicals above that present in carbonium ions and the apparent fact that electron-withdrawing groups have little or no additional effect on cation radicals relative to carbonium ions. For the first point, it is instructive to consider the resonance forms that can be reasonably drawn for the 4-methoxytriphenylaminium radical cation and the 4-methoxytriphenylmethyl carbonium ion as shown in Chart I. Resonance forms not involving the substituted rings are not shown since they would always be equivalent. Forms I–IV for the cation radical, where the unpaired electron and positive charge are localized on the central nitrogen and the ring positions ortho and para to it, are matched by forms I–IV for the carbonium ion. Forms V for each are also reasonably substantial contributors since the methoxy group can readily accommodate the positive charge and unpaired electron. In the cation radical, forms VI–VIII show the charge on the oxygen and the unpaired electron ortho and para to the methoxy group. Equivalent forms for the carbonium ion such as VI would require an unreasonable triplet state configuration; VII and VIII are not shown, but the same reasoning would apply. Clearly, the cation radical would be predicted to be considerably more stable based on consideration of these resonance forms. The remarkable stabilization of these cation radical systems by strong electron donors is further verified by the fact that the coupling rate for 4-dimethylaminotriphenylamine is so slow as to be immeasurable;[30] thus, this substituent stabilizes the radical to such an extent that decomposition is negligible. This is to be anticipated, since the unpaired electron and positive charge would be fairly equally divided between the two amine nitrogens.

The same type of comparison is shown in Chart II for the corresponding nitro derivatives. Here, forms I–IV are again equivalent for both, and when further electron distributions such as V and VI for the cation radical and V for the carbonium ion are considered, one sees that any further resonance effect would not be anticipated in either case. The net effect is that the strong electron-donating substituents, acting as ortho–para directors, spread the electron density around the substituted ring at the expense of the unsubstituted rings. The electron-withdrawing groups, acting as meta directors, only overlap the effect of the amine nitrogen and thus the electron density in the unsubstituted rings is proportionately higher. This is shown pictorially below with the directing power of each substituent shown by asterisks. The same picture can be gleaned from HMO calculations with electron densities represented by the

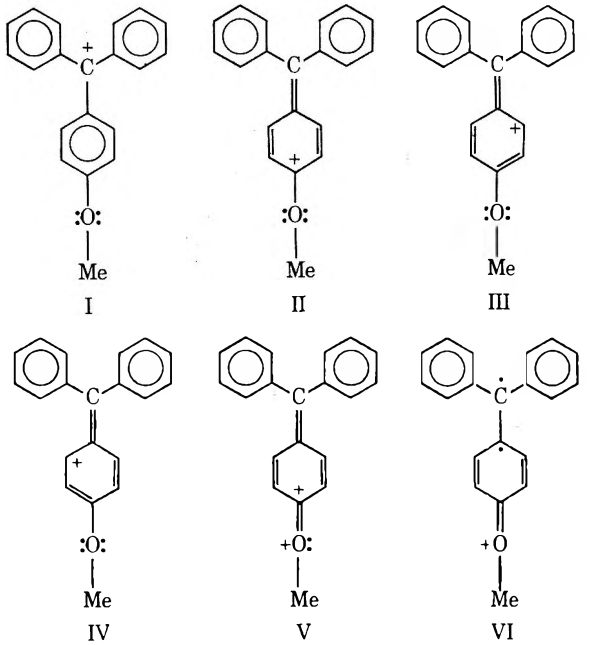
CHART I

RESONANCE FORMS FOR THE 4-METHOXYTRIPHENYLAMINIUM CATION RADICAL AND THE 4-METHOXYTRIPHENYLMETHYL CARBONIUM ION

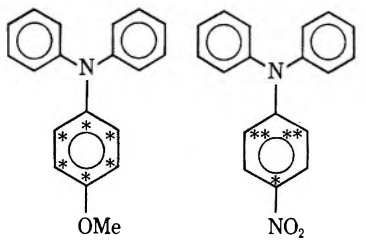
Cation Radical



Carbonium Ion



(28) Y. Okamoto and H. C. Brown, *J. Amer. Chem. Soc.*, **79**, 1909 (1957).
(29) J. W. Timberlake and M. L. Hodges, *Tetrahedron Lett.*, 4147 (1970).
(30) R. F. Nelson, unpublished data.



squares of the atomic orbital coefficients in the frontier orbital (HFMO). It should be stressed that the

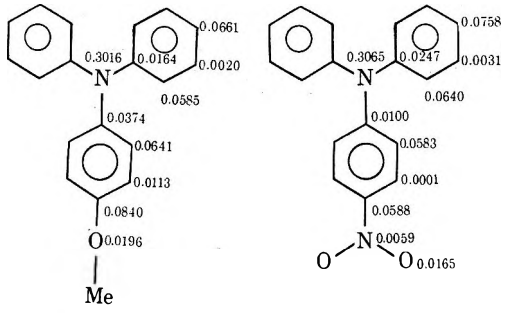
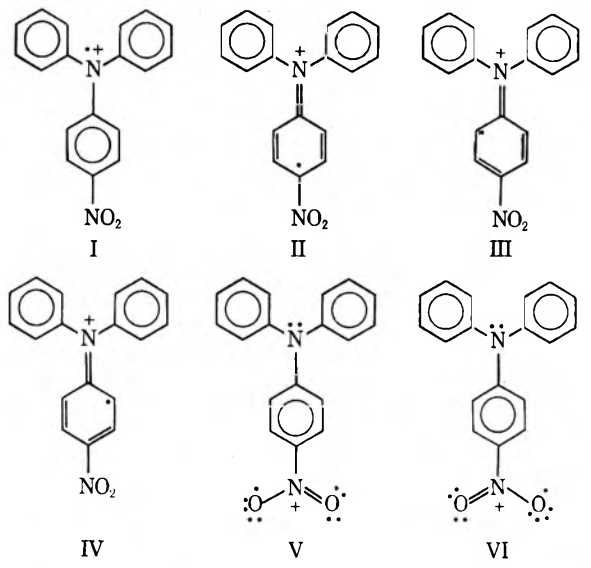


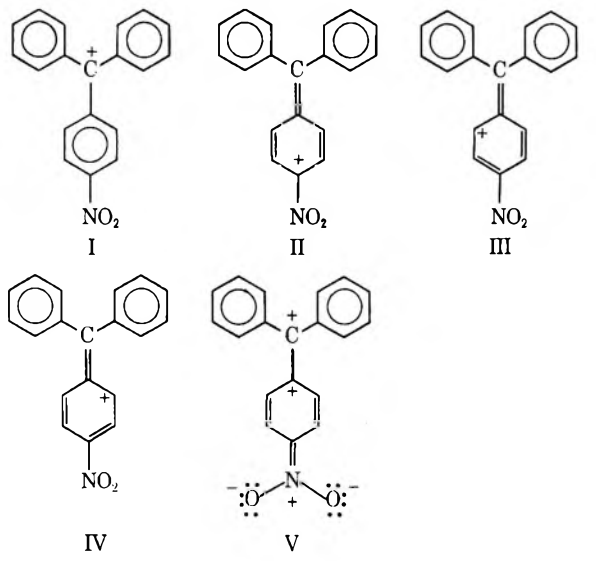
CHART II

RESONANCE FORMS FOR THE 4-NITROTRIPHENYLAMINIUM CATION RADICAL AND THE 4-NITROTRIPHENYLMETHYL CARBONIUM ION

Cation Radical



Carbonium Ion



numbers above are only valid in a relative sense, but they do confirm the results of the resonance arguments presented previously.

It is interesting to note that a plot of the open para site unpaired electron densities *vs.* the coupling rate constants actually gives a fairly satisfactory linear plot, again with the exception of molecules with strong electron-donating substituents. Thus, such coupling rate data, when correlated with other physicochemical properties such as epr coupling constants, may be useful in deriving new HMO heteroatom parameters for various substituents in cation radicals. Such studies are presently under way for several series of organic cation radicals.

Aside from the strong electron donors, only two other points seem grossly out of line. The formyl derivative, 17, appears to be much less stable than would have been predicted from the σ value of 0.22. The phenyl derivative 9, on the other hand, is more stable than would have been predicted from previous data; this is no doubt due to the increase in the breadth of the π system realized by introduction of an added phenyl group. This added delocalization is verified by simple HMO calculations which show appreciable electron density in the phenyl substituent ring, even with a fairly severe twist angle between it and the adjacent ring. Delocalization of the unpaired electron into a phenyl ring is a "bonus" not to be unexpected in cation radical systems.

Although the data presented here are hardly conclusive, the following corrected σ values for cation radicals ($\sigma \cdot^+$?) are suggested with the full realization that they will no doubt be refined and/or corrected in future studies.

R	$\sigma \cdot^+$	R	$\sigma \cdot^+$
OCH_3	−1.4	OC_6H_5	−1.0
OC_2H_5	−1.35	C_6H_5	−0.4
$NHCOCH_3$	−1.2	CHO	0.5–0.6

Although the above argument based on resonance stabilization and HMO data for substituents 1–4 seems sound, an alternate possibility would be that the plot in Figure 1 could consist of two linear regions, one composed of substituents 1–4 and the other comprised of the remaining functional groups.[31] This raises the possibility of different mechanisms being operative in the two linear regions; this certainly cannot be excluded at this point. Investigation of alternate mechanisms to the one proposed are being actively pursued by various electrochemical methods. One alternate mechanism is the previously mentioned radical–parent reaction, which might be occurring for compounds 1–4 due to the enhanced radical stability, thus allowing time for diffusion away from the electrode out into solution where collision with parent molecules is more likely.

Another possibility is that the dimerization step (eq 2 in Scheme I) is actually composed of two processes (this is almost certainly the case) with two attendant rate constants

$$2 \text{ cation radicals} \xrightarrow{k_1} \text{dimer dication} \xrightarrow{k_2} \text{benzidine} + 2H^+$$

It has been assumed that k_1 is the rate-determining step in all these systems and that the proton loss (k_2) is rela-

(31) This possibility was suggested by a referee.

tively rapid in all cases; it is possible that for some substituents (1–4?) the k_2 step is, in fact, rate determining. This alternative is being investigated by taking measurements of the coupling rates for 4-methoxy- and 4-methyltriphenylamine and the corresponding para-deuterated analogs. If proton loss is rate determining in these systems, then a primary isotope effect should be seen.

These mechanistic alternatives are being explored more fully, but it is felt that the radical–radical pathway is operative in these amine systems and that resonance stabilization through electron delocalization will require different substituent parameters from those for carbonium ions in some cases.

In summary, then, it appears that cation radical stabilities are fairly well predicted by existing σ^+ values in the literature, with the exception of the formyl, phenyl, and strong electron-donating substituents. Studies now in progress on the coupling rates of electrochemically generated carbazole cation radicals, as well as spectroscopic studies on several aromatic amine cation radical systems, should yield a reliable set of reactivity parameters to describe the effects of different functional groups upon cation radical stabilities.

Acknowledgments.—Financial support for this work through NSF Grant No. GP-20606 is gratefully acknowledged. Helpful discussions with Drs. R. W. Fish and R. I. Walter are also acknowledged. Special thanks are also due to Dr. R. N. Adams and Dr. D. E. Smith for their support and encouragement.

Chemistry of Santonic Acid. Oxidative and Reductive Modifications[1,2]

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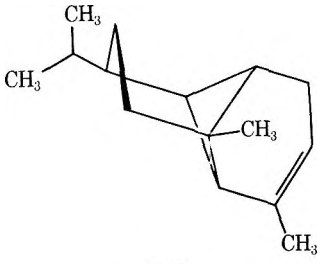
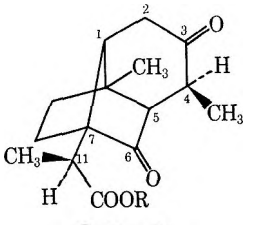
Received June 19, 1972

Reduction of santonic acid (**2**) with Na/Hg in aqueous base gives the previously reported "dihydrosantonic acid" which is now shown to be **4**. The C-11 epimer of **4** (*i.e.*, **6**) is similarly obtained from metasantonic acid (**5**), and is also found to be formed by epimerization of **4** during prolonged reductions of **2**. An acetoxy lactone (mp 204°) previously reported to be obtained on treatment of "dihydrosantonic acid" with acetic anhydride is shown to be **8** and was probably derived from **6** present as a contaminant in earlier preparations of **4**; a new acetoxy lactone, **7** (mp 140°), was obtained from pure **4**. An attempt to prepare "dihydrosantonide" by heating **4** in acetic acid at 145–150° gave **10**. Reduction of **2** with $NaBH_4$ gave **11**. Methyl ester **11a** gave mesylate **13a** with CH_3SO_2Cl and acetate **13b** with acetic anhydride–$HClO_4$. Mesylate **13a** on acetolysis (acetic acid, sodium acetate) gave epoxy acetoxy ester **14**, as evidenced by formation of **11** on hydrolysis. Heating either **11** with CH_3OH–H_2SO_4 or **13a** with collidine gave olefins **15** and **16a**. The presence of a dissymmetric β,γ-unsaturated ketone chromophore in **16a** gives rise to a very strong negative Cotton effect in the ORD and CD curves of **16a** which is of the magnitude observed for some other ketones of this type. Lithium–ammonia reduction of **17** yielded **18**, which gave 6β alcohol **3** on deketalization; similarly, Li–NH_3 reduction of **16** gave **19**. Reduction of **17** with $LiAlH_4$ afforded **20** and **21**. Treatment of **20** with HCl gave lactone **22**, which afforded 6α alcohol **23** on basic hydrolysis. Treatment of the mesylate of **18a** (**24**) with potassium *tert*-butoxide yielded sultone **25**, which gave **26** on hydrolysis. Deketalization of **24** afforded 3-keto mesylate **27**, which gave **28** on contact with Al_2O_3. Alkaline peroxide oxidation of **2** gave "aposantonic acid" (**29**), for which a stereostructure is proposed; a previously unreported keto lactone acid (**31**) formed by Baeyer–Villager oxidation of **2** was also obtained. Repetition of the previously reported hypobromite oxidation of **2** gave "oxysantonic acid," now formulated as **32** on the basis of analytical and spectroscopic data for several formerly reported derivatives of **32**.

The assignment of a tricyclo[4.4.0.0^{2,7}]decane structure to (−)-copaene (**1**)[3] and related naturally occurring sesquiterpenoids[4] has stimulated interest in the synthesis of this system.[5] In an attempt to achieve a synthesis of (+)-**1** *via* the route outlined in Scheme I, santonic acid (**2**)[6,7] was utilized as starting material for the preparation of suitable derivatives of **3**. Although



(−)-**1**



2, R = H
2a, R = CH_3

an example of the key 5 → 4 ring contraction step[8] has not been effected to date, the work described in this report has led to clarification of several previously reported transformations of santonic acid (**2**). These are discussed along with several additional reactions of **2** and related derivatives.

Reduction of Santonic Acid. A. Sodium Amalgam

(1) Abstracted from the Ph.D. Dissertation of D. S. Daniel, Washington University, 1970.

(2) A portion of this work has been outlined in a preliminary communication: A. G. Hortmann and D. S. Daniel, *Tetrahedron Lett.*, 2599 (1970).

(3) (a) G. Büchi, S. H. Feairheller, P. De Mayo, and R. E. Williams, *Proc. Chem. Soc.*, 214 (1963); *Tetrahedron*, **21**, 619 (1965); (b) V. H. Kapadia, B. A. Nagasampagi, V. G. Naik, and S. Dev, *Tetrahedron Lett.*, 1933 (1963); *Tetrahedron*, **21**, 607 (1965).

(4) *E.g.*, ylangene, O. Motl, V. Herout, and F. Sorm, *Tetrahedron Lett.*, 451 (1965); copadiene, V. H. Kapadia, V. G. Naik, M. S. Wadia, and S. Dev, *Tetrahedron Lett.*, 4661 (1967); mustakone, ref 3b.

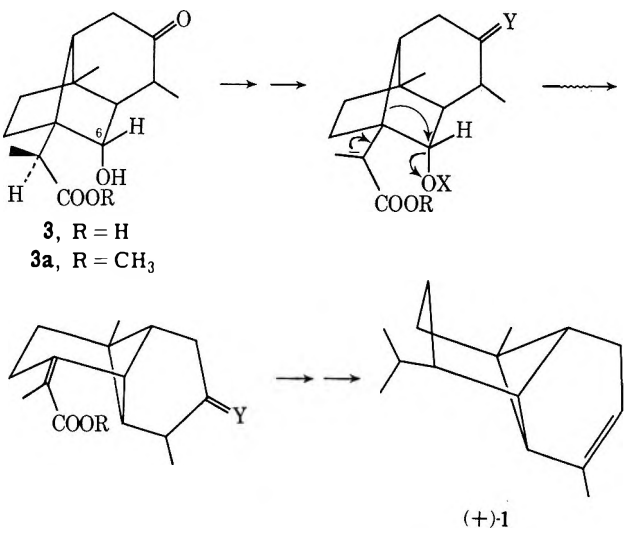
(5) A synthesis of (±)-copaene and (±)-ylangene has been described: C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *J. Amer. Chem. Soc.*, **89**, 4133 (1967).

(6) R. B. Woodward, F. J. Brutschy, and H. Baer, *ibid.*, **70**, 4216 (1948).

(7) For a review of santonic acid chemistry, see J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, New York, N. Y., 1952, pp 295–311. The stereochemistry at C-11 in santonin has since been shown to be 11*S*: J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.*, 335 (1962), and references cited therein.

(8) To our knowledge, the key ring-contraction step depicted in Scheme I has no precedent. Conceptually it may be viewed as analogous to the pinacol-type rearrangements observed for oxyanions derived from 1,2-diol monosulfonate esters. For a review, see D. Redmore and C. D. Gutsche, *Advan. Alicycl. Chem.*, **3**, 46 (1971).

SCHEME I



3, R = H
3a, R = CH_3

(+)-1

Reduction.—Following the suggestion[6] that "dihydrosantonic acid"[9-11] (DHS) is probably either **3** or its C-6 epimer, the reduction of santonic acid (**2**) with sodium amalgam (Na/Hg) was reinvestigated. Heating **2** under N_2 with 5% Na/Hg in 10% aqueous NaOH solution for 2 hr at reflux temperature afforded a crystalline acid in 91% yield which analyzed correctly for a dihydro derivative of **2** ($C_{15}H_{22}O_4$), could be readily reoxidized to **2** with Jones–Weedon reagent,[12] and has a broad ir absorption band at 3550–2550 cm^{-1} and ν_{max} at 3390, 3330, and 1700 cm^{-1}; the nmr spectrum of the product exhibits signals for methyl groups at δ 0.92 (s), 1.09 (d), and 1.12 (d), a quartet due to H-11 at 2.61, and a broad absorption band for three protons at 4.25–4.92. Esterification (CH_2N_2–ether) afforded "methyl dihydrosantonate" (methyl DHS) having mp 110–112° (lit.[11] mp 111–114°), ir ν_{max} 3570, 3440, and 1725 cm^{-1}, and nmr signals for C-methyl groups at δ 0.98 (s), 1.19 (d), and 1.23 (d), for H-11 at 2.76 (q), for $-OCH_3$ at 3.67 (s), and for two additional protons at 3.20 (br s). The latter two protons in the nmr spectrum of another sample of methyl DHS [which was prepared directly by treatment of methyl santonate (**2a**) with Na/Hg in absolute methanol] appeared at δ 2.92 (br s, 1 H) and 3.28 (br s, 1 H).[13]

Although the data described for DHS and methyl DHS are compatible with structures **3** and **3a** or their C-6 epimers, the disparity in chemical shift values for peaks attributable to a carbinyl proton (CHOH) in the acid (*ca.* δ 4.2–4.9) *vs.* the methyl ester (*ca.* δ 3.2–3.3) suggested that a –CHOH group was not present in either compound. Indeed, not one but *both* the protons appearing at δ 2.92 and 3.28 in methyl DHS were found to be readily exchangeable for deuterium, indicating that *two* hydroxyl groups must be present in methyl DHS, and furthermore, that both hydroxyls must be tertiary. On the basis of the data cited, DHS may therefore be assigned structure **4**.

Formation of the 1,2-cyclobutanediol moiety in **4** can be viewed as an example of an intramolecular pinacol reduction[14] of the 1,4-diketone system in **2**. Further support for structure **4** came from the observation that no significant exchange of hydrogen for deuterium occurred when DHS (**4**) was refluxed with 0.3 *M* NaOD in D_2O for 4 hr. (Similar treatment of santonic acid (**2**) led to formation of 9% 2-d_0, 29% 2-d_1, 36% 2-d_2, 20% 2-d_3 and 5% 2-d_4 as determined by mass spectroscopic analysis.)

Treatment of metasantonic acid (**5**), the 11*R* epimer of santonic acid (**2**),[15] with Na/Hg afforded dihydrometasantonic acid, which may be formulated as **6**. Both **6** and its methyl ester **6a** exhibit spectral characteristics similar to those described for **4** and **4a** and were readily reoxidized by Jones–Weedon reagent to **5** and **5a**; furthermore, addition of acetic-d_4 to the nmr sample solution of **6a** gave rise to a new broad singlet (2 H) at δ 6.3 and disappearance of the 1 H signals due to –OH which appeared at δ 3.69 and 4.78. No reduction products of metasantonic acid (**5**) have been reported previously.[7]

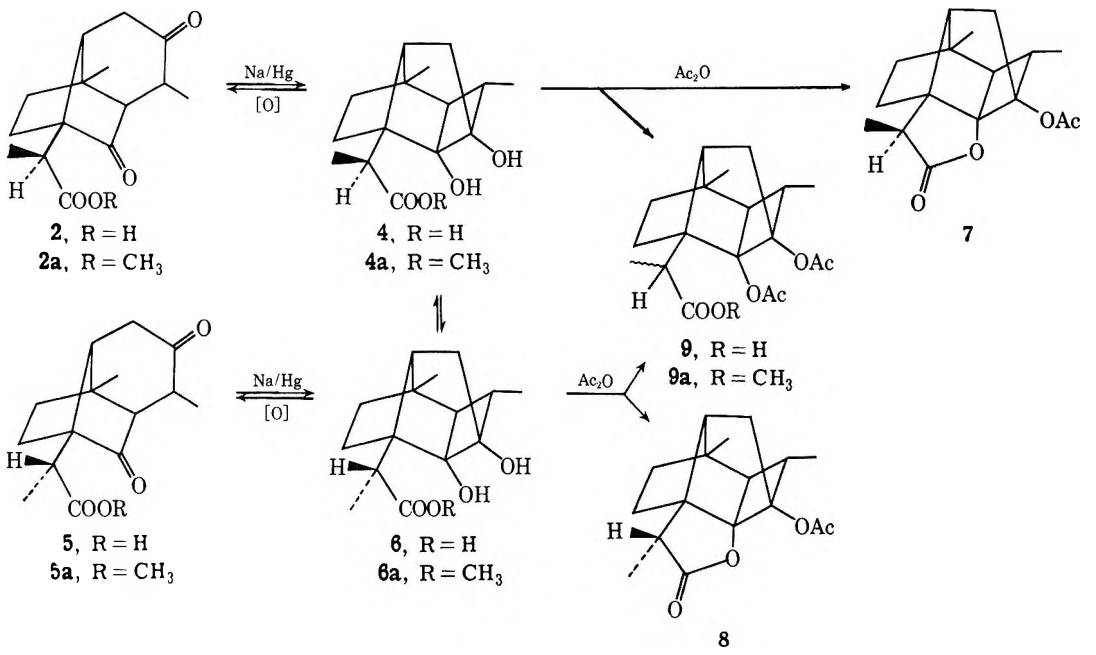
When the reduction of **2** was performed according to the procedure of Wedekind,[10] which calls for heating **2** in 10% NaOH solution at reflux in the presence of 5% sodium amalgam until H_2 liberation ceases (typically 20–48 hr), *mixtures* of **4** and **6** were obtained which contained >50% of **6** after 20 hr. In separate experiments prolonged treatment of **4** with aqueous hydroxide in the absence of reducing agent was also found to yield mixtures of **4** and **6** in which the ratios **4**:**6**[16] were found to be dependent upon the length of exposure; treatment of santonic acid (**2**) under similar conditions led to negligible amounts of metasantonic acid (**5**). Thus the formation of **6** during lengthy Na/Hg reductions of **2** occurs primarily by epimerization of **4**, possibly *via* a lactonic intermediate in which formation of an anion at C-11 would not be disfavored (as is the case for **2**) by the proximity of a carboxylate anion (Scheme II).

The likelihood that samples of "dihydrosantonic acid" used in at least some of the work reported in the earlier literature[9-11] contained substantial amounts of dihydrometasantonic acid (**6**) is indicated by the heretofore puzzling observation of Cannizzaro[9] that silver oxide oxidation of "dihydrosantonic acid" yields metasantonic acid. Repetition of this experiment using pure **4** afforded only **2** and unoxidized **4**.

In a similar vein, treatment of **4** with acetic anhydride under conditions approximating those reported by Wedekind[10] produced two acetate derivatives—an acetoxy lactone and a diacetoxy acid.[6,7,10] The acetoxy lactone (mp 140–142°) exhibits ir ν_{max} at 1780 and 1735 cm^{-1} and nmr peaks at δ 1.10 (d, 3), 1.13 (s, 3), 1.32 (d, 3), 2.04 (s, 3), 2.59 (q, 1), and 2.62 (q, 1) and may be reasonably formulated as **7**. The melting point of **7** did not agree with that of Wedekind's acetoxy lactone (mp 204°);[10] however, an acetoxy lactone obtained by treatment of dihydro*meta*santonic acid (**6**) with acetic anhydride under identical conditions had

(9) S. Cannizzaro, *Gazz. Chim. Ital.*, **6**, 341 (1876).
(10) E. Wedekind and O. Engel, *J. Prakt. Chem.*, **139**, 115 (1934).
(11) C. Harries and A. Stähler, *Chem. Ber.*, **37**, 258 (1904).
(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(13) The ester prepared from **2a** was otherwise identical spectroscopically to methyl DHS prepared from **2**.
(14) G. W. Griffin and R. B. Hager, *J. Org. Chem.*, **28**, 599 (1963). Also, *cf.* E. Wenkert and J. E. Yoder, *ibid.*, **35**, 2986 (1970); J. G. St. C. Buchanan and P. D. Woodgate, *Quart. Rev., Chem. Soc.*, **23**, 522 (1969).
(15) R. B. Woodward and P. Yates, *Chem. Ind. (London)*, 1391 (1954).
(16) The variation in the ratio of **4**:**6** with reaction time could be determined by working up aliquots of the reaction mixture, esterifying the crude mixtures of **4** and **6** obtained with CH_2N_2, and estimating the relative areas beneath the peaks due to the $-OCH_3$ group in **4a** and **6a**. A further check on the ratios of **4** to **6** was made by performing similar assays on mixtures of **2a** and **5a** obtained by oxidation of the mixtures of **4a** and **6a** after the latter had been assayed.

SCHEME II



spectral characteristics very similar to those of **7** and did correspond in melting point (204.5–206°) to that obtained from "dihydrosantonic acid" by Wedekind. Consequently, it may be concluded that Wedekind's acetoxy lactone having mp 204° is **8** and was derived from dihydrometasantonic acid, which was probably present as a contaminant in Wedekind's "dihydrosantonic acid."[17-20]

The diacetoxy acid obtained from **4** in low yield has spectral characteristics compatible with structure **9** and exhibits a melting point (235–237.5°) which is comparable with the melting point of Wedekind's diacetoxy acid (232°).[10] Similar agreement was found for the corresponding methyl ester **9a**, mp 150° (lit.[10] mp 151°). Owing to a lack of sufficient material, the diacetoxy acid obtained in very low yield by treatment of **6** with acetic anhydride was not completely purified and characterized, thus leaving the configuration of **9** at the carboxyl-bearing carbon open to question.[21]

(17) The acetoxy lactone, mp 204° (*i.e.*, **8**), had been prepared earlier[18] by treatment of "dihydrosantonic acid" with acetyl chloride. Cannizzaro also reported the formation of "dihydrosantonide," [18] $C_{15}H_{18}O_3$, mp 155–156°, upon heating "dihydrosantonic acid" with acetic acid at 140–150° in a sealed tube. "Dihydrosantonide" was also reportedly converted with acetic anhydride or acetyl chloride to the acetoxy lactone, mp 204°.[18,19] Hence "dihydrosantonide" must be the desacetyl lactone corresponding to **8** and may also be assumed to be in the meta series.

It is a matter for speculation whether "dihydrosantonide" was formed directly from metasantonic acid present in "dihydrosantonic acid," or whether epimerization at C-11 occurs during or after the formation of "dihydrosantonide" from **4**. (Acetic acid at elevated temperatures is known to catalyze epimerization at C-11 in the santonic acid and santonide series.[20])

(18) S. Cannizzaro and L. Valente, *Gazz. Chim. Ital.*, **8**, 309 (1878).

(19) See also ref 7, p 297.

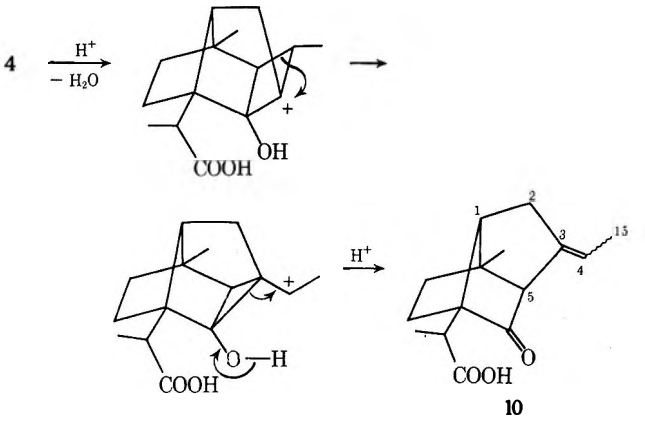
(20) R. B. Woodward and E. G. Kovach, *J. Amer. Chem. Soc.*, **72**, 1009 (1950), and references cited therein.

(21) An attempt to resolve this point by examining the product of basic hydrolysis of **9** followed by esterification (CH_2N_2–Et_2O) was unsuccessful, yielding a mixture of **4a** and **6a** in a ratio of 3:5 (nmr assay). The epimerization at C-11 observed during hydrolysis must occur at a stage prior to the actual formation of **4** since the conditions used were not sufficient (see Experimental Section) to cause isomerization of **4** to **6**.

Hydrolysis–esterification of **7** also led to a mixture of **4a** and **6a** (3:1), whereas similar treatment of **8** led to **6a** of >95% purity. [It is noteworthy that in earlier reports[10,18] hydrolyses of both "dihydrosantonide"[17] and the acetoxy lactone,[10,18] mp 204° (shown now to be in the meta series), as well as the diacetoxy acid,[10] mp 232° (*i.e.*, **9**), were claimed to afford unspecified yields of pure dihydrosantonic acid (melting point and mixture melting point determinations).[19]]

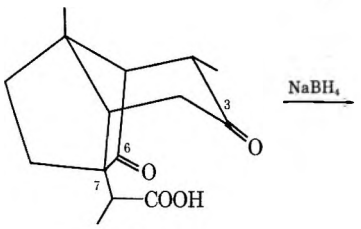
An attempt to prepare "dihydrosantonide" by heating **4** in a sealed tube with acetic acid[17,18] over a range of conditions yielded only starting DHS (**4**) and an olefinic acid to which structure **10** could be assigned on the basis of analytical and spectral data (see Experimental Section); a possible route for the formation of **10** is depicted in Scheme III. Prolonged heating apparently converted **10** to another olefinic product which was not isolated or characterized. No significant quantity of neutral material having spectral properties expected of "dihydrosantonide"[17,18] could be isolated. No attempt was made to prepare "dihydrosantonide" directly from **6** (from which it presumably originated in the earlier work[17]).

SCHEME III

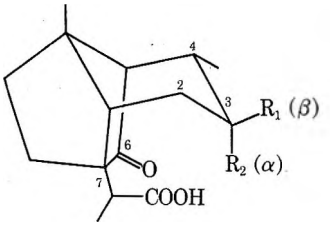


B. Sodium Borohydride Reduction.—In another approach to **3** or its C-6 epimer, santonic acid was reduced with $NaBH_4$. The dihydro derivative obtained was assigned structure **11** having hydroxyl at C-3 when it was found that the methyl ester **11a** exhibits only one strong carbonyl band at 1735 cm^{-1} (five-ring C=O and $COOCH_3$). Further confirmation of the location of the hydroxyl group followed from the observation that no significant incorporation of deuterium occurred when **11** was heated at reflux for 4 hr with 0.3 *M* NaOD in D_2O.

The hydroxyl group in **11** was assigned the α configuration on steric grounds. Models of **2** indicate that approaches of borohydride to the β face of the cyclohexane ring are less hindered than approaches to the α face, the latter being blocked by the C-6–C-7



2

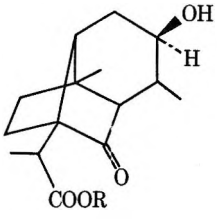


11, $R_1 = H$; $R_2 = OH$
12, $R_1 = OH$; $R_2 = H$

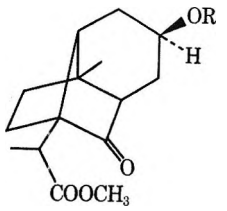
bridge carbons.[22] In addition, the observed half-width ($W_{1/2}$ = 7.5 Hz) of the nmr peak due to H-3 is in agreement with that expected for most reasonable conformations of **11** ($W_{1/2} \cong$ 6–12), and out of the range expected for H-3 in **12** ($W_{1/2} \geq$ 20) if it is assumed that the 6 ring in **12** will most likely be in a chair conformation.[23]

Several attempts were made to prepare **12** to aid in confirmation of the stereochemical assignments in the 3-OH series, as well as to open a possible route to **3** *via* base-induced hydride shift of H-3 to C-6.[24] In an initial approach, **11a** was converted into the 3α-mesylate **13a**. When subjected to acetolysis conditions, **13a** afforded not the desired 3β-acetoxy ester **12a** but the 6β-acetoxy-3α,6α-epoxy ester **14**. The structure of **14** was deduced from the following data: (a) the carbinyl proton (H-3) or **14** appears as a multiplet, $W_{1/2}$ = 7.5 Hz, at δ 4.05 suggesting that the orientation of H-3 relative to H-2, H-2′, and H-4 is similar to that in **11**; (b) hydrolysis of **14** affords **11**, and not a new alcohol (*viz.*, **12**); and (c) the acetate **14** is not identical with **13b**, which could be prepared by treatment of **11a** with acetic anhydride–$HClO_4$ and exhibits an nmr peak for its carbinyl proton at δ 4.99 (q, 1, J = 3.5 Hz).

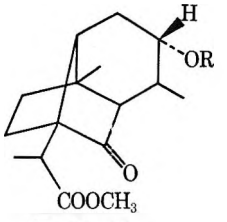
The acetoxy epoxy ester **14** presumably forms *via* formation of an intermediate C-3 carbonium ion which interacts readily with the carbonyl oxygen at C-6 to give an oxygen-bridged C-6 carbonium ion, which can react further with acetate ion to yield **14**. The formation of **14** and the nmr spectral characteristics of H-3 in **13b** and **14** conclusively support the configurational assignment at C-3 in **11**.



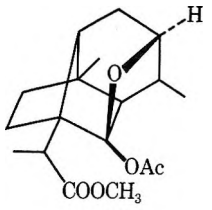
11, R = H
11a, R = CH_3



13a, R = OSO_2CH_3
b, R = $OCOCH_3$

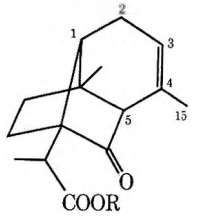


12, R = H
12a, R = $OCOCH_3$



14

15



16, R = H
16a, R = CH_3

As a second approach to **12**, hydroboration of the olefinic ester **16a** was tried. Heating either **11** with CH_3OH–H_2SO_4 or the mesylate **13a** with collidine[25] gave a crude mixture of olefins **15** and **16a** which could be separated by careful alumina chromatography and characterized spectroscopically (see Experimental Section).[26] Hydroboration of **16a** with diborane in THF[27] gave at least six compounds as determined by glpc. When treated with 9-borabicyclo[3.3.1]nonane,[28] **16a** was recovered unchanged. No additional attempts were made to prepare **12**.

C. Lithium–Ammonia Reduction.—No reduction products were observed when attempts were made to prepare **3** *via* $NaBH_4$ or Na/Hg reduction of **17**, the 3-ethylenedioxy derivative of santonic acid (**2**). The 6β-hydroxy-3-keto acid **3** was finally obtained by Li/NH_3 reduction[29] of **17** to **18** followed by acidic hydrolysis of the ketal function. Conclusive evidence

(22) Approach of borohydride to a carbonyl group is normally expected to occur by the least hindered route: H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 54–64.

(23) See M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(24) It was felt that the juxtaposition of H-3 to the carbonyl carbon (C-6) in **12** might favor an intramolecular Cannizzaro hydride shift. See, for example, W. C. Wildman and D. T. Bailey, *ibid.*, **91**, 150 (1969), and references cited therein; D. Arigoni, *Gazz. Chim. Ital.*, **92**, 884 (1962); *Chem. Abstr.*, **58**, 7981 (1963); A. J. Birch, C. W. Holzapfel, and R. W. Rickards, *Tetrahedron, Suppl.*, **8**, 359 (1966); J. J. Dugan, P. De Mayo, M. Nisbet, and M. Anchel, *J. Amer. Chem. Soc.*, **87**, 2768 (1965). In the case of **12** → **3** it was felt that the base-induced (and presumably reversible) transformation might be effected to favor **3** by using 3 molar equiv of a base strong enough to irreversibly convert any **3** formed to its enolate anion, which could then be quenched under mild acidic conditions to obtain **3**.

(25) *Cf.* M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Loewenthal, *J. Org. Chem.*, **34**, 126 (1969). See also G. G. Hazen and D. W. Rosenberg, *ibid.*, **29**, 1930 (1964).

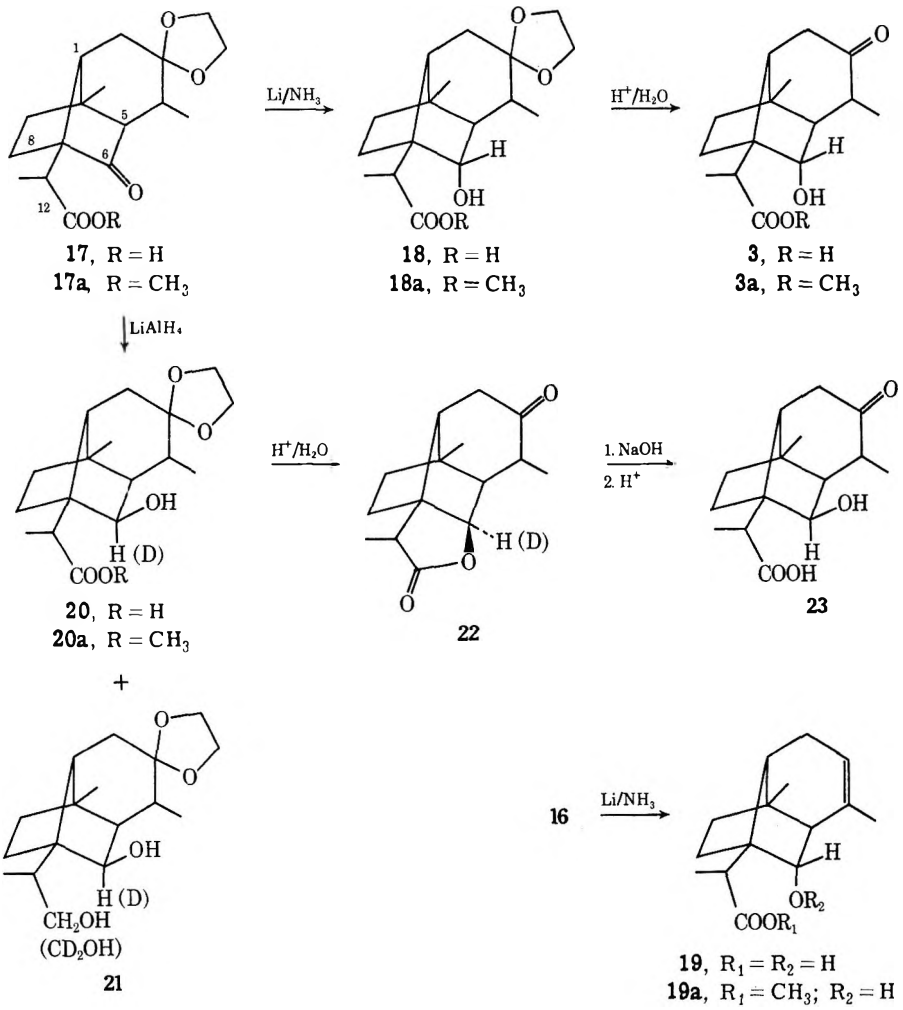
(26) The inherently dissymetric β,γ-unsaturated ketone chromophore of **16a** also gives rise, in the ORD and CD curves of **16a**, to a very strong negative Cotton effect of the order of magnitude observed for some other ketones of this type, *e.g.*, parasantonide and 3β-acetoxy-16α,17α-(17′-methylene)ethylenepregn-5-en-20-one. See A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 1945 (1962); P. Sunder-Plassman, P. H. Nelson, P. H. Boyle, A. Gruz, J. Iriate, P. Crabbé, J. A. Zderic, J. A. Edwards, and J. H. Fried, *J. Org. Chem.*, **34**, 3779 (1969).

(27) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

(28) E. F. Knights and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 5280, 5281 (1968).

(29) J. W. Huffman and J. T. Charles, *ibid.*, **90**, 6486 (1968).

SCHEME IV



for the 6β orientation of the hydroxyl group in **3** and **18** came from their nmr spectra. In each case H-6 appears as a broad singlet ($W_{1/2}$ = 3–4 Hz) indicating that $J_{6,5} \leqq 2$ Hz,[30] a value generally associated with H(exo)–H(endo) coupling of carbinyl protons in borneols.[31] See Scheme IV.

A similar Li/NH_3 reduction of **16** afforded **19**, a potentially more useful alternative to **3** as a starting material in Scheme I.

D. Lithium Aluminum Hydride Reduction.—Further support for the stereochemistry of **18** came from the observation that reduction of **17** with $LiAlH_4$ affords (in addition to diol **21**) an alcohol isomeric with **18** which could be tentatively assigned the 6α-hydroxy structure **20**. The configurational assignment at C-6 in **20** is based on the appearance of H-6 in the nmr spectrum as a doublet of doublets at δ 4.05 having $J_{6,5}$ = 5.5 Hz[31] and $J_{6,1}$ = 3.5 Hz.[32] The possibility that the reduction product might be a rearrangement product of **20** formed during the acidic work-up procedure could be eliminated when it was found that reduction of **17** with $LiAlD_4$ afforded a product which lacked a peak for the carbinyl proton at δ 4.05, but was otherise nearly identical with **20** in its nmr spectrum.

Attempts to remove the ketal function of **20** revealed that **20** was extraordinarily unreactive toward 3% HCl in boiling dioxane–H_2O, yielding only about 5–10% of the lactone **22**, along with unreacted **20**, after 16 hr. Lactone **22** and the alcohol **23** derived on hydrolysis of **22** both exhibited coupling patterns for H-6 (see Experimental Section) similar to that observed for H-6 in **20**, suggesting that **20**, **22**, and **23** probably have identical carbon skeletal structures, in spite of the vigorous acidic conditions required for the formation of **22**.[33]

Attempted Rearrangement of the Methanesulfonate of 18a.—Following Scheme I, the methanesulfonate ester **24** was prepared from **18a**. Treatment of **24** with potassium *tert*-butoxide in benzene led to the sultone **25** (2 H singlet for $-OSO_2CH_2CO-$ at δ 4.34; H-6 at δ 5.75) rather than the desired rearrangement product. Formation of **25** probably proceeds *via* generation of a sulfonyl-stabilized carbanion, which then displaces methoxide ion intramolecularly from the carbomethoxyl group. In contact with a trace of acid, **25** was deketalized to yield **26**.

In another preparation of mesylate **24**, work-up

(30) This assumes that there will be a contribution to $W_{1/2}$ of 2–4 Hz due to $J_{5,8}$ when H-6 is exo as in, *e.g.*, **3** or **18** (see examples in ref 31a–c).

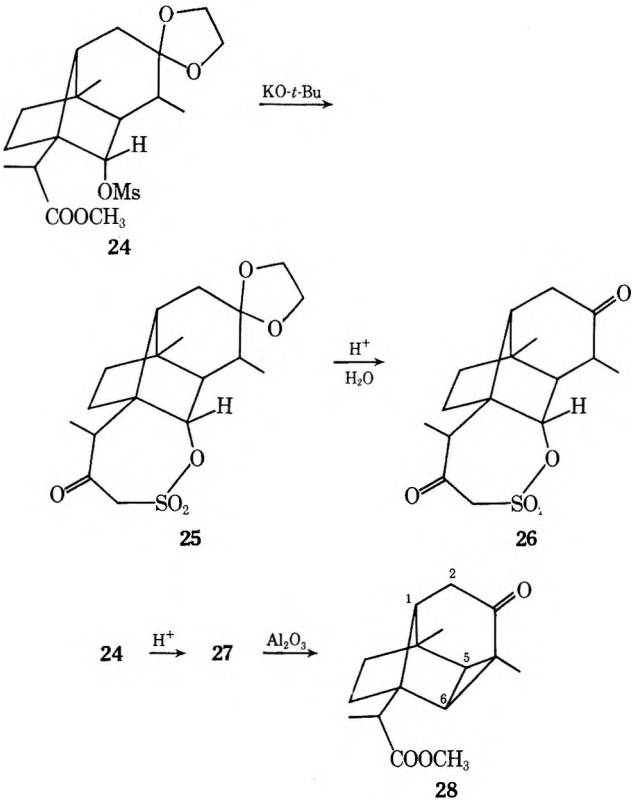
(31) Coupling constants for vicinal H(endo)–H(endo) protons in related borneols are typically in the range of about 5–10 Hz. For selected examples, see (a) H. Hikino, N. Suzuki, and T. Takemoto, *Tetrahedron Lett.*, 5069 (1967); (b) M. Kolbe and L. Westfelt, *Acta Chem. Scand.*, **21**, 585 (1967); (c) D. H. R. Barton and N. H. Werstiuk, *J. Chem. Soc. C*, 148 (1938).

(32) Coupling constants for H(2-endo)–H(7-anti) protons in norbornanes are typically 3–4 Hz: L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 334.

(33) In contrast to the ease of oxidation of **18a** to **17a**, **20** and **23** were found to be inert to Jones–Weedon reagent, and to form, with stronger oxidants, mixtures of products which were not readily characterizable. Thus a direct oxidative correlation of **20** and **23** with **2** could not be made.

under acidic conditions resulted in a mixture (~1:1) of **24** and a related mesylate which was probably **27**, the 3-keto analog of **24**. Attempted chromatography of the mixture on neutral alumina afforded the cyclopropyl ketone **28** having *two* quaternary methyl groups: nmr δ 1.03 (s, 3), 1.12 (s, 3), 1.24 (d, 3), 2.68 (q, 1), 3.63 (s, 3), and the AB portion of an ABX pattern centered at 2.19 ($J_{2,2'}$ = 16.5 Hz, $J_{2,1} = J_{2',1}$ = 3 Hz);[34] ir 1735 ($COOCH_3$) and 1685 cm^{-1} (cyclopropyl C=O).[35]

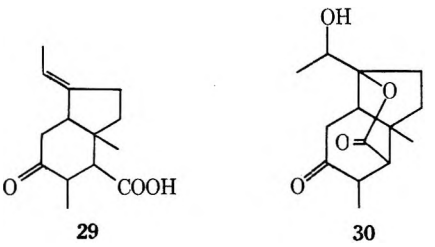
Further attempts to effect the desired rearrangement outlined in Scheme I using the tosylate (and related sulfonate esters) of **18a** and **19a** are currently in progress.



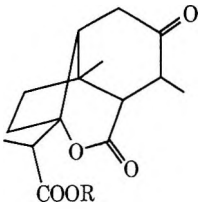
Oxidation of Santonic Acid.—The demonstrated utility of nmr spectroscopy in determination of the location and orientation of functional groups in santonic acid derivatives encouraged us to turn to a reinvestigation of the products of several previously reported oxidations of **2**.[36]

A. Alkaline Hydrogen Peroxide Oxidation.—Oxidation of **2** ($C_{15}H_{20}O_4$) with alkaline H_2O_2 was reported by Wedekind and Jäckh to yield "aposantonic acid," $C_{14}H_{20}O_3$, which on chromium oxide oxidation afforded a diketo lactone ($C_{14}H_{18}O_4$).[36] Consideration of these data led Woodward, *et al.*,[6] to propose a possible course of the oxidation which resulted in the formulation of aposantonic acid as **29**.

The proposed structure places the double bond and carboxyl group in the relationship required by the additional observation that reaction of **29** with perbenzoic acid affords a hydroxy lactone (*viz.*, **30**)[6] which (presumably) is related to the diketo lactone[36] reported earlier. To date the structures of **29** and **30** have rested entirely on analytical data and structural arguments.



Repetition of the alkaline peroxide oxidation of **2** under conditions similar to Wedekind's[36] gave a new crystalline acid ($C_{15}H_{20}O_5$) having ir bands at 1745 (cyclopentanone C=O or γ-lactone) and 1715 cm^{-1} (COOH) and an nmr spectrum which was similar in its essential features to that of **2**. On these bases the new product was assigned structure **31**; the three alternative lactones resulting from Bayer–Villiger oxidation at either C-3 or C-6 could be rejected as possible structures since no carbinyl protons(s) appears in the δ 3.5–5.5 region of the nmr spectrum of **31**. Esterification of the remaining crude product with CH_2N_2, followed by chromatography, afforded (in addition to **31a**) a compound having analytical, ir, and nmr spectral data in accord with structure **29a** (methyl aposantonate): ir 1735, 1715, and 820 cm^{-1}; nmr δ 0.95 (d, 3), 0.99 (s, 3), 1.60 (br d, 3), 3.75 (s, 3), and 5.35 (br q).



31, R = H
31a, R = CH_3

Further examination of the nmr spectrum of **29a** revealed a trans relationship between H-2 and H-3 ($J_{2,3}$ = 12.5 Hz)[23] leading to the detailed stereostructure shown for **29a** on the basis of conformational analysis (6-ring assumed to be in chair form) and consideration of the relative stabilities of B *vs.* C under conditions conducive to epimerization at C-3 which are probably operative during the oxidation.

The lactone **31** was probably overlooked in the earlier work,[36] since even when the conditions reported were followed as closely as possible an nmr assay of the crude oxidation product showed the ratio of **2**:**29**:**31** to be 2:1:1. When the lactone **31** was treated with base for several hours, an nmr spectrum of the product showed no olefinic protons, thus ruling out the possibility that aposantonic acid (**29**) is derived from **31** by a decarboxylative β-elimination process, and suggesting that **29** probably arises from **2** by an independent (and possibly stereospecific) fragmentation process (Scheme V) similar to that proposed earlier.[6]

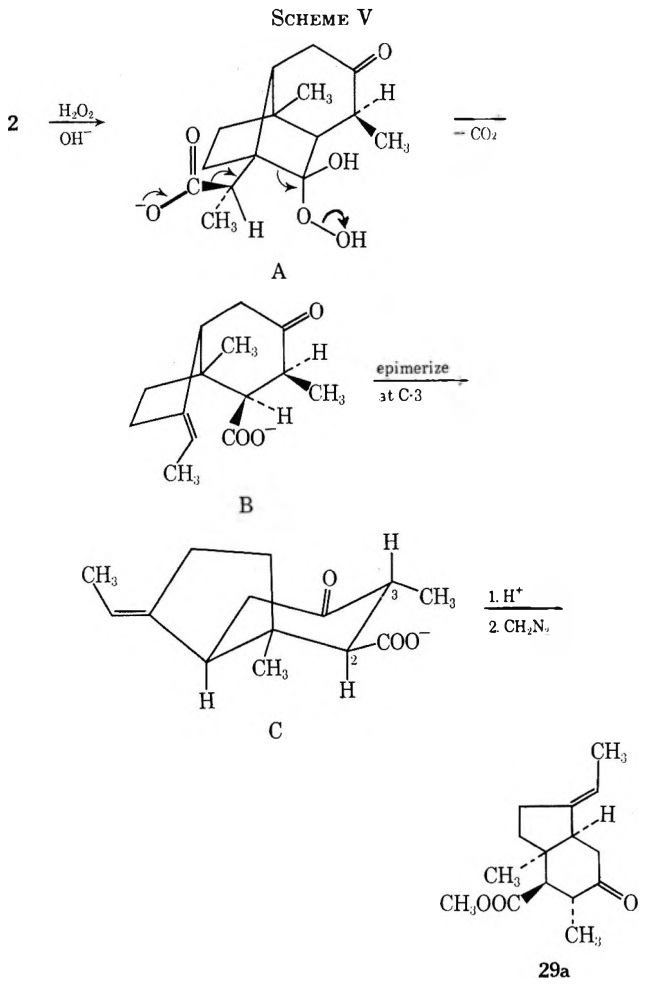
B. Potassium Hypobromite Oxidation.—Oxidation of santonic acid (**2**) with potassium hypobromite was reported[36] to give a compound referred to as "oxy-

(34) The ABX system is not H-5, H-6, and H-1, since the range for coupling observed for cis vicinal protons on cyclopropyl rings is typically 4.7–12.6 Hz. [See ref 32, p 286, and also S. A. Monti, D. J. Bucheck, and J. C. Shepard, *J. Org. Chem.*, **34**, 3080 (1969).] The resonance peaks for H-5 and H-6 in **28** apparently occur with the remaining protons in the δ 1.90–1.25 region; this seems unusual when compared with the chemical shifts observed for cyclopropyl protons located β to a carbonyl group in some other bridged systems. *Cf.* S. A. Monti, *ibid.*, **35**, 380 (1970).

(35) W. G. Dauben and R. E. Wolf, *ibid.*, **35**, 374 (1970).

(36) E. Wedekind and I. Jäckh, *J. Prakt. Chem.*, **139**, 129 (1934).

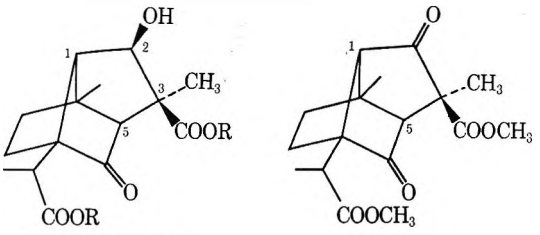
SCHEME V

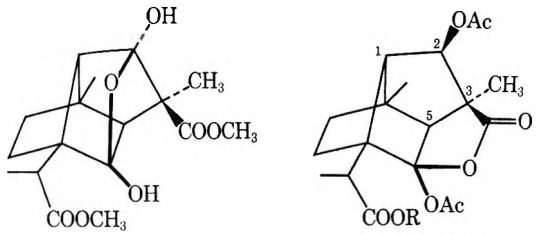


santonic acid" which analyzed as a hemihydrate, $C_{15}H_{20}O_6 \cdot {}^1/_2H_2O$. Treatment of oxysantonic acid with CH_2N_2 afforded a compound ($C_{17}H_{24}O_6$) described as a methoxy monomethyl ester. Oxysantonic acid also formed a diacetoxy acid, $C_{19}H_{24}O_8$, which yielded the corresponding monomethyl ester ($C_{20}H_{26}O_8$) on treatment with CH_2N_2.

When the hypobromite oxidation of **2** was repeated, a recrystallized product having the melting point reported for oxysantonic acid was obtained in 14% yield. The acid gave a negative $FeCl_3$ test, indicating that oxysantonic acid is not an enolized α diketone, *i.e.*, 2-oxosantonic acid. Esterification with CH_2N_2 afforded a dimethyl ester (3 H singlets at δ 3.68, 3.72) having *two* quaternary C-methyl groups (3 H singlets at δ 1.33, 1.61), an unaltered $-CH(CH_3)COOR$ side chain (3 H doublet at 1.42; 1 H quartet at 3.28), and a hydrogen-bonded secondary hydroxyl function [1 H doublet for –OH at 5.08 (J = 7 Hz) which disappears on addition of acetic acid-d_4]. On these bases the gross structure **32a** could be tentatively assigned to the dimethyl ester. Additional support for structure **32a** came from the appearance of the carbinyl proton (H-2) at δ 4.49 as a doublet of doublets (J = 7, 4 Hz) which collapses to a simple doublet owing to coupling of H-2 with H-1 ($J_{2,1}$ = 4 Hz) upon exchange of the –OH proton for deuterium. Finally, H-1 appears at δ 2.54 as a doublet of doublets owing to coupling with H-2 ($J_{1,2}$ = 4 Hz) and additional long-range coupling[32] with H-5 ($J_{1,5}$ = 2.5 Hz); H-5 in turn occurs as a simple doublet ($J_{1,5}$ = 2.5 Hz) at δ 2.36.

Jones–Weedon oxidation[12] of **32a** afforded **33** in which both H-1 and H-5 absorb coincidently at δ 2.72 (2 H, singlet); no signal for CHOH appears in the nmr spectrum of **33**. Compound **33** analyzed as **33**·H_2O and probably exists as the oxygen-bridged dihemiketal **33a** having one of its carbomethoxyl groups strongly hydrogen bonded [ir ν_{max} 3380, 3500–2500 (br), 1735, 1710, and 1683 cm^{-1}].

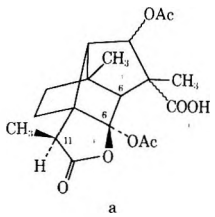




Treatment of **32** with acetic anhydride gave the diacetoxy acid obtained previously;[36] the derived methyl ester also corresponded in analysis and melting point to that reported. The diacetoxy acid exhibits ir and nmr spectral characteristics consonant with structure **34**: ν_{max} 1800, 1760, 1745, and 1710 cm^{-1}; nmr δ 1.22 (s, 3), 1.28 (d, 3), 1.48 (s, 3), 2.06 (s, 3), 2.11 (s, 3), 2.37 (dd, 1, $J_{1,2}$ = 4, $J_{1,5}$ = 2 Hz, H-1), 3.10 (d, 1, $J_{5,1}$ = 2 Hz, H-5), 3.26 (q, 1, H-11), and 5.33, (d, 1, $J_{2,1}$ = 4 Hz, H-2).[37]

The incorporation of the COOH group located at C-3 into the lactol acetate moiety of **34** establishes the configuration at C-3 of **32** and its derivatives. The configuration depicted for C-2 is based on the magnitude of the coupling interaction between H-1 and H-2 in **32a**, **34**, and **34a**. The observed coupling in each compound ($J_{1,2}$ = 4 Hz) is consistent with the

(37) The alternate structure a could be rejected for **34** on the basis of

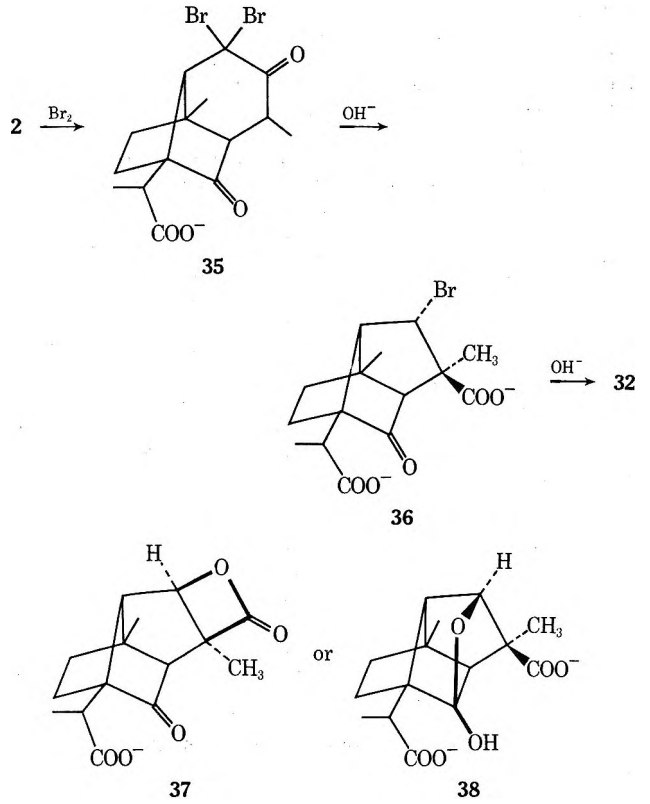


a

a comparison of the chemical shift values for H-11 in γ-lactones **7** (δ 2.62), **8** (δ 2.57), and **22** (δ 2.65) with those observed for the diacetate **34** (δ 3.26) and the diacetate methyl ester **34a** (δ 3.35). The latter values are closer to those observed (*e.g.*, δ 3.50 for **14**) for H-11 in structures having two oxygen substituents at C-6 and a freely rotating $-CH(CH_3)COOR$ side chain (which probably prefers a rotational orientation with H-11 near C-6). Although a has an additional 6-OAc which is not present in **7** and **22**, consideration of the distance of the 6-OAc group from H-11 in models of a, and its probable preferred rotational conformation (C=O oriented away from H-11) suggests that a deshielding effect due to 6-OAc of *ca.* 0.7 ppm at H-11 in a lactone such as a is improbable and would not satisfactorily explain the difference in δ values for H-11 in a *vs.* **7** or **22**.

dihedral angle of 40° found between H-1 and H-2 in Drieding models of **32**; a model of the structure epimeric to **32** at C-2 shows a dihedral angle of 85° between H-1 and H-2 corresponding to an expected coupling of $J_{1,2} \sim 0$ Hz.[23] The observation that the the 2-OH group in **32a** is hydrogen bonded is also in accord with its proposed cis orientation with respect to the 3-$COOCH_3$ group. (Hydrogen bonding of the 2-OH group with the carbonyl at C-6 is sterically impossible.)

Oxysantonic acid (**32**) probably rises *via* Favorskii rearrangement of 2,2-dibromosantonic acid (**35**) to yield **36**, followed by replacement of bromine by hydroxyl *via* propiolactone **37** or by initial attack of hydroxide at C-6 in **36** to yield an intermediate C-2–C-6 oxygen-bridged hemiketal of **32**, *i.e.*, **38**.[38]



Experimental Section[39–41]

(11*S*)-1,7-Cyclo-3,6-dioxo-4,5β-eudesman-12-oic Acid (2) (Santonic Acid).—This method is a modification of the procedure reported.[6] A solution of 100 g (0.41 mol) of α-santonin, 144 g of NaOH, and 600 ml of H_2O was heated at reflux under N_2 for 7 hr, cooled, acidified with concentrated HCl, and extracted with CH_2Cl_2. The organic phase was washed, dried, filtered, and evaporated *in vacuo*, affording 109 g of a brown gum. Trituration with ether followed by recrystallization gave 62.6 g (58%) of santonic acid (**2**): mp 173.5–179° (lit.[6] mp 170–172°); ir 1740 (C=O), 1725 (C=O), and 1710 cm^{-1} (C=O); nmr δ 1.12 (d, 3, J = 6.7 Hz, H-15), 1.37 (s, 3, H-14), 1.37 (d, 3, J = 7 Hz, H-13), 1.6–1.9 (m, 3), and 2.87 (q, 1, J = 7 Hz, H-11); nmr (DMSO-d_6) δ 0.95 (d, 3, J = 6.5 Hz), 1.22 (d, 3, J = 7 Hz), 1.32 (s, 3), and 2.74 (q, 1, J = 7 Hz).

Methyl (11*S*)-1,7-Cyclo-3,6-dioxo-4,5β-eudesman-12-oate (2a) (Methyl Santonate).—Addition of CH_2N_2 in Et_2O to a solution of **2** in Et_2O followed by concentration of the mixture gave a yellow oil which crystallized from CH_3OH–H_2O to yield **2a**: mp 66–67.5° (lit.[20] mp 86°); ir 1740, 1730, and 1715 cm^{-1}; nmr δ 1.10 (d, 3, J = 6.5 Hz, H-15), 1.31 (d, 3, J = 7 Hz, H-13), 1.38 (s, 3, H-14), 2.81 (q, 1, J = 7 Hz, H-11), and 3.65 (s, 3, $-OCH_3$).

Exchange Reaction of 2 in 0.28 *M* NaOD in D_2O.—A solution of **2** (135 mg) in 0.28 *M* NaOD was heated at reflux under N_2 for 10 hr, cooled, acidified with 0.4 ml of glacial acetic acid, and extracted with CH_2Cl_2 after dilution with 50 ml of H_2O. The organic extracts were washed with H_2O, dried, filtered, and concentrated to yield 127 mg of **2**-d_3: nmr δ 1.13 (s, 3), 1.35 (d, 3, J = 7 Hz), 1.38 (s, 3), and 2.84 (q, 1, J = 7 Hz). Overall, with the exception of the singlet at δ 1.13, loss of 2 H multiplets at 2.65 and 2.15, and appearance of a new sharp singlet at 2.15 (H-5), the spectrum of **2**-d_3 is very similar to the nmr spectrum of **2**.

Another exchange carried out under identical conditions, except for being 4 hr in duration, also showed a singlet at δ 1.13 in place of a doublet in the spectrum of **2**. Mass spectral analysis of recrystallized material indicated the presence of 9% of **2**-d_0, 29% of **2**-d_1, 36% of **2**-d_2, 20% of **2**-d_3, and 5% of **2**-d_4.

Treatment of Santonic Acid (2) with Concentrated Aqueous KOH.—A solution of 1.0 g (0.004 mol) of santonic acid (**2**) in 20 ml of 40% KOH was heated at reflux for 48 hr under N_2, acidified with concentrated HCl, and extracted with Et_2O. The ethereal layer was washed, dried, filtered, and concentrated *in vacuo* to leave 0.94 g of approximately 90% pure santonic acid (**2**) (nmr assay). Repeated recrystallization from CH_3OH–H_2O gave 0.21 g of **2**, mp 163–174°. Mixture melting point with authentic santonic acid showed no depression (mmp 158–171.5°) while a mixture melting point with metasantonic acid (**5**) was depressed (mmp 137–157°).

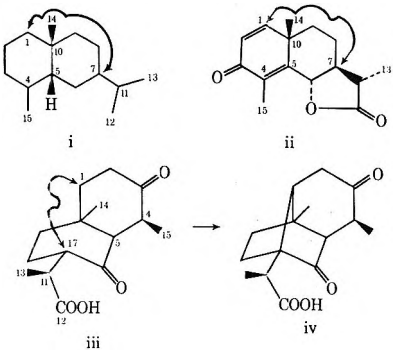
(38) The basic conditions used in the H_2O_2 and KOBr oxidations are not sufficiently strong to cause significant isomerization of **31** or **32** at C-11 to yield the corresponding 11*R* epimers (meta series). Similarly, epimerization at C-2 during the formation of aposantonic acid (**29**) is considered unlikely.

(39) Boiling points are uncorrected; melting points are uncorrected and were determined on samples in unsealed capillary tubes employing a Thomas-Hoover melting point apparatus. Infrared spectra were obtained on approximately 10% solutions in $CHCl_3$ using a Perkin-Elmer Model 457 grating spectrophotometer or a Perkin-Elmer Model 21 recording spectrophotometer. Mass spectra were determined using a Varian M-66 instrument with an ionizing potential of *ca.* 70 eV; precise mass determinations have a precision of ±0.03 amu. Nmr spectra were obtained on approximately 20–30% solutions in $CDCl_3$ (unless otherwise stated) using a Varian A-60A spectrometer; peak positions are reported in δ (parts per million) downfield from tetramethylsilane at δ 0.00 as internal standard. Complete ir and nmr spectra of most of the compounds described appear in the Ph.D. Thesis of D. S. Daniel (ref 1). Microanalyses were performed by Mikroanalytisches Laboratorium, Vienna, Austria, and Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

(40) In the normal work-up procedure, all organic extracts were washed with brine or water and dried over anhydrous magnesium sulfate. Recrystallizations, unless otherwise noted, were carried out using ethyl acetate–petroleum ether (bp 63–69°). Column chromatographic separations were carried out using Woelm alumina, neutral, activity 1; Alcoa Alumina, F-20 (basic); Fisher silica gel, Grade 923; or Davison silica gel, Grade 923. Evaporative distillations were done using a Kontes Bantamware micromolecular still, K-284500, or a noncommercial still of similar design. Short-path distillations were accomplished with a Kontes Bantamware short-path distillation apparatus, K-284800 (Kontes Glass Co., Vineland, N. J.).

(41) The compounds described are systematically named and numbered as cyclic eudesmanes where the new ring is formed between the C-1 and C-7 positions as in i. The orientation of the new bond at C-1 and C-7 is designated as α (based on the α,β-convention used in steroid systems and extended to the eudesmane structure *prior* to cyclization) and is implicit since the absolute configuration for α-santonin (ii) at C-10 is known and only one possibility exists for the orientation of the newly formed ring (iii). Trivial names from the original usage are used where applicable and no ambiguity emerges.

The nomenclature and numbering system used for the eudesmanes (i) are essentially those of W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4549 (1956), and further modifications in accord with the "IUPAC–IUB 1967 Revised Tentative Rules for Nomenclature of Steroids," *J. Org. Chem.*, **34**, 1517 (1969).



1,7-Cyclo-6β-hydroxy-3-oxo-4,5β-eudesman-12-oic Acid (3).—The procedure described below for the preparation of **18** by Li/NH_3 reduction of **17** was scaled down using 220 mg (0.71 mmol) of **17**. Evaporation of the NH_3 was followed by addition of dilute HCl and extraction with ether. A normal work-up followed by recrystallization afforded 140 mg (74%) of **3**: mp 186–191°; ir (Nujol) 3470 (OH), 1730 (C=O), and 1700 cm^{-1} (CO-OH); nmr (DMSO-d_6/$(CD_3)_2CO$) δ 1.03 (d, 3, J = 6.7 Hz, H-15), 1.15 (d, 3, J = 7 Hz, H-13), 1.20 (s, 3, H-14), 1.50 (s), and 3.33 (s, 1, $W_{1/2}$ = 3 Hz, CHOH).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.34; H, 8.15.

(11*S*)1,7:3α,6α-Biscyclo-3β,6β-dihydroxy-4,5β-eudesman-12-oic Acid (4) (Dihydrosantonic Acid). Method A.—To a solution of 300 mg (1.14 mmol) of santonic acid (**2**) in 10 ml of 2% NaOH was added 3.21 g of 5% sodium amalgam.[42] The mixture was heated at reflux under N_2. The temperature was monitored during the course of the reaction. The duration of the reaction was 350 min (*i.e.*, until the activity of the amalgam had ceased—no hydrogen evolution). The temperature climbed from 25 to 91° during the first 15 min, then from 91 to 101° over the next 25 min, and remained at 101°. The mixture was cooled, decanted from the mercury, washed with CH_2Cl_2, acidified with concentrated HCl, and extracted with Et_2O. The organic layer was washed, dried, filtered, and evaporated *in vacuo* to afford 304 mg of partially crystalline material which contained **4** and **6** in a ratio of *ca.* 20:1 as determined by nmr assay (see Table I) of the methyl esters **4a** and **6a** (276 mg) formed by

TABLE I

SODIUM AMALGAM REDUCTION OF SANTONIC ACID (2)

Time, hr	Ratio of diol esters (4a/6a)	Ratio of oxidized esters (2a/5a)
2.5	~10	~10
5	3.5	3.7
10	2.1	1.8
20	0.8	0.9
5.8[a]	~20	~20

[a] Conditions used in method A for the preparation of **4**; the concentration of NaOH at the outset was 2% instead of 10%.

treatment of the crude product with CH_2N_2 in Et_2O. As a further check of purity, the ester mixture was dissolved in 5 ml of acetone at 0–5° and treated with 1 ml of Jones–Weedon reagent.[12] The mixture was stirred for 15 min; isopropyl alcohol, H_2O, and NaCl were added, and the solution saturated in NaCl was extracted with ether. The organic layer was washed, dried, filtered, and concentrated *in vacuo* to afford 238 mg of methyl santonate (**5a**) in greater than 95% purity as estimated by nmr analysis.

Method B.—To a solution of 5.0 g (0.019 mol) of santonic acid (**2**) in 150 ml of 10% aqueous NaOH was added 40.0 g of 5% sodium amalgam. The mixture was heated at reflux under N_2 for 2 hr, cooled, decanted from the mercury, washed with CH_2Cl_2, acidified with concentrated HCl, filtered, washed, and air dried, yielding 4.59 g (91%) of dihydrosantonic acid (**4**): mp 170.8–182.5° (lit.[10] mp 190–192°); ir (Nujol mull) 3390 (OH), 3330 (OH), and 1700 cm^{-1} (C=O); nmr (DMSO-d_6) δ 0.92 (s, 3, H-14), 1.09 (d, 3, J = 7 Hz, H-13 or H-15), 1.12 (d, 3, J = 6.8 Hz, H-15 or H-13), 2.61 (q, 1, J = 7 Hz, H-11), and 4.25–4.92 (broad band, OH).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.48; H, 8.32.

Reduction of Santonic Acid (2) with Na/Hg over Varying Lengths of Time.—The procedure followed was that of method A except that 4.0 g of 5% sodium amalgam and 0.3 g of **2** were heated at reflux with 10 ml of 10% aqueous NaOH under N_2 for varying lengths of time. The mixture was processed as in method A for the preparation of **4** by forming the diol methyl esters and oxidizing the diols (Jones–Weedon reagent). Determination of the ratio of products at each stage was accomplished by integration of the areas of the OCH_3 peaks (diol esters, δ 3.65 for **4a**, 3.70 for **6a**; diketo esters, δ 3.62 for **2a**, 3.67 for **5a**) in the expanded nmr spectra (See Table I.)

(42) W. R. Brasen and C. R. Hauser, "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 509.

Jones–Weedon Oxidation of 4 to 2.—To a solution of 72 mg (0.27 mmol) of **4** in 5 ml of acetone at 0° was added 0.4 ml of Jones–Weedon reagent.[12] After a few minutes of stirring, the excess chromic acid was destroyed with methanol. The solution was saturated with NaCl and extracted with Et_2O. The ethereal layer was washed, filtered, and evaporated *in vacuo* to give 55 mg (77%) of crystalline material having an nmr spectrum identical with that of authentic **2**.

Silver Oxide Oxidation of 4.—To a solution of 1.0 g of **4** in 1.5 ml of 10% NaOH under N_2 was added 4 ml of 20% $AgNO_3$ and 20 ml of H_2O. The mixture was brought to pH 10 with 4 ml of saturated Na_2CO_3 solution, heated at reflux for 10 min (*i.e.*, until the mirror which had formed disappeared and a solid conglomerated at the bottom of the flask), cooled, and filtered, yielding 850 mg of gray metallic solid. The yellow filtrate was cooled, acidified by dropwise addition of concentrated HNO_3, and extracted with Et_2O. The Et_2O extracts were washed, dried, filtered, and evaporated *in vacuo* to leave 1.05 g of oily solid which was treated with CH_2N_2. The nmr spectrum of the esterified product indicated the presence of methyl santonate (**2a**) and methyl dihydrosantonate (**4a**) in a ratio of 1.6:1. No compounds of the metasantonic acid series were evident in the nmr spectrum.

When the reaction was carried out according to the procedure of Cannizzaro,[9] *i.e.*, heated at reflux for 1 hr, only polymeric material and an oil with an uninterpretable nmr spectrum was obtained.

Methyl (11*S*)-1,7;3α,6α-Biscyclo-3β,6β-dihydroxy-4,5β-eudesman-12-oate (4a) (Methyl Dihydrosantonate). Method A.—Diazomethane in Et_2O was added to the Et_2O extract of **4** (500 mg, 1.9 mmol) prepared by method A, affording 464 mg (88%) of crude **4a**. Several recrystallizations afforded 128 mg of pure **4a**: mp 110.4–112° (lit.[11] mp 111–114°); ir 3570 (OH), 3440 (OH), and 1725 cm^{-1} (C=O); nmr δ 0.98 (s, 3, H-14), 1.19 (d, 3, J = 7 Hz, H-13 or H-15), 1.23 (d, 3, J = 7 Hz, H-15 or H-13), 2.76 (q, 1, J = 7 Hz, H-11), 3.67 (s, 3, $-OCH_3$), and 3.20 (s, 2, OH).

Method B.—Following the procedure outlined by Harries and Stähler,[11] an ice-cooled solution of 1.0 g (0.0036 mol) of methyl santonate (**2a**) in 25 ml of absolute CH_3OH under N_2 was treated with 30 g of 3% Na/Hg. The mixture was stirred for 7 hr with gradual warming to room temperature, filtered, and concentrated *in vacuo*. The residue was dissolved in ether and the ether solution was washed, dried, filtered, and evaporated *in vacuo*, yielding 0.84 g (83%) of crude material which gave 0.39 g (39%) of recrystallized **4a**, mp 107–111° (lit.[11] mp 111–114°); the nmr spectrum was identical with that of **4a** prepared by method A except that two broad 1 H singlets for OH appeared at δ 2.92 and 3.28 in lieu of the 2 H signal at δ 3.20. Shaking the nmr sample with 1 drop of D_2O resulted in a decrease in the total area for the signals at δ 2.92 and 3.28. Exposure to a trace of hydrochloric acid shifted the signals to δ 3.07 and 3.45, respectively.

(11*R*)-1,7-Cyclo-3,6-dioxo-4,5β-eudesman-12-oic Acid (5) (Metasantonic Acid).—A mixture of 4.73 g (0.019 mol) of β-santonin and 60 ml of 17% NaOH under N_2 was heated at reflux for 4 hr, cooled, acidified with HCl, and extracted with Et_2O. The extracts were washed, dried, filtered, and evaporated *in vacuo* to leave 5.68 g of oil which crystallized from ethyl acetate to yield 2.38 g (45%) of metasantonic acid (**5**): mp 165–169° (lit.[9] mp 164–167° dec); ir 1740, 1725, and 1710 cm^{-1}; nmr δ 1.13 (d, 3, J = 6.8 Hz, H-15 or H-13), 1.15 (d, 3, J = 7.4 Hz, H-13 or H-15), 1.40 (s, 3, H-14), and 2.78 (q, 1, J = 7 Hz, H-11).

(11*R*)-1,7;3α,6α-Biscyclo-3β,6β-dihydroxy-4,5β-eudesman-12-oic Acid (6) (Dihydrometasantonic Acid).—A solution of 1.0 g (0.004 mol) of metasantonic acid (**5**) in 30 ml of 10% NaOH was heated at reflux under N_2 with 11.15 g of 5% sodium amalgam for 2 hr. A normal work-up procedure afforded 1.06 g of dihydrometasantonic acid (**6**) as white crystals: mp 163.5–177°; ir (Nujol mull) 3470 (OH), 3260 (OH), and 1687 cm^{-1} (acid C=O); nmr (DMSO-d_6) δ 0.94 (s, 3, H-14), 0.97 (d, 3, J = 6.8 Hz), 1.08 (d, 3, J = 6.5 Hz), 1.96 (q, 1, J = 7 Hz, H-4), and 2.60 (q, 1, J = 7 Hz, H-11).

Methyl (11*R*)-1,7;3α,6α-Biscyclo-3β,6β-dihydroxy-4,5β-eudesman-12-oate (6a) (Methyl Dihydrometasantonate).—A solution of CH_2N_2 in Et_2O was added to 946 mg (3.6 mmol) of dihydrometasantonic acid (**6**) in ether. Concentration of the solution left 1.06 g of an oil which was evaporatively distilled (twice) and the fractions boiling at 106° (0.1 mm) to 112° (0.08 mm) (bath temperature) were collected to afford 866 mg (87%) of methyl dihydrometasantonate (**6a**): ir 3560 (OH), 3360 (OH), 1740 (C=O), and 1700 cm^{-1} (C=O); nmr δ 1.01 (s, 3, H-14), 1.10 (d, 3, J = 7 Hz, H-15 or H-13), 1.17 (d, 3, J = 7 Hz, H-13 or H-15),

2.09 (q, 1, J = 7 Hz, H-4), 2.78 (q, 1, J = 7 Hz, H-11), 3.26 (s, 1, OH), 3.69 (s, 3, $-OCH_3$), and 4.78 (s, 1, OH). When 1 drop of acetic acid-d_4 was added the 1 H peak at δ 3.26 disappeared and a 2 H peak was found at δ 4.8; upon addition of a second drop, the 2 H peak at 4.8 ppm disappeared and a broad 2 H singlet appeared at 6.3 ppm.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 67.30, 67.25; H, 8.18, 7.99.

Oxidation of 6 to 5. Method A. Jones–Weedon Oxidation.—A solution of 500 mg (1.8 mmol) of **6** in acetone was oxidized as described for dihydrosantonic acid (**2**) to yield 164 mg (35%) of pure metasantonic acid (**5**), mp 147–165° dec. A mixture melting point with santonic acid was depressed (mmp 137–156°), but with metasantonic acid was not depressed (mmp 152.5–164.5°).

Method B. *N*-Bromoacetamide Oxidation.[43]—To a solution of 500 mg (1.8 mmol) of dihydrometasantonic acid (**6**) in 0.5 ml of H_2O and 8 ml of acetone was added 660 mg of *N*-bromoacetamide under N_2 with cooling in an ice bath. The solution was stirred in the dark for 12 hr. The bromine formed was destroyed with 0.1 *N* sodium thiosulfate and the solution was diluted with saturated NaCl solution and extracted with ether. The extracts were washed, dried, filtered, and concentrated *in vacuo* to leave 540 mg of oil which was recrystallized from ethyl acetate to yield 170 mg (36%) of metasantonic acid (**5**) as white crystals, mp 157–168°. A mixture melting point with an authentic sample of metasantonic acid was not depressed (mmp 155–165°).

Oxidation of 6a to 5a.—A solution of 720 mg (2.6 mmol) of methyl dihydrometasantonate (**6a**) in acetone was treated with Jones–Weedon reagent[12] as described for the oxidation of **4** to **2**. The crude product (670 mg, 62%), after recrystallization from methanol, afforded 175 mg of pure **5a**: mp 101–102.8° (lit.[7] mp 101.5–102.5°); ir 1735, 1725, and 1710 cm^{-1}; nmr (CCl_4) δ 1.08 (d, 3, J = 7.2 Hz, H-13), 1.04 (d, 3, J = 6.5 Hz, H-15), 1.38 (s, 3, H-14), 2.64 (q, 1, J = 7.0 Hz, H-11), and 3.58 (s, 3, $-OCH_3$).

Formation of 7 and 9 by Treatment of Dihydrosantonic Acid (4) with Acetic Anhydride.—By analogy with the procedure described by Wedekind and Engel,[10] a mixture of 2.0 g (0.008 mol) of **4** and 27 ml of acetic anhydride was heated at reflux under N_2 for 1 hr, cooled, poured into ice water, and extracted with methylene chloride. The organic layer was evaporated *in vacuo;* the residual solid was dissolved in ether and the solution was washed with saturated $NaHCO_3$ (three 30-ml portions) and brine, dried, filtered, and evaporated *in vacuo* to leave 2.09 g of solid. Several recrystallizations yielded 0.71 g (31%) of **(11*S*)-1,7;3α,6α-biscyclo-3β-acetoxy-4,5β-eudesmane 12,6β-lactone (7)** as white crystals: mp 140–141.8°; ir 1780 (lactone C=O) and 1735 cm^{-1} (acetate C=O); nmr δ 1.10 (d, 3, J = 7 Hz, H-15), 1.13 (s, 3, H-14), 1.32 (d, 3, J = 7.8 Hz, H-13), 2.04 (s, 3, $-OCOCH_3$), 2.59 (q, 1, J = 7 Hz, H-4), and 2.62 (q, 1, J = 7.8 Hz, H-11).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.31; H, 7.64. Found: C, 70.48; H, 7.53.

Treatment of the mother liquor, dissolved in ether, with sodium bicarbonate (as above), followed by concentration of the ethereal layer and crystallization yielded another 0.76 g of acetoxy lactone **7**.

The combined aqueous layers were acidified with concentrated HCl and extracted with Et_2O. The organic extracts were washed, dried, filtered, and evaporated *in vacuo* to leave 200 mg of solid. Two recrystallizations afforded 35 mg of **1,7;3α,6α-biscyclo-3β,6β-diacetoxy-4,5β-eudesman-12-oic acid (9)** (**diacetoxydihydrosantonate**): mp 235–237.5° (lit.[10] mp 232°); ir 1735 (acetate C=O) and 1705 cm^{-1} (acid C=O); nmr δ 0.98 (d, 3, J = 7 Hz, H-15), 1.05 (s, 3, H-14), 1.18 (d, 3, J = 7 Hz, H-13), 2.08 (s, 3, $-OCOCH_3$), 2.12 (s, 3, $-OCOCH_3$), 2.76 (q, 1, J = 7 Hz, H-11), and 1.67 (br s).

Anal. Calcd for $C_{19}H_{26}O_6 \cdot {}^1/_2H_2O$: C, 63.51; H, 7.52. Found: C, 63.82; H, 7.43.

Methyl 1,7;3α,6α-Biscyclo-3β,6β-diacetoxy-4,5β-eudesman-12-oate (9a).—The diacetoxy acid **9** (14.2 mg) was treated with CH_2N_2–Et_2O. Concentration of the solution yielded 8.9 mg (62%) of methyl diacetoxydihydrosantonate (**9a**): mp 150° (lit.[10] mp 151°); nmr (microcavity tube) δ 0.98 (d, J = 7 Hz), 1.05 (s, H-14), 1.15 (d, J = 7 Hz), 2.09 (s, unresolved, but separated into two peaks when the nmr sweep width was expanded, two $-OCOCH_3$), 2.70 (q, J = 7 Hz, H-11), and 3.65 (s, $-OCH_3$).

(43) E. P. Oliveto, H. L. Herzog, M. A. Jevnik, H. E. Jorgensen, and E. B. Hershberg, *J. Amer. Chem. Soc.*, **75**, 3651 (1953).

Hydrolysis of 7.—A mixture of 100 mg of **7** in 1 ml of dioxane and 2 ml of 10% NaOH under N_2 was heated at reflux for 2 hr, cooled, acidified with concentrated HCl, and extracted with ether. The product was esterified (CH_2N_2), yielding 165 mg of oil which consisted of a mixture of **4a** and **6a** in a ratio of 3:1 (nmr assay).

Hydrolysis of 9.—A mixture of 50 mg of **9** and 2 ml of 10% NaOH under N_2 was heated at reflux for 2 hr, cooled, acidified by dropwise addition of concentrated HCl, and extracted with ether. Treatment with CH_2N_2 and concentration *in vacuo* gave 40 mg of oil which consisted of a mixture of **4a** and **6a** in a ratio of 3:5 (nmr assay).

(11*R*)-1,7;3α,6α-Biscyclo-3β-acetoxy-4,5β-eudesmane 12,6β-Lactone (8).—A solution of 131 mg (0.79 mmol) of dihydrometasantonic acid (**6**) and 3 ml of acetic anhydride was heated at reflux for 5.25 hr, cooled, and extracted with methylene chloride. The organic extract was washed, dried, filtered, and evaporated *in vacuo* to leave 129 mg of solid. The solid was dissolved in ether, washed with saturated $NaHCO_3$ and NaCl solutions, dried, filtered, and evaporated *in vacuo* to afford 113 mg (49%) of the acetoxy lactone. Several recrystallizations yielded 70 mg of pure **8**: mp 204.5–206° (lit.[10] mp 204°); ir 1780 (C=O) and 1735 cm^{-1} (C=O); nmr δ 1.08 (d, 3, J = 7 Hz, H-15 or H-13), 1.17 (d, 3, J = 7 Hz, H-13 or H-15), 1.19 (s, 3, H-14), 2.02 (s, 3, $-OCOCH_3$), and 2.57 (two overlapping q, 2, J = 7 Hz, H-11 and H-4).

Hydrolysis of 8.—A solution of 44 mg (0.15 mmol) of acetoxy lactone **8** in 1 ml of dioxane and 1 ml of 10% NaOH was heated at reflux for 1 hr under N_2, cooled, acidified with HCl, and extracted with ether. The extracts were washed, dried, filtered, and treated with CH_2N_2 to give an oil which contained >95% methyl dihydrometasantonate (**6a**) (nmr assay).

1,7-Cyclo-3-ethylidene-6-oxo-*A*-5β-noreudesman-12-oic Acid (10).—Dihydrosantonic acid (**4**) was prepared in the usual manner from 5.0 g (0.019 mol) of santonic acid (**2**), then dissolved in 30 ml of glacial acetic acid, sealed in a glass tube, and heated at 145–150° for 4 hr. The contents of the tube were dissolved in methylene chloride and washed successively with H_2O, $NaHCO_3$ (saturated), and H_2O, dried, filtered, and evaporated *in vacuo* to leave 1.33 g of semisolid material which gave 0.52 g of yellow solid on recrystallization. Several additional recrystallizations afforded analytically pure **10**: mp 144.2–146.5°; ir 3400–2910, 1725, 1705, and 835 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 248 (89.4), 230 (39.3), 202 (47.1), 175 (62.5), 147 (100), 146 (89.4), 55 (32.2) 43 (32), 41 (63.2), and 18 (36.9); nmr[44] δ 1.06 (s, 3, H-14), 1.43 (d, 3, J = 7 Hz, H-13), 1.75 (dt, 3, $J_{15,4}$ = 7, $J_{15,2}$ = $J_{5,2'}$ = 2 Hz,[45] H-15), 2.06 (apparent q, 1, $J_{1,5}$ = $J_{1,2}$ = $J_{1,2'}$ = 2 Hz, H-1), 2.45 (apparent q), probably a sextet, or possibly two overlapping quintets (*i.e.*, high-intensity central signals) of AB pattern where $\nu_1 - \nu_{2'} \cong 2$ Hz with $J_{2,15}$ = 2, $J_{2',15}$ = 2, $J_{2,1}$ = 2, $J_{2',1}$ = 2 Hz, H-2, H-2'), 2.91 (q, 1, J = 7 Hz, H-11), 3.16 (d, 1, $J_{1,5}$ = 2 Hz, H-5), and 5.46 (apparent qtd, 1, $J_{4,15}$ = 7, $J_{4,2}$ = 2, $J_{4,2'}$ = 2, $J_{4,x}$ = 1 Hz, H-4).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.11.

An nmr spectrum of the mother liquor from recrystallization (of the 1.33 g of semisolid) indicated a 2:1 ratio of **10** to a new olefinic compound (br m at 5.05 ppm) which was not investigated further. (In another experiment run for 20 hr at 160° the crude product was found to consist almost entirely of the same olefin.)

The $NaHCO_3$ wash solution was acidified and extracted to afford 3.09 g of oil which consisted of **10** and **4** in a 4:3 ratio (nmr assay). Trituration with $CHCl_3$ left 1.02 g of **4**; the soluble material was nearly entirely **10** (nmr assay) but could be crystallized only with difficulty.

1,7-Cyclo-3α-hydroxy-6-oxo-4,5β-eudesman-12-oic Acid (11).—A solution of 2.0 g (0.008 mol) of santonic acid (**2**) in 28 ml of anhydrous isopropyl alcohol containing 1.55 g of $NaBH_4$ was stirred at room temperature and under N_2 for 17 hr.

The reaction mixture was acidified with dilute HCl and extracted with ether. The ether extracts were washed, dried, filtered, and evaporated *in vacuo* to leave 2.55 g of oil. Crystal-

(44) The nmr spectrum was run at 100 Mz on a Varian HA-100 spectrometer; all couplings cited were confirmed by spin-decoupling experiments.

(45) The coupling of $J_{15,2}$ = 2 Hz is an example of homoallylic coupling. See, for instance, $J_{6,12}$ = 1.8 Hz observed for γ-metasantonin, A. G. Hortmann, D. S. Daniel, and J. Schaefer, *J. Org. Chem.*, **33**, 3988 (1968); $J_{2,9} \cong$ 1 Hz in methyl isokhusenate, G. A. Neville and I. C. Nigam, *Tetrahedron Lett.*, 837 (1969).

lization afforded 1.15 g (55%) of 11: mp 86–113°; ir 3600, 3300–2800, 1705, and 1460 cm^{-1}; nmr δ 1.02 (d, 3, J = 7 Hz, H-15), 1.04 (s, 3, H-14), 1.28 (d, 3, J = 7 Hz, H-13), 3.37 (q, 1, J = 7 Hz, H-11), 4.05 (br m, 1, $W_{1/2}$ = 7.5 Hz, CHOH), and 1.35–2.33 (m, 9).

An analytical sample was prepared by recrystallization from ethanol–water, mp 93–108.4°. Drying *in vacuo* [40° (0.4 mm) over P_2O_5] changed the melting point to 140–144.5°.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Calcd for $C_{15}H_{22}O_4 \cdot 1/4H_2O$: C, 66.5; H, 8.2. Found: C, 66.62; H, 8.01.

Treatment of 11 with CH_2N_2 in ether afforded the methyl ester **11a**: mp 93.3–94.5°; ir 3610, 3450, and 1735 cm^{-1}; nmr δ 1.03 (d, 3, J = 6.5 Hz, H-15), 1.03 (s, 3, H-14), 1.25 (d, 3, J = 7 Hz, H-13), 2.06 (q, 1, J = 6.5 Hz, H-4), 3.42 (q, 1, J = 7 Hz, H-11), 3.63 (s, 3, $-OCH_3$), 4.04 (br m, 1, J = 3.5 Hz, $W_{1/2}$ = 7.8 Hz, CHOH), and 1.35–2.35 (m, 7).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.64; H, 8.59.

Methyl 1,7-Cyclo-3α-methanesulfonyloxy-6-oxo-4,5β-eudesman-12-oate (13a).—To a cold solution of 3.37 g (0.001 mol) of **11a** in 40 ml of anhydrous pyridine was added 10 ml of methanesulfonyl chloride. The mixture was kept at 10° for 24 hr, poured into ice water, and extracted with ether. The extracts were washed with 10% HCl and brine, dried, filtered, and evaporated *in vacuo* to leave 5.9 g of oil. Chromatography on alumina (80 g, neutral, 1.5 × 45 cm) using benzene as eluent yielded 3.08 g (72%) of mesylate **13a**: ir 1730, 1355, 1180, and 1155 cm^{-1}; nmr (CCl_4) δ 1.07 (s, 3, H-14), 1.10 (d, 3, J = 7 Hz, H-15), 1.22 (d, 3, J = 7 Hz, H-13), 1.43 (br s), 2.48 [t (dd), 1, $J_{1,5}$ = 2, $J_{4,5}$ = 2 Hz, H-5); 3.04 (s, 3, $-OSO_2CH_3$), 3.37 (q, 1, J = 7 Hz, H-11), 3.57 (s, 3, $-OCH_3$), 3.91 (br m, 1, CHOR), and 1.3–2.4 (m, 8).

Further elution of the column with chloroform yielded 1.13 g of starting hydroxy ester **11a**.

Methyl 3α-Acetoxy-1,7-cyclo-6-oxo-4,5β-eudesman-12-oate (13b).—A solution of 350 mg (1.3 mmol) of **11a** in 15 ml of acetic anhydride containing 50 μl of 70% $HClO_4$ was stirred in an ice bath for 13 hr, added to ice water, and extracted with ether. The extracts were washed successively with NaCl, $NaHCO_3$, 10% NaOH, and saturated NaCl solutions, dried, filtered, and evaporated *in vacuo* to yield 424 mg of brown oil. The oil was passed through 10 g of alumina (neutral, 1 × 14 cm): fraction 1 (benzene, 75 ml), 239 mg of acetate *via* nmr (*vide infra*); fraction 2 (chloroform, 50 ml), 98 mg of acetate **13b** and at least two other compounds that were not identified. The first fraction was evaporatively distilled (twice) to afford 208 mg (52%) of acetate **13b**: bp 84° (bath temperature) (0.09 mm); ir 1785 (shoulder) and 1735 cm^{-1}; nmr (CCl_4) δ 0.92 (d, 3, J = 7 Hz, H-15), 1.11 (s, 3, H-14), 1.38 (d, 3, J = 7 Hz, H-13), 1.94 (s, 3, $-OCOCH_3$), 3.09 (q, 1, J = 7 Hz, H-11), 3.59 (s, 3, $-OCH_3$), and 4.99 (br q, 1, J = 3.5 Hz, CHOR).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.48; H, 7.55. Found: C, 67.45; H, 8.23.

Hydrolysis of 13b.—A solution of 169 mg of **13b** in 8 ml of 40% ethanol containing 6% NaOH was heated at reflux under N_2 for 3 hr. Work-up afforded 11 in >80% yield.

Methyl 6β-Acetoxy-1,7-cyclo-3α,6α-epoxy-4,5β-eudesman-12-oate (14).—A mixture of 3.08 g (0.009 mol) of mesylate **13a**, 50 ml of glacial acetic acid, and 4.0 g of anhydrous sodium acetate was heated at reflux under N_2 for 2 hr, cooled, diluted with H_2O, and extracted with CH_2Cl_2. The organic extract was washed, dried, filtered, and evaporated *in vacuo* to yield 2.53 g (91%) of oil. Crystallization afforded 1.95 g (70%) of 14: mp 79.6–83.6°; ir 1760, 1730, and 1100 cm^{-1}; nmr δ 1.08 (s, 3, H-14), 1.10 (d, 3, J = 7 Hz, H-15 or H-13), 1.27 (d, 3, J = 7 Hz, H-13 or H-15), 2.05 (s, 3, $-OCOCH_3$), 2.63 (dd, 1, $J \cong 3$, $J \sim 1.5$ Hz, H-5), 3.50 (q, 1, J = 7 Hz, H-11), 3.65 (s, 3, $-OCH_3$), and 4.05 (br m, 1, $W_{1/2}$ = 7.3 Hz, H-3). An analytical sample had mp 79.5–81°.

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.06; H, 8.08.

Hydrolysis of 14.—A mixture of 1.53 g of **14** and 1.94 g of NaOH in THF–H_2O (3:2) was heated at reflux under N_2 for 6 hr and cooled. Extraction with ether afforded 1.35 g of neutral oil which was identical (nmr) with methyl ester **11a**. The basic aqueous solution was acidified and extracted with ether to yield 0.16 g of oil which was identical in its nmr spectrum with hydroxy acid **11**.

Dehydration of 11a. Method A.—A solution of 26.4 g (0.1 mol) of santonic acid (**2**) was reduced with $NaBH_4$ as described above. A solution of the crude alcohol **11a** in CH_3OH (350 ml) containing 0.5 ml of concentrated H_2SO_4 was refluxed for 2.5 hr and worked up as usual to afford, after esterification (CH_2N_2) and distillation at reduced pressure, 18.5 g of oil, bp 90–144° (0.15–0.22 mm). Chromatography on alumina (Alcoa F-20) yielded 14.3 g of a mixture of two olefins (5:1 ratio) and 3.37 g (13%) of recrystallized **11a**. The olefin mixture was rechromatographed four times on large alumina columns. Fractions containing the olefin eluted first were combined (650 mg) and distilled twice to afford 505 mg of **methyl 1,7-cyclo-6-oxo-4,5β-eudesm-2-en-12-oate (15)**: bp 64–70° (bath temperature) (0.11 mm); ir 1735, 1640, and 670 cm^{-1}; nmr δ 1.08 (d, 3, J = 7 Hz, H-15), 1.09 (s, 3, H-14), 1.50–2.7 (m, 7), 1.33 (d, 3, J = 7 Hz, H-13), 2.88 (q, 1, J = 7 Hz, H-11), 3.67 (s, 3, $-OCH_3$), 5.50 (ddd, 1, $J_{3,2}$ = 10, $J_{3,4}$ = 2, $J_{3,1}$ = 1 Hz, C=CH), and 5.75 (ddd, 1, $J_{2,3}$ = 10, $J_{2,1}$ = 5.25, $J_{2,4}$ = 2 Hz, CH=C). An analytical sample of **15** was prepared by glpc (6-ft column, 1% SE-30 on Anakrom AS).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.25; H, 8.22.

The fractions containing the olefin eluted last from the columns were combined (7.4 g) and distilled to afford 4.49 g of **methyl 1,7-cyclo-6-oxo-5β-eudesm-3-en-12-oate (16a)**: bp 62–72° (0.06 mm); ir (film) 1735, 1670, and 815 cm^{-1}; nmr (CCl_4) δ 0.97 (s, 3, H-14), 1.33 (d, 3, J = 7 Hz, H-13), 1.70 (dt, 3, $J_{15,3}$ = 1.2, $J_{15,2}$ = $J_{15,2'}$ = 2.3 Hz, H-15), 2.17 (m, 3), 2.97 (q, 1, J = 7 Hz, H-11), 3.58 (s, 3, $-OCH_3$), and 5.33 (br s, 1, $W_{1/2}$ = 8 Hz, C=CH, H-3); ORD[46] (*c* 0.62, cyclohexane) $[\alpha]_{228}$ 0°, $[\alpha]_{237}$ +40,300°, $[\alpha]_{245}$ +35,800°, $[\alpha]_{273}$ +53,600°, $[\alpha]_{298}$ 0°, $[\alpha]_{314}$ −42,300°, $[\alpha]_{328}$ −20,900°, $[\alpha]_{350}$ = −8200°; CD[46] (*c* 0.62, cyclohexane) $[\theta]_{216}$ 0°, $[\theta]_{223.5}$ +42,700°, $[\theta]_{242}$ +6,100°, $[\theta]_{254}$ 0°, $[\theta]_{295}$ −70,100°, $[\theta]_{328}$ −1600°.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; mol wt, 262.157. Found: C, 73.10; H, 8.27; mol wt, 262.193 (mass spectrum).

Method B.[25]—A solution of 200 mg of **11a**, 20 ml of anhydrous dimethylformamide, and 5 ml of collidine was cooled under N_2 and 2 ml of methanesulfonyl chloride was added. The mixture was stirred at room temperature (23°) for 12 hr and heated at 90–100° for 2 hr, cooled, poured into ice water, and extracted with ether. The extracts were washed with 20% HCl and brine, dried, filtered, and evaporated *in vacuo* to afford 218 mg of brown oil. The nmr spectrum indicated the presence of three compounds, *viz.*, **11a** (<5%), **15** (<5%), and **16a** (>90%).

Hydrolysis of 16a.—A mixture of 711 mg of **16a**, 10 ml of dioxane, and 20 ml of 10% NaOH was heated at reflux under N_2 for 2 hr. A normal work-up procedure afforded 678 mg of product which upon crystallization from ethyl acetate gave **1,7-cyclo-6-oxo-5β-eudesm-3-en-12-oic acid (16)** as white rods: mp 181.6–183°; nmr δ 0.84 (s, 3, H-14), 1.26 (d, 3, J = 7 Hz, H-13), 1.78 (dt, 3, $J_{15,3}$ = 1.2, $J_{15,2}$ = $J_{15,2'}$ = 2.3 Hz, H-15), 2.93 (q, 1, J = 7 Hz, H-11), 5.44 (br s, 1, $W_{1/2}$ = 7.5 Hz, H-3, C=CH), and 10.83 (s, 1, OH).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.49; H, 8.10.

Attempted Hydroboration of Methyl 1,7-Cyclo-6-oxo-5β-eudesm-3-en-12-oate (16a). Method A.[26]—To a cold (salt–ice bath) solution of 512 mg (1.9 mmol) of **16a** in 10 ml of anhydrous THF under N_2 was added 4 ml of 1.0 *M* borane in THF over 10 min; the solution was stirred at room temperature for 12 hr, H_2O was added dropwise until foaming ceased, and 5 ml of 10% NaOH and 5 ml of 30% H_2O_2 were added. After stirring for 1 hr at room temperature, the solution was extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo*, yielding 452 mg of oil: nmr (CCl_4) δ 1.12 (d, $J \sim 7$ Hz), 1.19 (s), 1.29 (s), 1.68 (br s), 2.59 (q, J = 7 Hz), 4.12 (dd, J = 7, 1.5 Hz), 4.34 (dd, J = 7, 1 Hz), 5.28 (br s), and 5.50 (br s). The ratio of the last four signals was about 5:4.5:1.3:0.5. Vpc analysis (6-ft column, 1% SE-30/Anakrom AS) indicated at least six compounds.

Method B.—The procedure of Knight and Brown[27] was followed in preparing 9-borabicyclo[3.3.1]nonane. A solution of 200 mg (0.76 mmol) of **16a** in 1 ml of THF was added by means of a syringe to the solution of 9-borabicyclo[3.3.1]nonane. The resulting reaction mixture was stirred at room temperature for 20 hr; H_2O was added followed by 1 ml of 10% NaOH and 1 ml of

(46) The ORD and CD curves were measured using a Durrum-Jasco Model J-20 spectropolarimeter.

30% H_2O_2. The resulting basic solution was warmed for 10 min and extracted with ether. The extracts were washed with 10% HCl and brine, dried, filtered, and evaporated *in vacuo* to afford 435 mg of oil; the nmr spectrum showed mainly **16a** and *ca.* 20% of 1,5-cyclooctadiene.

1,7-Cyclo-3-ethylenedioxy-6-oxo-4,5β-eudesman-12-oic Acid (17).—In a boiling flask equipped with a Dean–Stark trap, 52.8 g (0.2 mol) of santonic acid (**2**), 1.0 g of *p*-toluenesulfonic acid, and 100 ml of ethylene glycol in 1.05 l. of benzene were heated at reflux for 10 hr. The benzene was removed *in vacuo*, and 60 g of KOH, 300 ml of methanol, and 150 ml of H_2O were added. The solution was heated at reflux for 1 hr, cooled, evaporated *in vacuo*, acidified with dilute acetic acid, and extracted with CH_2Cl_2. The combined extracts were washed, dried, filtered, and evaporated *in vacuo*, affording 69.5 g of solid. Recrystallization yielded 51.7 g (83%) of santonic acid ketal (**17**): mp 146–149.6°; ir 1740 and 1705 cm^{-1}; nmr δ 0.99 (d, 3, J = 6.5 Hz, H-15), 1.22 (s, 3, H-14), 1.49 (d, 3, J = 7 Hz, H-13), 1.3–2.6 (complex m, 8), 3.33 (q, 1, J = 7 Hz, H-11), and 3.98 (m, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.26; H, 7.86.

A solution of 100 mg (0.33 mmol) of **17** in 5 ml of acetone, 2 ml of water, and 5 drops of concentrated H_2SO_4 was heated at reflux under N_2 for 1 hr, cooled, and concentrated *in vacuo*, affording 70 mg (82%) of crude material having an nmr spectrum identical with that of authentic **2**. Recrystallization gave **2**, mp 165–177°, mmp 168–174° with authentic **2**.

Methyl 1,7-Cyclo-3-ethylenedioxy-6-oxo-4,5β-eudesman-12-oate (17a).—A solution of 1.60 g (0.005 mol) of **17** in ether was treated with CH_2N_2. Distillation afforded 1.3 g (78%) of **17a**: bp 172–185° (1.3 mm); ir 1740 (shoulder) and 1725 cm^{-1}; nmr δ 0.87 (d, 3, J = 7 Hz, H-15), 1.17 (s, 3, H-14), 1.34 (d, 3, J = 7 Hz, H-13), 3.17 (q, 1, J = 7 Hz, H-11), 3.62 (s, 3, $-OCH_3$), and 3.93 (m, 4, $-OCH_2CH_2O-$).

1,7-Cyclo-3-ethylenedioxy-6β-hydroxy-4,5β-eudesman-12-oic Acid (18).—Following a procedure analogous to that of Huffman and Charles,[29] a solution of 2.24 g (0.007 mol) of **17** in 40 ml of anhydrous THF was added to 500 ml of distilled liquid NH_3 in a flask equipped with a Dry Ice–acetone condenser; NH_4Cl (57 g) was then added. This was followed by addition of 6.4 g of Li wire in small pieces over 20 min at −60°. The mixture was stirred for 1 hr and warmed to room temperature. After evaporation of most of the NH_3 and addition of water, glacial acetic acid was added dropwise to the cooled mixture until the pH was 6. Extraction with CH_2Cl_2 followed by a normal work-up procedure afforded 2.45 g of white solid. Recrystallization gave 1.85 g (82%) of the hydroxy acid **18**: mp 198–201°; ir (Nujol) 3455 (OH), 3500–2600 (br, OH), and 1740 cm^{-1}; nmr (DMSO-d_6) δ 0.83 (d, 3, J = 6.5 Hz, H-15), 0.99 (s, 3, H-14), 1.08 (d, 3, J = 7 Hz, H-13), 1.32 (s), 2.78 (q, 1, J = 7 Hz, H-11), 3.82 (m, 4, $-OCH_2CH_2O-$), 4.26 (br s, 1, $W_{1/2}$ = 3 Hz, CHOH), and 11.69 (br s, 1, OH).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.81; H, 8.36.

The nmr spectrum of the mother liquor (333 mg) indicated a 7:3 ratio of unreduced **17** to 6β-hydroxy acid **18**. No 6α-hydroxy acid **20** was discernible.

Methyl 1,7-Cyclo-3-ethylenedioxy-6β-hydroxy-4,5β-eudesman-12-oate (18a).—Diazomethane in ether was added to a solution of 3.74 g (0.012 mol) of once-recrystallized acid **18**. Evaporation *in vacuo* gave an oil which was chromatographed on alumina (neutral) to remove small amounts of **17a**. The fractions containing **18a** were combined and a portion (0.21 g) was distilled using a sublimation apparatus to obtain an analytical sample: bp 80–82° (bath temperature) (0.10 mm); ir 3630, 3480, and 1725 cm^{-1} (C=O); nmr δ 0.90 (d, 3, J = 7 Hz, H-15), 1.05 (s, 3, H-14), 1.23 (d, 3, J = 7 Hz, H-13), 1.95 (s, 1, OH), 3.00 (q, 1, J = 7 Hz, H-11), 3.63 (s, 3, $-OCH_3$), 3.92 (m, 4, $-OCH_2CH_2O-$), and 4.48 (s, 1, $W_{1/2}$ = 4 Hz, CHOH).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.45; H, 8.51.

Oxidation of 18a to 17a.—To a cooled (ice bath) solution of 87 mg (0.27 mmol) of **18a** in 10 ml of acetone (distilled from chromic trioxide), 0.25 ml of Jones–Weedon reagent[12] was added dropwise over 10 min until a red color persisted. The mixture was stirred for 35 min. Methanol and H_2O were added and the mixture was extracted with ether. The extracts were washed with brine, dried, filtered, and evaporated *in vacuo* to afford 80 mg (92%) of **17a**: nmr δ 0.95 (d, 3), 1.00 (s, 3), 1.42 (d, 3), 3.28 (q, 1), 3.65 (s, 3), and 3.95 (m, 4).

1,7-Cyclo-6β-hydroxy-5β-eudesm-3-en-12-oic Acid (19).—A solution of 2.24 g (0.009 mol) of **16** in 30 ml of anhydrous THF was added to 500 ml of distilled liquid NH_3 in a flask cooled with a Dry Ice–acetone bath and fitted with a Dry Ice–acetone condenser. Ammonium chloride (53 g) was added,[29] followed (during 25 min) by 5.70 g of Li wire cut in small pieces. The cold mixture was stirred until the blue color had disappeared, and then warmed to room temperature. After evaporation of the NH_3, the mixture was cooled, treated with water, acidified with glacial acetic acid to pH 6, and extracted with CH_2Cl_2. A normal work-up afforded 2.99 g of yellowish oil which, after several recrystallizations, afforded 1.01 g (45%) of **19**: mp 126.5–128.5°; nmr δ 0.94 (s, 3, H-14), 1.22 (d, 3, J = 7 Hz, H-13), 1.52 (apparent br s), 1.71 (apparent br d, 3, J = 1.5 Hz, H-15), 2.77 (q, 1, J = 7 Hz, H-11), 3.73 (br s, 1, $W_{1/2}$ = 2.5 Hz, CHOH), 5.12 (br s, 1, $W_{1/2}$ = 6 Hz, CH=C, H-3), and 7.48 (s, 2, OH).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.98; H, 8.92.

Methyl 1,7-Cyclo-6β-hydroxy-5β-eudesm-3-en-12-oate (19a).—A solution of **19** in ether was treated with CH_2N_2. Several distillations using an evaporative still gave **19a**: bp 82–84° (bath temperature) (0.12 mm); ir 3630, 3510, 1730, and 805 cm^{-1}; nmr δ 0.93 (s, 3, H-14), 1.21 (d, 3, J = 7 Hz, H-13), 1.47 (br peak, 4, $W_{1/2}$ = 3.3 Hz), 1.71 (dt, 3, $J_{15,2}$ = 2.3, $J_{15,3}$ = 1.5 Hz, H-15), 2.46 (s, 1, OH), 2.78 (q, 1, J = 7 Hz, H-11), 3.64 (s, 3, $-OCH_3$), 3.73 (s, 1, $W_{1/2}$ = 2 Hz, CHOH), and 5.10 (br s, 1, $W_{1/2}$ = 7.5 Hz, CH=C, H-3).

A sample for elemental analysis was prepared by glpc (10.5-ft column, 2% SE-30 on Anakrom 60/70 ABS).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.29; H, 9.17.

Preparation of 20, 21, and 22 by Lithium Aluminum Hydride Reduction of 17.—A solution of 24.0 g (0.08 mol) of **17** in 225 ml of anhydrous THF was added dropwise during 2 hr to a mixture of 5.0 g of $LiAlH_4$ in 200 ml of anhydrous THF at −1 to −5° and under N_2. The mixture was stirred at 0° for 3 hr. Wet ether and aqueous $NaHCO_3$ solution were added dropwise and in succession at 0° and the resulting mixture was stirred for 1 hr, diluted further with H_2O, and extracted with ether. The organic layer was worked up as usual by washing with brine, drying, filtering, and evaporating *in vacuo* to yield 4.96 g of gummy tan solid. The solid was slurried in saturated Na_2CO_3 solution for 30 min. Extraction with ether and work-up as before afforded 2.40 g of solid. Recrystallization gave **1,7-cyclo-3-ethylenedioxy-4,5β-eudesmane 6α,12-diol (21)** as white prisms: mp 108.8–110.4°; ir 3610 and 3420 cm^{-1}; nmr δ 0.90 (d, 3, J = 6.7 Hz), 0.93 (d, 3, J = 6.7 Hz), 1.12 (s, 3, H-14), 1.21 (s), 1.72 (br d, 1, $J_{5,6}$ = 4.5 Hz, H-5), 2.78 (br s, 2, –OH), 3.51 (d, 1, $J_{12,12'}$ = 11.0, $J_{12,11}$ = 0 Hz, H-12), and 3.71 [dd (partially obscured), 1, $J_{12',11}$ = 11.0, $J_{12',11}$ ~ 5 Hz, H-12'], 3.76 (s, 4, $-OCH_2CH_2O-$), and 4.04 (dd, 1, $J_{6,5}$ = 4.5, $J_{6,1}$ = 3 Hz, CHOH).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.98; H, 9.33.

The diol **21** was also obtained in high yield by $LiAlH_4$ reduction of the hydroxy acid **20**.

The combined basic aqueous layers containing the acidic product after removal of **21** were cooled, acidified by addition of HCl, saturated with NaCl, and extracted with ether. The extracts were combined, washed, dried, filtered, and evaporated *in vacuo*, leaving 23.3 g of oil. The oil was dissolved in ethyl acetate, and petroleum ether (bp 30–60°) was added. Upon cooling to 0°, crystals were deposited. Filtration yielded 0.87 g of starting ketal **17** (nmr), mp 134–140°. The filtrate was concentrated, taken up in ether, washed with Na_2CO_3 and saturated NaCl solutions, dried, filtered, and evaporated *in vacuo* to leave 167 mg of diol **21** (nmr). The basic wash solutions were acidified and extracted as before to recover the bulk of the oily product (*ca.* 22 g). The oil was dissolved in 220 ml of dioxane. Hydrochloric acid (10%, 110 ml) was added and the resulting mixture was heated at reflux for 3 hr, cooled, saturated with NaCl, and extracted with ether. The extracts were washed with $NaHCO_3$ and saturated NaCl solutions, dried, filtered, and evaporated *in vacuo*, affording 20.8 g of oil. The oil was stirred with aqueous Na_2CO_3 for 2 hr and extracted with ether. The ether layer was processed as before to yield 0.45 g of solid which afforded **1,7-cyclo-3-oxo-4,5β-eudesmane 12,6α-lactone (22)** upon recrystallization: mp 173–175.5°; ir 1780 (C=O) and 1715 cm^{-1} (C=O); nmr δ 1.21 (d, 3, J = 7 Hz), 1.23 (d, 3, J = 7 Hz), 1.28 (s, 3, H-14), 2.65 (q, 1, J = 7 Hz, H-11), and 4.35 (dd, 1, $J_{6,5}$ = 7, $J_{6,1}$ = 2 Hz, CHO–).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.46; H, 7.91.

The aqueous bicarbonate layer remaining after removal of **22** was cooled to 0° and acidified by dropwise addition of HCl. Extraction with ether was followed by a normal brine wash. Drying, filtration, and concentration gave an oil which crystallized to yield 17.1 g (71%) of **1,7-cyclo-3-ethylenedioxy-6α-hydroxy-4,5β-eudesman-12-oic acid (20)** as white prisms: mp 112–116.5°; ir 3590, 3440, and 1705 cm^{-1}; nmr[44] δ 0.90 (d, 3, $J_{15,4}$ = 6.7 Hz, H-15), 1.13 (s, 3, H-14), 1.16 (d, 3, $J_{13,11}$ = 7 Hz, H-13), 1.78 [m, 2 (appears as br d, J = 5 Hz, at 60 MHz), H-1 and H-5], 2.13 (q, 1, $J_{4,15}$ = 6.7 Hz, H-4), AB parts of an ABX pattern centered at 1.51 (dd, 1, $J_{2,2'}$ = 13, $J_{2,1}$ = 2.5 Hz, H-2), and 2.29 (dd, 1, $J_{2',2}$ = 13, $J_{2',1}$ = 2.5 Hz, H-2′), 3.27 (q, 1, $J_{11,13}$ = 7 Hz, H-11), 3.78 (m, 4, $-OCH_2CH_2O-$), 4.05 (dd, 1, $J_{6,5}$ = 5.5, $J_{6,1}$ = 3.5 Hz, CHOH), and 6.94 (br s, 2, OH). An analytical sample of **20** had mp 117.9–118.5°.

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.69; H, 8.61.

The mother liquors afforded another 0.78 g of **20**.

Preparation of 22 by Treatment of 20 with HCl.—A mixture of 1.00 g (0.003 mol) of **20**, 10 ml of 10% HCl, and 20 ml of dioxane was heated at reflux under N_2. After 16 hr, a 20-ml aliquot was added to 10% NaOH solution. The solution was extracted with ether and the extracts were washed, dried, filtered, and evaporated *in vacuo* to afford 0.028 g of lactone **22** (nmr). The basic solution was cooled, acidified with HCl, extracted with ether, and worked up in the normal manner to leave 0.507 g of the starting acid **20** (nmr). The nmr spectrum was poorly resolved and at least 20% of other material could have gone undetected. After heating for 84 hr, the remaining mixture was worked up as for the aliquot to afford 0.067 g of lactone **22** and 0.238 g of acid **20**.

The acidic material (0.507 g) obtained from work-up of the aliquot was subjected to further acid treatment for 50 hr and worked up as before to yield 0.523 g of material containing lactone **22** and acid **20** in a ratio of ~2:3 by nmr assay.

Preparation of 20-6β-d_1 and 21-6β,12,12-d_3.—Ketal **17** (2.0 g, 0.007 mol) was reduced with 0.52 g of $LiAlD_4$ as described above for the preparation of **20**, **21**, and **22**, yielding 0.18 g of neutral diol, **21-6β,12,12-d_3**: mp 105–106.5°; nmr δ 0.88 (d, 3, J = 6.5 Hz, H-15), 0.93 (d, 3, J = 6.8 Hz, H-13), 1.12 (s, 3, H-14), 1.71 (br s, 1, $W_{1/2}$ = 2.5 Hz), 2.32 (q, 1, J = 7 Hz), 2.37 (q, 1, J = 7 Hz), and 3.78 (s, 4, $-OCH_2CH_2O-$). An additional 0.21 g of crystals were obtained from the mother liquor on evaporation and cooling.

Further processing as described for the $LiAlH_4$ reduction afforded trace amounts of lactone **22-d_3** followed by 0.87 g of **20-6β-d_1**: mp 111–112.9°; nmr δ 0.90 (d, 3, J = 6.5 Hz, H-15), 1.12 (s, 3, H-14), 1.14 (d, 3, J = 6.5 Hz, H-13), 1.77 (s, 2), 3.22 (q, 1, J = 6.7 Hz, H-11), and 3.75 (s, 4, $-OCH_2CH_2O-$). Another 0.76 g of crystals (mp 112–115°) was obtained from the mother liquor after concentrating and cooling.

Attempted Oxidation of 20 to 17.—A solution of 1.00 g of **20** in 20 ml of anhydrous DMF containing 1.00 g of anhydrous CrO_3[47] was treated with 100 λ of concentrated H_2SO_4 and stirred at room temperature for 5 days. The reaction was quenched by adding methanol to destroy the excess oxidant. The mixture was diluted with $NaHCO_3$ solution and extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo* to yield 246 mg of oil, whose nmr spectrum showed that the ratio of the area for CHOH to the area of $-OCH_2CH_2O-$ was 1:1 and the ratio of area for lactonic CHO– to CHOH was 1:4.

The aqueous layer was acidified with HCl and extracted with ether. The ether layer was worked up as above to obtain 880 mg of oil. An nmr spectrum of the oil was not readily interpreted; however, integration indicated that the areas for the lactonic CHO–, CHOH, and $-OCH_2CH_2O-$ protons were in a ratio of 1:3:8. Also, a signal at δ 1.28 could be assigned to H-14 of the lactone **22** and a signal at 1.12 assigned to a methyl group of the acid **20**.

Methyl 1,7-Cyclo-3-ethylenedioxy-6α-hydroxy-4,5β-eudesman-12-oate (20a).—A solution of **20** in ether was treated with CH_2N_2–Et_2O concentrated *in vacuo* to leave the methyl ester **20a**: bp 120–140° (bath temperature) (0.1 mm); ir 3413 and 1705 cm^{-1} (d); nmr δ 0.90 (d, 3, J = 6.5 Hz, H-15), 1.12 (s, 3, H-14), 1.30 (d, 3, J = 7 Hz, H-13), 1.78 (dd, 1, $J_{5,6}$ = 5.5, $J_{5,1}$ = 2, $J_{5,4}$ = 0 Hz, H-5), 2.11 (q, 1, J = 6.5 Hz, H-4), 3.10 (s, 1, OH), 3.25 (q, 1, J = 7 Hz, H-11), 3.67 (s, 3, $-OCH_3$), 3.75 (s, 4, $-OCH_2CH_2O-$), and 4.02 (dd, 1, $J_{6,5}$ = 5.5, $J_{6,1}$ = 2.5 Hz, CHOH). An analytical sample was prepared by distilling an aliquot twice using an evaporative still and collecting the fraction boiling at 140–143° (bath temperature) (0.1 mm).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.60; H, 8.61.

Attempted Oxidation of 20a to 17a.—To an ice-cooled solution of 258 mg of **20a** in 10 ml of anhydrous DMF was added 120 mg of CrO_3.[47] The mixture was stirred until dissolution was complete (30 min). Three drops of concentrated H_2SO_4 was added. The solution was stirred at room temperature for 7 hr, treated with aqueous $NaHSO_3$, and extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo* to yield 210 mg of oil; the nmr spectrum had the usual peaks for **20a** plus C-methyl peaks for a related compound in minor amount. However, the ratio of the peaks at δ 3.63 (s, $-OCH_3$), 3.73 (s, $-OCH_2CH_2O-$), and 3.98 (dd, J = 5.5, J = 2.5 Hz, CHOH) was 2:2:1.

Attempted Ketalization of 22.—A mixture of 243 mg of the lactone **22**, 20 ml of benzene, 10 ml of ethylene glycol, and 9.81 mg of *p*-toluenesulfonic acid was heated at reflux for 48 hr using a Dean–Stark trap to collect water formed. The benzene was distilled and 10 ml of 20% KOH and 20 ml of methanol were added. The resulting solution was heated at reflux under N_2 for 1 hr, cooled, acidified with acetic acid, and extracted with CH_2Cl_2. The organic phase was washed, dried, filtered, and evaporated *in vacuo* to afford 238 mg of oily solid. Recrystallization from ethyl acetate yielded 96 mg of white crystals, mp 169.5–174.5°. The product was identical with **23** in its nmr spectrum (see below). The mother liquor gave a poorly defined nmr spectrum in which **20** could not be clearly identified.

1,7-Cyclo-6α-hydroxy-3-oxo-4,5β-eudesman-12-oic Acid (23).—A mixture of 315 mg (1.3 mmol) of lactone **22** and 5 ml of 10% NaOH was warmed to 57° over 3 hr under N_2 until the solid had dissolved; the solution was cooled, acidified by dropwise addition of HCl, and extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo*, leaving 354 mg of solid. Recrystallization afforded 213 mg (63%) of **23**: mp 181–183.5°; ir (Nujol) 3320 (OH) and 1705 cm^{-1} (C=O); nmr (DMSO-d_6) δ 0.80 (d, 3, J = 6.7 Hz, H-15), 1.00 (d, 3, J = 7 Hz, H-13), 1.07 (s, 3, H-14), 1.15–2.2 (m, 8), 3.11 (q, 1, J = 7 Hz, H-11), 3.60 (dd, 1, $J_{6,5}$ = 5.5, $J_{6,1}$ = 2.5 Hz, CHOH), and 6.0 (br s, OH).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.49; H, 8.21.

Methyl 1,7-Cyclo-3-ethylenedioxy-6β-methanesulfonyloxy-4,5β-eudesman-12-oate (24).—To an ice-cooled solution of 336 mg (1.04 mmol) of **18a** in 7 ml of anhydrous pyridine was added 1 ml of methanesulfonyl chloride. The mixture was kept at 10° for 38 hr, and then treated with ice water and extracted with CH_2Cl_2. The extracts were washed with H_2O, dilute acetic acid (10%), and saturated $NaHCO_3$ solution, dried, filtered, and evaporated *in vacuo* to leave 366 mg (88%) of **24**: nmr δ 1.00 (d, 3, J = 7 Hz, H-15), 1.09 (s, 3, H-14), 1.22 (d, 3, J = 7 Hz, H-13), 2.99 (s, 3, $-OSO_2CH_3$), 3.13 (q, 1, J = 7 Hz, H-11), 3.63 (s, 3, $-OCH_3$), 3.94 (m, 4, $-OCH_2CH_2O-$), and 5.53 (s, 1, H-6).

Methyl 1,7-Cyclo-3-ethylenedioxy-6α-methanesulfonyloxy-4,5β-eudesman-12-oate (C-6 Epimer of 24).—To a solution of 1.05 g (0.003 mol) of **20a** in 20 ml of anhydrous pyridine at 0° under N_2 was added 0.5 ml of methanesulfonyl chloride. The mixture was stirred for 45 min (formation of a precipitate occurred), poured into cold 10% HCl, and extracted with ether. The extracts were washed with dilute HCl and brine, filtered, and evaporated *in vacuo* to leave a solid which upon recrystallization afforded 1.09 g (81%) of the C-6 epimer of **24**: mp 122–123°; ir 1730 (C=O), and 1360 and 1178 cm^{-1} ($-SO_2O-$); nmr δ 0.88 (d, 3, J = 6.5 Hz, H-15), 1.10 (s, 3, H-14), 1.13 (d, 3, J = 7 Hz, H-13), 1.77 (dd, 1, $J_{5,6}$ = 5.5, $J_{5,1}$ = 2 Hz, H-5), 2.10 (q, 1, J = 6.5 Hz, H-4), 3.04 (s, 3, $-SO_2CH_3$), 3.22 (q, 1, J = 7 Hz, H-11), 3.63 (s, 3, $-OCH_3$), 3.93 (8 lines, 3, –CHO– and A_2 of A_2B_2 for $-OCH_2CH_2O-$), and 4.32 (8 lines, 2, B_2 of A_2B_2 for $-OCH_2CH_2O-$).

Anal. Calcd for $C_{19}H_{30}O_7S$: C, 56.71; H, 7.51; S, 7.51. Found: C, 56.61; H, 7.48; S, 7.65.

1,7-Cyclo-3-ethylenedioxy-13-oxo-4,5β-13-homoeudesmane 13a,6β-Sultone (25).—A solution of 256 mg (0.64 mmol) of **24** in 10 ml of dry benzene was added to 380 mg of potassium *tert*-butoxide (Ventron, powder) in 10 ml of dry benzene. The mixture was heated at reflux under N_2 for 1 hr, cooled, poured into ice water, and extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo* to afford 134 mg (57%) of sultone **25**: ir 1715, 1370, and 1160 cm^{-1}; nmr δ 0.95 (d, 3, J = 6.5 Hz), 1.06 (d, 3, J = 7 Hz), 1.14 (s, 3, H-14), 1.59 (br s,

(47) G. Snatzke, *Chem. Ber.*, **94**, 729 (1961).

$W_{1/2}$ = 6.5 Hz), 2.35 (qd, 1, $J_{4,15}$ = 7, $J_{4,5}$ = 2 Hz, H-4), 3.29 (q, 1, J = 7 Hz, H-11), 3.97 (m, 4, $-OCH_2CH_2O-$), 4.34 (s, 2, H-13a), and 5.75 (s, 1, H-6). A sample for elemental analysis, mp 130.5–132° dec, was prepared by recrystallization from ethanol.

Anal. Calcd for $C_{18}H_{26}O_6S$: C, 58.37; H, 7.08; S, 8.63. Found: C, 58.42; H, 6.78; S, 9.52, 8.68.

A new crystalline material formed when the sultone **25** was left at room temperature in the presence of a trace of acid. Recrystallization from methanol afforded 3-oxo sultone **26**: mp 137–141° dec; ir 1715, 1370, and 1165 cm^{-1}; nmr δ 1.14 (d, J = 7 Hz), 1.20 (d, 3, J = 6.5 Hz), 1.27 (s, 3, H-14), 2.76 (dq, 1, $J_{4,15}$ = 7, $J_{4,5}$ = 2.5 Hz, H-4), 3.18 (q, 1, J = 7 Hz, H-11), 4.31 (s, 2, H-13a), and 4.56 (br, 1, $W_{1/2}$ = 3 Hz, CHO–).

Anal. Calcd for $C_{16}H_{22}O_5S$: C, 58.88; H, 6.79; S, 9.81. Found: C, 59.06; H, 7.04; S, 9.51.

Methyl 1,7;4,6α-Biscyclo-3-oxo-5β-eudesman-12-oate (28).—Mesylate **24** was prepared as described using 207 mg (0.64 mmol) of the ester **18a**. In the work-up procedure the ethereal solution was washed with 10% HCl instead of acetic acid as described above. An nmr spectrum of the oil obtained (228 mg) indicated that partial loss of the ketal function had occurred resulting in formation of two mesylates, *viz.*, **24** and **27**, in a ratio of *ca.* 1:1. The oil was chromatographed on 9 g of alumina to afford, after distillation, 104 mg of **28**: bp 72–75° (bath temperature) (0.10 mm); ir 1735, 1685, 1465, 1380, 875, and 855 cm^{-1}; nmr δ 1.03 (s, 3, H-15), 1.12 (s, 3, H-14), 1.24 (d, 3, J = 7 Hz, H-13), 2.14 (dd, A of ABX, 1, $J_{2,2'}$ = 16.5, $J_{2,1}$ = 3.0 Hz), 2.25 (dd, B of ABX, 1, $J_{2',2}$ = 16.5, $J_{2',1}$ = 3.0 Hz), 2.68 (q, 1, J = 7 Hz, H-11), and 3.63 (s, 3, $-OCH_3$); in benzene the doublet at 2.14 ppm was shifted to 2.07 ppm. The outer low-intensity doublets (J = 3 Hz) of the AB portion of the ABX system were partially obscured by other resonance peaks.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.67; H, 8.52.

Alkaline Peroxide Oxidation of Santonic Acid (2).—To a cooled solution of 3.00 g (0.012 mol) of **2** in 15 ml of 10% NaOH was added 20 ml of 15% H_2O_2. The solution was left at 10° for 38 hr, acidified by dropwise addition of 4 *N* HCl (15 ml), and extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo*, yielding 3.88 g of solid. Recrystallization from benzene and four times from ethyl acetate afforded 229 mg of 1,7-cyclo-*B*-homo-6a-oxa-3,6-dioxo-4,5β-eudesman-12-oic acid (**31**): mp 181–183° dec; ir 1745 and 1715 cm^{-1}; nmr δ 1.08 (d, J = 6.5 Hz, H-15), 1.35 (d, J = 7 Hz, H-13), 1.44 (s, 3, H-14), 3.04 (q, 1, J = 7 Hz, H-11), and 9.63 ppm (s, 1.3, –COOH).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.05.

The mother liquors were combined, treated with CH_2N_2–Et_2O, and evaporated *in vacuo* to give 2.06 g of oil. The oil was chromatographed on neutral alumina. Rechromatography on silica gel of the fractions eluted from alumina with petroleum ether and CCl_4 afforded, on elution with $CHCl_3$ (following elution with CCl_4 and benzene), 0.134 g of **29a** (see below) and 1.21 g of a mixture of **31a** and **29a** in a ratio of ~12:1. Distillation of the 0.134-g fraction afforded 0.124 g of methyl 1β,3α-dimethyl-7-ethylidene-4-oxo-5β-bicyclo[4.3.0]octane-2-carboxylate (**29a**) (methyl aposantonate): bp 62–72° (bath temperature) (0.06 mm); mp 71–73°; ir 1735, 1715, and 820 cm^{-1}; nmr δ 0.95 (d, 3, J = 6.0 Hz, 3-CH_3), 0.99 (s, 3, 1-CH_3), 1.60 (dt, 3, J = 7, 1.5 Hz, C=CHCH_3), 2.51 [d, 1, $J_{2,3}$ = 12.5 Hz, H-2 (upfield half of doublet partially obscured)], 2.92 (dq, 1, $J_{3,2}$ = 12.5, J_{3,CH_3} = 6 Hz), 3.75 (s, 3, $-OCH_3$), and 5.35 (br q, 1, J = 7 Hz, C=C**H**-CH_3).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.92; H, 8.76.

Two distillations of the 1.21-g mixture followed by glpc separation afforded 67 mg of the lactone ester **31a**: mp 111.8–127°; nmr δ 1.06 (d, 3, J = 6.75 Hz, H-15), 1.30 (d, 3, J = 7 Hz, H-13), 1.43 (s, H-14), 3.00 (q, 1, J = 7 Hz), and 3.70 (s, 3 $-OCH_3$). An analytical sample was prepared by glpc (6-ft column, 1% SE-30 on Anakrom AS).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 64.99; H, 7.40.

The reaction was repeated following as closely as possible the procedure given by Wedekind and Jäckh.[36] Santonic acid (**2**, 3.00 g) in 50 ml of 2% KOH in the cold was treated with 40 ml of 15% H_2O_2 for 24 hr. The resulting solution was acidified with 10% HCl, saturated with NaCl, and extracted with ether. The extracts were washed with brine, dried, filtered, and evaporated *in vacuo* to afford 2.91 g of oil; the nmr spectrum indicated santonic acid (**2**), olefin **29**, and lactone **31** in a ratio of 2:1:1.

Treatment of Santonic Acid (2) with Potassium Hypobromite.—By analogy with the procedure of Wedekind and Jäckh,[36] a solution of 10 ml of Br_2 in 600 ml of 5% KOH was added to a solution of 10.0 g (0.04 mol) of **2** in 200 ml of 5% KOH at room temperature. Within 30 min solid formed. After 24 hr, the mixture was filtered to yield 100 mg of carbon tetrabromide, mp 90–92°. The filtrate, after 13 days, was cooled and acidified with HCl. Sodium bisulfite and NaCl were added and the mixture was extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo* to afford 9.9 g of white solid. A solution of 3.47 g of the solid in ethyl acetate was diluted with petroleum ether until the solution became cloudy. The solution was warmed gently on the hot plate until a slight amount of brown oil began to form; upon cooling, crystals began to form. Filtration gave 0.46 g (14%) of 2(3 → 4β)*abeo*-1,7-cyclo-2α-hydroxy-6-oxo-5β-eudesmane-3,12-dioic acid (**32**) (oxysantonic acid): mp 211–213° (sealed tube) (lit.[36] mp 215° dec); ir (Nujol mull) 3600–2600, and a broad absorption band at 1786–1690 having peaks (shoulders) at 1768, 1745, 1735, and 1718 cm^{-1}. A second crop of crystals yielded another 0.12 g of the diacid.

Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Calcd for $C_{15}H_{20}O_6 \cdot {}^1/_4H_2O$: C, 59.8; H, 6.7. Found: C, 59.77, 59.62; H, 6.87, 6.81.

Dimethyl 2-(3 → 4β)*abeo*-1,7-Cyclo-2α-hydroxy-6-oxo-5β-eudesmane-3,12-dioate (32a).—A solution of 0.211 g (0.71 mmol) of **32** in ether was treated with CH_2N_2 to yield 0.230 g (100%) of the dimethyl ester **32a**: nmr δ 1.33 (s, 3, H-14), 1.42 (d, 3, J = 7 Hz, H-13), 1.61 (s, 3, H-15), 2.36 (d, 1, $J_{5,1}$ = 2.5 Hz, H-5), 2.54 (dd, 1, $J_{1,2}$ = 4, $J_{1,5}$ = 2.5 Hz, H-1), 3.28 (q, 1, J = 7 Hz, H-11), 3.68 (s, 3, $-OCH_3$), 3.72 (s, 3, $-OCH_3$), 4.49 (dd, 1, $J_{2,OH}$ = 7, $J_{2,1}$ = 4 Hz, H-2), and 5.08 (d, 1, $J_{OH,2}$ = 7 Hz, OH). The signal at δ 5.08 disappeared upon addition of one drop of acetic acid-d_4; the doublet of doublets at δ 4.49 became a doublet ($J_{2,1}$ = 4 Hz) and a broad absorption band appeared at δ 9.47.

Dimethyl 2(3 → 4β)*abeo*-1,7-Cyclo-2,6-dioxo-5β-eudesmane-3,12-dioate (33).—To a cold solution of 84 mg (0.26 mmol) of **32a** in 5 ml of acetone was added 0.5 ml of Jones–Weedon reagent.[12] After the solution was stirred for 24 min, excess oxidant was destroyed with methanol, H_2O was added, and the solution was extracted with ether. The extracts were washed with brine, dried, filtered, and evaporated *in vacuo* to leave 61 mg (73%) of yellow oil. The oil was passed through silica gel using chloroform as eluent. Concentration of the eluate *in vacuo* gave dihemiketal **33a**: ir (Nujol) 3500–2500 (br band with max at 3380), 1735, 1710, and 1683 cm^{-1}; nmr δ 1.35 (s, 3, H-14), 1.39 (d, 3, J = 7 Hz, H-13), 1.58 (s, 3, H-15), 2.72 (s, 2, H-1 and H-5), 3.07 (q, 1, J = 7 Hz, H-11), 3.66 (s, 3, $-OCH_3$), and 3.72 (s, 3, $-OCH_3$). An analytical sample was prepared by recrystallization from CH_3OH–H_2O, mp 207–211°.

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Calcd for $C_{17}H_{22}O_6 \cdot H_2O$: C, 59.99; H, 7.11. Found: C, 60.19, 60.20; H, 7.38, 7.16.

2(3 → 4β)*abeo*-1,7-Cyclo-4α,6α-carbonyloxy-2α,6-diacetoxy-5β-eudesman-12-oic Acid (34).—A solution of 529 mg of **32** in 5 ml of pyridine and 2.5 ml of acetic anhydride was stirred at room temperature for 62 hr, diluted with ice water, and extracted with ether. The extracts were washed with dilute HCl and brine, dried, filtered, and evaporated *in vacuo* to leave 600 mg of oil. Crystallization from benzene–petroleum ether followed by ethyl acetate–petroleum ether afforded 129 mg of the diacetoxy acid **34**: mp 194.5–196° (lit.[36] mp 192° dec); ir 1800, 1760, 1745, and 1710 cm^{-1}; nmr δ 1.22 (s, 3, H-14), 1.28 (d, 3, J = 7 Hz, H-13), 1.48 (s, 3, H-15), 2.06 (s, 3, $-OCOCH_3$), 2.11 (s, 3, $-OCOCH_3$), 2.37 (dd, 1, $J_{1,2}$ = 4, $J_{1,5}$ = 2 Hz, H-1), 3.10 (d, 1, $J_{5,1}$ = 2 Hz, H-5), 3.26 (q, 1, J = 7 Hz, H-11), and 5.33 (d, 1, $J_{2,1}$ = 4 Hz, H-2).

Anal. Calcd for $C_{19}H_{24}O_8$: C, 59.97; H, 6.36. Found: C, 60.14; H, 6.32.

Methyl 2(3 → 4β)*abeo*-1,7-Cyclo-4α,6α-carbonyloxy-2α,6β-diacetoxy-5β-eudesman-12-oate (34a).—A solution of 208 mg of the diacetoxy acid **34** in ether was treated with CH_2N_2 to afford 204 mg of diacetoxy ester **34a**: mp 139.5–140.8° (lit.[36] mp 142°); nmr δ 1.22 (s, 3, H-14), 1.22 (d, 3, J = 7 Hz, H-13), 1.43 (s, 3, H-15), 2.02 (s, 3, $-OCOCH_3$), 2.08 (s, 3, $-OCOCH_3$), 2.18 (dd, 1, $J_{1,2}$ = 4 Hz, $J_{1,5}$ = 2.5 Hz, H-1), 3.03 (d, 1, $J_{5,1}$ = 2.5 Hz, H-5), 3.35 (q, 1, J = 7 Hz, H-11), 3.93 (s, 3, $-OCH_3$), and 5.17 (d, 1, $J_{2,1}$ = 4 Hz, H-2).

Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.98; H, 6.68.

Registry No.—**2**, 510-35-0; **3**, 36492-45-2; **4**, 29598-38-7; **5**, 34167-05-0; **6**, 29598-40-1; **6a**, 29598-41-2; **7**, 36539-92-1; **9**, 36492-47-4; **10**, 36492-48-5; **11**, 36492-50-9; **11a**, 36492-49-6; **13a**, 36492-51-0; **13b**, 36563-78-7; **14**, 36492-52-1; **15**, 36492-53-2; **16**, 36492-54-3; **16a**, 36492-55-4; **17**, 36492-56-5; **17a**, 36492-57-6; **18**, 36492-58-7; **18a**, 36492-59-8; **19**, 36492-60-1; **19a**, 36492-61-2; **20**, 36492-62-3; **20-6β-d_1**, 36492-63-4; **20a**, 36492-64-5; **21**, 36492-65-6; **21-6β-12,12-d_3**, 36492-66-7; **22**, 36492-67-8; **23**, 36492-68-9; **24**, 36492-69-0; **24** C-6 epimer, 36492-70-3; **25**, 36492-71-4; **26**, 36492-72-5; **28**, 36492-73-6; **29a**, 36492-74-7; **31**, 36492-75-8; **31a**, 36492-76-9; **32**, 36492-77-0; **32a**, 36492-78-1; **33**, 36492-79-2; **34**, 36492-80-5; **34a**, 36594-88-4.

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Notes

Synthesis of Diterpenoid Acids. XII.[1] Preparation of a Lactone Related to *cis*-Dehydrodeisopropylabietic Acid

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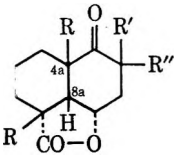
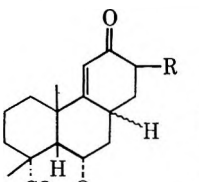
We have described the preparation of the bicyclic cis keto lactone **1a** as an intermediate in the synthesis of diterpenoid acids.[2] In the present work we have added an aromatic ring C in the hope that it would then be possible to epimerize the bridgehead hydrogen,[1,3] and thus obtain diterpenoid acids related to abietic acid.

The Robinson–Mannich annelation failed with **1a**. However, the hydroxymethylene compound **1b** reacted with trimethyl-3-oxobutylammonium iodide in the presence of base to give the diketo aldehydo lactone **1c**, which, after prolonged treatment with sodium ethoxide, underwent an aldol cyclization to form **2a**. Apparently the formation of the third ring is hindered by the presence of the lactone, since the cyclization went more smoothly in the presence of aqueous base; in the work-up of this reaction the lactone was reclosed by heating the crude product in benzene with *p*-toluenesulfonic acid.[4]

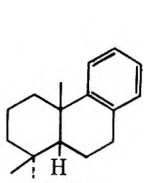
We also prepared **2a** from **1a** by an approach similar to that used by Dutta in his synthesis of *cis*-dehydrodeisopropylabietic acid (**3**).[3] Compound **1a** was converted in poor yield to the Mannich base **1d**, whose



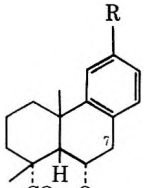
1a, R = CH_3; R′ = R″ = H
b, R = CH_3; R′R″ = C(OH)H
c, R = CH_3; R′ = CHO; R″ = $CH_2CH_2C(=O)CH_3$
d, R = CH_3; R′ = $CH_2N(CH_3)_2$; R″ = H
e, R = CH_3; R′ = $CH_2N^+(CH_3)_3I^-$; R″ = H
f, R = CH_3; R′R″ = CH_2
g, R = H; R′R″ = $CHSC_4H_9$



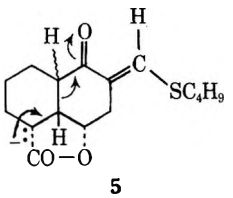
2a, R = H
b, R = $COOC_2H_5$



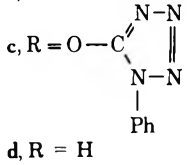
3



4a, R = OCH_2Ph
b, R = OH



5



c, R = O—C(=N—N)—N(Ph)—N
d, R = H

methiodide **1e** condensed with acetoacetic ester to give crude **2b**. By carrying out the Mannich reaction of **1a** in refluxing isoamyl alcohol we obtained the methylene derivative **1f**, which condensed with acetoacetic ester to give **2b** and **2a** in poor yields. The structures of compounds **1b–f**, **2a**, and **2b** are based on spectral and analytical data.

The preparation of **2a** *via* the formyl derivative **1b** is more satisfactory than the one *via* the methylene derivative **1f** and was the one normally used. However, the product from both routes melted over a range of 5°. The nmr spectra showed that the main product

(1) Part XI: A. Kröniger and D. M. S. Wheeler, *Tetrahedron*, **28**, 255 (1972).
(2) A. C. Ghosh, K. Mori, A. C. Rieke, S. K. Roy, and D. M. S. Wheeler, *J. Org. Chem.*, **32**, 722 (1967).
(3) C. T. Mathew, G. C. Banerjee, and P. C. Dutta, *J. Org. Chem.*, **30**, 2754 (1965).
(4) S. K. Roy and D. M. S. Wheeler, *J. Chem. Soc.*, 2155 (1963).

(signal for vinyl proton at 6.05 ppm) was contaminated by a closely related second product (vinyl signal at 6.15 ppm). We attribute the mixture to the existence of **2a** in two forms epimeric at C_8.

We attempted to prepare *cis*-dehydrodeisopropylabietic acid[3] by aromatizing ring C, removing the phenol, and cleaving the lactone. Treatment of **2a** with cupric bromide in benzyl alcohol[5] gave the benzyl ether **4a**, which was hydrogenolyzed to the phenol **4b**. The phenolic group was removed by hydrogenolysis of the phenyltetrazolyl ether (**4c**)[7] to give **4d**. Our **4d** had a similar melting point and an identical infrared spectrum to **4d** of known stereochemistry previously prepared by Mahapatra and Dodson[8-10] using an entirely different route. This confirms that the stereochemistries we assigned earlier[2] and those in the present paper are correct.[11]

In trying to remove the lactone group by oxidation at C_7 followed by hydrogenolysis (*cf.* ref 13) we were not able to oxidize **4d** with chromic acid even under strong conditions. Other attempts to remove the lactone also failed. We also were unsuccessful in applying to **2a** the route used by Dutta and coworkers in their synthesis of **3**.[3]

The presence of sp^2 carbons at the C_5 and C_6 positions of **1b**, **4c**, and **4d** restricts rotation about the C_5–C_6 bond.[14] Studies with models suggest that the most stable conformation of these compounds is not that of **1a**[15] but rather one in which the C_8–O bond is axial to ring B; ring B is in a twist-boat conformation, while ring A is a chair. In such a conformation the dihedral angle of C_8–H with each of the C_7–H's is 60° (J_{calcd} = 2.5 Hz[16]) and the angle C_8H–$C_{8a}H$ is about 10° (J_{calcd} = 9.5 Hz[16]). These calculated coupling constants are consistent with the observed values. The conformation we have deduced for **4c** and **4d** differs from that normally adopted by compounds related to isodehydroabietic acid.[17]

Since it is well established that resin acids with ring C aromatic are readily oxidized by chromic acid,[9,18] the resistance of **4d** to oxidation was unexpected. Examination of the conformation of **4d** indicates a 1,4 interaction between the C_4 α H and the C_7 α H, which would, presumably, be relieved by oxidation of C_7 to a ketone. The initial stage of the oxidation of a benzylic position by chromic acid involves the removal of a hydride ion or hydrogen atom by the oxidant.[19] It seems likely that of the two hydrogens at C_7, removal of the α hydrogen (axial to ring B) would enable the developing radical or positive charge to fulfill better the stereoelectronic conditions for conjugation with the ring than would the removal of the 7β hydrogen. However, in the conformation adopted by **4d** the 7α H is on the concave side of the molecule and so not easily accessible to attack by the reagent.[20] In view of our failure to cleave the lactone **4d** to the corresponding acid and the length of the synthesis to **4d**, we have abandoned this approach to synthesizing diterpenoid acids in favor of another route.[1]

(5) Our use of benzyl alcohol in place of methyl alcohol[6] was to facilitate the cleavage of the phenolic ether at the next stage.

(6) A. W. Fort, *J. Org. Chem.*, **26**, 765 (1961).

(7) W. J. Musliner and J. W. Gates, *J. Amer. Chem. Soc.*, **88**, 4271 (1966).

(8) R. M. Dodson, personal communication.

(9) S. N. Mahapatra and R. M. Dodson, *Chem. Ind. (London)*, 253 (1963).

(10) We are grateful to Dr. R. M. Dodson for informing us of his synthesis of **4d** and for supplying us with a copy of its infrared spectrum.

(11) In earlier work,[2] we assigned the stereochemistry of the product **1a** on the basis that, in the methylation of **1g**, the lactone ring controlled the stereochemistry at C_1 and that the stereochemistry at C_{8a} was not affected by the reaction. It was possible that the latter assumption was incorrect (see **5**).[12]

(12) We thank Drs. N. A. LeBel and M. J. T. Robinson for pointing out this possibility to one of us (D. M. S. W.).

(13) A. E. Lickei, A. C. Rieke, and D. M. S. Wheeler, *J. Org. Chem.*, **32**, 1647 (1967).

(14) In this paragraph we use decalin numbering for compounds **4b** and **4c** as well as for **1b**.

(15) G. A. Gallup, M. L. Maheshwari, S. K. Roy, and D. M. S. Wheeler, *Tetrahedron*, **24**, 5769 (1968).

(16) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 50.

(17) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).

(18) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958).

(19) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Menlo Park, Calif., 1972, pp 285–288.

(20) R. B. Woodward, F. A. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(21) Unless otherwise stated infrared spectra were determined for chloroform solutions on Perkin-Elmer 137 and 237 infrared spectrometers, and nmr spectra on $CDCl_3$ solutions on Varian A-60 and A-60D spectrometers.

Experimental Section[21]

***cis*-Decahydro-6-formyl-8α-hydroxy-1β,4a-dimethyl-5-oxonaphthalene-1α-carboxylic Acid Lactone (1b).**—Sodium hydride (0.45 g, 51.7% suspension in oil) was added to a cooled solution (0°) of the keto lactone **1a** (0.45 g) in ethyl formate (5 ml) in a nitrogen atmosphere. A drop of dry methanol was added and the mixture was stirred at 0° for 1.5 hr. Ether (5 ml) was added, the stirring was continued for 3.5 hr, and the mixture was treated with water (10 ml) and then extracted with ether. The combined ethereal solutions were extracted with aqueous sodium hydroxide (2 *N*). The combined aqueous extracts were acidified and extracted with ethyl acetate. The ethyl acetate solution was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to yield a brown oil which crystallized on treatment with ether to give **1b**: mp 119–122° (0.51 g); ν_{max} 1760, 1640, and 1580 cm^{-1}; nmr δ 0.70–2.60 (13 H, m, with s at 1.22 and 1.33 and d, J = 6.5 Hz at 2.37), 2.80 (2 H, d, J = 3.5 Hz, =CCH_2CO–), 4.85–5.20 (1 H, d of t, J = 3.5 and 6.5 Hz, OCH), and 7.55 (1 H, broad s, C=CH). This product was used in the following reaction without further purification.

***cis*-Decahydro-6-formyl-6-(3′-butanone)-8α-hydroxy-1β,4a-dimethyl-5-oxonaphthalene-1α-carboxylic Acid Lactone (1c).**—A solution of trimethyl-3-oxobutylammonium iodide (15 g) in methanol (20 ml) was added dropwise (20 min) in a nitrogen atmosphere to a cooled mixture (0°) of sodium methoxide (from 0.30 g of sodium) in methanol (10 ml) and the formyl compound **1b** (3.2 g obtained from 2.5 g of **1a**) in methanol (25 ml). The mixture was stirred for 25 hr at room temperature, and the solvent was removed under reduced pressure. The residue was treated with saturated aqueous sodium chloride (20 ml, pH *ca.* 8), and the mixture was acidified and then extracted with ethyl acetate. The ethyl acetate solution was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and concentrated. The residue in benzene was chromatographed on Florisil and the product eluted in ether was obtained as an oil (3.6 g) which crystallized from ether to give material with mp 149–156° (2.4 g). Further crystallization from chloroform–ether gave **1c**: mp 152–153°; ν_{max} 1730, 1720, and 1705 cm^{-1} (sh); nmr ($CHCl_3$) δ 0.80–4.00 (22 H, m with s at 1.30, 1.40, and 2.13) and 4.80–5.10 (1 H, m, HCO–).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55; O, 24.97. Found: C, 67.17; H, 7.37; O, 25.52.

***cis*-Decahydro-6-methylene-8α-hydroxy-1β,4a-dimethyl-5-oxonaphthalene-1α-carboxylic Acid Lactone (1f).**—A mixture of the keto lactone **1a** (0.88 g), dimethylamine hydrochloride (0.50 g), paraformaldehyde (0.52 g) in isoamyl alcohol (25 ml), and concentrated hydrochloric acid (4 drops) was refluxed in a nitrogen atmosphere for 5 hr, and then diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were dried (Na_2SO_4) and the solvent was removed to give a neutral product (2.74 g, contains isoamyl alcohol) which was chromatographed on Florisil. The material (1.12 g) eluted in ethyl

acetate crystallized from ether–light petroleum to give the methylene compound, **1f**, mp 134–135° (0.40 g) and 123–130° (0.15 g). The former material was recrystallized further from ethanol for analysis: ν_{max} 1775, 1694, and 1620 cm^{-1}; nmr δ 0.80–2.70 (13 H, m, with s at 1.22 and 1.30), 3.00–3.30 (2 H, m, $-CH_2CO-$), 4.75–5.20 (1 H, m, OCH), 5.30–5.50 (1 H, m, =CH), and 6.18–6.38 (1 H, m, =CH).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.56; H, 7.90.

The aqueous portion from the reaction was treated with potassium carbonate at 0°, the solution was saturated with sodium chloride, and the basic product was isolated by extraction with ethyl acetate. Evaporation of the dried (Na_2SO_4) ethyl acetate solution gave the Mannich base **1d** (0.04 g), mp 94–99°, ν_{max} 1775, 1705, and 1620 cm^{-1} (weak). This compound with methyl iodide gave a yellow methiodide **1e**, mp 125° dec.

The preparation of **1f** was also carried out by refluxing **1a**, paraformaldehyde, and dimethylamine hydrochloride in dimethoxyethane for 68 hr.

***cis*-10α-Hydroxy-1β,4a-dimethyl-6-oxo-1,2,3,4,4a,6,7,8,8a,9,-10,10a-dodecahydrophenanthrene-1α-carboxylic Acid Lactone (2a).** A.—A mixture of the diketo aldehydo lactone **1c** (2.7 g, mp 152–155°, from 2.5 g of the keto aldehyde **1b**), potassium hydroxide (8.0 g), methanol (100 ml), and water (50 ml) was stirred under nitrogen for 70 hr. The solvent was evaporated, the residue was treated with water (100 ml), and the mixture was acidified to pH 2 with concentrated hydrochloric acid. The product was extracted with ethyl acetate and the ethyl acetate solution was washed with water and dried (Na_2SO_4). Removal of the solvent gave the crude product as a brown residue. A solution of the residue in benzene with *p*-toluenesulfonic acid was refluxed for 16 hr with a water separator; it was then washed with dilute aqueous sodium carbonate and water and dried (Na_2SO_4). Evaporation of the solvent gave a dark brown oil (2.2 g) whose infrared spectrum did not show a band corresponding to a saturated ketone but did show strong absorption corresponding to an unsaturated ketone. Chromatography of this oil on Florisil and elution with ethyl acetate gave a brown oil (1.8 g) which solidified on trituration with ether. Two crystallizations from ether gave the unsaturated ketone **2a**: mp 158–163° (1.1 g); nmr δ 1.00–2.90 (20 H, m with overlapping singlets at 1.30 and 1.40), 4.80–5.20 (1 H, m, –OCH), and 6.05 (d, J = 2 Hz, =CH) and 6.15 (d, J = 3 Hz, =CH) (the two peaks together integrate to 1 H). After several recrystallizations from methanol–hexane (with a trace of ether) the ketone **2a** was obtained as needles: mp 168.5–173° (with slight decomposition); ν_{max} 1770, 1665, and 1605 cm^{-1}; spectrum identical with that of material, mp 169–175° from B.

B.—In a typical procedure, a solution of the methylene compound, **1f** (0.80 g), in ethanol (25 ml) was added at 0° under N_2 to a stirred mixture of ethyl acetoacetate (0.56 g), and sodium ethoxide (from 0.2 g of sodium) in ethanol (5 ml) which had been stirred for 1 hr at 0°. The mixture was stirred for 8 hr and refluxed for 9 hr. Water was added to the mixture, which was concentrated under vacuum on a water bath, more water was added, and the product was extracted in ethyl acetate. The ethyl acetate was dried and evaporated to yield crude product (0.51 g), ν_{max} 1773, 1713 (very weak), 1665, and 1608 cm^{-1}, which tlc showed contained two major fractions. The aqueous mixture was acidified and then extracted with ethyl acetate to yield further product [0.48 g, ν_{max} 1762, 1710, 1660, and 1603 cm^{-1} (weak)] which was a complex mixture (tlc).

The material obtained in the first ethyl acetate extraction of several reactions was chromatographed repeatedly on Florisil. The product **2b** corresponding to the faster running tlc spot was eluted in benzene: mp 171–174° (yield about 5%) raised after crystallization from ether–light petroleum to mp 174–175°; ν_{max} 1767, 1663, and 1625 cm^{-1}; λ_{max} 247 nm (ϵ 11,000) and 315 (3000); nmr δ 0.90–3.35 (21 H, m, with sharp peaks at 1.05, 1.24, 1.33, 1.38, 1.44, and 1.56), 4.00–4.70 (2 H, m, OCH_2-CH_3), 4.90–5.35 (1 H, m, –OCH), 7.07 (1 H, s, =CH), and 7.83 (1 H, s, –OH). Structure **2b** is assigned to this compound.

Anal. Calcd for $C_{20}H_{28}O_5$: C, 69.34; H, 7.57. Found: C, 69.31; H, 7.41.

Later fractions from the column eluted in benzene–ether (3:1) gave material which after crystallization from ether had mp 163–169° (yield less than 5%) raised by crystallization from ethanol–ether to mp 169–175°; ν_{max} 1772, 1663, and 1603 cm^{-1} (identical with material **2a**, mp 168.5–173°, prepared in A above); nmr ($CHCl_3$) δ 0.8–3.0 (m, with strong s at 1.29 and weak s at 1.42), 4.90–5.20 (m, –OCH), and 6.05 (d, with trace of d at 6.18, C=CH). (The nmr spectrum was very similar to the nmr spectrum of the major component of the product with mp 158–163° in A above.)

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.47; H, 8.08. Found: C, 74.35; H, 8.21.

***cis*-12-Benzyloxy-6α-hydroxydehydrodeisopropylabietic Acid Lactone (4a).**—A solution of the unsaturated ketone **2a** (1.1 g) in benzyl alcohol (25 ml) was heated with cupric bromide (1.6 g) at 70° for 2.5 hr in a N_2 atmosphere. Ether was added to the cooled mixture, which was filtered. The ether was removed under reduced pressure and the benzyl alcohol was removed by steam distillation. The residue was dissolved in chloroform and the chloroform solution was washed, dried (Na_2SO_4), and concentrated. A solution of the brown residue in benzene was chromatographed on Florisil, and the material eluted in benzene–ether (1:1) crystallized from ether to give **4a**: mp 176° (780 mg), raised after further crystallizations from ether–chloroform and ether to 179.5–180.5°; ν_{max} 1760 cm^{-1}; nmr δ 0.8–2.5 (13 H, m with s at 1.17 and 1.32 and d, J = 7 Hz, at 2.28), 3.0–3.2 (2 H, $-CH_2$ aromatic, d, J = 4 Hz), 4.75–5.20 (3 H, m, $PhCH_2O$ + OCH), 6.6–7.2 (3 H, m, $C_{arom}H$), and 7.38 (5 H, s, $C_{arom}H$).

Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23; O, 13.24. Found: C, 79.22; H, 7.25; O, 13.10.

***cis*-12-(5′-1′-phenyl-1-*H*-tetrazolyloxy)-6α-hydroxydehydrodeisopropylabietic Acid Lactone (4c).**—A solution of the benzyl ether **4a** (0.75 g) in methanol (200 ml) and concentrated sulfuric acid (2 drops) was hydrogenated in the presence of palladium on charcoal (10%, 0.2 g). After an uptake of 45 ml of H_2 (in 15 min) the solution was filtered, and the filtrate was concentrated to a small volume and extracted with chloroform. The chloroform solution was washed with water, dried (Na_2SO_4), and evaporated to yield the phenol **4b**: mp 214–216° (0.55 g); ν_{max}^{Kbr} 1740 cm^{-1}; nmr peaks (deuterioacetone, material was poorly soluble) δ 0.70–3.00 (16 H, m, with s at 0.80 and 0.92), 4.6–4.9 (1 H, m, –OCH), and 6.1–6.8 (3 H, m, $C_{arom}H$).

A mixture of the phenol **4b** (0.53 g), 5-chloro-1-phenyl-1*H*-tetrazole (0.36 g), anhydrous potassium carbonate (1.0 g), and dimethylformamide (40 ml) was heated at 80° for 8 hr in a N_2 atmosphere, and then diluted with ethyl acetate (200 ml). The ethyl acetate solution was washed with ice–water several times, the aqueous phase was back extracted with ethyl acetate, and the back extracts were washed with water. The combined ethyl acetate solutions were dried (Na_2SO_4) and evaporated to yield an oil. Any remaining traces of dimethylformamide were removed *in vacuo* and the residue was crystallized on treatment with ether and light petroleum, yielding the ether **4c** as a pale yellow solid, mp 139–141° (750 mg). The product after three crystallizations from methanol was colorless: mp 142–143°; ν_{max} 1765 cm^{-1}; nmr δ 1.00–2.50 (13 H, m, with s at 1.25 and 1.32 and d, J = 7 Hz, at 2.38), 3.20 (2 H, d, J = 4 Hz, $C_{arom}CH_2-$), 5.00–5.35 (1 H, d of t, J = 4 and 7 Hz, –OCH), and 7.20–8.00 (8 H, m, $C_{arom}H$).

Anal. Calcd for $C_{24}H_{24}O_3N_4$: C, 69.21; H, 5.81; N, 13.45. Found: C, 69.15; H, 5.75; N, 13.62.

***cis*-6α-Hydroxydehydrodeisopropylabietic Acid Lactone (4d).**—A solution of the tetrazolyl ether **4c** (0.70 g) in ethanol (200 ml) was shaken in a hydrogen atmosphere at 45 psi at 28° for 21 hr in the presence of palladium on charcoal (10%, 0.50 g). The solution was filtered and the filtrate was concentrated. A solution of the residue (0.69 g) in benzene was chromatographed on Florisil, and the product **4d** (0.30 g) was eluted in benzene and some early fractions of benzene–ether (98:2). Crystallization from ether–light petroleum gave **4d**: mp 151–152° (0.23 g); ν_{max} 1760 cm^{-1}; nmr δ 1.00–2.50 (13 H, m, with s at 1.18 and 1.32, and d, J = 7 Hz, at 2.33), 3.17 (2 H, d, J = 4 Hz, $C_{arom}CH_2-$), 4.90–5.25 (1 H, d of t, J = 4 and 7 Hz, –OCH), and 7.10–7.40 (4 H, m, $C_{arom}H$). Dodson's compound had mp 154–155° and the infrared spectra (Nujol) of his compound and ours were identical.

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.68; H, 7.81. Found: C, 79.35; H, 7.90.

The lactone **4d** was recovered unchanged (a) on treatment with chromium trioxide in 90% acetic acid at room temperature for 16 hr; (b) on heating with chromium trioxide in glacial acetic acid for 5 hr on a steam bath; and (c) on refluxing with selenium dioxide in 95% acetic acid for 70 hr.

Registry No.—**1b**, 36794-36-2; **1c**, 36807-65-5; **1d**, 36807-66-6; **1e**, 36807-67-7; **1f**, 36807-68-8; **2a**,

36803-46-0; **2b**, 36803-47-1; **4a**, 36807-69-9; **4b**, 36807-70-2; **4c**, 36807-71-3; **4d**, 36807-72-4.

Acknowledgments.—This work was supported by grants from the National Cancer Institute (CAO 5796) the Research Council of the University of Nebraska, and the American Cancer Society.

Photochemical Syntheses of Spiro[4.5]decane-1,6-dione

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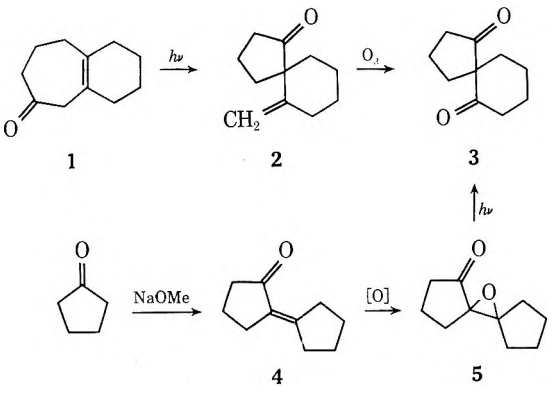
Received May 24, 1972

Recently the photoisomerization of the β,γ-unsaturated ketone bicyclo[5.4.0]undec-1(7)-en-3-one (**1**) to the β,γ-unsaturated spiro ketone 6-methylenespiro-[4.5]decan-1-one (**2**) was reported.[1] We now wish to describe the ozonolysis of **2** to the spiro 1,3 diketone **3** and the facile photochemical synthesis of **3**.



1 2 3 4 5

The structure of the spiro ketone **2** was proved by physical methods and by catalytic reduction of the exocyclic methylene group to two isomeric methyl ketones, one of which is known.[2] To confirm that the exocyclic methylene group was attached to the six-membered ring, **2** was ozonized to yield the spiro 1,3 diketone **3**. The infrared spectrum of **2** showed $\bar{\nu}_{max}$ at 1735 cm^{-1} due to the carbonyl stretching frequency of a cyclopentanone, whereas **3** had $\bar{\nu}_{max}$ at 1732 and 1698 cm^{-1} due to cyclopentanone and cyclohexanone rings, respectively.

Since it is well known in the steroid series that photolysis of α,β-epoxy ketones yields 1,3 diketones,[3] photolysis of the epoxy ketone **5** should yield the desired spiro 1,3 diketone **3**. The precursor required for this photorearrangement was the ketone **5**. This epoxy ketone **5** can be readily obtained by an aldol condensation of cyclopentanone followed by epoxidation. Epoxidation of the aldol product **4** with perbenzoic acid or with 30% hydrogen peroxide and base gave the epoxide **5** in low yield; however, *m*-chloroperbenzoic acid gave **5** in 47% yield.

Direct irradiation of **5** in benzene, hexane, ether, and methanol with a medium-pressure mercury arc (Hanovia type L), using a Pyrex filter, afforded the spiro 1,3 diketone **3** in 25% yield. A second unidentified product **6** was also observed in trace amounts such that the ratio of formation of **3**:**6** was 7:1.

Photolysis of **5** in the presence of a series of photosensitizers such that the sensitizer absorbed >90% of the light gave the following results: benzaldehyde (E_T = 72 kcal)[4] and benzophenone (69 kcal)[4] led to a substantial decrease in the rate of formation of **3**, whereas acetone (77 kcal)[5] and acetophenone (74 kcal)[4] led to an increase in the rate of reaction. These results indicate that a triplet state with an energy level above 72 kcal and below 74 kcal leads to the spiro 1,3-diketone **3**. Furthermore, sensitized photolysis of **5** also leads to the formation of **3** and **6** in the ratio of 7:1. Since the product distribution in such sensitized runs provides a "fingerprint" characteristic of the triplet, it would be exceedingly fortuitous for another species to give the same "fingerprint," and we therefore conclude that the triplet is the reacting species in the direct runs as well.[6]

Photolysis of **5** in the presence of the quenchers piperylene, naphthalene, and biphenyl indicated a slight increase in the rate of photoisomerization in the case of naphthalene. These results indicate that the triplet state has an extremely short lifetime and does not undergo diffusion-controlled quenching. The increase in the rate of reaction in the case of naphthalene is probably due to sensitization of the singlet state of **5**.[7]

The photorearrangement described here offers a rapid method for the synthesis of the spiro[4.5]decanes found as the skeletons of a number of interesting sesquiterpenes.[8,9] Furthermore, this method should be general and provide an alternative synthetic route to spiro molecules.

Experimental Section[10]

Ozonolysis of 6-Methylenespiro[4.5]decan-1-one (2).—A solution of 30 mg (0.183 mmol) of 6-methylenespiro[4.5]decan-1-one,[1] one drop of water, and 10 ml of ethyl acetate was stirred at 0° for 10 min while ozone was passed through the solution. Then 1.0 ml of water and 0.2 g of zinc dust were added, and the mixture was stirred at room temperature overnight. The ethyl acetate solution was filtered, washed with water until neutral, dried

(1) J. R. Williams and G. M. Sarkisian, *Chem. Commun.*, 1564 (1971).
(2) K. Grimm, P. S. Venkataramani, and W. Reusch, *J. Amer. Chem. Soc.*, **93**, 270 (1971).
(3) O. Jeger, K. Schaffner, and H. Wehrli, *Pure Appl. Chem.*, **9**, 555 (1964).
(4) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1967, p 132.
(5) P. J. Wagner and G. S. Hammond, "Advances in Photochemistry," Vol. 5, W. A. Noyes, Jr., G. S. Hammond, and J. N. Pitts, Jr., Ed., Interscience, New York, N. Y., 1968, p 21.
(6) H. E. Zimmerman and R. L. Morse, *J. Amer. Chem. Soc.*, **90**, 954 (1968).
(7) P. J. Wagner, *Mol. Photochem.*, **3**, 169 (1971).
(8) I. Yoshioka and T. Kimura, *Chem. Pharm. Bull.*, **13**, 1430 (1965).
(9) J. Marshall and P. Johnson, *J. Amer. Chem. Soc.*, **89**, 2750 (1967).
(10) Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer fitted with sodium chloride prisms. Ultraviolet spectra were determined in methanol with a Cary 14 recording spectrometer. Nmr spectra were obtained with Varian A-60-A and XL100 spectrometers. The mass spectra were on an AE1 MS-9 mass spectrometer at an ionizing energy of 70 eV. Microanalysis were performed by Micro-Analysis Inc., Wilmington, Del.

(Na_2SO_4), and concentrated. The product was separated by preparative vpc[11] to yield 10 mg (33%) of spiro[4.5]decane-1,6-dione as a clear oil: bp 238–241° dec; ir ($CHCl_3$) 1732 (cyclopentanone C=O), 1698 cm^{-1} (cyclohexanone C=O); mass spectrum (70 eV) *m/e* (rel intensity) 166 (38, M^+), 148 (14), 138 (35), 137 (20), 121 (21), 111 (100), 110 (90), 95 (34), 91 (27), 67 (52), 55 (74), 44 (95), 41 (67).

Preparation of 2-Cyclopentylidenecyclopentan-1-one Oxide (5).—A solution of 2.84 g (85% pure, 0.0140 mol) of *m*-chloroperbenzoic acid in 60 ml of chloroform was added slowly to an ice-cold solution of 2.00 g (13.3 mmol) of 2-cyclopentylidenecyclopentan-1-one (**4**)[12] in 20 ml of chloroform. This mixture was stirred at 3° for 18 hr. The reaction mixture was then filtered, washed with $NaHCO_3$ solution and brine until neutral, dried (Na_2SO_4), and concentrated. The residue was chromatographed on 50 g of silica gel (activity IV, 27.8 × 2.3 cm), with 9:1 hexane–ethyl acetate. The product obtained (1.04 g, 47%) crystallized from hexane to give holohedral plates of 2-cyclopentylidenecyclopenten-1-one oxide (**5**): mp 38–40°; uv max (EtOH) 307 nm (ε 43); ir ($CHCl_3$) 1743 (cyclopentanone C=O), 1160, 960 cm^{-1}; nmr ($CDCl_3$) δ 2.6–1.4 (m); mass spectrum (70 eV) *m/e* (rel intensity) 166 (50, M^+), 148 (40), 138 (55), 125 (21), 110 (100), 109 (32), 96 (34), 95 (75), 91 (44), 67 (80), 66 (40), 55 (65), 44 (48), 41 (64).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.27; H, 8.54.

Preparation of Spiro[4.5]decane-1,6-dione (3).—A solution of 132 mg of 2-cyclopentylidenecyclopentan-1-one oxide (**5**) in 110 ml of acetone was stirred with a stream of nitrogen and irradiated with a 450-W Hanovia lamp through a Pyrex filter. The reaction was stopped after 90 min. The acetone solution was concentrated and preparative vpc[13] was used to collect 6 mg of an unidentified oil, **6**,[14] 15 mg of reactant, and 40 mg (30%) of spiro[4.5]decane-1,6-dione (**3**) as a clear oil: bp 238–240° dec; uv max (EtOH) 287 nm (ε 126); ir ($CHCl_3$) 1732 (cyclopentanone C=O) and 1698 cm^{-1} (cyclohexanone C=O); nmr ($CDCl_3$) δ 2.9–1.1 (m); mass spectrum (70 eV) *m/e* (rel intensity) 166 (62, M^+), 148 (19), 138 (33), 137 (25), 121 (19), 111 (100), 110 (91), 95 (50), 91 (28), 67 (55), 55 (67), 44 (100), 41 (66).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.25; H, 8.74.

The spiro[4.5]decane-1,6-dione was shown to be identical (boiling point, ir, mass spectrum) with the diketone **3**, previously prepared by ozonolysis of the spiro[4.5]undecene **2**. Nmr spectra indicate that **3** and **6** are the only products. The low yield of **3** obtained is due to preparative vpc. Similar results were obtained when **5** was photolyzed in benzene, hexane, ether, and methanol.

Quenching Studies with 2-Cyclopentylidenecyclopentan-1-one Oxide (5).—In a typical experiment approximately 0.010 g of **5** was weighed into a 5-ml volumetric flask. The sample was dissolved in benzene, and 0.5-ml aliquots were placed in 7-mm Pyrex test tubes. Quenchers were added to prepare the following solutions: 0.01, 0.1, and 2.0 *M* piperylene; 0.01 and 0.1 *M* naphthalene; and 2 *M* biphenyl. The test tubes were degassed with nitrogen and irradiated on a merry-go-round with a 450-W Hanovia lamp. The resulting solutions were analyzed by vpc.[11]

Sensitization Studies with 2-Cyclopentylidenecyclopentan-1-one Oxide (5).—The same procedure was used as in the quenching studies, except that the solutions were prepared so that the sensitizer absorbed over 90% of the light at 313.0 nm. The following solutions were used: 0.0615 *M* acetophenone, 0.0324 *M* benzophenone, 0.258 *M* benzaldehyde, and acetone (neat).

Registry No.—**3**, 36803-48-2; **5**, 36803-49-3.

Acknowledgment.—We acknowledge partial support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Mr. Kuhlman of Wyeth Laboratories for the mass spectra.

(11) The column (6 ft × 0.25 in.) used was packed with 20% Carbowax 20M on 60–80 mesh Chromosorb P.

(12) O. Wallach, *Ber.*, **29**, 2955 (1896).

(13) The column (4 ft × 0.25 in.) used was packed with 20% Carbowax 20M on 60–80 mesh Chromosorb WAW DMCS.

(14) This product is currently under investigation.

Studies in Purine Chemistry. XVI. A One-Step Synthesis of 7-Aryltheophyllines[1,2]

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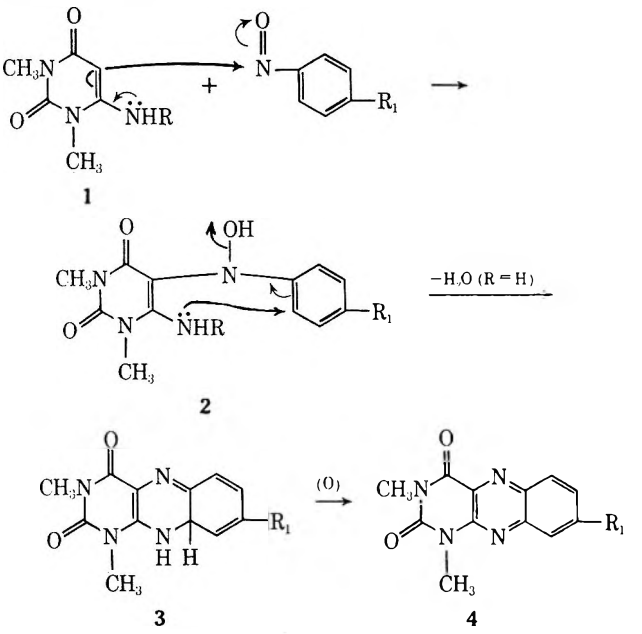
Received August 18, 1972

Some time ago we described a new route to 1,3-dimethylalloxazines which involves the condensation of 1,3-dimethyl-6-aminouracil (**1**, R = H) with nitrosobenzenes in the presence of acetic anhydride.[4] A reasonable intermediate in this condensation is the hydroxylamine **2**; the intramolecular dehydrative-cyclization step (**2** to **3**) is presumably facilitated by prior acetylation of the hydroxylamine. Dehydrogenation with excess nitrosobenzene then gives **4**. It appeared that the use of a 6-alkylamino derivative of **1** (R = alkyl) would prevent the final aromatization step (**3** to **4**) and lead to a synthesis of 1,3-dimethyl-5-acetyl-10-alkylleucoflavins.



1 2 3 4

We have found, however, that the reaction of 1,3-dimethyl-6-methylaminouracil (**1**, R = CH_3) with nitrosobenzene in the presence of acetic anhydride gave 7-phenyltheophylline (**8**, R_1 = H; Ar = C_6H_5).[5] Analogous reactions were observed with 1,3-dimethyl-6-ethylaminouracil (**1**, R = C_2H_5) and with 1,3-dimethyl-6-benzylaminouracil (**1**, R = $CH_2C_6H_5$) in condensations with nitrosobenzene and with *p*-chloronitrosobenzene; in all cases, the α-C atom of the 6-alkylamino group becomes the 8-carbon atom of the

(1) Part XV: E. C. Taylor, G. P. Beardsley, and Y. Maki, *J. Org. Chem.*, **36**, 3211 (1971).

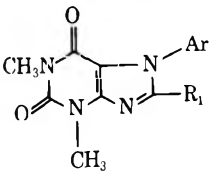
(2) This investigation was supported by the U. S. Army Medical Research and Development Command (Contract No. DA-49-193-MD-2777) and is Contribution No. 1089 in the Army research program on malaria.

(3) Kumamoto University, Kumamoto, Japan.

(4) E. C. Taylor, F. Sowinski, T. Yee, and F. Yoneda, *J. Amer. Chem. Soc.*, **89**, 3369 (1967).

(5) H. Dolman, J. van der Goot, G. H. Mos, and H. D. Moed, *Recl. Trav. Chim. Pays-Bas*, **83**, 1215 (1964), have reported the preparation of this compound by arylation of theophylline with *p*-chloronitrobenzene, followed by reduction and reductive diazotization. This is the only 7-aryltheophylline previously reported.

TABLE I
7-ARYLTHEOPHYLLINES[c]

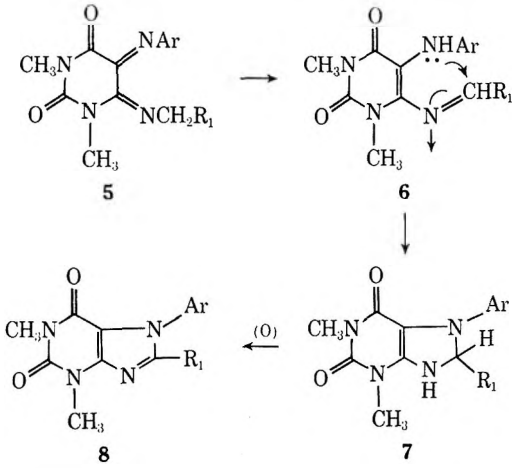


Registry no.	R_1	Ar	Yield, %	Recrystn solvent	Mp, °C[a]
960-61-2	H	C_6H_5	31	Ethanol	195.5[b]
36748-65-9	H	*p*-ClC_6H_4	48	1-Propanol	245.2
36748-66-0	CH_3	C_6H_5	38	Methanol	235.0
36748-67-1	CH_3	*p*-ClC_6H_4	40	Methanol	250.5
36748-68-2	C_6H_5	C_6H_5	48	Ethanol	221.3
36748-69-3	C_6H_5	*p*-ClC_6H_4	70	1-Propanol	267.6

[a] All melting points are corrected and were determined on a Mettler FP-1 apparatus. [b] Lit. mp 193–194.5° (ref 5). [c] Satisfactory analytical values (±0.3% in C, H, N) were reported for all compounds in the table: Ed.

final 7-aryltheophylline.[6] Results are summarized in Table I.

We suggest that this new purine synthesis involves the intermediacy of a 5-hydroxylamino derivative (**2**, R = CH_3, C_2H_5, $CH_2C_6H_5$) which suffers dehydration in the acetic anhydride medium to give the diimine **5**. Prototropic rearrangement would then give the monoimine **6**, which is ideally disposed for intramolecular cyclization to **7**. Subsequent dehydrogenation by excess arylnitroso compound would then lead to the 7-aryltheophylline **8** and an arylhydroxylamine. Since



azoxybenzene (and 4,4′-dichloroazoxybenzene) were also isolated from reactions involving nitrosobenzene and *p*-chloronitrosobenzene, respectively, a further reaction of the hydroxylamine with unreacted arylnitroso compound must occur, indicating the ultimate participation of 3 mol of the latter. Utilization of this stoichiometry significantly improved the yields of the 7-aryltheophyllines.

Experimental Section

7-Aryltheophyllines. General Procedure.—A solution of 0.01 mol of the 1,3-dimethyl-6-alkylaminouracil[7] and 0.03 mol of nitrosobenzene (or *p*-chloronitrosobenzene) in 30 ml of acetic anhydride was heated under gentle reflux for 30 min and poured into 500 ml of water, and the resulting solution was neutralized with aqueous ammonia[8] and allowed to stand overnight at room temperature. The yellow solid which had separated was collected by filtration, washed well with ether to remove coprecipitated azoxybenzene (or 4,4′-dichloroazoxybenzene), and recrystallized as specified in Table I.

(6) For other purine syntheses in which the α-C atom of a 6-alkylamino substituent becomes C-8 in the final product, see, for example, (a) W. Pfleiderer and H.-U. Blank, *Angew. Chem., Int. Ed. Engl.*, **5**, 666 (1966); (b) H. Goldner, G. Dietz, and E. Carstens, *Justus Liebigs Ann. Chem.*, **691**, 142 (1966).

(7) 1,3-Dimethyl-6-methylaminouracil and 1,3-dimethyl-6-ethylaminouracil: W. Pfleiderer and K.-H. Schundehutte, *Justus Liebigs Ann. Chem.*, **612**, 158 (1958). 1,3-Dimethyl-6-benzylaminouracil: H. Bredereck, H. Herlinger, and W. Resemann, *Chem. Ber.*, **93**, 236 (1960).

(8) In the condensation of 1,3-dimethyl-6-methylaminouracil with nitrosobenzene there was no precipitate at this stage; the alkaline solution was extracted with ether and the ether extracts were evaporated to a small volume and cooled to give 7-phenyltheophylline.

Synthesis of Myosmine and Nornicotine, Using an Acyl Carbanion Equivalent as an Intermediate[1a]

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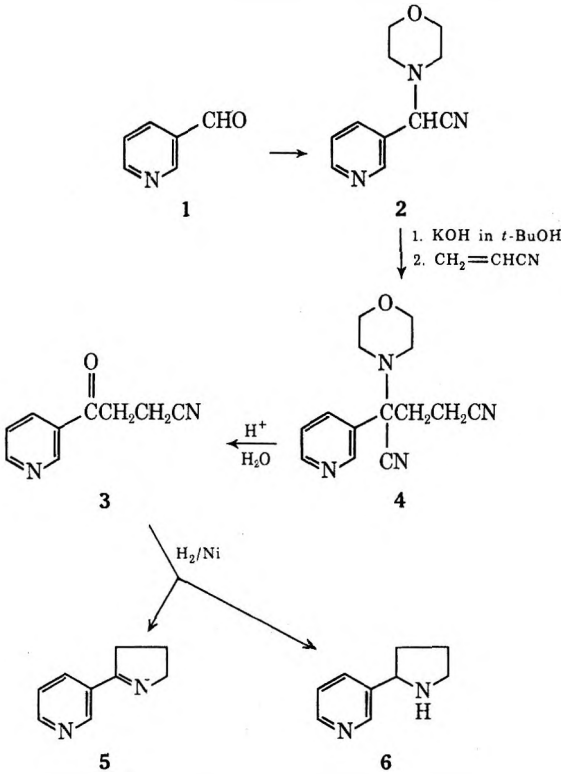
Received August 28, 1972

Myosmine (**5**) has been isolated from tobacco smoke and is a minor component of the alkaloids of *Nicotiana tabacum*.[2] It has been synthesized by several methods[3] and on reduction affords nornicotine (**6**).



For our studies on the metabolism of the tobacco alkaloids we required a synthesis of these alkaloids

(1) (a) This investigation was supported by Research Grant GM-13246 from the National Institutes of Health; (b) Contribution No. 122 from this laboratory.

(2) R. L. Stedman, *Chem. Rev.*, **68**, 153 (1968).

(3) (a) E. Späth and L. Mamoli, *Ber.*, **69**, 757 (1936); (b) C. F. Woodward, A. Eisner, and P. G. Haines, *J. Amer. Chem. Soc.*, **66**, 911 (1944); (c) M. L. Stein and A. Burger, *ibid.*, **79**, 154 (1957); (d) R. V. Stevens, M. C. Ellis, and M. P. Wentland, *ibid.*, **90**, 5576 (1968); (e) B. P. Mundy, B. R. Larsen, L. F. McKenzie, and G. Braden, *J. Org. Chem.*, **37**, 1635 (1972).

which would enable us to introduce an appropriate isotope at specific positions.

The key step in our four-step synthesis from pyridine-3-aldehyde (1) is the 1,4 addition of the anion of α-morpholino-α-(3-pyridyl)acetonitrile (2), an acylcarbanion equivalent,[4] to acrylonitrile, affording γ-cyano-γ-morpholino-γ-(3-pyridyl)butyronitrile (4). The scope of this novel addition is being investigated. Compound 2 was obtained by the addition of aqueous potassium cyanide to the iminium salt formed by heating pyridine-3-aldehyde with morpholine perchlorate in morpholine.[5] Hydrolysis of 4 with aqueous acetic acid[6] yielded 3-cyano-1-(3-pyridyl)propan-1-one (3). Hydrogenation of this β-ketonitrile in ethanolic ammonia in the presence of Raney nickel at 3-atm pressure for 24 hr yielded a mixture of myosmine (30%) and nornicotine (60%), separated by preparative thin layer chromatography. The overall yield of the combined alkaloids from pyridine-3-aldehyde was 67%.

Experimental Section

Melting points are corrected. Microanalyses were carried out by Clark Microanalytical Laboratories, Urbana, Ill. Mass spectra were determined on an Hitachi Perkin-Elmer RMU-6D mass spectrometer.

α-Morpholino-α-(3-pyridyl)acetonitrile (2).—Pyridine-3-aldehyde (Aldrich Chemical Co.) (6.95 g) was added to a solution of morpholine perchlorate (13.3 g) in morpholine (64 ml) and the mixture was heated at 80° for 1 hr. Potassium cyanide (4.5 g), dissolved in a minimum amount of water, was added and the mixture was heated at 100° for an additional hour. The cooled reaction mixture was added to aqueous potassium carbonate (10%) and extracted with $CHCl_3$ (4 × 50 ml). The combined extract was washed with aqueous $NaHSO_3$ and then dried ($MgSO_4$). Evaporation yielded 2 as a colorless oil (12.4 g, 92%) which crystallized on standing. Crystallization from cyclohexane afforded 2 as colorless plates, mp 53–54.5°, mass spectrum *m/e* 203 (parent peak).

Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 65.62; H, 6.20; N, 20.33.

γ-Cyano-γ-morpholino-γ-(3-pyridyl)butyronitrile (4).—Acrylonitrile (0.61 g) dissolved in *tert*-butyl alcohol (30 ml) was added slowly (during 30 min) to a stirred solution of 2 (1.89 g) in *tert*-butyl alcohol (100 ml) which contained 11 drops of a methanolic solution of KOH (30%), the reaction being carried out at room temperature under N_2. After stirring for an additional 5 min the reaction mixture was diluted with an equal volume of water and extracted with $CHCl_3$ (4 × 50 ml). The residue obtained on evaporation of the dried ($MgSO_4$) extract was crystallized from a mixture of $CHCl_3$ and Et_2O, affording 4 as colorless prisms (2.14 g, 90%), mp 120–121°, mass spectrum *m/e* 256 (parent peak), 202 (M − CH_2CH_2CN).

Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.21; H, 6.46; N, 21.70.

3-Cyano-1-(3-pyridyl)propan-1-one (3).—Compound 4 (1.70 g) was dissolved in a mixture of acetic acid (10 ml), water (5 ml), and tetrahydrofuran (1.5 ml) and warmed at 53° for 24 hr. The reaction mixture was made basic with solid K_2CO_3 and extracted with $CHCl_3$. The residue obtained on evaporation of the dried ($MgSO_4$) extract was crystallized from Et_2O, affording the β-ketonitrile 3 as colorless plates (0.96 g, 90%), mp 66–67°.

Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.80; H, 5.13; N, 17.53.

Myosmine (5) and Nornicotine (6).—The β-ketonitrile 3 (2.31 g), dissolved in ethanol (200 ml) which had previously been saturated with ammonia, was hydrogenated at room temperature in the presence of Raney nickel (one spoonfull) at 3-atm pressure for 24 hr. The filtered mixture was acidified with HCl and evaporated to dryness *in vacuo*. The residue was made basic with aqueous K_2CO_3 and extracted with CH_2Cl_2. The liquid obtained on evaporation of the dried ($MgSO_4$) extract was subjected to preparative tlc on silica gel PF-254 (Merck), developing with the mixture of $CHCl_3$, ethanol, and concentrated NH_3 (85:14:1). The higher zone (R_f 0.63) on extraction with $CHCl_3$ afforded myosmine (0.64 g, 30%), identical (nmr, ir, tlc) with an authentic specimen. It afforded a dipicrate, mp 183–185° (lit.[3a] mp 184–185°). The lower zone (R_f 0.20) yielded *dl*-nornicotine (1.29 g, 60%), identical with an authentic specimen.

By reducing the duration of the hydrogenation the yield of myosmine was increased at the expense of the nornicotine.

Registry No.—**2**, 36740-09-7; **3**, 36740-10-0; **4**, 36740-11-1; **5**, 532-12-7; **6**, 5746-86-1.

(4) (a) G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, **93**, 5286 (1971), describe the use of protected aldehyde cyanohydrins for the synthesis of ketones; (b) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969), has reviewed other acyl carbanion equivalents.

(5) D. J. Bennett, G. W. Kirby, and V. A. Moss, *J. Chem. Soc. C*, 2049 (1970), prepared α-aryl-α-morpholinoacetonitriles by this method, and utilized them for the synthesis of [*formyl*-^2H]-labeled aldehydes by quenching the carbanions, generated from these nitriles with base, with deuterium oxide, followed by acid hydrolysis.

(6) Hydrolysis of 4 with hydrochloric acid resulted in the formation of 4-(3-pyridyl)-4-oxobutanoic acid.

An Improved Synthesis of Arylacetylenes

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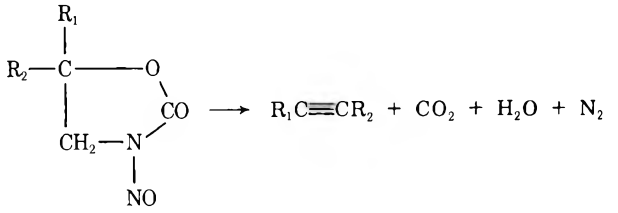
Received July 20, 1972

Studies of the alkaline decomposition of the readily prepared[1] 5,5-disubstituted 3-nitroso-2-oxazolidones (1)



$R_1 = C_6H_5$; $R_2 = H$
$R_1 = C_6H_5$; $R_2 = CH_3$
$R_1 = R_2 = C_6H_5$
$R_1 = C_6H_5CH_2$; $R_2 = CH_3$

have provided preparative pathways to rather elusive organic structures, *i.e.*, vinyl ethers,[2] vinylsilanes,[3] and vinyl halides.[3] Newman[1] has previously reported obtaining mixtures of acetylenes and carbonyl compounds in a ratio of about 2:1 from the methanolic KOH decompositions of **1a–c**. We wish to report that butylamine in ether quantitatively converts **1a**, **1b**, or **1c** to phenylacetylene, 1-phenylpropyne, and diphenylacetylene, respectively. When an aryl ring is not present in the 5 position of the nitroso oxazolidone, as in **1d**, little acetylenic product is obtained (less than 4%), and a mixture of carbonyl compounds is produced.[4] That this reaction provides an excellent general preparative route to arylacetylenes is illustrated in the following papers.[5,6]

(1) M. S. Newman and A. Kutner, *J. Amer. Chem. Soc.*, **73**, 4199 (1951).

(2) M. S. Newman and A. O. M. Okorodudu, *J. Org. Chem.*, **34**, 1220 (1969).

(3) M. S. Newman and C. D. Beard, *J. Amer. Chem. Soc.*, **91**, 5678 (1969).

(4) Newman[1] has observed the same results with various 5,5-dialkyl-substituted nitroso oxazolidones.

(5) M. S. Newman and L. F. Lee, *J. Org. Chem.*, **37**, 4468 (1972).

(6) T. B. Patrick, J. M. Disher, and W. J. Probst, *ibid.*, **37**, 4467 (1972).

Experimental Section

The nitroso oxazolidones **1a–d** were prepared by the method of Newman.[1] The structures of all intermediates in these syntheses were established by nmr, ir, and agreement of physical constants with published data.

5-Benzyl-5-methyl-2-oxazolidone was obtained in 53% yield: mp 103°; nmr ($CDCl_3$) τ 8.60 (s, 3, CH_3), 7.05 (s, 2, CH_2C_6H), 6.65 (2 d, AB pattern of C-4 hydrogens), 3.59 (s, 1, O=CNH), 2.70 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; O, 16.75; N, 7.33. Found: C, 69.15; H, 6.90; N, 7.20.

5-Benzyl-5-methyl-3-nitroso-2-oxazolidone was obtained in 80% yield: mp 80°; nmr τ 8.49 (s, 3, CH_3), 7.00 (s, 2, $CH_2C_6H_5$) 6.0–6.7 (2 d, 2, C-4 hydrogens, AB pattern), 2.72 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{12}O_3N_2$: C, 60.00; H, 5.45; O, 21.82; N, 12.73. Found: C, 59.91; H, 5.56; N, 12.51.

Decompositions.—To a stirred solution of 0.10 mol of the nitroso oxazolidone in 100 ml of dried ether at room temperature, 0.10 mol of butylamine was added in one portion. The evolved gases were passed through a $Ba(OH)_2$ solution trap and the nitrogen was measured by displacement of water. The theoretical nitrogen volume was obtained within 2 hr. The ether solution was washed with dilute HCl and then H_2O, dried (Na_2SO), and concentrated. Distillation gave a 99–100% yield of the arylacetylene. Vpc, ir, and nmr analyses failed to indicate any trace contaminates. The physical properties were in agreement with published data.

Registry No.—**1d**, 36783-10-5; 5-benzyl-5-methyl-2-oxazolidone, 36838-64-9; butylamine, 109-73-9.

Acknowledgment.—The authors are grateful to Professor James Wilt, Loyola University, Chicago, Ill., for providing the nmr facilities.

Synthesis and Metalation of 2-Ethynylthiophene

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Initiation of a study designed to develop new and improved syntheses of naturally occurring acetylenes[1] required us to prepare 2-ethynylthiophene (**1**). After many attempts to prepare **1** by dehydrohalogenation of α,α-dichloro-2-ethylthiophene using described literature procedures[2] were found to give only small amounts of impure **1**, we pursued other means of preparing the title compound.

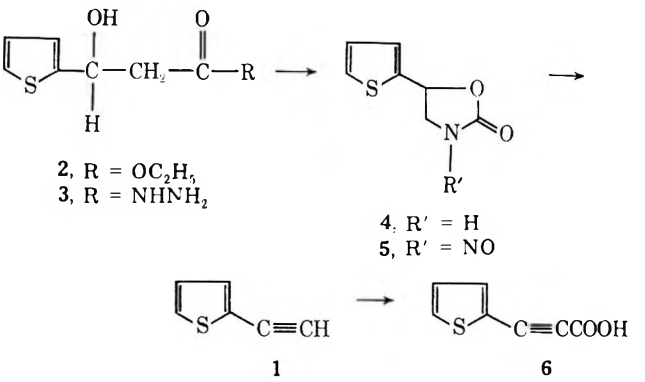
A successful route to **1** is shown in Scheme I. The conversion of **2** → **1** occurred in 57% overall yield. Best results were obtained when 5-(2-thienyl)-3-nitroso-2-oxazolidone (**5**) was used immediately following its preparation. Basic decomposition of 5-substituted 3-nitroso-2-oxazolidones to yield acetylenic compounds has been developed by Newman and coworkers,[3] and proves to be a very useful procedure for preparing various types of acetylenes.

(1) F. Bohlmann, "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, p 977.

(2) (a) A. Vaitiekunas and F. F. Nord, *J. Org. Chem.*, **19**, 902 (1954); (b) A. J. Osbar, A. Vaitiekunas, and F. F. Nord, *J. Amer. Chem. Soc.*, **77**, 1911 (1955).

(3) (a) M. S. Newman and A. Kutner, *J. Amer. Chem. Soc.*, **73**, 4199 (1951). (b) See accompanying papers by M. S. Newman and L. F. Lee, *J. Org. Chem.*, **37**, 4468 (1972), and H. P. Hogan and J. Seehafer, *ibid.*, **37**, 4466 (1972).

SCHEME I



Metalation of thiophene derivatives having more than one acidic position has received increased attention for both synthetic and theoretical reasons.[4] Metalation of **1**, which has both an acidic acetylenic hydrogen and an acidic hydrogen on the thiophene 5 position, with *n*-butyllithium followed by carbonation and acidification of the reaction mixture gave a 73% yield of 2-thienylpropiolic acid. Spectral evidence for reaction at the thiophene 5 position was not found. Lithium 2-thienylacetylide seems to have more synthetic utility than sodium 2-thienylacetylide, since it is reported that the latter compound yields only small amounts of carbonation product.[2b]

Competitive metalation of equal molar amounts of **1** and phenylacetylene with insufficient amounts of *n*-butyllithium showed that the ratio of lithium 2-thienylacetylide to lithium phenylacetylide was 2.4:1, indicating that **1** is more acidic than phenylacetylene. The ratio was determined by nmr analysis of the carbonation products. The pK_a of **1** was thus determined to be 22.4[5] using a value of 23.2 for the pK_a of phenylacetylene.[6] The J (^{13}CH) values of 257 for **1** and 246 for phenylacetylene are in agreement with the greater acidity found for **1**.[7]

Experimental Section

3-Hydroxy-3-(2-thienyl)propionic Acid Hydrazide (3).—Anhydrous hydrazine (2.4 g, 0.09 mol) was added to a mixture of 15 g (0.08 mol) of ethyl 3-hydroxy-3-(2-thienyl)propionate[8] and 10 ml of methanol. After 1 hr, the entire contents had solidified. Recrystallization from methanol furnished pure **3** (13.0, g, 93%), mp 139–140°.

Anal. Calcd for $C_7H_{10}N_2O_2S$ (mol wt 186): C, 45.2; H, 5.4; N, 15.1. Found: C, 45.2; H, 5.5; N, 14.8.

5(2-Thienyl)-2-oxazolidone (4).—A solution of 10.0 g (0.05 mol) of **3** in 30 ml of 6 *N* hydrochloric acid was treated at −5° with a solution of 4.0 g of sodium nitrite in 10 ml of water during 30 min. The mixture was stirred for 30 min and gave a positive nitrous acid test. The cold solution was extracted with three 100-ml portions of 3:1 benzene–chloroform. The dried organic solution ($MgSO_4$) was heated at reflux until nitrogen evolution ceased (1.5 hr). Solvents were removed and the remaining brown oil was crystallized from hexane–ether to yield 6.4 g (71%) of pure **4**, mp 92–94°.

(4) (a) D. W. H. MacDowell, R. A. Jourdenais, R. Naylor, and G. E. Paulovicks, *J. Org. Chem.*, **36**, 2683 (1971), and references cited therein; (b) D. W. H. MacDowell and A. T. Jefferies, *ibid.*, **35**, 871 (1970), and references cited therein; (c) P. L. Kelly, S. F. Thames, and J. E. McCleskey, *J. Heterocycl. Chem.*, **9**, 141 (1972).

(5) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 3.

(6) A. Streitwieser, Jr., and D. M. E. Reuben, *J. Amer. Chem. Soc.*, **93**, 1794 (1971).

(7) A. Streitwieser, Jr., R. A. Caldwell, and W. R. Young, *ibid.*, **91**, 529 (1969).

(8) R. Schuetz and W. Houff, *ibid.*, **77**, 1833 (1955).

The nmr spectrum ($CDCl_3$) showed absorptions at δ 3.6–4.1 (m, 2 H, CH_2), 5.8–6.1 (m, 6.7 (broad, NH), and 7.1–7.7 (m, 3 H, C_4H_3S–).

Anal. Calcd for $C_7H_7NO_2S$: C, 49.7; H, 4.1; N, 8.3. Found: C, 49.9; H, 4.3; N, 8.4.

5-(2-Thienyl)-3-nitroso-2-oxazolidone (5).—A mixture of 4.0 g (0.23 mol) of 4 in 40 ml of dry ether and 4.2 g of sodium bicarbonate was treated at −60° with 2.0 g of N_2O_4. The mixture was allowed to come to room temperature and then filtered. The solvent was removed on a rotary evaporator and the yellow solid thus obtained was converted immediately into 2-ethynylthiophene.

A small sample of 5 was dried *in vacuo* for 20 min and gave a melting range of 60–65° with gas evolution. An nmr spectrum ($CDCl_3$) showed absorptions at δ 4.0–4.8 (CH_2), 6.1–6.4 (CH), and 7.3–7.9 (C_4H_3S–).

2-Ethynylthiophene (1).—The product obtained from the previous reaction was dissolved in methanol (50 ml) and treated with sodium methoxide solution until gas evolution stopped. The mixture was poured into water, extracted with ether, and dried. The dried extracts from three runs were combined and distilled. The yield of 1 was 6.0 g (79%), bp 54–60° (20 mm), n^{24}D 1.5882 (lit.[2a] n^{20}D 1.5886).

The infrared spectrum showed strong absorption at 3300 cm^{-1} (C≡CH) and medium absorption at 2100 cm^{-1} (C≡C). The nmr spectrum (CCl_4) showed absorption at δ 3.18 (C≡CH) and 6.8–7.4 (C_4H_3S–).

2-Thienylpropiolic Acid (6).—To a solution of 0.50 g (4.6 mmol) of 1 in dry ether was added 1.2 ml (6.7 mmol) of freshly prepared ethereal *n*-butyllithium (1.6 *N*). After 3 hr, 3 g of Dry Ice was added to the mixture with stirring. Water (5 ml) was added to the mixture and the contents were extracted with ether. The water layer was acidified to give 0.5 g (72%) of 6 which had mp 130–133° dec after drying (lit.[2b] mp 130–133°). Unreacted 1 accounted for the balance of the material. The infrared spectrum (KBr) showed absorptions at 3000 (broad, acid), 2200 (C≡C), and 1675 cm^{-1} (C=O). The nmr spectrum (acetone-d_6) showed absorption at δ 7.4–7.6 (1 H), 7.8–8.2 2 H, (m, C_4H_3S–), and 9.9 (s, 1 H, COOH).

Competitive Metalation of 2-Ethylthiophene (1) **and Phenylacetylene.**—A freshly prepared ethereal solution of 1.6 *N* *n*-butyllithium (1.8 ml, 2.9 mequiv) was added under a dry nitrogen atmosphere to a solution of 0.32 g (3.0 mequiv) of 1 and 0.31 g (3.0 mequiv) of phenylacetylene in 10 ml of dry ether. After 3–4 hr, 1 g of powdered Dry Ice was added to the mixture. Water (5 ml) was added and the layers were separated. The acidified water layer was extracted with ether and worked up to give a mixture of 6 and phenylpropiolic acid, δ 7.6–8.0 (m, 5 H, C_6H_5–). A complete material balance was obtained.

Analysis of the mixture was accomplished by integration of the aromatic region of the nmr spectrum using the one-proton resonance of 6 at δ 7.4–7.6 as a standard. The ratio of 6 to phenylpropiolic acid was determined to be 2.4:1 from an average of six experiments.

Registry No.—1, 4298-52-6; 3, 20795-13-5; 4, 20805-23-6; 5, 36740-08-6.

Acknowledgment.—Financial support for this project was supplied by the Office of Research and Projects, Southern Illinois University.

The Synthesis of Arylacetylenes. 3,5-Di-*tert*-butylphenylacetylene[1]

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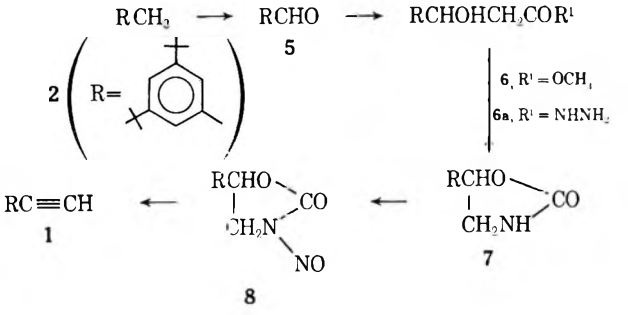
In connection with a research program designed to provide molecules of the rotaxane type[2] we required a quantity of 3,5-di-*tert*-butylphenylacetylene (1). As starting material 3,5-di-*tert*-butyltoluene (2) was readily available.[3] Our first route involved oxidation of 2 to 3,5-di-*tert*-butylbenzoic acid (3), which was converted into 3,5-di-*tert*-butylacetophenone (4). Hopefully reaction of 4 with phosphorus pentachloride followed by treatment of the dichloride (or chloro olefin) produced with strong base should yield 1. Although 4 was readily prepared, all attempts to convert 4 in good yield to 1 were unsuccessful. A similar failure to convert 2-acetylthiophene to 2-thienylacetylene in good yield is reported.[4]

The successful route is illustrated in Scheme I. The good overall yield of 41% (all yields of pure material)

SCHEME I



from 2 to 1 indicates that this route deserves serious consideration for the synthesis of arylacetylenes.

The conversion of 5 to 8 was accomplished essentially as described.[5] On treatment of 8 with butylamine[6] a 95% yield of 1 was obtained. This reagent proved superior to the aqueous alcoholic alkali previously used for the synthesis of phenylacetylene.[5,6a]

Experimental Section[7]

3,5-Di-*tert*-butylbenzaldehyde (5).—A solution of 228 g of 2, 300 g of *N*-bromosuccinimide, and 1 g of benzoyl peroxide in 600 ml of CCl_4 was heated at reflux for 4 hr. After filtration the CCl_4 was removed on a rotary evaporator and the residue was added to a solution of 430 g of hexamethylenetetramine in 300 ml of water and 300 ml of ethanol. This solution was refluxed for 4 hr, 200 ml of concentrated HCl was added, and refluxing was continued for 30 min. The organic product was isolated as usual to yield a residue which was recrystallized from Skellysolve B [petroleum ether (bp 60–68°)] to yield 153 g (63% from 2) of 5,[8] mp 84–85°.

(1) Research sponsored by the Air Force Office of Scientific Research, Air Force Systems Command, U. S. Air Force, under Grant No. AFOSR-72-2237. The U. S. Government is authorized to reproduce and distribute reprints for Governmental purposes notwithstanding any copyright notation hereon.

(2) G. Schill, "Catenanes, Rotaxanes, and Knots," Academic Press, New York, N. Y., 1971.

(3) J. Geuze, C. Ruinard, J. Soeterbroek, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **15**, 301 (1956).

(4) See accompanying article by T. Patrick, J. M. Disher, and W. J. Probst, *J. Org. Chem.*, **37**, 4467 (1972).

(5) M. S. Newman and A. Kutner, *J. Amer. Chem. Soc.*, **73**, 4199 (1951).

(6) Private communication from Father H. P. Hogan. See accompanying article by H. P. Hogan and J. Seehafer, *J. Org. Chem.*, **37**, 4466 (1972).

(6a) NOTE ADDED IN PROOF.—Recently, 5 has been converted into 1 by the method of E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 3769 (1972).

(7) All melting points are uncorrected. Analyses were performed by M-H-W Laboratory, Garden City, Mich. 48135. The phrase "worked up as usual" means that an ether–benzene solution of the products was washed with aqueous acid and/or alkali and saturated salt solution, and was filtered through anhydrous magnesium sulfate. The solvents were then removed on a rotary evaporator and the residue was treated as described. All experiments were repeated at least once. All new compounds gave ir, nmr, and mass spectra consistent with the assigned structures.

(8) W. M. Schubert and R. G. Minton, *J. Amer. Chem. Soc.*, **82**, 6188 (1960).

Methyl β-(3,5-Di-*tert*-butylphenyl)-β-hydroxypropionate (6).—A mixture of 136 g (0.625 mol) of 5, 400 ml of benzene, and 44 g (0.705 g-atom) of activated zinc[9] was heated until 200 ml of benzene had distilled. After 200 ml of dry ether was added, 96 g (0.634 mol) of methyl bromoacetate was added during 5 hr to the refluxing mixture. After refluxing for 10 hr more, the cooled reaction mixture was treated with 1 l. of NH_4OH and the organic products were isolated as usual. A small amount of the crude residue was crystallized from Skellysolve B to yield the analytical sample of 6, mp 66–67°. The remainder was treated as described below to yield 6a.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.9; H, 9.7. Found: C, 73.9; H, 9.7.

β-(3,5-Di-*tert*-butylphenyl)-β-hydroxypropionic Acid Hydrazide (6a).—To a solution of 80.0 g of crude 6, obtained as above, in 60 ml of ethanol was added 10.0 g of anhydrous hydrazine. The mixture was heated until a clear solution resulted. After cooling, the resulting crystalline hydrazide was recrystallized from benzene–ethanol to yield 66.7 g (82.5% from 5) of pure 6a, mp 143–145°.

Anal. Calcd for $C_{17}H_{28}N_2O_2$: C, 69.8; H, 9.6; N, 9.6. Found: C, 69.5; H, 9.4; N, 9.8.

5-(3,5-Di-*tert*-butylphenyl)oxazolidone (7).—To a stirred mixture of 32.0 g of 6a, 200 ml of 6 *N* hydrochloric acid, and 50 ml of chloroform at 0–5° was added 12.0 g of sodium nitrite during 30 min. After stirring for 30 min the excess nitrous acid was destroyed with sodium sulfite. The organic product was taken into three 100-ml benzene extracts, which were washed with saturated salt solution and dried by pouring through magnesium sulfate. This benzene solution was added to 50 ml of refluxing benzene in a flask arranged so that the nitrogen evolved could be collected and measured over water. After nitrogen evolution had ceased the solvent was distilled and the residue was crystallized from Skellysolve B–ether to yield 27.1 g (90%) of 7, mp 167.5–168.5°.

Anal. Calcd for $C_{17}H_{25}NO$: C, 74.1; H, 9.2; N, 5.1. Found: C, 74.1; H, 9.2; N, 5.1.

5-(3,5-Di-*tert*-butylphenyl)-3-nitrosooxazolidone (8).—By method B,[5] 10.5 g of 7 in 50 ml of pyridine on treatment with 5.9 g of nitrosyl chloride in 30 ml of acetic anhydride was converted into 10.8 g (93.5%) of 8, mp 193–195° dec, after recrystallization of crude 8 from acetone.

Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.1; H, 8.0; N, 9.2. Found: C, 67.1; H, 7.9; N, 8.9.

3,5-Di-*tert*-butylphenylacetylene (1).—To a refluxing solution of 4.90 g (0.066 mol) of butylamine in 100 ml of chloroform was added 20.0 g (0.066 mol) of 8 during 30 min. About 95% of the theoretical nitrogen was evolved. After removal of solvent, distillation yielded 13.4 g (95%) of 1, mp 87.0–88.5°. When a similar experiment was done in refluxing ether the yield was 78%.

Anal. Calcd for $C_{16}H_{22}$: C, 89.7; H, 10.4. Found: C, 89.7; H, 10.4.

Registry No.—1, 36720-94-2; 6, 36763-76-5; 6a, 36720-95-3; 7, 36720-96-4; 8, 36720-97-5.

(9) L. F. Fieser and W. S. Johnson, *J. Amer. Chem. Soc.*, **62**, 576 (1940).

Reaction of Naphthalene Dianions with Tetrahydrofuran and Ethylene[1a]

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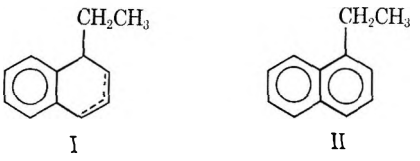
In the course of our work with reactions of arene anion radicals, a frequently observed minor product from many reactions of sodium or lithium naphthalene in THF was identified as a mixture of 1-ethyldihydronaphthalenes (I). Identity was confirmed through aromatization to the known 1-ethylnaphthalene (II)



I II

and conversion to its picrate complex. The recent work of Bates and coworkers on the cleavage of THF into ethylene and acetaldehyde enolate by strong bases[2] led us to consider this reaction as a source of the two-carbon fragment. The anion radical of naphthalene is not a particularly strong base,[3] but the dianion should be considerably stronger. The observations that the amounts of ethylidihydronaphthalene formed in THF solutions of potassium or sodium naphthalene were always very small at most, while lithium naphthalene solutions sometimes exhibited as much as 5% after standing for several days, coupled with the fact that the lithium anion radical is most prone to disproportionate to a mixture of dianion and neutral arene,[4] strongly supported this hypothesis (see Table I). Warming a solution of naphthalene in

TABLE I
YIELDS OF 1-ETHYLDIHYDRO- AND 1-ETHYLNAPHTHALENE[a]

Solvent	Metal	Naphthalene/metal ratio	Addend	Ethylated material, % yield[b]
THF	Li	0.22		54
Tetrahydropyran	Li	0.22		0
THF	Li	1.04		7
THF	K	0.33		~5
THF	Na	0.33		~5
1,2-Dimethoxyethane	Li	0.22		24
1,2-Dimethoxyethane	Li	0.22	750 mg of *n*-butyl vinyl ether	33
Tetrahydropyran	Li	0.29	750 mg of *n*-butyl vinyl ether	~10

[a] See Experimental Section for details. [b] Relative to original naphthalene concentration.

THF containing a fourfold excess of lithium yielded ethylene, easily identified through its dibromide, and similar treatment of 2-methyltetrahydrofuran yielded ethylene and propylene in a 1:15 ratio. Bates observed only propylene formation from the "α-cleavage" reaction of 2-methyltetrahydrofuran with butyllithium.[2] (The "β-cleavage reaction" reported by Bates for this substrate[2] probably also occurred in our reaction, but we did not search for the 4-penten-1-ol product.)

Noting that solutions of excess lithium and naphthalene in THF readily give rise to a large amount of naphthalene dianion at 25°,[5] we carried out the series of

(1) (a) Supported in part by the Public Health Service (Research Grant No. RO1-AM11419 from the National Institute of Arthritis and Metabolic Diseases). (b) Alfred P. Sloan Research Fellow, 1968–1972.

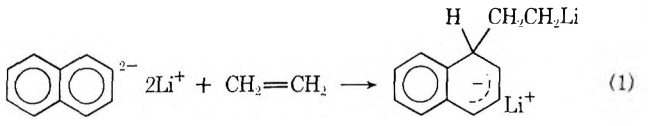
(2) R. B. Bates L. M. Kroposki, and D. E. Potter *J. Org. Chem.* **37**, 560 (1972).

(3) S. Bank and B. Bockrath *J. Amer. Chem. Soc.* **93**, 430 (1971); G. Levin, C. Sutphen and M. Szwarc, *ibid.*, **94**, 2652 (1972).

(4) M. Szwarc, *Progr. Phys. Org. Chem.*, **6**, 323 (1968).

(5) G. Henrici-Olive and S. Olive, *Z. Physik. Chem.*, **43**, 327 (1964); **42**, 145 (1964).

experiments listed in Table I. As expected, the highest yields of ethylated naphthalene derivatives were obtained under conditions where the concentration of dianion would be expected to be greatest, but surprisingly, a considerable amount of ethylation product is obtained with lithium in 1,2-dimethoxyethane (DME). This can be rationalized on the basis of the well-known formation of methoxide ion and methyl vinyl ether from DME and strong base,[6] and the report of Suga, *et al.*, that treatment of lithium naphthalene in THF with alkyl vinyl ethers affords a convenient synthesis of 1-ethylnaphthalene.[7] [Incidentally, using Suga's procedure (3:1 ratio of lithium to naphthalene in THF at 60°) we were able to produce a 30% yield of ethylated material in *the absence* of vinyl ether. Addition of butyl vinyl ether actually results in a slight decrease in yield.] Cleavage of ethers at the C–O bond by strong reducing agents is a well-known phenomenon[8] and a vinyl ether would be expected to cleave mainly between the alkyl carbon and oxygen, in analogy with phenyl alkyl ethers,[8] thus furnishing acetaldehyde enolate, one of the two-carbon fragments from THF. Considerable doubt is cast on the enolate ion as the source of the ethyl group, however, by the following experiment. A stream of ethylene was bubbled through a solution of lithium and naphthalene (3:1 ratio) in tetrahydropyran for 1 hr at 25°. A yield of 45% 1-ethyldihydronaphthalenes and 7% 1-ethylnaphthalene was realized. No ethylated material is formed in the absence of ethylene in tetrahydropyran even at 60° (see Table I). Apparently, the naphthalene dianion adds readily to ethylene, as shown in eq 1. That some sort of lithium



(1)

derivative of the adduct survives for some time is clear from the fact that quenching the reaction mixture with CO_2 or methyl iodide rather than water results in a sharp diminution in yield of ethylated material. (With CO_2 there was simply a large decrease in total amount of material with retention time longer than naphthalene, presumably owing to formation of water-soluble carboxylate salts; with methyl iodide several products of longer retention than ethylnaphthalene now appeared. These were not investigated further.) Further addition of the intermediate alkyllithium to ethylene would not be expected on the basis of work by Bartlett, *et al.*, who noted that primary alkyllithiums are relatively unreactive toward ethylene.[9] Also of note is the fact that reaction of the dianion with 2-methyltetrahydrofuran produces only a trace of ethylated product and no readily identifiable products from propylene in accord with the observed sluggishness of attack of secondary and tertiary alkyllithiums upon substituted ethylenes.[10] Apparently, the lithium salt of the dianion of naphthalene (and presumably other alkali metal salts) approaches the reactivity toward ethylene of secondary and tertiary alkyllithiums. (An alternative mechanism could involve electron transfer from the dianion to ethylene, followed by combination of the resulting radical pair, but distinguishing this from carbanion addition would be difficult.)

The ethylated material from reaction of the lithium dianion in DME, and tetrahydropyran plus butyl vinyl ether, appears not to arise in some manner from acetaldehyde enolate, but most likely from ethylene derived from vinyl carbon–oxygen cleavage of vinyl ether. Thus, reaction of the dianion with butyl vinyl ether in tetrahydropyran yields a large amount (72%) of *n*-butyl alcohol, a modest amount (12%) of ethylated material, and an easily detectable amount of ethylene. Apparently, at least in these systems, the major mode of cleavage of vinyl ethers is opposite to that of phenyl alkyl ethers.[8,11] The actual manner in which such cleavage occurs and such questions as whether vinyl radicals or anions are initially produced must await further work.

Experimental Section[12]

Isolation and Identification of Ethyldihydronaphthalenes from Sodium Naphthalene in THF.—A sample (*ca.* 100 ml) of about 0.4 *M* sodium naphthalene in THF that was 3 weeks old (originally prepared using a slight excess of naphthalene over sodium) was added rapidly to 100 ml of water, and the organic material was extracted with ether and dried with magnesium sulfate. Removal of solvent at reduced pressure yielded a yellow oil, which was dissolved in ethanol and cooled to crystallize out naphthalene. After eight such repeated crystallizations the residual material showed only two peaks other than naphthalene on gas chromatography (5 ft × 0.25 in. SE-30, 150°). These two peaks were collected by preparative gc. The material from the first peak after naphthalene exhibited a complex nmr spectrum and had a mass spectrum (70 eV) of *m/e* 158, 129, and 128. Treatment of this material with DDQ (Aldrich) in CCl_4 for 30 min at 75° transformed it into material identical in retention time with that of the second, much smaller, peak after naphthalene. It was further identified as 1-ethylnaphthalene by nmr [triplet, 1.31 (3.0 H); quartet, 3.06 (2.0 H); multiplet, 7.0–8.2 (7.0 H)], mass spectrum (70 eV, *m/e* 156, 141, 115), and conversion to a picrate complex, mp 97–99° (lit.[14] mp 99°). That the first peak was initially a mixture principally of isomers of 1-ethyl-1,2- and 1-ethyl-1,4-dihydronaphthalene was confirmed by comparing its gc retention time with that of authentic material obtained by treating freshly prepared sodium naphthalene with ethyl bromide.[15]

(6) See, for example, J. F. Garst and F. E. Barton, II, *Tetrahedron Lett.*, 587 (1969).

(7) K. Suga, S. Watanabe, and T. Pai Pan, *Aust. J. Chem.*, **21**, 2341 (1968).

(8) J. J. Eisch, *J. Org. Chem.*, **28**, 707 (1963).

(9) P. D. Bartlett, S. J. Tauber, and W. P. Weber, *J. Amer. Chem. Soc.*, **91**, 6362 (1969).

(10) P. D. Bartlett, S. Friedman, and M. Stiles, *ibid.*, **75**, 1771 (1953).

(11) (a) Eisch did report production of a trace of phenyllithium in the cleavage of anisole with lithium biphenyl in THF,[8] and Morton and Lanpher noted that potassium sand cleaved anisole predominantly (60%) to phenylpotassium and methoxide ion.[11b] (b) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **23**, 1636 (1958). (c) A referee has suggested an alternative mechanism in which the dianion adds to the double bond of the vinyl ether to eventually yield a 1- or 2-(1-naphthyl)ethyl butyl ether, followed by reductive cleavage of this ether[11d] to ethylnaphthalene and butoxide. This, however, would not account for production of ethylene. (d) D. J. Cram and C. K. Dalton, *J. Amer. Chem. Soc.*, **85**, 1268 (1967).

(12) Gas chromatographic measurements were made on a Varian Model 200 (0.125-in. columns, flame ionization detector), utilizing internal standards and determining peak areas by cutting and weighing. Preparative gas chromatography was carried out with a Varian A-90 instrument. The nmr measurements were done with either a Varian A-60A or an HA-100-D modified by a Digilab FTS-3 Fourier transform system,[13] and mass spectrometric measurements were done with a AEI MS-902.

(13) We would like to thank the National Science Foundation for Grant No. GP 28061 for the purchase of this equipment.

(14) H. Cristol, R. Jacquier, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 248 (1958).

(15) J. F. Garst, J. T. Barbas, and F. E. Barton, II, *J. Amer. Chem. Soc.*, **90**, 7159 (1968); G. D. Sargent and G. A. Lux, *ibid.*, **90**, 7160 (1968).

Reaction of Lithium Naphthalene Dianion with THF.—To 200 ml of dry THF was added 1.28 g (0.10 mol) of naphthalene and 2.1 g (0.30 mol) of lithium. The mixture was degassed and covered with argon, and then stirred. The solution rapidly turned green and became reddish brown after 1 hr at 25°. The solution was then refluxed for 4 hr and the effluent gases were collected for 2 hr in cooled CCl_4 and then for 2 hr in a solution of bromine in CCl_4. The solution was then cooled and quenched with water. Analysis by gc revealed 1-ethyldihydronaphthalenes, 9%, 1-ethylnaphthalene, 19%, and 72% of naphthalene and dihydronaphthalenes. Analysis by nmr of the CCl_4 solution of effluent gases showed only a sharp singlet at δ 5.3 which moved to 3.70 on addition of bromine. Authentic 1,2-dibromoethane showed an identical nmr spectrum and had a gc retention time on several columns identical with that of this material and with the material obtained by collecting the effluent gases in bromine–CCl_4.

Reaction of lithium naphthalene dianion with 2-methyltetrahydrofuran was carried out in identical fashion except that 2.8 g (0.40 mol) of lithium was used. The nmr spectrum of the material collected in bromine–CCl_4 was identical with that of 1,2-dibromopropane plus a small peak at the position of 1,2-dibromoethane. Analysis of the mixture of dibromides by gc indicated the ratio of dibromoethane to dibromopropane to be *ca.* 1:15. Quenching of the lithium naphthalene solution with water and gc analysis indicated only a very small amount of ethylation products and some even smaller peaks at longer retention time.

Effects of Solvent and Metal on Yield of Ethylated Material.—Ampoules containing 0.320 g (2.5 mmol) of naphthalene in 5.0 ml of different dry solvents and 2.5–7.5 mmol of different alkali metals plus, in some cases, 0.75 g (7.5 mmol) of butyl vinyl ether, were prepared and sealed under nitrogen. After stirring at 25° until deep colors had formed, they were heated at 65° for 13 hr. They were then cooled, opened, quenched with a small amount of water, dried with magnesium sulfate, and analyzed for 1-ethyldihydro- and 1-ethylnaphthalene by gc. The results are shown in Table I.

Reaction of lithium naphthalene dianion with butyl vinyl ether in THF was carried out according to the procedure of Suga, *et al.*[7] A mixture of 3.2 g (25 mmol) of naphthalene, 0.70 g (0.10 mol) of lithium, and 10 g (100 mmol) of butyl vinyl ether in 50 ml of THF under nitrogen was stirred for 1 hr at 25°, then heated at reflux for 3 hr. It was then cooled and quenched with methanol. Usual work-up and analysis by gc indicated ethyldihydronaphthalenes, 6%, and 1-ethylnaphthalene, 3%, relative to the original amount of naphthalene. A reaction carried out in identical fashion except for the absence of butyl vinyl ether afforded a 16% yield of ethyldihydronaphthalenes and a 14% yield of 1-ethylnaphthalene.

Reaction of Lithium and Naphthalene with Ethylene in Tetrahydropyran.—A mixture of 6.25 g (0.049 mol) of naphthalene and 1.05 g (0.15 mol) of lithium in 50 ml of dry tetrahydropyran was stirred at 25° under nitrogen for 3 hr and then ethylene was bubbled through the solution for 1 hr by means of a glass-frit inlet tube. Quenching the solution with water, drying with magnesium sulfate, and analysis by gc revealed a 45% yield of ethyldihydronaphthalenes and 7% of 1-ethylnaphthalene. A control experiment, carried out in identical fashion except for addition of ethylene, yielded no detectable amount (less than 0.1%) of ethylated product.

Reaction of Lithium, Naphthalene, and Butyl Vinyl Ether in Tetrahydropyran.—In a glass ampoule equipped with glass-covered stirring bar were sealed 0.32 g (2.5 mmol) of naphthalene, 0.080 g (11.4 mmol) of lithium, and 0.300 g (3.0 mmol) of butyl vinyl ether in 5.0 ml of dry tetrahydropyran under vacuum. The mixture was stirred for 48 hr at 25°. Analysis by gc of the gas in the ampoule indicated a modest amount of ethylene. Analysis of the water-quenched solution indicated 2.17 mmol (72%) of *n*-butyl alcohol and a 12% (relative to naphthalene) combined yield of ethyldihydro- and ethylnaphthalene.

Registry No.—THF, 109-99-9; ethylene, 74-85-1; 1-ethylnaphthalene, 1127-76-0; 1-ethyl-1,2-dihydronaphthalene, 34599-49-0; 1-ethyl-1,4-dihydronaphthalene, 36789-17-0; lithium naphthalene dianion, 34488-61-4; 2-methyltetrahydrofuran, 96-47-9; butyl vinyl ether, 111-34-2.

Synthesis of 5-Vinylcyclohexa-1,3-diene by a Nickel-Catalyzed Cooligomerization of Acetylene and Butadiene

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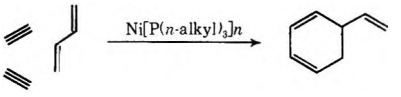
5-Vinylcyclohexa-1,3-diene is the major product formed (*ca.* 60% yield based on acetylene) when acetylene and butadiene are cooligomerized by nickel(0)–tri-*n*-alkylphosphine complexes. By-products are benzene (*ca.* 20% yield based on acetylene) and small amounts of 1,3,6-cyclooctatriene, styrene, 4-vinylcyclohexene, 1,5-cyclooctadiene, and several unidentified compounds. Isolation of 5-vinylcyclohexa-1,3-diene may be achieved by fractional distillation, under diminished pressure, of the volatile portion of the reaction mixture or by preparative glpc. This compound was previously obtained in moderate yield by pyrolysis of 1,3,5-cyclooctatriene.[1,2] As a preparative method, the synthesis described here appears more attractive.



Substituted derivatives of 5-vinylcyclohexa-1,3-diene have previously been prepared by nickel(0)-*tert*-phosphine catalyzed mixed oligomerizations of substituted acetylenes with butadiene.[3,4] However, the identities of reaction products from acetylene and butadiene were not reported, apparently because the course of the reaction was rather ill defined.[5] In yet earlier studies with $(R_3P)_2Ni(CO)_2$ complexes (R = OPh, OMe) as catalysts, acetylene and butadiene yielded small amounts of cyclooctatriene (presumably the 1,3,6 isomer) and a compound believed to be 4,5-divinylcyclohexene.[6] The principle process occurring in this study was a dimerization of butadiene.[6]

The relative simplicity of the product mixtures obtained here results largely from the choice of the *tert*-phosphine. As shown in Table I, the highest selectivity to 5-vinylcyclohexa-1,3-diene occurs with tri-*n*-alkylphosphines at R_3P:Ni mole ratios between 1:1 and 4:1. At low butadiene to acetylene mole ratios, reaction times are shortened and reaction temperatures below 25° may be used, but the selectivity to 5-vinylcyclohexa-1,3-diene suffers and the benzene yield increases.

The nickel catalyst is conveniently prepared *in situ* by treating $Ni(acac)_2$ with $AlEt_3$ at −78° in the presence of the *tert*-phosphine and the monomers, although

(1) W. R. Roth and B. Peltzer, *Justus Liebigs Ann. Chem.*, **685**, 56 (1965).
(2) W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).
(3) P. Heimbach, K.-J. Ploner, and F. Thömel, *Angew. Chem., Int. Ed. Engl.*, **10**, 276 (1971).
(4) W. Brenner, P. Heimbach, K.-J. Ploner, and F. Thömel, *ibid.*, **8**, 753 (1969).
(5) W. Brenner, P Heimbach, and G. Wilke, *Justus Liebigs Ann. Chem.*, **727**, 194 (1969).
(6) H. W. B. Reed, *J. Chem. Soc.*, 1931 (1954).

TABLE I

ACETYLENE–BUTADIENE COOLIGOMERIZATIONS CATALYZED BY NICKEL COMPLEXES[a]

Catalytic system	Reaction conditions: Mole ratio, C_4H_6: C_2H_2	Temp, °C	Time, hr	Products: % Yield based on acetylene: VCHD[b]	COT[b]	PhH	Sty[b]	% Yield based on butadiene: VCH[b]	COD[b]	Yield, g, of others[c]
$Ni(acac)_2$, $3AlEt_3$	4	25	42	4	1	5	<1	<1	*d*	<0.01
$Ni(acac)_2$, $2PEt_3$, $3AlEt_3$	4	25	6	59	<1	16	5	<1	*d*	0.11
$Ni(acac)_2$, $2PPh_3$, $3AlEt_3$	4	25	69	46	2	26	1	1	1	0.09
$Ni(acac)_2$, $2P(OPh)_3$, $3AlEt_3$	4	25	17	<1	<1	2	1	<1	<1	<0.01
$Ni(acac)_2$, $P(n\text{-}Bu)_3$, $3AlEt_3$	4	25	16	61	<1	22	1	<1	*d*	0.06
$Ni(acac)_2$, $4P(n\text{-}Bu)_3$, $3AlEt_3$	4	25	6	66	<1	15	1	<1	*d*	0.06
$Ni(acac)_2$, $8P(n\text{-}Bu)_3$, $3AlEt_3$	4	25	22	41	<1	12	1	<1	*d*	0.02
$Ni(acac)_2$, $2P(n\text{-}Bu)_3$, $3AlEt_3$	1	25	3	56	1	22	1	<1	*d*	0.32
$Ni(1,5\text{-}COD)_2$, $2P(n\text{-}Bu)_3$	4	25	4	52	<1	18	ND[e]	<1	ND	ND
$(Et_3P)_2Ni(o\text{-tolyl})Br$, MeOH	5	50	18	27	<1	17	2	<1	<1	0.12
$Ni(acac)_2$, $2P(n\text{-}Bu)_3$, MeOH	4	70	16	50	<1	32	4	ND	ND	ND
$Ni(acac)_2$, $2P(n\text{-}Bu)_3$	4	80	6	45	<1	10	1	1	<1	ND
$(Et_3P)_2NiCl_2$, MeOH	4	90	44	15	<1	12	ND	ND	<1	ND
PBu_3	4	80	5	*d*	*d*	0.5	*d*	0.5	*d*	*d*

[a] Reaction mixtures normally contained 200 mmol of butadiene and *ca.* 0.4 mmol of nickel complex. [b] Abbreviations are as follows: VCHD = 5-vinylcyclohexa-1,3-diene; COT = 1,3,6-cyclooctatriene; Sty = styrene; VCH = 4-vinylcyclohexene; COD = 1,5-cyclooctadiene. [c] Others are unidentified compounds which were detected by glpc. [d] The product was not detected by glpc. [e] ND denotes that the product yield was not determined.

the preformed nickel(0) complex $Ni(1,5\text{-}COD)_2$ plus the *tert*-phosphine gave comparable results. The true nature of the catalytically active species in solution has not been established. At −20°, a red-brown crystalline solid formed in reaction mixtures containing triphenylphosphine, but the solid decomposed while being filtered in a drybox. Treating a product mixture, containing triethylphosphine as the *tert*-phosphine ligand, with tetrachloroethylene resulted in the formation of a 23% yield of *trans*-$(Et_3P)_2Ni(CCl{=}CCl_2)Cl$. This organonickel compound can arise by an oxidative addition of tetrachloroethylene to a $(Et_3P)_n$-Ni(0) complex.[7]

Alternatively, the catalyst may be formed *in situ* from nickel(II) complexes at higher temperatures without the aid of organometallic or metal hydride reducing agents (Table I). The actual reducing agent in this case must be either acetylene, the *tert*-phosphine, or methanol, when present. In earlier reported attempts to catalyze a reaction of acetylene with butadiene using $(n\text{-}Pr_3P)_2NiX_2$ complexes, no distillable products were obtained, but $Ni(acac)_2$ afforded cyclooctatetraene by acetylene cyclotetramerization.[6] At higher temperatures, thermal Diels–Alder reactions of butadiene with itself to yield 4-vinylcyclohexene and between acetylene and butadiene to form 1,4-cyclohexadiene may also occur.

On standing, 5-vinylcyclohexa-1,3-diene undergoes spontaneous dehydrogenation to styrene and slowly polymerizes. During glpc analyses of reaction mixtures with an injection port temperature of 250°, the thermal isomerizations of 5-vinylcyclohexa-1,3-diene to tricyclo[2.2.2.$0^{2,6}$]oct-7-ene and of 1,3,6-cyclooctatriene to 1,3,5-cyclooctatriene were observed.[1,2] These isomerizations are avoided at an injection port temperature of *ca.* 90°. Treatment of 5-vinylcyclohexa-1,3-diene with maleic anhydride in benzene affords the Diels–Alder adduct 7-vinylbicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride.

(7) R. G. Miller, D. R. Fahey, and D. P. Kuhlman, *J. Amer. Chem. Soc.*, **90**, 6248 (1968).

Experimental Section[8]

All reactions were carried out under a nitrogen atmosphere with anhydrous reagents and in dry deoxygenated solvents. Triethylaluminum was used as a 25 weight % solution in cyclohexane and was purchased from Texas Alkyls. The complexes $Ni(1,5\text{-}COD)_2$,[9] *trans*-$(Et_3P)_2Ni(o\text{-tolyl})Br$,[10] and *trans*-$(Et_3P)_2NiCl_2$[11] were prepared by published procedures. Phillips pure grade butadiene was used, and acetylene was passed through two −78° traps to remove acetone.

Acetylene–butadiene reactions were conducted in aerosol compatibility bottles, *i.e.*, thick-walled glass vessels of 3-oz capacity fitted with a stainless steel cap and sealed by a neoprene rubber O-ring. The cap was fitted with a pressure gauge, a gas inlet–outlet port, and a vertical tubular serum-stoppered port encompassing a "ball" type stopcock through which a 12-in syringe needle could be passed.

Cooligomerization of Acetylene with Butadiene to 5-Vinylcyclohexa-1,3-diene. A. By $Ni(acac)_2$, $AlEt_3$, and a *tert*-Phosphine.—To a previously dried pressure bottle was added 0.10 g (0.39 mmol) of $Ni(acac)_2$, 10.0 ml of cyclohexane, and the desired quantity of a *tert*-phosphine. The bottle was capped, flushed with nitrogen, partially evacuated, and cooled to −78°. Then 10.8 g (200 mmol) of butadiene and 1.3 g (50 mmol) of acetylene were introduced followed by 0.80 ml of 25% $AlEt_3$ in cyclohexane by syringe through the vertical port. The ball valve was closed, and the mixture was warmed to 25° and magnetically stirred until the pressure dropped from *ca.* 70 to <15 psig. The unreacted gases were vented, and the crude mixture, spiked with ethylbenzene as a standard, was analyzed by glpc isothermally at 95 and at 140°. Results are reported in Table I. Typical retention times at 95° follow: cyclohexane (1.4 min), 1,4-cyclohexadiene (3.5), 4-vinylcyclohexene (4.2), benzene (4.7), 5-vinylcyclohexa-1,3-diene (5.7), tricyclo[2.2.2.$0^{2,6}$]oct-7-ene (7.1), 1,3,6-cyclooctatriene (9.2), 1,5-cyclooctadiene (10.5), 1,3,5-cyclooctatriene (14.1), styrene (20.6), and several un-

(8) Boiling and melting points are uncorrected. Infrared and nuclear magnetic resonance spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer and a Varian T-60 spectrometer, respectively. Mass spectra of pure compounds were obtained on a CEC 21-110 high-resolution instrument. Mass spectra of components in mixtures were obtained with a CEC 21-130 spectrometer coupled to a Perkin-Elmer F-11 gas chromatograph *via* a Phillips-Becker molecular separator. Gas chromatographic analyses were performed on a Hewlett-Packard Model 5750 instrument, and yields were obtained using ethylbenzene as an internal standard with appropriate corrections being made for relative response factors. A 20 ft × 0.125 in. column packed with 20% 1,2,3-tris(2-cyanoethoxy)propane on 60/80 Chromosorb P was used in both chromatographs.

(9) B. Bogdanović, M. Kröner, and G. Wilke, *Justus Liebigs Ann. Chem.*, **699**, 1 (1966).

(10) J. Chatt and B. L. Shaw, *J. Chem. Soc.*, 1718 (1960).

(11) K. A. Jensen and B. Nygaard, *Acta Chem. Scand.*, **3**, 474 (1949).

known compounds (>25). 1,4-Cyclohexadiene, 4-vinylcyclohexene, benzene, 1,5-cyclooctadiene, and styrene were identified by comparison of glpc retention times with those of authentic samples and by combination glpc–mass spectral analysis. Tricyclo[2.2.2.0^{2,6}]oct-7-ene was identified by combination glpc–mass spectral analysis and by its known[1,2] formation from 5-vinylcyclohexa-1,3-diene at elevated temperatures. 5-Vinylcyclohexa-1,3-diene, 1,3,6-cyclooctatriene, and 1,3,5-cyclooctatriene were isolated by preparative glpc and were identified from their mass and nmr spectra. 5-Vinylcyclohexa-1,3-diene could also be isolated by distillation: bp 63–66° (90 mm) [lit.[2] bp 43–46° (42 mm)]; ir identical with that reported in the literature;[2] nmr (neat) τ 4.40 (m, 5, CH=CH$_2$ and CH=CHCH=CH), 5.15 (m, 2, CH=CH$_2$), 7.25 (m, 1, CHCH$_2$), and 8.00 ppm (m, 2, CHCH$_2$); mass spectrum (70 eV) *m/e* (rel intensity) 106 (49), 105 (31), 91 (100), 79 (51), 78 (80), 77 (41), 51 (26), 39 (25), and 29 (25). Identification of 1,3,6-cyclooctatriene is based upon the following: nmr (CCl_4) τ 3.8 (d, 2, J = 9 Hz, CH=CHCH=CH), 4.27 (m, 4, CH=CHCH=CH and CH$_2$-CH=CHCH$_2$), and 3.15 ppm (dd, 4, J = 7, 3.5 Hz, CH$_2$CH=CHCH$_2$); mass spectrum (70 eV) *m/e* (rel intensity) 106 (27), 91 (49), and 78 (100). Identification of 1,3,5-cyclooctatriene is based upon the following: nmr (CCl_4) τ 4.23 (broad d, 6, CH=CHCH=CHCH=CH) and 7.50 ppm (broad s, 4, CH$_2$-CH$_2$); mass spectrum (70 eV) *m/e* (rel intensity) 106 (24), 91 (52), and 78 (100).

B. By Ni(1,5-COD)$_2$ and P(*n*-Bu)$_3$.—A predried pressure bottle was charged with 0.10 g (0.36 mmol) of Ni(1,5-COD)$_2$ and capped in a drybox. After the bottle was partially evacuated and cooled to −78°, 0.80 mmol of P(*n*-Bu)$_3$ in 6 ml of cyclohexane was syringed into the bottle, and the ball stopcock was closed. Then 12.7 g (235 mmol) of butadiene and 1.5 g (58 mmol) of acetylene were added, the bottle was warmed to 25°, and the reaction was carried out and analyzed as in A. The yield of 5-vinylcyclohexa-1,3-diene was 52%.

C. By Nickel(II) Complexes at Elevated Temperatures.—A predried pressure bottle was charged with cyclohexane, the nickel(II) compound (if any), a *tert*-phosphine (if any), 1–2 ml of methanol (if any), butadiene, and acetylene as in A. As the mixture was stirred, its temperature was increased (the bottle was immersed in a heated oil bath) until the system pressure began to decrease. After no further reaction was apparent, the reaction solution was cooled and then analyzed as in A. Results are reported in Table I.

Treatment of a Cooligomerization Product Mixture with Tetrachloroethylene.—A cooligomerization reaction was carried out as in A except with 0.30 g (1.2 mmol) of Ni(acac)$_2$, 0.27 g (2.3 mmol) of PEt$_3$, and 2.4 ml of 25% AlEt$_3$ in cyclohexane. After 1 hr at 25°, the cooligomerization was complete, and a product distribution comparable to those shown in Table I for tri-*n*-alkylphosphines was obtained (by glpc analysis). This crude reaction mixture was treated with 3.2 g (19 mmol) of tetrachloroethylene, and the resulting solution was stirred overnight at 25° while unreacted gases were allowed to vent. Concentration of the solution under vacuum left a brown sludge which was chromatographed on acid-washed alumina. A viscous yellow oil was eluted with 50% ether in pentane and was rechromatographed. Elution with benzene afforded 0.12 g (23%) of *trans*-(Et$_3$P)$_2$Ni(CCl=CCl$_2$)Cl which, after recrystallization from MeOH, was found to be identical in all respects with an authentic sample.[7]

7-Vinylbicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Anhydride.—A solution of 1.49 g (14.1 mmol) of 5-vinylcyclohexa-1,3-diene and 1.50 g (15.3 mmol) of maleic anhydride in 2 ml of benzene was stirred at 25° for 48 hr. Pentane (10 ml) was added, and a mushy solid was collected by filtration. The solid was washed with ice water until the filtrate no longer gave a positive test with Congo red paper. Recrystallization of the solid from hot cyclohexane afforded 1.68 g (58%) of the product: mp 81–83°; ir (Nujol) 1840 (m) and 1765 (vs) (C=O), 1628 (m) (C=C), 1375 (m), 1350 (w), 1300 (w), 1258 (m), 1245 (m), 1225 (s), 1210 (w), 1175 (w), 1086 (s), 1063 (w), 1042 (w), 1018 (w), 990 (w), 958 (s), 938 (s), 924 (s), 908 (s), 902 (s), 866 (w), 833 (m), 823 (m), 778 (w), 754 (s), 697 (m), and 687 cm^{-1} (m); nmr ($CDCl_3$) τ 3.75 (m, 2, CH=CH), 4.60 (m, 1, CH=CH$_2$), 5.10 (m, 2, CH=CH$_2$), 6.85 (broad s, 4, bridgehead CH), 7.6, 8.05, and 8.8 ppm (broad multiplets, 3, CH$_2$CH); mass spectrum (70 eV) *m/e* (rel intensity) 204 (0.2), 96 (12), 78 (100), and 54 (70).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.7; H, 6.0.

Registry No.—5-Vinylcyclohexa-1,3-diene, 3725-32-4; acetylene, 74-86-2; butadiene, 106-99-0; Ni(1,5-COD)$_2$, 1295-35-8; P(Bu)$_3$, 998-40-3; *trans*-(Et$_3$P)$_2$Ni(*o*-tolyl)Br, 26521-33-5; *trans*-(Et$_3$P)$_2$NiCl$_2$, 15638-51-4; 7-vinylbicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride, 36749-22-1; nickel, 7440-02-0.

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Ozonolysis of the 7-Phenylnorcaranes

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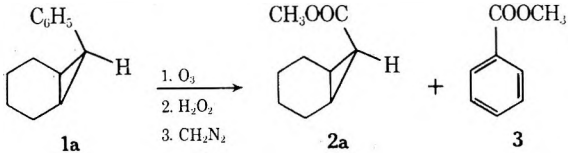
Conflicting reports of Hodgkins,[1] Closs,[2] Jensen,[3] and Ledlie[4] concerning the stereochemical assignments of the 7-phenylnorcaranes **1a** and **1b** have prompted us to reinvestigate the stereochemistry of these compounds. The structural assignments found in the literature have been based primarily on nmr data. In this paper we present the first conclusive chemical evidence supporting Closs', Jensen's, and Ledlie's assignments.

Reduction of a mixture of the 7-phenyl-7-chloronorcaranes[1] employing triphenyltin hydride yields 80% **1a**, ~1% **1b**, and 19% olefin. The olefin was removed with ozone.[1] Then work-up and distillation resulted in a sample of **1a** which was 99% pure. Subjecting **1a** to ozonization[5] furnishes a mixture of two acids which are converted to their corresponding methyl esters **2a** and **3** to facilitate their separation and identification. Preparative gas chromatography employing a 30% SE-30 column allowed separation of



1a **2a** **3**

these materials. Compound **3** was produced in 20% yield and was identified as methyl benzoate by comparison of its ir spectrum with that of authentic material. **2a** was formed in 14% yield and was identified as *endo*-7-carbomethoxynorcarane, thereby identifying **1a** as the endo isomer of 7-phenylnorcarane. **2a** analyzed correctly for $C_9H_{14}O_2$ and exhibited an absorption band in its ir spectrum at 1734 cm^{-1} due to the C=O stretch of the ester function. Further evidence supporting the structure of compound **2a** was obtained

(1) J. E. Hodgkins, J. D. Woodyard, and D. L. Stephenson, *J. Amer. Chem. Soc.*, **86**, 4080 (1964).
(2) G. L. Closs and J. J. Coyle, *J. Org. Chem.*, **31**, 2759 (1966).
(3) F. R. Jensen and D. B. Patterson, *Tetrahedron Lett.*, 3837 (1966).
(4) D. R. Ledlie and S. MacLean, *J. Org. Chem.*, **34**, 1123 (1969).
(5) Y. S. Shabarov, V. K. Potapov, R. Y. Levina, and E. G. Treshchova, *Vestn. Mosk. Univ., Khim., Ser. 2*, **18**, 61 (1963); *Chem. Abstr.*, **59**, 7397*h* (1963).

by comparing its ir spectrum with that of an authentic sample.

Authentic **2a** was prepared by treating the known *endo*-norcarane-7-carboxylic acid[6,7] with diazomethane. The resulting ester analyzed correctly for $C_9H_{14}O_2$. Authentic 7-carbomethoxynorcarane displayed an absorption band in its ir spectrum at 1734 cm^{-1} as did **2a**. Its nmr spectrum exhibited absorptions at 3.58 ppm (3 protons, singlet) and 0.8–2.1 ppm (11 protons, multiplet).

When **1a** is treated with a 10% solution of potassium *tert*-butoxide in dimethyl sulfoxide,[2] *exo*-7-phenylnorcarane (**1b**) is obtained, which, after work-up and distillation, resulted in a sample of **1b** which was 97% pure. When **1b** was treated in turn with ozone, hydrogen peroxide,[5] and diazomethane, it furnished a 24% yield of *exo*-7-carbomethoxynorcarane (**2b**) and a 13% yield of methyl benzoate. The products were separated by preparative gas chromatography employing a 20% Carbowax 1500 column. Methyl benzoate was identified as before. Compound **2b** was identified as *exo*-7-carbomethoxynorcarane on the basis of a correct elemental analysis and by comparing its ir spectrum (1728 cm^{-1}, ester carbonyl) with that of an authentic sample.

Authentic *exo*-7-carbomethoxynorcarane was prepared in the same manner as its endo isomer. Authentic *exo*-7-carbomethoxynorcarane exhibits nmr absorptions at 3.57 ppm (3 protons, singlet) and 1.0–2.3 ppm (11 protons, multiplet). These data indicate that **1a** and **1b** are indeed the endo and exo isomers, respectively, of 7-phenylnorcarane, and are in complete agreement with the conclusions reached by Closs, Jensen, and Ledlie. We are presently investigating the ozonization of other bicyclo[*n*.1.0] systems as a function of structure and reaction temperature.

Experimental Section

An F & M gas chromatograph, Model 810, equipped with a 7 ft by 0.25 in. 20% Carbowax 1500 column operated at 125°, was employed for separation of methyl benzoate from *exo*-7-carbomethoxynorcarane. A 6 ft by 0.25 in. 30% SE-30 column was operated at 160° to achieve separation of methyl benzoate and *endo*-7-carbomethoxynorcarane. Ir spectra were obtained using a Beckman Model 10 grating ir spectrophotometer with potassium bromide cells. Nmr spectra were recorded in carbon tetrachloride with a Varian A-60 spectrometer employing tetramethylsilane as an internal reference. A Welsbach ozonator, Model T-816, generating a stream of 3% ozone at a flow of 1 l./min was used for all ozonolyses. The elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. All boiling points are uncorrected.

Ozonolysis[5] of *endo*-7-Phenylnorcarane (1a).—A stream of 3% ozone was bubbled through a 250-ml gas wash bottle containing a magnetically stirred mixture of 2.0 g of **1a** (99% pure) in 100 ml of 95% acetic acid until a test in water showed no turbidity. The time required for this reaction when carried out at 25° was 2.5 hr. After completion of the reaction, 10 ml of 30% hydrogen peroxide was added, and the solution was allowed to stir at room temperature overnight. The mixture was then heated in an oil bath at 95° for 4 hr, the acetic acid removed by vacuum distillation, and the residue extracted four times with 5-ml portions of hot hexane. Evaporation of the hexane furnished 0.92 g of a mixture of two acids. These acids were treated with diazomethane and the resulting esters were separated by preparative gas chromatography employing a 6 ft by 0.25 in. column containing 30% SE-30 on Chromosorb P operated at 160°. The faster eluting compound (**3**) was proven to be methyl benzoate by comparison of its ir and nmr spectra with reference spectra. The slower eluting compound, **2a**, was collected and found to have ir and nmr spectra identical with those of an authentic sample of *endo*-7-carbomethoxynorcarane (see below). The yield of esters **2a** and **3** based on **1a** was 14 and 20%, respectively. The yields were calculated by comparing the area found under the vpc curves with those obtained from standard samples.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.21; H, 9.20.

Ozonolysis of *exo*-7-Phenylnorcarane (1b).—Ozonolysis of **1b** was carried out in exactly the same manner described for **1a**. A yield of 0.72 g of a mixture of two acids was obtained. These acids were treated with diazomethane and the resulting esters were separated by preparative gas chromatography employing a 7 ft by 0.25 in. column containing 20% Carbowax 1500 on Chromosorb P operated at 125°. The faster eluting compound (**3**) was proven to be methyl benzoate by comparison of its ir and nmr spectra with reference spectra. The slower eluting compound, **2b**, was collected and found to have ir and nmr spectra identical with those of an authentic sample of *exo*-7-carbomethoxynorcarane (see below). The yield of esters **2b** and **3** based on **1b** was 24 and 13%, respectively. The yields were calculated by comparing the area found under the vpc curves with those obtained from standard samples.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.16; H, 9.19.

***exo*-7-Carbomethoxynorcarane (2b).**—*exo*-Norcarane-7-carboxylic acid[6] was methylated by dissolving 5 g of the acid in 50 ml of ether and treating the solution with an excess of diazomethane.[8] The solution was allowed to stand in the dark for 30 min. The unreacted diazomethane was treated with a dilute solution of acetic acid in ether. The ether was evaporated and the residue distilled *in vacuo* to give 4.31 g (78%) of **2b**, bp 99° (15 mm), $n^{28}D$ 1.4700.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.30; H, 9.23.

***endo*-7-Carbomethoxynorcarane (2a).**—*endo*-Norcarane-7-carboxylic acid[6] was methylated in the same manner as its exo isomer except that only 0.4 g of the acid was used, and the reaction was allowed to stand in the dark for 2.5 hr after the diazomethane was added. A yield of 0.36 g (71%) of **2a**, bp 95° (15 mm), was isolated.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.03; H, 9.12.

Registry No.—**1a**, 10503-37-4; **1b**, 10503-36-3; **2a**, 36744-58-8; **2b**, 36744-59-9; **3**, 93-58-3.

Acknowledgment.—The authors wish to acknowledge the financial support (Grant AE-361) of the Robert A. Welch Foundation.

(6) P. S. Skell and R. M. Etter, *Proc. Chem. Soc. London*, 443 (1961).
(7) H. Musso and U. Biethan, *Chem. Ber.*, **97**, 2282 (1964).
(8) F. Arndt, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 165.

Cycloaddition Reactions of Vinylketene Thioacetals

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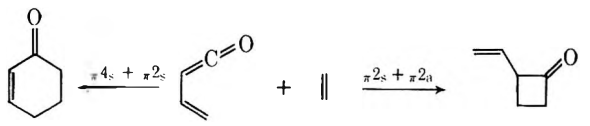
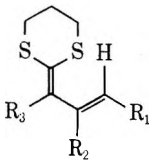
The relative unavailability of vinylketenes from readily available precursors coupled with their tendency to ring close has precluded their use in synthesis. An obvious application would be in cyclohexenone synthesis by Diels–Alder addition of olefins to a vinylketene, but here an additional complication arises in that vinylcyclobutanones could arise by a $_{\pi}2_s + _{\pi}2_a$ process in competition with the desired $_{\pi}4_s + _{\pi}2_s$ process.[1]

(1) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, pp 163–168.



A solution to these problems can be found in the now-familiar approach of using stable reagents which bear the critical functionality masked in a fashion which permits the required reactions to occur.[2] In the work described here the vinylketene equivalents employed are unsaturated ketene thioacetals (vinylketene thioacetals) **1a–c**.



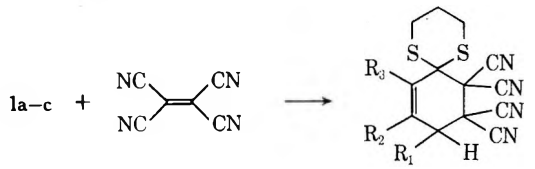
1

	R_3	R_2	R_1
a	CH_3	CH_3	H
b	Ph	H	H
c	$-(CH_2)_4-$		CH_3

These vinylketene thioacetals retain the diene system necessary for the 4 + 2 cycloaddition while the expected adducts of such reactions can be converted to cyclohexenones by a variety of hydrolytic methods.[3] Previous work on simple ketene thioacetals did not indicate a tendency toward 2 + 2 cycloaddition;[4] so vinylcyclobutanone formation as a competing process should be unimportant.

The compounds studied were all prepared by the recently developed method employing addition of 2-lithio-2-trimethylsilyl-1,3-dithiane to α,β-unsaturated aldehydes and ketones.[5] Addition occurs exclusively at the carbonyl group and elimination of Me_3SiOLi is spontaneous under the reaction conditions to afford good yields of **1a–c**. Compound **1c** was prepared from 1-acetylcyclohexene in 87% yield while **1a** (from tiglaldehyde) and **1b** (from cinnamaldehyde) were available from previous studies.

The first dienophile examined toward cycloaddition to **1a–c** was tetracyanoethylene (TCNE). Each of the vinylketene thioacetals reacted with TCNE in methylene chloride at room temperature within minutes to afford the corresponding 4 + 2 adducts **2a–c** in good yield (71–83%).



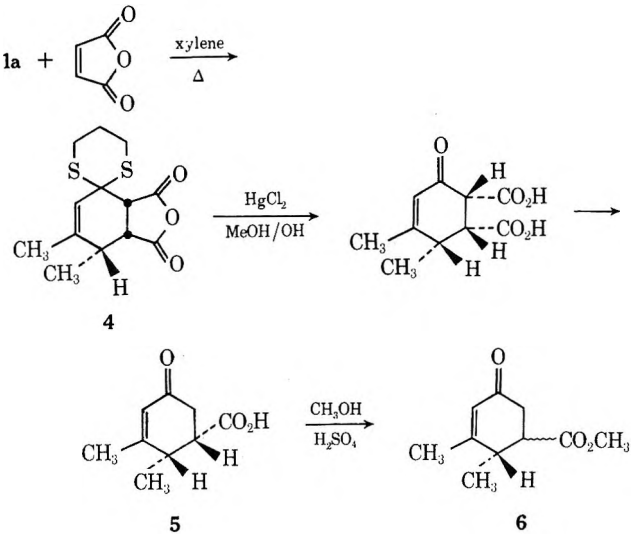
2a–c

The nmr spectra of the adducts fully supported their formulation as 4 + 2 cycloaddition products. In particular, the presence in the nmr spectrum of **2a** of signals for an allylic methyl group (δ 1.90) and a vinyl proton (δ 5.60) is consistent with the assigned structure.

It was considered to be of interest to ascertain the effect of the sulfur substituents on reactivity in 4 + 2 cycloadditions, since it was not obvious whether they should activate the diene by electron release from the lone pairs or deactivate it by stabilization of the diene through d_π–p_π overlap.[6] Destabilization of the required s-cis conformation by the sulfur substituents should also retard the rate of cycloaddition.[7] To determine the relative importance of these various factors a competition reaction was carried out in which the vinylketene thioacetal **1b** was allowed to compete with *trans*-1-phenylbutadiene (**3**) for a deficiency of TCNE. One equivalent of TCNE was added to a solution containing 1 equiv of **1b** and 1 equiv of **3** in methylene chloride at 25°. The product which was isolated was exclusively **2b** and was formed in 87% yield. In a similar competition study between **1c** and 2,3-dimethyl-1,3-butadiene, 0.5 equiv of TCNE was added to a dichloromethane solution containing 1 equiv of each diene. Again the only adduct detected was that from the vinylketene thioacetal.

The implications from these experiments are, at least toward highly electrophilic olefins, that sulfur substituents on the diene activate the diene toward Diels–Alder cycloaddition to a substantial degree.[8]

Development of the desired cyclohexenone synthesis proceeded in a direct fashion using **1a** as the substrate and maleic anhydride as the dienophile. Refluxing a xylene solution of **1a** and maleic anhydride for 3 hr and evaporating the solvent afforded the crystalline adduct **4** in 60% yield. Hydrolysis of the dithioacetal protecting group was effected with mercuric chloride in 90% aqueous methanol at reflux for 15 hr. Under these conditions the initial product, a β-keto acid, underwent decarboxylation to yield **5**. Since it was determined by nmr that the crude product of the hydrolysis–decarboxylation was a mixture of **5** and its methyl ester **6**, the entire mixture was esterified to **6** in methanol containing a catalytic amount of sulfuric acid. The desired cyclohexenonecarboxylic ester was isolated as a mixture of epimers in 58% overall yield from **4**.



(2) E. J. Corey, B. W. Erickson, and R. Noyori, *J. Amer. Chem. Soc.*, **93**, 1724 (1971), and references cited therein.

(3) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971); E. Vedejs and P. L. Fuchs, *ibid.*, **36**, 366 (1971).

(4) F. A. Carey and J. R. Neergaard, *ibid.*, **36**, 2731 (1971).

(5) F. A. Carey and A. S. Court, *ibid.*, **37**, 1926 (1972); D. Seebach, B. T. Grobel, A. K. Beck, M. Braun, and K. H. Geiss, *Angew. Chem., Int. Ed. Engl.*, **11**, 443 (1972).

(6) For a review of reactivity in Diels–Alder reactions see J. Sauer, *ibid.*, **6**, 16 (1967).

(7) C. A. Stewart, *J. Org. Chem.*, **28**, 3320 (1963).

(8) Diels–Alder addition of olefins to a dienyl sulfide has recently been reported: D. A. Evans, C. A. Bryan, and C. L. Sims, *J. Amer. Chem. Soc.*, **94**, 2891 (1972).

Less reactive dienophiles such as diethyl maleate, diphenylacetylene, and *p*-benzoquinone did not react with **1a**. Of the three vinylketene thioacetals examined in this study **1a** was the only one to give an adduct with maleic anhydride. Failure of **1b** and **1c** to react with maleic anhydride is presumably due to electronic and steric effects, respectively.

Experimental Section

Nmr spectra were recorded on a Hitachi Perkin-Elmer R-20 spectrometer in $CDCl_3$ and chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Infrared spectra were measured on a Perkin-Elmer 337 grating instrument as KBr discs for solids and pressed films for liquids. Melting points are corrected and were determined on a Thomas-Hoover apparatus. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionizing potential of 70 eV.

Microanalyses were performed by Alfred Bernhardt, Engelskirchen, West Germany.

Vinylketene thioacetals **1a** and **1b** were previously reported, while 2-[1-methyl-1-(1-cyclohexenyl)]methylene-1,3-dithiane (**1c**) was prepared in 87% yield from 1-acetyl-1-cyclohexene according to the general procedure described in ref 5.

The analytical sample was obtained by preparative tlc to yield **1c** as a colorless liquid: nmr ($CDCl_3$) δ 1.4–1.8 (m, 4), 1.9 (s, 3, CH_3C=), 1.9–2.2 (m, 6), 2.6–3.0 (q, 4, SCH_2), 5.34 (m, 1, vinyl H).

Anal. Calcd for $C_{12}H_{18}S_2$: C, 63.66; H, 8.01. Found: C, 63.74; H, 7.89.

General Procedure for Reactions of 1a–c with Tetracyanoethylene.—Tetracyanoethylene was added to an equal molar amount of the vinylketene thioacetal in methylene chloride (3 ml per 2 mmol of 1) at 25° and the solution was stirred for 15–30 min and evaporated.

2a.—The residue obtained after evaporation was washed with ether to afford the pure adduct in 71% yield: mp 169–170°; nmr ($CDCl_3$) δ 1.60 (d, 3, J = 7 Hz, CH_3CH), 1.90 (s, 3, C=C), 2–4 (m, 7, SCH_2CH_2 and CH_3CH), 5.6 (br s, 1, C=CH).

Anal. Calcd for $C_{15}H_{14}N_4S_2$: C, 57.29; H, 4.48; S, 20.40. Found: C, 57.43; H, 4.35; S, 20.53.

2b.—Purified adduct, mp 183°, was obtained in 83% yield by washing the material remaining after evaporation with ether: nmr ($CDCl_3$) δ 4.40 (s, 1, PhCH), 6.0 (m, 2, HC=CH), 7.45 (s, 5, Ph); mass spectrum m/e (rel intensity) 326 (12), 234 (100), 160 (42).

The analytical sample, mp 183°, was obtained by recrystallization from ether. *Anal.* Calcd for $C_{19}H_{14}N_4S_2$: C, 62.95; H, 3.89; S, 17.70. Found: C, 62.76; H, 3.87; S, 17.90.

2c.—The crude product was purified by preparative tlc on silica gel using ether as the developing solvent to yield white crystals, mp 168–169° (72% yield). The nmr spectrum was characterized by three broad, complex multiplets at δ 1.6–2.4, 2.5–3.2, and 3.3–4 and a doublet (J = 1–2 Hz) at δ 1.99 assigned to the allylic methyl group; mass spectrum m/e (rel intensity) 354 (26), 179 (20), 106 (100), 91 (31).

Anal. Calcd for $C_{18}H_{18}N_4S_2$: C, 60.98; H, 5.12; S, 18.09. Found: C, 60.97; H, 5.20; S, 18.02.

An authentic sample of the adduct of TCNE and **3** was prepared in the same fashion as the adducts of **1** in 77% yield: mp 155°; nmr ($CDCl_3$) δ 3.2 (br, 2, allylic CH_2), 4.3 (br, 1, PhCH), 6.0 (s, 2, vinyl CH), 7.4 (s, 5, Ph).

Anal. Calcd for $C_{16}H_{10}N_4$: C, 74.40; H, 3.90. Found: C, 74.22; H, 3.77.

Reaction of 1a with Maleic Anhydride.—A solution of 4.0 g (21.7 mmol) of **1a** and 2.1 g (21.5 mmol) of maleic anhydride in 50 ml of xylene was refluxed for 3 hr. The xylene solution was concentrated under vacuum. The crystalline adduct which resulted was filtered and washed with ether to yield 3.6 g (60%) of **4**: nmr ($CDCl_3$) δ 1.43 (d, 3, J = 7 Hz, CH_3CH), 1.87 (s, 3, CH_3C=), 1.9–2.2 (m, 2, SCH_2CH_2), 2.5–3.3 (m, 5, SCH_2 and CH_3CH), 3.5 (d, d, 1, J = 8, 5 Hz, HC=CO), 4.06 (d, 1, J = 8 HzHCC=O), 5.75 (br s, 1, C=CH).

The analytical sample was obtained by recrystallization from chloroform–ethanol, mp 114–115°.

Anal. Calcd for $C_{13}H_{16}O_3S_2$: C, 54.90; H, 5.67; S, 22.55. Found: C, 54.97; H, 5.46; S, 22.66.

Conversion of 4 to Methyl 2,3-Dimethyl-4-oxo-3-cyclohexenecarboxylate (6).—A solution of 500 mg (1.75 mmol) of **4** in 45 ml of methanol containing 5 ml of water and 1.05 g (3.9 mmol) of mercuric chloride was refluxed for 15 hr under nitrogen, cooled, and filtered through Celite. The Celite was washed thoroughly with methanol and the combined filtrates were evaporated. The residue (448 mg) exhibited peaks in the nmr at δ 3.7 attributable to a methyl ester and at 9.2 for the carboxylic acid. This product was taken up in 50 ml of methanol, several drops of sulfuric acid were added, and the solution was refluxed for 6 hr. The methanol was removed on the rotary evaporator and the product was taken up in methylene chloride. The solution was washed with water, dried ($MgSO_4$), filtered, and evaporated to yield 317 mg of **6**. The nmr spectrum of this product was identical with that of the purified product (190 mg, 58%) obtained by preparative tlc on silica gel with 75% ether–25% hexane. The nmr spectrum clearly showed that a mixture of epimers was present by the doubling of the $-OCH_3$ and CH_3CH signals: nmr ($CDCl_3$) δ 1.1 and 1.25 (2, d, J = 7 Hz, CH_3CH), 2.0 (2, d, CH_3C=C), 2.5–3 (m, CHC=O and CH_3CH), 3.70 and 3.75 (2, s, OCH_3), and 5.80 (br, s, vinyl H); mass spectrum m/e (rel intensity) 182 (18), 123 (100), 96 (65), 95 (28).

The analytical sample was obtained by preparative glpc on Carbowax at a column temperature of 200°.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.86; H, 7.72.

Registry No.—**1a**, 36744-60-2; **1b**, 36744-61-3; **1c**, 36736-49-9; **2a**, 36736-50-2; **2b**, 36736-51-3; **2c**, 36748-70-6; **3**–TCNE adduct, 36748-71-7; **4**, 36744-62-4; **6**, 36748-72-8.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Ring Contraction in a Synthesis of 2-Piperazinemethanethiol[1]

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The reaction of the disodium salt of *N,N'*-ethylenebis-*p*-toluenesulfonamide (**1**) with 2,3-dibromo-1-propanol has recently been shown to give hexahydro-1,4-bis(*p*-tolylsulfonyl)-1*H*-1,4-diazepin-6-ol[2] (**2**) instead of 1,4-bis(*p*-tolylsulfonyl)-2-piperazinemethanol (**4**) as originally reported[3] and subsequently assumed by other investigators.[4,5] The error was confirmed[2] by a comparison of **2** with an authentic sample of **4** (which was prepared from ethyl 1,4-dibenzyl-2-piperazinecarboxylate[6] in three steps). The intermediacy of *N*-2,3-epoxypropyl-*N,N'*-ethylenebis-*p*-toluenesulfonamide in the formation of **2** was suggested.[2] The firm identity of **2** cast considerable doubt on the structures of intermediates and products in the re-

(1) This investigation was supported by U. S. Army Medical Research and Development Command (Contract No. DADA17-69-C-9033).

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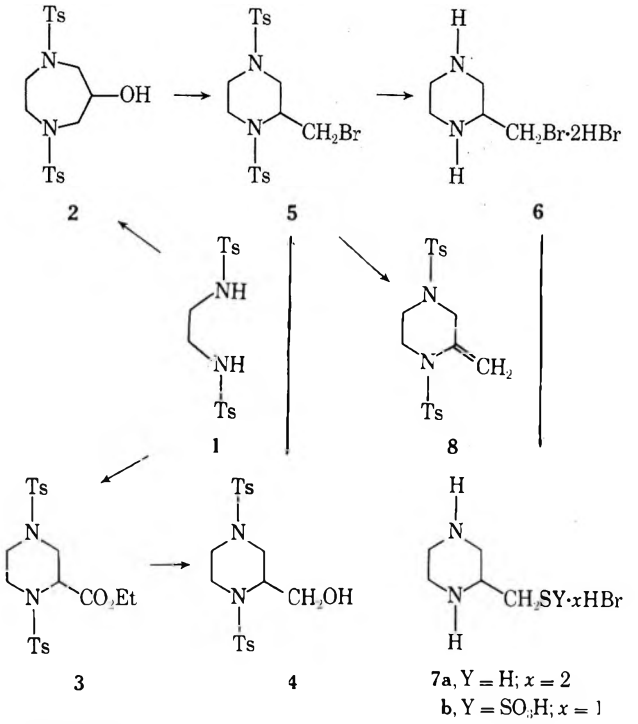
ported[4] synthesis of 2-piperazinemethanethiol dihydrobromide (**7a**) and the corresponding thiosulfate **7b**. The pmr spectrum of a sample of the hydroxy intermediate used in the synthesis of **7a,b** agreed with pmr data reported[2] for authentic **2**. These findings prompted an investigation of other structures in the sequence.

An unambiguous synthesis of **4** from **1** was performed, combining successively (1) the condensation[3a] of the preformed disodium salt of **1** with ethyl 2,3-dibromopropionate in *N,N*-dimethylformamide (DMF) and (2) the lithium aluminum hydride reduction[2] of the resulting ethyl 1,4-bis(*p*-tolylsulfonyl)-2-piperazinecarboxylate (**3**). Treatment of **4** with dibromotriphenylphosphorane[7] afforded 2-(bromomethyl)-1,4-bis(*p*-tolylsulfonyl)piperazine (**5**), which, unexpectedly and fortuitously, was identical (melting point and mixture melting point, ir and pmr spectra) with the product obtained earlier[4] by the treatment of **2** (thought at that time to be **4**) with thionyl bromide.

The pmr spectrum was clearly consistent with **5**. Thus, it was shown that bromodehydroxylation of **2** with thionyl bromide resulted in ring contraction, similar examples of which effected with thionyl chloride[8] and with phosphorus tribromide[9] have recently been reported and for which activated aziridinium intermediates were proposed. The pmr spectrum of the thiol[4] derived from **5** *via* the detosylated bromide **6** was consistent with the originally assigned structure **7a**. In a resynthesis of **5** from **2**, dibromotriphenylphosphorane was shown to be an effective reagent for the rearrangement. An attempted alkylation of the sodium salt of 2-oxazolidinone[10] with **5** resulted in dehydrobromination; the isolated product was shown by elemental and spectral (pmr, mass) analysis to be 2-methylene-1,4-bis(*p*-tolylsulfonyl)-piperazine (**8**).



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Experimental Section[11]

Ethyl 1,4-Bis(*p*-tolylsulfonyl)-2-piperazinecarboxylate (3).—The disodium salt of **1** was prepared by the addition of pulverized **1**[4] (96.0 g, 0.260 mol) to a warm solution of sodium methoxide (28.0 g, 0.518 mol) in methanol (700 ml) and dilution of the resulting clear solution with ether (700 ml): yield 106 g (99%). The salt was suspended in DMF (500 ml), and a solution of ethyl 2,3-dibromopropionate (66.7 g, 0.256 mol) in DMF (500 ml) was added. The mixture was stirred at 90–110° for 3 hr, cooled, and added to water (12 l.). The precipitate that formed was recrystallized twice from ethanol to give **3**, mp 152.5–155° (lit.[2] mp 150.9–154.9°), in 83% yield (75.6 g).

2-(Bromomethyl)-1,4-bis(*p*-tolylsulfonyl)piperazine (5). A. From 4.—Dibromotriphenylphosphorane was prepared by the dropwise addition of a solution of bromine (1.92 g, 12.0 mmol) in acetonitrile (10 ml) to a partial solution of finely divided triphenylphosphine (3.14 g, 12.0 mmol) in acetonitrile (40 ml) at 10–15°. The mixture was allowed to warm to 25°, and **4** (4.24 g, 10.0 mmol) was added. The resulting solution was kept at 25–30° for 2 hr, refluxed for 2 hr, and allowed to cool. The cooled mixture, from which product had begun crystallizing, was treated with water (1.5 ml), stirred for ~10 min, and reheated to boiling. Water (~8.5 ml) was added to the hot solution until solid began forming, and the mixture was left to cool and stand overnight. The crystallized solid was collected and dried *in vacuo* (25–30°, P_2O_5). A small second crop was obtained from the filtrate diluted with water to incipient cloudiness. The two crops (3.47 and 0.37 g, mp of each ~200°) were combined and recrystallized from acetonitrile to give pure **5**, mp 204–206°, in 68% yield (3.29 g): pmr ($CDCl_3$) ~δ 2.0–2.5 (m, 8, includes CH_3 singlets at 2.40 and 2.44, and CH_2Br), 2.9–4.4 (m, 7, NCH), 7.1–7.8 (m, 8, aromatic CH). *Anal.* Calcd for $C_{19}H_{23}BrN_2O_4S_2$: C, 46.81; H, 4.75; N, 5.75. Found: C, 46.93; H, 4.86; N, 5.59. This compound was identical (melting point, mixture melting point, ir, pmr) with the product obtained earlier by the action of thionyl bromide on **2**, which had been erroneously assigned structure **4**.[4]

B. From 2.—Dibromotriphenylphosphorane (12.0 mmol) was prepared in acetonitrile (50 ml) for use *in situ* as described under A, and **2** (4.24 g, 10.0 mmol) was added. The mixture, which contained a small amount of insoluble solid, was stirred at 25–30° for 18 hr and was then refluxed for 6 hr, complete solution occurring shortly after heating was started. Examination of the reaction mixture during the 18-hr and 6-hr periods by thin layer chromatography [Merck silica gel H, ethyl acetate–benzene (1:1), iodine-vapor detection] showed the appearance of **5** during the heating period, but after 4 hr unchanged **2** was still present. The reaction solution was poured into water (200 ml), and the solid that formed was collected and dried *in vacuo* (25–30°, P_2O_5): wt 5.79 g, mp 130–138°. [A small amount (0.56 g) of solid that separated from the filtrate was identified as triphenylphosphine oxide.] Two recrystallizations of the crude solid from acetonitrile gave 1.44 g (29%) of pure **5**, mp 204–206°, whose identity was attested by a comparison (ir, tlc, melting point, mixture melting point) with **5** prepared from **4**. A work-up of the filtrate from the first recrystallization (precipitation by addition of water and recrystallization from acetonitrile) gave a slightly less pure crop (1.35 g, mp 202–204°), which increased the yield to 59%.

2-Methylene-1,4-bis(*p*-tolylsulfonyl)piperazine (8).—A solution of 2-oxazolidinone (0.435 g, 5.00 mmol) in DMF (10 ml) was added dropwise to a stirred suspension of sodium hydride (0.21 g of 57% dispersion in oil, 5.0 mmol) in DMF (8 ml). After 30 min, **5** (2.44 g, 5.00 mmol) and sodium iodide (0.1 g) were added. The mixture was stirred at 25–30° for 4 days, then poured into water to give **8**, mp 148–150°, in 62% yield (1.52 g). The analytical sample, mp 150.5–151.5°, was recrystallized successively from ethyl acetate and ethanol: mass spectrum *m/e*

(11) Melting points were determined with a Mel-Temp apparatus, ir spectra with a Perkin-Elmer 521 spectrometer, pmr spectra with a Varian XL-100-15 spectrometer, and mass spectra with a Hitachi Perkin-Elmer RMU-6D-3 spectrometer. Hexahydro-1,4-bis(*p*-tolylsulfonyl)-1*H*-1,4-diazepin-6-ol (**2**, from 2,3-dibromo-2-propanol) and 1,4-bis(*p*-tolylsulfonyl)-2-piperazinemethanol (**4**) were prepared by slight modifications of literature[2] procedures.

406 (molecular ion); pmr (DMSO-d_6) ~ δ 2.36 (s, 3, CH_3), 2.43 (s, 3, CH_3), 2.8–3.8 (pair of triplets, 4, NCH_2CH_2N), 3.22 [s, 2, $NCH_2C(N)<$], 5.1 (d, 2, $>CH_2$), 7.1–7.7 (m, 8, aromatic CH). *Anal.* Calcd for $C_{19}H_{22}N_2O_4S_2$: C, 56.14; H, 5.45; N, 6.89. Found: C, 56.22; H, 5.27; N, 6.70.

The structure assigned to the previously described[4] 2-piperazinemethanethiol hydrobromide (**7a**) was confirmed by pmr (D_2O, DSS internal standard) data: ~δ 2.8–3.2 (m, 2, CH_2S), 3.1–4.1 (m, 7, NCH).

Registry No.—**5**, 36748-77-3; **7a**, 36748-78-4; **8**, 36748-79-5.

Acknowledgment.—The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute for microanalytical and spectral data and to Mrs. Martha Thorpe for interpretation of pmr data.

A New High Yield Procedure for Thiocyanogen and Thiocyanates

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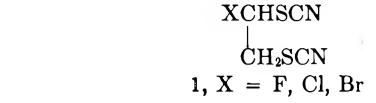
We report here a new high yield procedure for the preparation of thiocyanogen and thiocyanates, and the use of this procedure to synthesize three new haloalkylene bisthiocyanates.

The procedure consisted of the use of a two-solvent system (water and water-immiscible hydrocarbon) for the reaction between a thiocyanate salt and a halogen. The thiocyanogen formed in the aqueous phase was extracted into the hydrocarbon phase. With sodium thiocyanate and chlorine as the reactants, and toluene as the hydrocarbon solvent, 85–90% yields of thiocyanogen were routine. The thiocyanogen solution, after physical separation from the water phase and sodium chloride and without drying, could be used immediately or stored at reduced temperature for subsequent use.

The efficacy of this procedure was undoubtedly due to the presence of the water-immiscible phase during the generation of thiocyanogen, which extracted and preserved the thiocyanogen as it was formed. Until now, anhydrous conditions were generally considered to be essential for the satisfactory preparation of thiocyanogen.[1-3] Although aqueous systems (without a water-immiscible phase) have been tried, the conversions to thiocyanogen were not reported.[4-7]

Many well-known reactions of thiocyanogen have become economically feasible as a result of the two-solvent procedure, which depends on sodium thiocyanate and chlorine rather than the customary silver or lead thiocyanate, and bromine.

Also, a previously unknown reaction, the synthesis of haloalkylene bisthiocyanates,[8] has been carried out for the first time. The fluoro, chloro, and bromo analogs (**1**), crystalline solids with pungent odors, were prepared in good yield by the addition of thiocyanogen, prepared by the two-solvent procedure, to the corresponding vinyl halides, with diisopropyl peroxydicarbonate as the catalyst. Earlier attempts to add thiocyanogen to vinyl bromide and other halogenated olefins had been unsuccessful.[3]



1, X = F, Cl, Br

Experimental Section[9,10]

Preparation of Thiocyanogen Solution.—Addition of 28.9 g (0.407 mol) of gaseous chlorine beneath the surface of a well-stirred mixture of 379 g of toluene, 50 g of water, and 64.9 g (0.800 mol) of sodium thiocyanate over a period of 1 hr with the temperature at 2–8° gave a mixture of yellow toluene layer and wet sodium chloride. After filtration, toluene wash of the cake, and physical separation of the water layer, 475 g of the upper toluene phase was obtained, containing 42.6 g of thiocyanogen, a 90% yield (iodimetric assay). The yellow solution, although wet, was moderately stable at reduced temperature. Thus, in 17 hr at 0–2°, the concentration of such a thiocyanogen solution fell from 0.57 to 0.54 *N*.

Chloroethylene Bisthiocyanate (CET).—To all of the above thiocyanogen solution at 0–5° was added the catalyst solution, 2.15 g (0.0104 mol) of diisopropyl peroxydicarbonate (PPG Industries, Inc.) in 13 g of toluene. After the apparatus was flushed with nitrogen, 28.6 g (0.457 mol) of vinyl chloride was added as a gas beneath the liquid surface at 0–5°. The solution was heated to 50° in 15 min and held at 50–57° for 2 hr. An exotherm lasting 20 min raised the temperature from 50 to 57°. Iodimetric titration showed that less than 2% thiocyanogen remained. The slurry was filtered to remove parathiocyanogen. The yellow filtrate contained 55.1 g of CET, a 77% overall yield based on sodium thiocyanate.

Crystalline CET was recovered by removing the toluene solvent at reduced pressure, mp 46–46.5° (from ethanol). It was soluble in cold methanol, acetonitrile, methylene chloride and benzene, and hot ethanol, and difficulty soluble in hot water and petroleum ether (bp 30–60°).

Anal. Calcd for $C_4H_3ClN_2S_2$: C, 26.89; H, 1.69; N, 15.68; S, 35.89; Cl, 19.85. Found: C, 27.00; H, 1.60; N, 15.84; S, 35.84; Cl, 19.15.

Bromoethylene Bisthiocyanate (BET).—BET was prepared in 70% overall yield by the addition of 62.9 g (0.59 mol) of vinyl bromide to the same quantity of catalyst-containing thiocyanogen solution as above, followed by heating for 1 hr at 35–37°, filtration, and removal of solvent, mp 43.5–44° (from ethanol).

Anal. Calcd for $C_4H_3BrN_2S_2$: C, 21.53; H, 1.35; Br, 35.82; N, 12.56; S, 28.74. Found: C, 21.73; H, 1.25; Br, 36.19; N, 12.58; S, 28.45.

Fluoroethylene Bisthiocyanate (FET).—In order to contain the volatile vinyl fluoride, the reaction was carried out in an autoclave, within a glass liner. Excess vinyl fluoride (14.7 g,

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(7) J. H. Clayton and B. Baun (to the Manchester Oxide Co., Ltd.), U. S. Patent 2,212,175 (1940).

(8) Although the preferred Chemical Abstracts name for such a compound is haloalkylene thiocyanate, there is some precedent for either bis- or di- as a multiplying prefix (K. L. Loening, Chemical Abstracts Director of Nomenclature, private communication).

(9) All melting points are corrected. The ir spectra were recorded on a Perkin-Elmer Model 521 spectrophotometer. The nmr spectra were run on both the Varian A-60 and HA-100 instruments. The uv spectrum was recorded with a Cary 14 spectrophotometer.

(10) Thiocyanogen has been characterized as "probably highly toxic," See N. Irving Sax, "Dangerous Properties of Industrial Materials," 3rd ed, Reinhold, New York, N. Y., 1968, p 1160. No difficulty was experienced in this work, but the toluene solution of thiocyanogen should be considered irritating to the skin, and highly irritating to the eye.

0.32 mol) was added as a liquid to 190 g of frozen benzene solution containing 14.5 g of thiocyanogen and 0.8 g of catalyst at −80°. After heating for 2 hr at 40–54°, under a nitrogen pressure of 625 psi, venting, and removal of solvent, the residue was extracted with methylene chloride to provide a 57% overall yield of crystalline FET, mp 35.5–36° (from ethanol).

Anal. Calcd for $C_4H_3FN_2S_2$: C, 29.62; H, 1.86; F, 11.71; N, 17.28; S, 39.53. Found: C, 29.65; H, 1.57; F, 11.4; N, 17.08; S, 39.19.

Spectra.—The three haloalkylene bisthiocyanates had mostly similar ir spectra with the following bands in common: 2900 (s), 2150–2160 (s, sharp),[11] 1415–1425 (s), 1245 (s), 1150 (m), 900 (s), and 408 cm^{-1} (w). Distinctive bands were seen at 1300 (m), 1010 (m), and 632 cm^{-1} (m) for FET, 702 cm^{-1} (m) for CET, and 660 cm^{-1} (m) for BET.

CET had a weak absorption band in the near-ultraviolet region [ϵ_{243} 151 (in methanol)].

The nmr spectra were all consistent with the proposed structures. For BET and CET, the CH_2's were equivalent, giving only a doublet; the CH was a triplet. FET showed an extra coupling from the fluorine, so that the CH was a doubled triplet, and the CH_2 showed a slight nonequivalence. The CH and CH_2 peak positions and $CHCH_2$ couplings (absolute values) were as follows: BET, δ 5.27, 3.79 (J = 7.0 Hz); CET, δ 5.36, 3.70 (J = 6.7 Hz); FET, δ 6.10, ~3.63 (J = 6.0 Hz). In addition, for FET the CHF coupling was 47.2 Hz.

Registry No.—Thiocyanogen, 505-14-6; CET, 24689-89-2; BET, 26799-59-7; FET, 26799-60-0.

Acknowledgment.—We thank Mr. N. B. Colthup, Mr. J. Koren, Dr. J. E. Lancaster, and Mrs. M. T. Neglia for their assistance in interpreting the ir, uv, and nmr spectra.

(11) Organic thiocyanates (RSCN) show a medium–strong sharp ir band at 2170–2135 cm^{-1} caused by the C≡N stretch vibration. Organic isothiocyanates (RNCS) have a very strong broader ir band at 2150–2050 cm^{-1} caused by the out-of-phase N=C=S vibration. See N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, p 201.

Preparation of the Diels–Alder Adducts of Methyl Vinyl Sulfone and Cyclopentadiene and of Their Dihydro Derivatives[1]

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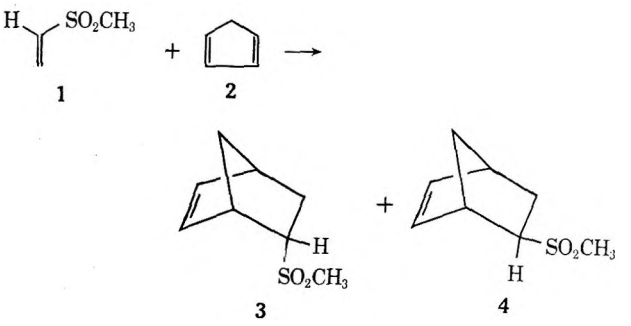
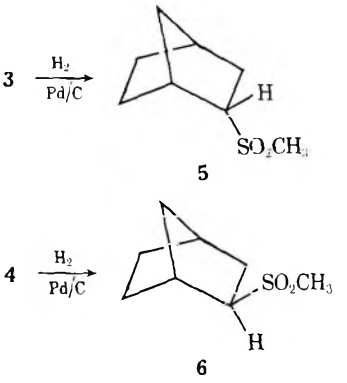
In the course of another problem[2] a need arose for relatively large quantities of the Diels–Alder adducts of methyl vinyl sulfone and cyclopentadiene and the corresponding dihydro derivatives and for a knowledge of the respective stereochemistries in each series. The methyl vinyl sulfone–cyclopentadiene reaction was investigated previously by Snyder,[3] but mention was made only of one adduct isomer, mp 55–56°, and no data or speculation concerning its stereochemistry were reported. Also, the addition of methyl mercaptan to norbornene followed by hydrogen peroxide oxidation has been reported by Davies[4] to afford only *exo*-2-methylsulfonylbicyclo[2.2.1]heptane.

The ambient temperature reaction of methyl vinyl sulfone (1)[5] with cyclopentadiene (2) was monitored by means of nmr, and the formation of two cycloadducts **3** and **4** was observed. Chromatography on silica gel



afforded pure samples of each isomer. In accord with the endo rule[6] and on the basis of chemical shift data, the structure of the major cycloadduct, mp 55–55.5°, was assigned to the *endo*-methylsulfonyl isomer **3**. The $-SO_2CH_3$ nmr absorption of **3** is observed at a higher field than the corresponding absorption of the minor cycloadduct **4**, mp 41.5–42.5°. The shielding of endo protons or of protons attached to endo functional groups in bicyclo[2.2.1]hept-2-enes and inversely the deshielding of exo protons or of protons attached to exo functional groups are well-recognized phenomena.[7] However, care should be taken to ensure that these effects are due predominantly to the anisotropy of the double bond and not to that of the 5–8 σ bond.[8] Thus, removal of the double bond by hydrogenation should result in a downfield shift for the *endo*-methylsulfonyl hydrogens and an upfield shift for the *exo*-methylsulfonyl hydrogens.[7,8] The expected chemical shifts were indeed observed as can be seen in Table I. Further confirmation of the above structural assignments was obtained by comparison of the *exo*-methylsulfonyl isomer **6** with authentic material.[4] The two sulfones were identical in all respects.



(1) Grants from The Research Corp. and The Petroleum Research Fund, administered by The American Chemical Society, are gratefully acknowledged.

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TABLE I
CHEMICAL SHIFT VALUES

Compd no.	$\delta_{TMS}^{CDCl_3}$ (SO_2CH_3)[a]
3	2.798 ± 0.002
5	2.831 ± 0.002
4	2.897 ± 0.002
6	2.814 ± 0.002

[a] Chemical shifts were obtained from average line frequencies and calibrated by the side-band method with the aid of a Hewlett-Packard Model 4204A audiooscillator and a Model 5216A frequency counter.

It is of interest to note that **6** is reported to fail to undergo potassium *tert*-butoxide induced epimerization.[4] We have confirmed this observation and have noted that **5** may be converted readily into **6** under these conditions. While **6** cannot be epimerized, both its methine and methyl hydrogens α to the sulfone moiety readily undergo deuterium exchange.

Thus pure **6** is available *via* the Davies route[4] or *via* cycloaddition of methyl vinyl sulfone with cyclopentadiene followed by hydrogenation of the mixture of **3** and **4** and subsequent epimerization, and pure **5** may be prepared by hydrogenation of pure **3**.

The ease of epimerization of **5** led us to examine the similar reaction with the unsaturated isomers **3** and **4**. Treatment of either isomer with potassium *tert*-butoxide in *tert*-butyl alcohol afforded the identical mixture containing 79 ± 2% of **4** and 21 ± 2% of **3**. Thus **3**, the major product of the Diels–Alder reaction, may be crystallized from the crude reaction mixture, and the minor isomer **4** may be obtained by direct chromatography of the crude mixture or of an enriched mixture obtained by epimerization.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 475 spectrometer. Nmr spectra were measured at 60 Mc using tetramethylsilane as an internal standard unless otherwise stated. All microanalyses were determined by MHW Laboratories, Garden City, Mich., except for the deuterium analysis, which was determined by Mr. Josef Nemeth, Department of Chemistry, University of Illinois.

***endo*- and *exo*-5-Methylsulfonylbicyclo[2.2.1]hept-2-ene (3 and 4).**—To a magnetically stirred solution of 1.70 g (25.7 mmol) of cyclopentadiene in 50 ml of carbon tetrachloride was added 2.65 g (25.0 mmol) of methyl vinyl sulfone. The reaction vessel was sealed, and the mixture was stirred for 4 days at ambient temperature. The solvent was removed to yield 4.22 g of a viscous pale yellow oil. The crude adduct was triturated with 20 ml of petroleum ether (bp 30–60°) to give 3.98 g (23.1 mmol, 92.4%) of a semisolid mixture of the two epimers. This mixture was chromatographed on silica gel with increasing percentages of ether–petroleum ether to give 1.06 g (28% of the mixture) of *exo*-5-methylsulfonylbicyclo[2.2.1]hept-2-ene, a colorless viscous oil, bp 94.5° (0.10 mm), which subsequently solidified, mp 40.5–41.5°. Recrystallization from chloroform–*n*-hexane gave white plates: mp 41.5–42.5°; $\nu_{max}^{CCl_4}$ strong 1318 and 1141 cm^{-1} (SO_2); weak 3065 (HC=C), 2985, 1337, and 1296 cm^{-1}; near-ir λ_{max}^{EtOH} 1.657 μ (ϵ 0.637); $\delta_{TMS}^{CDCl_3}$ 1.30–2.30 (m, 4, methylene), 2.65–2.95 (m, 1, $>CHSO_2CH_3$), 2.897 (s, 3, SO_2CH_3), 2.90–3.18 (m, 1, bridgehead), 3.20–3.40 (m, 1, bridgehead), 6.02–6.40 (seven-line pattern, 2, HC=CH).

Anal. Calcd for $C_8H_{12}O_2S$: C, 55.79; H, 7.02; S, 18.61. Found: C, 55.69; H, 6.97; S, 18.50.

Further elution of the column gave 2.79 g (72% of the mixture) of *endo*-5-methylsulfonylbicyclo[2.2.1]hept-2-ene as white crystals, mp 54–55°. Recrystallization from chloroform–*n*-hexane gave white plates: mp 55.0–55.5° (lit.[3] mp 55–56°); $\nu_{max}^{CCl_4}$ strong 1321 (with a shoulder at 1316, SO_2) and 1143 cm^{-1} (SO_2); weak 3065 (HC=C), 1337, 1286, and 1124 cm^{-1}; near-ir λ_{max}^{EtOH} 1.657 μ (ϵ 0.569); $\delta_{TMS}^{CDCl_3}$ 1.17–2.40 (m, 4, methylene), 2.798 (s, 3, SO_2CH_3), 2.90–3.17 (m, 1, bridgehead), 3.20–3.45 (m, 1, bridgehead), 3.40–3.75 (m, 1, $>CHSO_2CH_3$), 5.97–6.40 (eight-line pattern, 2, HC=CH).

Anal. Calcd for $C_8H_{12}O_2S$: C, 55.79; H, 7.02; S, 18.61. Found: C, 55.90; H, 6.99; S, 18.60.

Hydrogenation of *endo*- and *exo*-5-Methylsulfonylbicyclo[2.2.1]hept-2-ene.—A solution of 500 mg (2.91 mmol) of *endo*-5-methylsulfonylbicyclo[2.2.1]hept-2-ene in 30 ml of ethyl acetate was hydrogenated over 10% palladium on powdered charcoal (30 psi) at ambient temperature for 1 hr. The catalyst was removed by filtration, and the solvent was evaporated to afford 490 mg (2.81 mmol, 96.9%) of white crystals, mp 72–74°. Recrystallization from carbon tetrachloride–*n*-hexane gave *endo*-2-methylsulfonylbicyclo[2.2.1]heptane as white plates: mp 73–75°; $\nu_{max}^{CCl_4}$ strong 1328, 1315, and 1148 cm^{-1}; medium 2970 cm^{-1}; weak 2882, 1279, and 1119 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.17–2.60 (m, 9, methylene and bridgehead), 2.61–2.90 (m, 1, bridgehead), 2.831 (s, 3, SO_2CH_3), 3.11–3.58 (m, 1, $>CHSO_2CH_3$).

Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.10; S, 18.40. Found: C, 55.03; H, 8.10; S, 18.30.

The same procedure was carried out using the *exo*-methylsulfonyl isomer to give 0.5 g (2.87 mmol, 95.3%) of white crystals, mp 71–72°. Recrystallization from carbon tetrachloride–*n*-hexane gave *exo*-2-methylsulfonylbicyclo[2.2.1]heptane as white crystals: mp 75–76.5° (lit.[4] mp 75°); $\nu_{max}^{CCl_4}$ strong 1322, 1316, and 1147 cm^{-1}; medium 2968 and 1332 cm^{-1}; weak 2880, 1277, 1161, and 947 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.02–2.29 (m, 8, methylene), 2.29–2.57 (m, 1, bridgehead), 2.814 (s, 3, SO_2CH_3), 2.66–3.11 (m, 2, bridgehead and $>CHSO_2CH_3$).

Deuteration of *exo*-2-Methylsulfonylbicyclo[2.2.1]heptane.—A mixture of 1.00 g (5.74 mmol) of *exo*-2-methylsulfonylbicyclo[2.2.1]heptane, 35 ml of 10% sodium deuterioxide in deuterium oxide, and 10 ml of tetrahydrofuran was refluxed for 6 days under a nitrogen atmosphere. The tetrahydrofuran was evaporated, and the residual solution was extracted with chloroform. The chloroform layer was washed with deuterium oxide and dried over anhydrous magnesium sulfate. Removal of the solvent afforded 0.812 g (4.55 mmol, 79.3%) of pale yellow oil, which subsequently solidified. The crude product, on recrystallization from chloroform–*n*-hexane, afforded 0.742 g (4.16 mmol, 72.5%) of *endo*-2-deuterio-2-trideuteriomethylsulfonylbicyclo[2.2.1]heptane as white plates: mp 79.5–80.5°; $\nu_{max}^{CCl_4}$ strong 1312 and 1146 cm^{-1}; medium 2965, 1158, and 696 cm^{-1}; weak 2878 and 1297 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.00–2.26 (m, 8, methylene), 2.30–2.60 (m, 1, bridgehead), 2.67–2.92 (m, 1, bridgehead).

Anal. Calcd for $C_8H_{10}D_4O_2S$: 28.6 atom % excess D. Found: 27.9 atom % excess D.

Base-Catalyzed Epimerization of *endo*- and *exo*-2-Methylsulfonylbicyclo[2.2.1]heptane (5 and 6).—To a solution of 300 mg (1.72 mmol) of *endo*-2-methylsulfonylbicyclo[2.2.1]heptane in 10 ml of dry *tert*-butyl alcohol was added 20 ml of 0.60 *N* potassium *tert*-butoxide in *tert*-butyl alcohol. The solution was refluxed for 24 hr and then quenched with water. After removal of the *tert*-butyl alcohol, the aqueous mixture was extracted with chloroform. Evaporation of the solvent afforded 274 mg (1.57 mmol, 91.4%) of pale yellow crystals. Comparison of nmr and ir spectra and a mixture melting point determination indicated that the product was exclusively the *exo*-methylsulfonyl isomer. The same procedure using 300 mg (1.72 mmol) of the exo isomer gave 282 mg (1.62 mmol, 94.0%) of the starting sulfone.

Base-Catalyzed Epimerization of *endo*- and *exo*-5-Methylsulfonylbicyclo[2.2.1]hept-2-ene (3 and 4).—Under a nitrogen atmosphere a solution of 300 mg (1.74 mmol) of *endo*-5-methylsulfonylbicyclo[2.2.1]hept-2-ene in 10 ml of 0.60 *N* potassium *tert*-butoxide in *tert*-butyl alcohol was refluxed for 7 days and then quenched with water. After removal of the *tert*-butyl alcohol by rotary evaporation, the aqueous mixture was extracted with chloroform. The chloroform layer was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 214 mg (1.24 mmol, 71.3%) of a pale yellow oil consisting of 79 ± 2% *exo*- and 21 ± 2% *endo*-methylsulfonyl isomers.

Registry No.—**1**, 3680-02-2; **2**, 542-92-7; **3**, 35495-35-3; **4**, 35495-36-4; **5**, 36736-13-7; **6**, 24584-19-8; *endo*-2-deuterio-2-trideuteriomethylsulfonylbicyclo[2.2.1]heptane, 36736-15-9.

A Simultaneous Diels–Alder and Friedel–Crafts Reaction[1]

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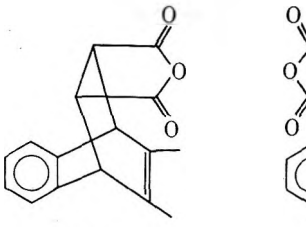
In the condensation of 2,3-dimethylnaphthalene with maleic anhydride in the presence of aluminum chloride four Diels–Alder adducts and three Friedel–Crafts condensation products are theoretically possible. In examining this reaction we have found that two adducts (**1** and **2**) and one condensation product (**3**) are formed.



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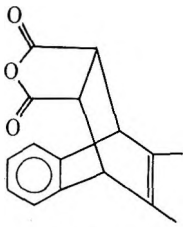
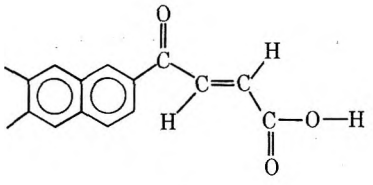
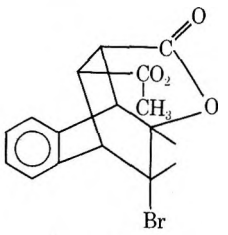


2 (exo)



3



4

So far this seems to be the first system found where maleic anhydride is involved in competing Diels–Alder and Friedel–Crafts reactions although these concurrent condensations have been noted between dicyanoacetylene and benzene.[3]

The thermal reaction of 2,3-dimethylnaphthalene and maleic anhydride was investigated by Kloetzel and Herzog who obtained a product melting at 177–178°.[4] They showed that addition had occurred at the 1,4 positions of the methyl-substituted, more electron-rich ring of the naphthalene but left unsettled whether their material was mainly **1** or **2**.

Yates and Eaton found that this Diels–Alder reaction was accelerated by aluminum chloride and obtained a 40% yield of product melting at 175–178° dec.[5] They converted their material into a bromolactone **4** and assigned structure **1** to the adduct.

Since a closely related keto acid on treatment with lead tetraacetate has been found to give a keto lactone *via* a carbonium ion rearrangement[6] the exo–endo assignment made by Yates and Eaton appeared in doubt if **2** gave a bromonium ion rearrangement. The work was reinvestigated, but no rearrangement was found. However, it was found that both the thermal reaction and the aluminum chloride catalyzed reaction gave two adducts, one melting at 193–195° and the other melting at 176–177°. Although the melting point of the latter corresponded to that reported for **1** by Yates and Eaton, pmr data indicated its structure was **2** and the higher melting isomer was **1**.

The pmr spectra showed that each compound had four aromatic protons corresponding to structures **1** and **2** and not the other two possible adducts. The higher melting adduct had the more shielded bridge protons which indicated they were in the shielding cone of the benzene moiety corresponding to **1**. Williams[7] has studied pmr spectra of rigid cyclic ketones in deuteriochloroform and noted how various peaks shift in going to a benzene solution. His work suggested that a similar effect might be found in the spectra of rigid cyclic anhydrides and would enable one to distinguish between adducts such as **1** and **2**. The complexing in benzene solution leads one to predict that the methyl groups in **1** would have greater shifts due to solvent shielding in going from chloroform to benzene, but bridgehead and bridge proton shifts would be almost identical. The data obtained are given in the table below and the solvent shifts were consistent with assigned structures.

TABLE I

Proton	Adduct[a]	Observed resonance, cps $CDCl_2$	Observed resonance, cps C_6H_6	Shift
Bridge	a	197	145	52
	b	205	155	50
Bridgehead	a	253	230	23
	b	247	226	21
Methyl	a	108	88	20
	b	110	80	30

[a] a = higher melting adduct; b = lower melting adduct.

The structures of the two adducts were also checked chemically by lactonization studies. The higher melting adduct was subjected to an iodolactonization reaction and gave two products, one melting at 167° and the other at 316°. The lower melting product gave a positive Beilstein test, slowly produced a violet color in acetic acid, and gave upon stirring with powdered zinc in acetic acid the starting anhydride. This substance was assigned the iodolactone structure **5**. The higher melting product gave a negative Beilstein test and a single ir carbonyl absorption at 1776 cm^{-1} which is characteristic of a γ-lactone. Therefore this compound was assigned structure **6**.

The lower melting adduct would not undergo lactone formation but yielded its dicarboxylic acid.

Both adducts were converted into monomethyl esters by warming with methanol. These esters were

(1) The first group of workers investigated the condensation of maleic anhydride and 2,3-dimethylnaphthalene to get suitable starting materials for the synthesis of compounds of pharmacological interest while the second investigated the reaction since they felt the structure proof of the reported product seemed ambiguous. In the course of this research it was discovered that the two independent investigations overlapped in part as well as supplemented each other and a joint publication seemed desirable.

(2) National Science Foundation Summer Research Participant, 1966 and 1968.

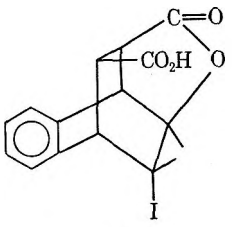
(3) E. Ciganek, *Tetrahedron Lett.*, **No. 34**, 3321 (1967).

(4) M. C. Kloetzel and H. L. Herzog, *J. Amer. Chem. Soc.*, **72**, 1991 (1950).

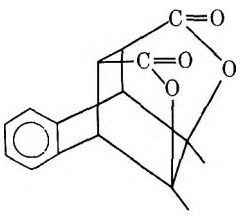
(5) P. Yates and P. Eaton, *ibid.*, **82**, 4436 (1960).

(6) C. M. Cimarusti and J. Wolinsky, *ibid.*, **90**, 113 (1968).

(7) D. H. Williams, *Excerpta Med. Found. Int. Congr. Ser.*, **No. 132**, 159 (1966).



5



6

then treated with iodine in a basic solution. The half-ester from the higher melting adduct quickly discharged the iodine color and gave an iodolactone whereas the half-ester of the lower melting adduct did not react with iodine in the presence of sodium carbonate.

The higher melting adduct was converted into a diacid and then to a bromolactonic acid which on treatment with diazomethane gave an ester whose melting point checked that reported by Yates and Eaton for **4**. It appears that material reported earlier[3,4] were mixtures of **1** and **2**.

Since the resonance of the methyl groups in **1** and **2** distinctly differed, the Diels–Alder reaction could be followed by pmr. In both the thermal and the aluminum chloride catalyzed reaction the ratio of the two adducts were found to be 2:1 in favor of the higher melting adduct. When either adduct alone was heated in boiling benzene for a week, the pmr spectra showed a slow formation of 2,3-dimethylnaphthalene in each case but the other adduct was not detectable. This indicated the adduct ratio was due to kinetic control and one isomer was not accumulating owing to a readily reversible reaction in boiling benzene.

The finding that the adduct ratio was approximately the same in both the thermal and the catalyzed reaction is not in agreement with the observation that the proportion of the endo adduct is enhanced by catalysis with aluminum chloride.[8]

It is of interest that in the competing Friedel–Crafts and Diels–Alder reaction different rings are attacked. In the first reaction a steric factor appears to overrride electronic considerations important in the latter reaction. The planes of the reactants need not be parallel in the transition state of the Friedel–Crafts reaction as they do in the Diels–Alder reaction, and it is doubtful the two reactions have similar transition states.

The keto acid **3** coming from the aluminum chloride catalyzed reaction was a yellow solid whose pmr spectrum indicated a trans double bond. Hydrogenation of the acid gave the known β-2(6,7-dimethylnaphthoyl)-propionic acid.[9]

Experimental Section

Nmr spectra were obtained with Varian A-60 and A-60A spectrometers. Spectra were obtained from 16% solutions in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. Melting points were measured in a copper block as well as with standardized thermometers. Analyses were performed in St. Louis or by Galbraith Laboratories, Knoxville, Tenn.

endo-**1,4-(2′,5′-Diketo-3′,4′-tetrahydrofurano)-2,3-dimethyl-1,4-dihydronaphthalene** (1).—To a filtered solution of 39 g (0.25 mol) of 2,3-dimethylnaphthalene and 29 g (0.30 mol) of maleic anhydride in 1.6 l. of methylene chloride was added 33 g (0.25 mol) of anhydrous aluminum chloride over a 1–1.5-hr period. After stirring the mixture for an additional 3 hr, tetrahydrofuran was cautiously added to it until the deep red coloration of the solution was removed. The resulting solution was evaporated to about 500 ml and cooled overnight. The viscous mixture was diluted with an equal volume of cold acetone and filtered. The product was washed with acetone and air-dried. In four runs, yields ranged from 13 to 19%: mp 193–195°, nmr ($CDCl_3$) δ 1.80 (s, 6 H), 3.28 (m, 2 H), 4.20 (m, 2 H), 7.25 (m, 4, ArH); ir (mull) 1835 (C=O, asymmetric), 1754 cm^{-1} (C=O, symmetric).

Anal. Calcd for $C_{15}H_{14}O_3$: 75.57; H, 5.55. Found: C, 75.28; H, 5.61.

2,3-Dimethylnaphthalene (15.6 g) and maleic anhydride (19.6 g) were refluxed in 100 ml of benzene. Samples were removed, and the ratio of the adducts and percentage of reactions given in the discussion were calculated from integration of the methyl peaks. When samples of the purified adducts were heated in benzene for a week, more 2,3-dimethylnaphthalene was produced from 1 than from **2**.

exo-**1,4-(2′,5′-Diketo-3′,4′-tetrahydrofurano)-2,3-dimethyl-1,4-dihydronaphthalene** (2).—A 1000-ml erlenmeyer flask covered by a watch glass containing 104 g (0.66 mol) of 2,3-dimethylnaphthalene and 600 g (6.12 mol) of maleic anhydride was heated on a steam bath for 2 days. To the hot reaction mixture enough water was added to form a mushy layer on top of the water. The crude product was collected by filtration, washed with hot water and air-dired, and then washed with hot benzene and dried: mp 178–180°; nmr ($CDCl_3$) δ 1.80 (s), 1.82 (s), 3.28 (m), 3.41 (m), 4.11 (m), 4.22 (m), 7.25 (m). The mixture was placed in 800 ml of benzene and heated 10 min; any insoluble matter was removed. The filtrate was cooled to 50–60° and filtered at that temperature to give 3.3 g (2%), mp 175–176°, of exo anhydride **2**. Yields of **2** were increased to a maximum of 19% by using the filtrate from previous runs as the recrystallization solvent: nmr ($CDCl_3$) δ 1.82 (s, 6 H), 3.41 (m, 2 H), 4.11 (m, 2 H), 7.20 (s, 4 ArH); ir (mull) 1835 (C=O, asymmetric), 1754 cm^{-1} (C=O, symmetric).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.36; H, 5.63.

Iodolactonization of 1 in Aqueous Potassium Hydroxide.—The endo anhydride (15.70 g, 0.0616 mol) was placed in 1100 ml of 1% aqueous potassium hydroxide and the solution boiled until almost homogeneous. The few remaining undissolved crystals were removed by filtration. The solution was cooled to room temperature; the pH was adjusted with 6 *N* hydrochloric acid to 7.3 and 21 g (0.250 mol) of sodium bicarbonate added. To the resulting solution was added 120 ml of a solution of 18.0 g (0.0708 mol) of iodine and 37.0 g (0.222 mol) of potassium iodide This mixture was left to stand in the dark for 1 day. The resulting solid was filtered, washed with water, and air-dried to yield 3.5 g of the dilactone (**6**) (18.7%), mp 315–319°, which was recrystallized from acetonitrile to give 2.8 g of large colorless crystals, mp 315–316°, ir (mull) 1775 cm^{-1} (C=O, lactone).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.83; H, 5.35.

To the filtrate from the iodolactonization was added 6 *N* hydrochloric acid to pH 4. The resulting solid was heated with acetone, filtered, and dried, giving 4.6 g (22.4%) of iodolactone (**5**), mp 161–163°, which was recrystallized (methanol) to give 3.0 g of product, mp 166–167°. The analytical sample was prepared by washing with dilute hydrochloric acid, followed by warm water. It was then air-dried and recrystallized (methanol) giving a white solid, mp 171–173° (sealed tube), ir (mull) 1775 (C=O, lactone), 1680 cm^{-1} (C=O, carboxylic acid).

Anal. Calcd for $C_{16}H_{15}IO_4$: C, 48.26; H, 3.80. Found: C, 48.50; H, 4.03.

Attempted Iodolactonization of 2 in Aqueous Potassium Hydroxide.—The adduct **2**, mp 175–176°, was subjected to the same iodolactonization as above. The reaction mixture was adjusted to pH 4 with 6 *N* hydrochloric acid. The resulting solid was filtered, washed with water, and dried to yield 13.35 g (82.4% yield) of a white solid, mp 180–185°. It was recrystallized from methanol giving 10.0 g of the diacid of **2**, mp 241–243° (sealed tube). The analytical sample was prepared by washing with dilute hydrochloric acid, followed by warm water, air-dried, and recrystallized (methanol) to give a white solid, mp 241–243° (sealed tube).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.43; H, 6.38.

(8) T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 2032 (1966).

(9) R. H. Martin and J. Senders, *Bull. Soc. Chim. Belg.*, **64**, 221 (1955).

Preparation of the Diacid of 2.—The exo anhydride (**2**), 5.0 g (0.0196 mol), was dissolved in 500 ml of boiling 1% aqueous potassium hydroxide, filtered, and cooled to room temperature. The solution was adjusted to a pH of 4 with 6 *N* hydrochloric acid. The resulting mixture was filtered, washed with water, and air-dried, giving 4.5 g (84%) of a colorless solid, mp 242–244° (sealed tube). This substance was identical with the product of the attempted iodolactonization of **2**.

Zinc Reduction of the Iodolactone (5).—Exactly 1.0 g (0.0025 mol) of the iodolactone (**5**) was dissolved in 250 ml of glacial acetic acid. Excess zinc dust (0.64 g, 0.076 g-atom) was added, and the suspension was stirred for 10 hr. The unconsumed zinc was removed and the filtrate diluted with water to the cloud point. The solution was heated until homogeneous, cooled, and then filtered. The resulting white crystals were washed with cold glacial acetic acid and air-dried giving 0.25 g (39%) of the endo anhydride (**1**), mp 193–195°.

Half-Esters.—A 0.21-g sample of the exo anhydride, mp 175–177°, was heated in methanol until all of the solid dissolved. Evaporation of the 10 ml of solvent to dryness gave 0.25 g of the exo half-ester: mp 169–172°; pmr ($CDCl_3$) 1.77 (s, 6 CH_3), 3.10 (d, 2, J = 1 Hz), 3.38 (s, 3, OCH_3), 3.32 (d, 2, J = 1 Hz), and 7.20 (m, 4, ArH).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.19; H, 6.27.

The higher melting endo adduct was similarly converted into a half-ester, mp 187–189° (lit.[5] mp 184–185°). The pmr of this half-ester was similar to that of the exo isomer, but no coupling between the bridge and bridgehead protons was observed and the integration suggested the acidic proton might lie in the aromatic region: pmr ($CDCl_3$) 1.83 (s, 6) 3.00 (s, 2), 3.64 (s, 3), 3.92 (s, 2), 7.18 (m, 4.6).

The half-esters were dissolved in 5 ml of 5% sodium carbonate and treated with an iodine stock solution.[10] The exo half-ester (0.18 g) did not decolorize the first four drops of iodine, and 0.12 g was recovered unchanged. When 0.37 g of the endo half-ester, mp 187–189°, was similarly treated, the iodine was immediately decolorized and a precipitate formed: yield 0.13 g; mp 105–110° dec; pmr ($CDCl_3$) 1.83 (s, 3), 2.35 (s, 3), 2.95 (m, 2), 3.7 (m, 1), 3.80 (s, 3), 4.17 (d, 1, J = 1 Hz), 7.34 (m, 4, ArH).

Anal. Calcd for $C_{17}H_{17}IO_4$: C, 49.53; H, 4.16. Found: C, 49.31; H, 3.99.

A 2-g sample of the endo anhydride was heated in 40 ml of 5% sodium carbonate until solution was effected. Cooling, acidification, and drying gave 2.10 g of a solid; 1 g of this acid was added to 75 ml of 0.1 *N* sodium bicarbonate. This solution was diluted with 75 ml of water and filtered. Bromine was added dropwise to the filtrate until the bromine color persisted. After 30 min the solution was acidified, decolorized with a trace of sodium bisulfite, and filtered, yield 0.90 g, mp 215–218°. Recrystallization from ethanol did not improve the product: pmr (acetone-d_6) 1.61 (s, 3), 2.05 (s, 4), 2.93 (m, 2), 4.01 (m, 2), 7.36 (m, 4); ir 1770 cm^{-1} (C=O, lactone).

Anal. Calcd for $C_{16}H_{15}BrO_4$: C, 54.70; H, 4.27. Found: C, 54.49; H, 4.19.

A solution of 0.35 g of this bromolactone acid was treated with an ethereal solution of diazomethane. The product was recrystallized from ethanol and gave 0.20 g of solid, mp 191–193°. A mixture of this solid and a sample of the methyl bromolactone (lit.[5] mp 191.5–192°) prepared by the method of Yates and Eaton[6] melted without depression.

Preparation of 3.—A mixture of 3.9 g of a 2,3-dimethylnaphthalene, 2.5 g of maleic anhydride, and 3.4 g of aluminum chloride in 400 ml of methylene chloride was allowed to react at room temperature. After decomposition of the complex with acid, 10% sodium carbonate was used to make the solution basic and extract a yellow acid. Acidification, filtration, and recrystallization from acetic acid gave 0.70 g of **3**: mp 188–189°; pmr (dimethyl sulfoxide-d_6) 2.40 (s, 6), 6.68 (d, 1, J = 16 Hz), 7.61 and 7.83 (4), 8.00 (d, 1, J = 16 Hz), 8.50 (s, 1); ir (KBr) 1760, 1690 (C=O, acid), 1670 cm^{-1} (C=O, ketone). The analytical sample melted at 190–191° to give a red liquid.

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.35; H, 5.47.

Hydrogenation of 0.25 g of the acid over 10% palladium on charcoal gave 0.16 g of white crystals, mp 182–183 dec (lit.[9] mp 179–180°). Authentic material was prepared by the method of Morten and Senders, but the use of methylene chloride in place of nitrobenzene as solvent for the aluminum chloride, 2,3-dimethylnaphthalene, and succinic anhydride gave much less tar and the product melted at 183–184° dec. A mixture of this material and that from the hydrogenation melted at 183–184° dec, and the products had identical spectra.

Analysis of the material left from the extraction of **3** showed a 33% yield of **1** and **2** in which the ratio of **1** to **2** was 2:1.

Registry No.—**1**, 36736-37-5; **1** half-ester iodide, 36808-03-4; **1** bromolactone, 36808-04-5; **2**, 36736-38-6; **2** diacid, 36808-06-7; **2** half-ester, 36807-55-3; **3**, 36807-56-4; **5**, 36807-57-5; **6**, 36803-78-8.

Acknowledgment.—This investigation was supported in Missouri through Contract No. DA 18-108-CML-6601 and DA 18-035-AMC-382A from the U. S. Army Research and Development Laboratories, Edgewood Arsenal, Maryland.

(10) C. S. Rondestvedt, Jr., and C. D. Ver Nooy, *J. Amer. Chem. Soc.*, **77**, 4878 (1955).

The Utilization of Magnesium Enolates in the Michael Reaction

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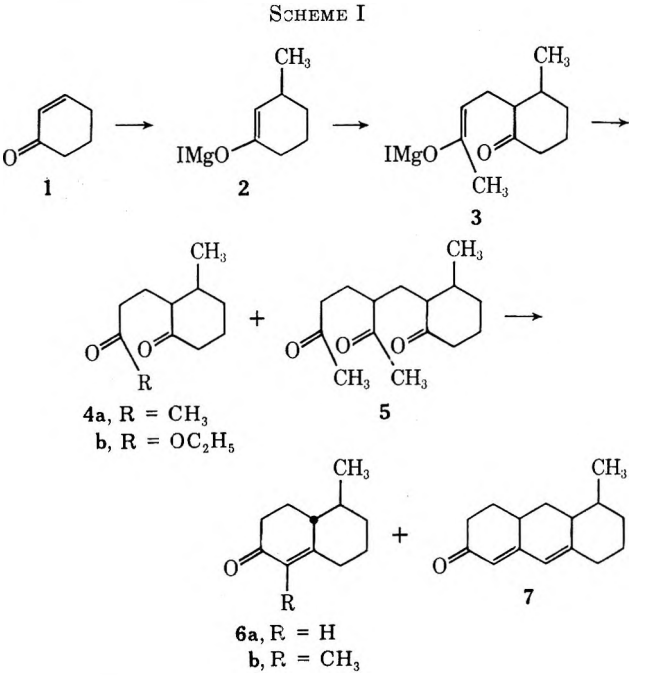
The Michael reaction of magnesium enolates has recently been demonstrated to be a potential side reaction in the conjugate addition of Grignard reagents to α,β-unsaturated ketones.[2] We wish to report the application of this observation to the stereospecific synthesis of 2,3-disubstituted cyclohexanones and 1,5-substituted $\Delta^{1,9}$-octal-2-one derivatives.

SCHEME I



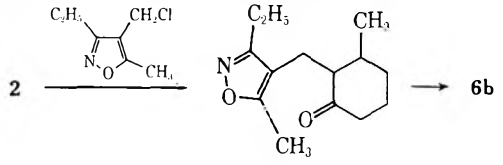
(1) National Science Foundation Undergraduate Research Participant, Summer 1972.

(2) R. A. Kretchmer, *J. Org. Chem.*, **37**, 2744 (1972); (b) R. A. Kretchmer, *ibid.*, **37**, 2747 (1972); (c) E. P. Kohler and W. D. Peterson, *J. Amer. Chem. Soc.*, **55**, 1073 (1933).

An ether solution of magnesium enolate **2** was generated by the cuprous chloride catalyzed addition of methylmagnesium iodide to 2-cyclohexenone (**1**) (Scheme I). Addition of methyl vinyl ketone then afforded a crude product which was treated with KOH in aqueous methanol to give **6a** in 11% overall yield. In addition, dienone **7** was also isolated in 14% yield. The relatively low yield of **6a** presumably reflects the fact that the initially formed Michael adduct **3** may react further with methyl vinyl ketone to give products such as **5** instead of **4a**. The formation of dienone **7**, which would result from base-catalyzed cyclization of **5**, appears to confirm this latter process.

Reaction of magnesium enolate **2** with ethyl vinyl ketone followed by base treatment afforded **6b** in 14% overall yield. The structure of **6b** was confirmed by alternate synthesis. This was accomplished by alkylation of 2[3] with 5-methyl-3-ethyl-4-chloromethylisoxazole[4] in the presence of hexamethylphosphoramide to give **8**, which was converted to **6b** by Stork's annelation procedure.[5]

In addition, the Michael reaction of **2** with ethyl acrylate was found to afford a 17% yield of keto ester **4b**. Although the yields of **4b**, **6a**, and **6b** are modest, this is mitigated by the stereospecificity, speed, and simplicity of the reaction sequence.



8

Experimental Section[6]

Preparation of 5-Methyl-$\Delta^{1,9}$-octal-2-one (6a).—A solution of methylmagnesium iodide was prepared under nitrogen by dropwise addition of a solution of 13.068 g (92.1 mmol) of methyl iodide in 150 ml of anhydrous ether into a flask containing 2.143 g (0.0881 g-atom) of magnesium turnings over a period of 25 min with stirring at ice-bath temperature. After the addition was completed, stirring was continued at room temperature for 2 hr. The mixture was then cooled to ice-bath temperature and 0.411 g (4.15 mmol) of cuprous chloride was added. A solution of 7.711 g (80.2 mmol) of 2-cyclohexenone (**1**) in 150 ml of anhydrous ether was next added dropwise over a period of 1.3 hr, with stirring and at ice-bath temperature. When addition was completed, a solution of 5.623 g (80.2 mmol) of methyl vinyl ketone in 30 ml of anhydrous ether was added rapidly in one portion. After stirring at room temperature for 1.5 hr, the mixture was treated with 200 ml of saturated NH_4Cl solution. The ether layer was separated and washed six times with 100-ml portions of water and once with 100 ml of saturated NaCl solution, and concentrated *in vacuo* to give 11.7 g of amber oil, ir (neat) 1706 cm^{-1}.

The crude product was dissolved in 300 ml of methanol and 15 ml of 45% aqueous KOH. The resulting mixture was refluxed under nitrogen for 20 hr. After cooling, the mixture was diluted with 300 ml of water and extracted with ether. The ether extract was washed with water, dilute HCl, and saturated NaCl solution, and dried. Concentration *in vacuo* followed by distillation through a 10-cm Vigreux column afforded 1.456 g (11%) of enone **6a** as a colorless oil, bp 84–86° (0.5 mm) [lit.[3a] bp 71–76° (0.1 mm)], which was identified by spectroscopic comparison with an authentic sample.[3a] The 2,4-dinitrophenylhydrazone had mp 190.5–192.5° and was undepressed upon admixture with that prepared from authentic 5-methyl-$\Delta^{1,9}$-octal-2-one.[3a]

The fractional distillation also afforded 2.401 g (14%) of dienone **7** as a yellow solid, bp 100–125° (0.5 mm). Material from a similar reaction was recrystallized twice from ether–hexane to give the analytical sample as a pale yellow solid: mp 102.0–103.5°; uv max (EtOH) 293 nm (ϵ 29,000); ir (CCl_4) 1662 (α,β-γ,δ-unsaturated C=O), 1622 (C=C), and 1588 cm^{-1} (C=C); nmr (CCl_4) δ 1.04 (3 H, br, W_H = 4.7 Hz, $CHCH_3$), 5.60 (1 H, br, W_H = 4.9 Hz, vinyl CH), and 5.97 (1 H, br, W_H = 5.3 Hz, vinyl CH); mass spectrum (70 eV) *m/e* 216 (M^+).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.38; H, 9.47.

Preparation of 1,5-Dimethyl-$\Delta^{1,9}$-octal-2-one (6b). A. From 2-Cyclohexenone by Isoxazole Annelation.—A solution of methylmagnesium iodide in 400 ml of ether was prepared by reaction between 28.703 g (0.202 mol) of methyl iodide and 5.140 g (0.211 g-atom) of magnesium turnings. To this was added 0.551 g (5.6 mmol) of cuprous chloride and the mixture was cooled at ice bath temperature. A solution of 17.697 g (0.184 mol) of 2-cyclohexenone (**1**) in 400 ml of ether was then added dropwise, over a period of 3 hr, with mechanical stirring, and under nitrogen. When addition was complete, a solution of 30.804 g (0.193 mol) of 5-methyl-3-ethyl-4-chloromethylisoxazole,[4] bp 109.0–111.0° (13 mm), in 90 ml of hexamethylphosphoramide was added. The resulting mixture was stirred at ice-bath temperature for 1 hr and at room temperature for an additional 14 hr. The mixture was then treated with 400 ml of saturated NH_4Cl solution. The ether layer was separated, washed five times with 200-ml portions of water and once with 200 ml of saturated NaCl solution, and dried. Concentration *in vacuo* followed by distillation through a 10-cm Vigreux column afforded 17.739 g (41%) of keto isoxazole **8** as a pale yellow oil: bp 134–143° (0.15–0.25 mm); ir (neat) 1709 (C=O) and 1633 cm^{-1} (isoxazole).

The keto isoxazole **8** was dissolved in 200 ml of absolute ethanol and stirred under a hydrogen atmosphere with 19 g of W-4 Raney nickel[7] for 16 hr. An additional 17 g of W-4 Raney nickel[7] was then added and stirring under hydrogen was continued for 12 hr (the reaction was followed by monitoring the disappearance of isoxazole absorption at 223 nm in the uv). Catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residual amber resin was dissolved in 250 ml of absolute methanol. After the solution was purged with nitrogen, 40.0 g of sodium methoxide was added, and the mixture was heated at reflux under nitrogen for 6 hr. The mixture was then diluted with 350 ml of water, and refluxing under nitrogen was continued for an additional 10 hr. After cooling, the mixture was diluted with 500 ml of water and extracted four times with 250-ml portions of ether. The combined ether extracts were washed three times with 250-ml portions of water and once with 250 ml of saturated NaCl solution, and dried. Concentration *in vacuo* followed by distillation through a 10-cm Vigreux column afforded 9.643 g (29% overall) of enone **6b** as a pale yellow liquid: bp 75–83° (0.10–0.15 mm); ir (neat) 1668 (C=O) and 1615 cm^{-1} (C=C); uv max (EtOH) 247 nm; nmr (CCl_4) δ 1.05 (3 H, br, $CHCH_3$) and 1.69 (3 H, s, vinyl CH_3). The 2,4-dinitrophenylhydrazone, after three recrystallizations from ethanol, had mp 192.5–193.5°.

Anal. Calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.47; H, 6.19; N, 15.62.

B. From 2-Cyclohexenone and Ethyl Vinyl Ketone.—A solution of magnesium enolate **2** was prepared in ether solution by cuprous chloride catalyzed reaction between 88.1 mmol[8] of methylmagnesium iodide and 7.711 g (80.2 mmol) of 2-cyclohexenone (**1**) as described above in the preparation of **6a**. To this was added 6.750 g (80.2 mmol) of ethyl vinyl ketone in one portion, at ice-bath temperature, and the mixture was allowed to stir at room temperature for 1 hr. The resulting mixture was

(3) (a) R. A. Kretchmer and W. M. Schafer, *J. Org. Chem.*, in press; (b) G. Stork, G. L. Nelson, F. Rouessac and O. Gringore, *J. Amer. Chem. Soc.*, **93**, 3091 (1971); (c) G. Stork, *Pure Appl Chem.*, **17**, 383 (1968).

(4) J. E. McMurry, Ph.D. Thesis, Columbia University, New York, N. Y., 1967.

(5) (a) G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967); (b) G. Stork and J. E. McMurry, *ibid.*, **89**, 5463 (1967); (c) G. Stork and J. E. McMurry, *ibid.*, **89**, 5464 (1967).

(6) Melting points are uncorrected. Magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Beckman IR-8 or a Perkin-Elmer 257 infrared spectrophotometer. Nmr spectra were determined with either a Varian A-60 or T-60 spectrometer using tetramethylsilane as internal standard. Uv spectra were determined on a Cary Model 11PM spectrophotometer. The mass spectra were obtained with a Varian MAT CH7 mass spectrometer. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

(7) A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.*, **68**, 1471 (1946).

(8) Calculated on the basis of the amount of magnesium employed.

then treated with 200 ml of saturated NH_4Cl solution. The ether layer was separated, washed six times with 75-ml portions of water and once with 75 ml of saturated NaCl, and dried. Concentration *in vacuo* afforded 13.5 g of oil which was dissolved in 250 ml of anhydrous methanol. To this was added a solution of 30 g of NaOH in 350 ml of water, and the resulting mixture was heated at reflux under nitrogen for 16 hr. After cooling, the mixture was extracted with ether. The ether extract was washed with water, 3 *M* HCl, and saturated NaCl solution, and then dried. Concentration *in vacuo* followed by distillation through a 10-cm Vigreux column afforded 1.985 g (14%) of **6b** as a colorless liquid, bp 97–117° (0.6–0.65 mm). This material was characterized by conversion to the 2,4-dinitrophenylhydrazone derivative, which, after recystallization from ethanol–ethyl acetate had mp 194.0–195.5°, undepressed on admixture with material prepared *via* the isoxazole route above.

Preparation of Keto Ester 4b.—An ether solution of magnesium enolate **2** was prepared under nitrogen by cuprous chloride catalyzed reaction between 89.9 mmol[8] of methylmagnesium iodide and 8.04 g (83.6 mmol) of 2-cyclohexenone (**1**), as described above in the preparation of **6a**. A solution of 8.37 g (83.6 mmol) of ethyl acrylate in 50 ml of ether was then added in one portion at ice-bath temperature, and the mixture was allowed to stir at room temperature under nitrogen for 30 min. The resulting mixture was next treated with dilute aqueous HCl. The ether layer was separated, washed five times with 100-ml portions of water and once with 100 ml of saturated NaCl solution, and dried. Concentration *in vacuo* afforded 15.19 g of amber oil which was distilled through a 10-cm Vigreux column to give 0.45 g (5%) of 3-methylcyclohexanone, bp 25° (0.25 mm), which was identified by spectroscopic comparison with an authentic sample.

The fractional distillation also afforded 2.94 g (17%) of keto ester **4b** as a pale yellow liquid, bp 88–93° (0.1–0.35 mm). Redistillation afforded the analytical sample as a colorless liquid: bp 100–102° (0.45–0.55 mm); ir (neat) 1711 (ketone C=O) and 1735 cm^{-1} (ester C=O); mass spectrum (70 eV) *m/e* 212 (M^+).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.94; H, 9.41.

Registry No.—**4b**, 36794-99-7; **6a** DNPH, 36795-00-3; **6b**, 32456-17-0; **6b** DNPH, 36795-02-5; **7**, 36795-03-6; **8**, 36795-04-7; 3-methylcyclohexanone, 591-24-2.

Rotational Isomerism in β,β-Dichlorovinyl Carbonyl Compounds

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In connection with a synthetic effort, we have prepared several of the title compounds, $Cl_2C{=}CHCOX$, where X = H (**1**), Cl (**2**), CH_3 (**3**), and OCH_3 (**4**).[2] These compounds show two bands in the carbonyl-stretching frequency region of their ir spectra. The studies of Dabrowski and coworkers on the related mono-β-chlorovinyl compounds[3a–c] suggest that this phenomenon is due to s-cis,s-trans[4] isomerism about the olefin–carbonyl bond.

Infrared absorption bands in the 1500–1800-cm^{-1} region and nmr chemical shifts are set out in Table I. Inspection of the ir data suggests that the higher frequency carbonyl band (A) should be assigned to the s-cis forms of the compounds and the lower one (B) to the s-trans form. As one would expect the relative intensity of band A (s-cis) increases with the size of X. Also, the relative strength of band B is usually apparently greater in the more polar solvent.[3b,c] The ketone **3** appears to be a particularly good example. There are four well-resolved double bond stretching bands in CCl_4 and C_2Cl_4; it is tempting to assign the two outer bands to the s-cis form and the two inner ones to the s-trans.[3b] But this simple picture is complicated when one considers all the data, especially for the ketone. In this compound, the relative intensity of band A to band B is in the order $CH_3CN > CH_2Cl_2 > CHCl_3 > CCl_4, C_2Cl_4$. Similarly, a careful inspection of the ester ≤ spectra indicates band B is probably actually more intense in CH_3CN. In addition, there are more than two bands in the C=C region for all the compounds.[5] The discussion below considers these facts.

In the aldehyde **1**, band B is much more intense than band A and is relatively stronger in CH_3CN. Since this is the least sterically hindered compound and the s-trans form is electronically favored,[3b] band A is assigned to $\nu_{C=O}$ (s-cis) and band B to $\nu_{C=O}$ (s-trans). The strongest C=C band, 1585 cm^{-1}, is assigned to $\nu_{C=C}$ (s-trans). These s-trans bands are near those found in the s-trans monochlorovinyl aldehyde (1692 and 1588).[3a] The s-cis C=C band is probably overlaid by the s-trans one; both the other bands between 1500 and 1600 cm^{-1} seem too strong to go with the weak s-cis C=O band.

In the acid chloride **2** the two well-resolved C=O bands are of comparable intensity. The relative intensity of band B is markedly greater in CH_3CN. These two bands are therefore assigned as for the aldehyde. Both shoulders on the very strong C=C band increase as band B increases, but, since it is difficult to judge intensities for these closely spaced absorptions, we are reluctant to assign any of them definitely to one conformer or the other.

The ketone **3** departs from the pattern of **1** and **2**. Bands A and B are well separated and of comparable intensity as in **2**, but the relative strength of band B *falls* with increasing solvent polarity. Both the highest and lowest band in the C=C region show the same behavior relative to the strongest C=C band. The Noack criterion, *viz.*, that $\nu_{C=O}$ in s-cis shifts less than that of $\nu_{C=O}$ in s-trans in going from CCl_4 to $CHCl_3$,[6] is no help in this case except that it may suggest that the conformers in this case are not very close to s-cis and s-trans. A quasi-s-trans rotamer must be considerably skewed from planarity in **3** due to interference between the methyl and the nearer β-chlorine.[7]

(1) NSF Predoctoral Fellow, 1966–1970.

(2) Our interest in these compounds stems from our discovery that they react with certain secondary amines to yield directly aminoethynyl carbonyl compounds: ethynylogous amides, "push–pull" acetylenes. *Cf.* H.-J. Gais, K. Hafner, and M. Neuenschwander, *Helv. Chim. Acta*, **52**, 2641 (1969). These results will be communicated shortly.

(3) (a) J. Terpinski and J. Dabrowski, *Bull. Akad. Pol. Sci., Ser. Sci. Chim.*, **17**, 355 (1969); (b) J. Dabrowski and K. Kamienska-Trela, *Bull. Chem. Soc. Jap.*, **39**, 2565 (1966); (c) J. Dabrowski and J. Terpinski, *J. Org. Chem.*, **31**, 2159 (1966).

(4) We recognize that both conformations may deviate from planarity; *cf.* A. J. Bowles, W. O. George, and W. F. Maddams, *J. Chem. Soc. B*, 810 (1969), and D. D. Faulk and A. Fry, *J. Org. Chem.*, **35**, 365 (1970).

(5) Factors other than rotational isomerism that may cause band splitting (*e.g.*, Fermi resonance) are discussed in ref 3b and c and references cited therein; see also ref 8.

(6) K. Noack, *Spectrochim. Acta*, **18**, 1625 (1962).

(7) (a) A sketch made to scale using reasonable values for bond lengths and contact radii (values from Pauling[7b]) or the use of models shows this; (b) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960.

TABLE I

SPECTRAL DATA FOR THE COMPOUNDS $Cl_2C{=}CHCOX$

X	Solvent	Ir absorption bands, cm^{-1} C=O[a]	Ir absorption bands, cm^{-1} C=C[a]	Nmr (δ)
H	CCl_4	1733 (w, shp) (A) 1688 (vs) (B)	1591 (s, sh) 1585 (s) 1569 (m)	6.25 (d, 1, J = 6.7 Hz, $Cl_2C{=}CH$) 9.56 (d, 1, J = 6.7 Hz, -CHO) (neat liquid)
	CH_3CN	1727 (w, brd) (A) 1687 (vs) (B)	1595 (s, sh) 1585 (s) 1570 (m, sh)	
Cl	CCl_4	1789 (s) (A) 1766 (s-vs) (B)	1575 (s, sh) 1570 (vs) 1557 (m, sh)	6.72 (s) (neat liquid)
	CH_3CN	1790 (m-s) (A) 1765 (vs) (B)	1576 (vs, sh) 1571 (vs) 1558 (m-s, sh)	
CH_3	CCl_4	1708 (s) (A) 1678 (m-s) (B)	1585 (s) 1577 (s, sh) 1574 (vs) 1557 (m, sh)	2.03 (s, 3, CH_3) 6.42 (s, 1, $Cl_2C{=}CH$) (neat liquid)
	C_2Cl_4	1707 (s) (A) 1676 (m-s) (B)	1583 (s) 1576 (s, sh) 1571 (vs) 1557 (m, sh)	
	$CHCl_3$	1701 (s) (A) 1671 (m-s) (B)	1584 (s) 1576 (s, sh) 1572 (vs) 1560 (m)	
	CH_2Cl_2	1702 (s) (A) 1673 (m-s) (B)	1584 (s, sh) 1576 (vs, sh) 1572 (vs) 1557 (m)	
	CH_3CN	1703 (s) (A) 1673 (m)	1587 (s, sh) 1574 (vs) 1569 (vs, sh) 1557 (m)	
OCH_3	CCl_4	1742 (vs) (A) 1718 (s)[b] (B)	1617 (m, sh) 1608 (vs)	3.59 (s, 3, OCH_3) 6.29 (s, 1, $Cl_2C{=}CH$) (neat liquid)
	CH_3CN	1733 (vs) (A) 1718 (s-vs, sh)[b] (B)	1618 (s, sh) 1609 (vs)	

[a] These designations refer to the generally accepted spectral regions and do not necessarily imply assignment; see discussion below. [b] The integrated intensity is probably actually greater in CCl_4.

Even in *trans*-4-chloro-3-buten-2-one, the s-trans conformer is not quite planar[3c] and the mesityl oxide is all s-cis.[6] It is noteworthy that band A in **3** is at higher, and band B at lower, frequency than in the monochlorovinyl ketone under the same conditions (C_2Cl_4 solution).[3b] It thus appears that at least one of the rotamers of **3** has a different nature from those of the monochloro ketones and possibly different from those of **1** and **2**.[8] Both the slightly smaller size of chlorine compared to methyl[7b] and differences in electronic structure probably account for the spectral differences between **2** and **3**.

Considerations similar for those for **3** may apply to the ester **4**. Changes in intensity are more difficult to gauge in **4** compared to **3**, and there is a lack of data on the related monochlorovinyl compounds.[9]

Overall we conclude that the compounds studied all show rotational isomerism. The exact nature of the conformers is however unclear, especially as X becomes large. A recently described matrix isolation technique might help elucidate this problem.[10]

Experimental Section

Spectral Analysis.—Ir spectra were taken on a Perkin-Elmer 225 grating infrared spectrophotometer in 0.1-mm KBr cells. Solutions were 50 mg/ml. Nmr spectra were taken on a Varian A-60A analytical nmr spectrometer.

Syntheses.—*Caution.* β-Chlorovinyl carbonyl compounds

(8) After the submission of this note, we found that we had overlooked a differing interpretation of the spectrum of the ketone **3** in the literature. Based on a film spectrum and the dipole moment of **3**, Searles, *et al.*, regard **3** as all quasi-s-trans: S. Searles, Jr., R. A. Sanchez, R. L. Soulen, and D. G. Kundiger, *J. Org. Chem.*, **32**, 2655 (1967). They assert band B is an overtone of the strong unsplit (in their spectrum) C-Cl band at 833 cm^{-1}. We re-examined our spectra with the following results and conclusions. In CS_2 and CCl_4 band B is more intense than the C-Cl absorption and the latter is split in CS_2 (832 and 817 cm^{-1}). There is no absorption near 785 cm^{-1}; thus the splitting of the C=C absorption cannot be due to Fermi resonance or an overtone. We believe it unlikely that s-trans **3** would have its C=O absorption ~20 cm^{-1} *higher* than s-trans **1** unless the former is highly skewed (and therefore effectively nonconjugated), a conclusion the above authors reject. The fact that s-cis **3** might well be *more* polar than the s-trans conformer, as stated by these authors, is consistent with out solvent effect data. Thus, we believe **3** to exist as two conformers, at least in solution. None of the compounds **1**, **2**, or **4** has a strong absorption at one-half the frequency of the weaker carbonyl band.

(9) A. N. Kurtz, W. E. Billups, R. B. Greenlee, A. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965), report only one C=O band for *cis*- and *trans*-3-chloropropenoyl chloride and the methyl esters. However, the resolving power of their instruments was probably less than that of ours.

(10) A. Krautz, T. D. Goldfarb, and C. Y. Lin, *J. Amer. Chem. Soc.*, **94**, 4022 (1972).

should be treated as vesicants. Solutions of 3,3-dichloropropenoate anion generate explosive chloroacetylene on warming.[11] The ketone **3** reacts with concentrated aqueous alkali to yield an explosive gas, probably also HC≡CCl.[12]

3,3-Dichloropropenal (1) was obtained by a reported method:[13] bp 38–39° (21 mm); 2,4-dinitrophenylhydrazone mp 164–165° [lit.[13] bp 85° (35 mm);[14] 2,4-DNP mp 164–165°].

4,4-Dichloro-3-buten-2-one (**3**) was prepared by acetylation of 1,1-dichloroethene,[15a,b] bp 59.5–60.0 (18 mm) [lit. bp 153–156° (atm),[15a] 45° (10 mm), 58° (15 mm)[15b]]. This material is stable at least 8 months at −15° if carefully freed from dissolved HCl by refluxing several hours in a 30-cm Vigreux column under vacuum, distilling (90% of once-distilled material boils within a 0.5° range), and purging the main fraction with nitrogen.

3,3-Dichloropropenoic acid was prepared by the haloform reaction (0–5°) on a mixture of 4,4,1-trichloro-3-buten-2-one and 4,4,4,1-tetrachloro-2-butanone, prepared analogously to **3**, using ordinary chlorine bleach (55% overall yield): white needles from CCl_4; mp 76–77° (lit.[16a,b] mp 76–77°); ir (CCl_4) 1742 (w, sh), 1706 (vs, C=O), 1598 cm^{-1} (vs, C=C); nmr (CCl_4) δ 6.38 (s, 1, Cl_2C=CH), 12.21 (s, 1, COOH); satisfactory analyses for C, H, and Cl.

3,3-Dichloropropenoyl chloride (2) was prepared in 75–80% yield by refluxing the acid 1.5 hr with a 75% excess of $SOCl_2$ and fractionating, colorless liquid, bp 51.6–52.2 (18 mm) [lit.[16b] bp 145° (atm)], no $SOCl_2$ by ir.

Methyl 3,3-dichloropropenoate (4) was prepared by Fischer esterification of the acid (10% H_2SO_4 in ~20-fold excess CH_3OH, 2-day reflux). Fractionation after the usual work-up gave a 75–80% yield of colorless liquid, bp 57.7–58.8° (18 mm). This compound has mp ~15°; the analytical sample, whose ir spectrum was identical with that of the distillate, was obtained by fractional freezing.

Anal. Calcd for $C_4H_4Cl_2O_2$: C, 31.00; H, 2.60. Found: C, 31.09; H, 2.61.

Registry No.—**1**, 2648-51-3; **2**, 20618-08-0; **3**, 5780-61-0; **4**, 2257-46-7.

(11) O. Wallach, *Justus Liebigs Ann. Chem.*, **203**, 83 (1880), and our observations.

(12) We surmise that this occurs by a reaction analogous to the "acid" cleavage of acetoacetic esters.

(13) M. S. Kharasch, O. Reinmuth, and W. A. Urry, *J. Amer. Chem. Soc.*, **69**, 1105 (1947).

(14) In view of the boiling points of the compounds **2**–**4**, this is almost surely a typographic error in ref 13.

(15) (a) O. Wichterle and J. Vogel, *Collect. Czech. Chem. Commun.*, **19**, 1197 (1954); (b) I. Heilbron, E. R. H. Jones, and M. Julia, *J. Chem. Soc.*, 1430 (1949).

(16) (a) F. Strauss, L. Kollek, and W. Heyn, *Ber.*, **63**, 1868 (1930); (b) O. Wallach, *Justus Liebigs Ann. Chem.*, **193**, 1 (1878).

2,3,4,5-Tetrahydro-1*H*-phosphorino[4,3-*b*]indoles and Derivatives[1]

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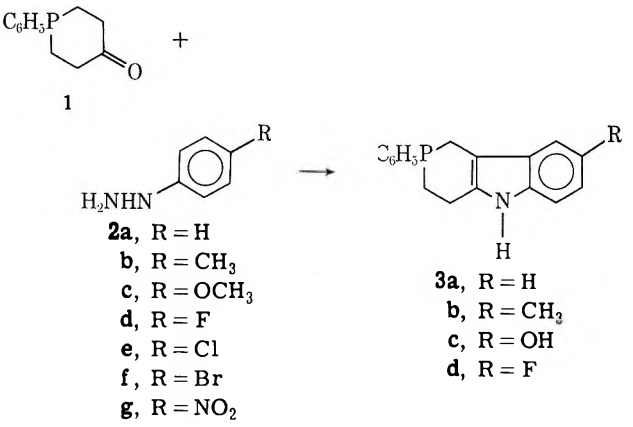
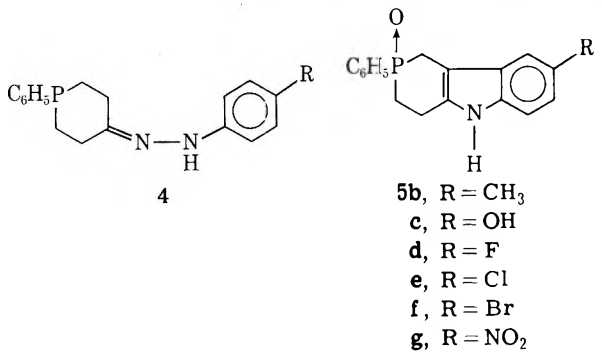
In view of the well-known biological activity of indoles[3,4] and the rarity of 2,3,4,5-tetrahydro-1*H*-phosphorino[4,3-*b*]indoles,[5] and because of our interest in fused C–P ring systems,[6] the need arose for the synthesis of the title class of phosphorus heterocycles. 1-Phenyl-4-phosphorinanone (**1**) was a logical starting material and an improved procedure for its preparation was developed.[7,8]



Condensation of the ketone **1** with various substituted phenylhydrazines **2** or phenylhydrazine hydrochlorides presumably produced phenylhydrazones, which were cyclized *in situ* using glacial acetic acid and concentrated hydrochloric acid[9] to give the corresponding 2,3,4,5-tetrahydro-2-aryl-1*H*-phosphorino-[4,3-*b*]indoles **3a**–**d**, all high-melting, crystalline solids. It was found that the subsequent indolization occurred readily when the original arylhydrazine had an electron-releasing substituent in the 4 position, as noted in the classic studies with simpler ketones.[10] The presence of a nitro group at the 4 position produces an opposite effect; only the oxide **5g** could be isolated in



low yield. Consequently, the particular hydrazone precursor **4** (R = NO_2) could be isolated and was characterized.

Formation of the corresponding phosphine oxides **5** occurred so rapidly in some condensations (from **2e**–**g** → **5e**–**g**) that the phosphines could not be obtained. Their data are reported in Table I along with the other oxides.

Quaternization of 2,3,4,5-tetrahydro-2-aryl-1*H*-phosphorino[4,3-*b*]indole compounds **3** occurs easily to give

(1) We gratefully acknowledge partial support by the National Institute of Health, Cancer Institute, CA 11967-08. We also thank the Research Foundation, Oklahoma State University, for preliminary support. We gratefully acknowledge the National Science Foundation Institution grant to purchase the XL-100 nmr unit, Grant NSF GP-17641.

(2) Research Associate, 1972.

(3) R. V. Heinzelman and J. Szumuszkovicz, "Progress in Drug Research," Vol. 6. E. Jucker, Ed., Birkhauser Verlag, Basel, 1963, p 75.

(4) R. J. Sundberg, "The Chemistry of Indoles," in "Organic Chemistry: A Series of Monographs," Vol. 14, A. T. Blomquist, Ed., Academic Press, New York, N. Y., 1970.

(5) The *P*-phenyl derivative of the parent compound is the only member reported; see M. J. Gallagher and F. G. Mann, *J. Chem. Soc.*, 5110 (1962).

(6) T. E. Snider and K. D. Berlin, *Phosphorus*, **1**, 59 (1971); C. C. Chen and K. D. Berlin, *J. Org. Chem.*, **36**, 2791 (1971).

(7) T. E. Snider, D. E. Morris, K. C. Srivastava, and K. D. Berlin, *Org. Syn.*, submitted.

(8) Pioneering work on the synthesis of this compound was done by R. P. Welcher, G. A. Johnson, and V. P. Wystrach *J. Amer. Chem. Soc.*, **82**, 4437 (1960).

(9) B. Robinson, *Chem. Rev.*, **69**, 227 (1969).

(10) D. Desaty and D. Keglevic, *Croat. Chem. Acta*, **36**, 103 (1964).

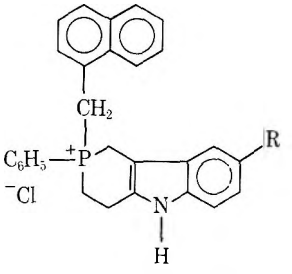
TABLE I

PHYSICAL DATA OF THE PHOSPHINES AND THE PHOSPHINE OXIDES

Compd	Mp, °C	Yield,[b] %
3a	115–116[c]	75
3b	155–156	48
3c	101–102[a]	36
3d	113–114	73
5b	203–204	10
5c	274–275[a]	
5d	184–186	3
5e	223–225	46
5f	230–232	52
5g	220–222 dec	20

[a] The compound 3c was found to contain some chloroform which was the solvent of recrystallization. It could not be obtained free of the solvent without decomposition by regular drying procedures under vacuum, and hence a good analysis could not be obtained on the phosphine. When recrystallized with methanol–ether, it formed the oxide 5c. Note that 3c is the 8-hydroxy compound rather than the 8-methoxy derivative expected from 2c. The acidic conditions for the cyclization apparently caused the ether cleavage, as the 8-methoxy compound could not be found in the reaction mixture. [b] Satisfactory analytical data (±0.4% for N, P, and halogen) were reported for all new compounds listed in the table. [c] Lit.[5] mp 113–114°.

phosphonium salts 6 using dry toluene as solvent. Reaction with 1-(chloromethyl)naphthalene was at phosphorus rather than nitrogen and was demonstrated *via* ^{31}P nmr spectroscopy. One set was selected for study; analysis of 3a and its salt 6a gave



6a, R = H
b, R = CH_3
c, R = OH
d, R = F

values of δ 25.8 and −13.8, respectively (from 85% H_3PO_4). These are typical values for phosphines and phosphonium salts.[11,12] Other data for the phosphonium salts are given in Table II.

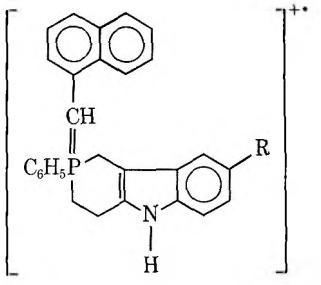
Very little literature is available on the mass spectrum of phosphonium salts.[12,13] Mass spectra of the phosphonium salts 6 do *not* show a peak for the molecular ion, but a peak for the cation fragment is present. For example, there is a major ion at *m/e* 406 (M^+ − Cl) and a strong peak at *m/e* 405 (M^+ − HCl), the latter of which could result by electron impact when the sample enters the ionization chamber. Similar results were obtained by Snider[12] on some other phosphonium salts. In the phosphonium salt the overall elimination of HCl could produce the cation of a Wittig reagent, the neutral structure of which is well known in solution.[14] Interestingly, a molecular ion for 1,1,4,4-tetraphenyl-1,4-diphosphoniacyclohexane dibromide (*m/e* 586) has been reported with the inlet temperature at 310° but intensities were not given.[13] The area of mass spectral analysis of phosphonium salts needs considerable work before any definitive conclusions can be made.

TABLE II

PHOSPHONIUM SALTS

Compd[a]	Mp, °C	Yield, %
6a	311–313	qt
6b	299–301	qt
6c	265–267	91
6d	276–278	qt

[a] Satisfactory analytical data (±0.4% for N, P) were reported for all new compounds listed in the table.



m/e 405

Experimental Section

All melting points are uncorrected and were taken in Pyrex capillary tubes in a Thomas-Hoover melting point apparatus. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Potassium bromide wafers were used for all solid compounds. The nmr spectra were obtained on a Varian Associates XL-100 spectrometer; chemical shifts are expressed in parts per million (δ) downfield from TMS. The ^{31}P spectra were recorded at 40.54 MHz. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Mass spectra were obtained on a LKB-9000 prototype, magnetic sector, mass spectrometer; we gratefully acknowledge support from NSF, GB-7731.

General Procedure for the Preparation of Tetrahydroarylphosphorinoindoles (3). 2,3,4,5-Tetrahydro-2-phenyl-1*H*-phosphorino[4,3-*b*]indole (3a).—Phenylhydrazine (2a, 4.54 g, 0.042 mol) was added to a stirred, boiling solution of 1-phenyl-4-phosphorinanone (1, 8.0 g, 0.042 mol) in glacial acetic acid (15 ml) under N_2. After addition, the reaction mixture was boiled for 2 hr and a solution of concentrated hydrochloric acid (25 ml) in glacial acetic acid (5 ml) was added to it. After addition, the reaction mixture was boiled for 2 hr, cooled to room temperature, and diluted (H_2O, 200 ml). The resulting mixture was neutralized (10% KOH solution) and then extracted thrice with 50-ml portions of ether. The combined ether extracts were washed (H_2O) and dried ($MgSO_4$). Removal of the solvent gave 8.2 g (75%) of white solid product, mp 111–114°, which was recrystallized from aqueous ethanol: mp 115–116° (reported[5] mp 113–114°); ir 3470 cm^{-1} (NH); nmr ($DCCl_3$) δ 1.97 (m, 2, CH_2), 2.42 (m, 2, CH_2), 3.02 (m, 2, CH_2), and 7.20 (m, 10, ArH and NH); *m/e* 265 (M^+). ^{31}P absorption occurred at δ 25.8 (in C_2H_5OH from 85% H_3PO_4).

General Procedure for the Preparation of the Phosphonium Salts (6). Preparation of Phosphonium Salt 6a.—1-(Chloromethyl)naphthalene (0.53 g, 0.003 mol) was added to a stirred, warm solution (100–110°) of 3a (0.53 g, 0.002 mol) in dry toluene (5 ml) under N_2. After addition, the reaction mixture was stirred at the same temperature for 8 hr, then cooled to room temperature and diluted with anhydrous ether (50 ml). Precipitated phosphonium salt was collected by filtration and was washed (anhydrous ether), giving 0.88 g (quantitative) of 6a,

(11) V. Mark, C. H. Dungan, M. M. Crutchfield, and J. R. Van Wazer, "Topics in Phosphorus Chemistry," Vol. 5, M. Grayson and E. J. Griffith, Ed., Interscience, New York, N. Y., 1967, p 227.

(12) T. E. Snider, Ph.D. Dissertation, Oklahoma State University, 1972.

(13) A. M. Aguiar, H. Aguiar, and D. Daigle, *J. Amer. Chem. Soc.*, **87**, 671 (1965).

(14) A. Maercker, "Organic Reactions," Vol. 14, A. C. Cope, Ed., Wiley New York, N. Y., 1965, p 270.

which was recrystallized from hot ethanol: mp 311–313°; mass spectrum *m/e* 406 (for the cation part of the molecule, the molecular ion peak at 441 was absent), 405 ($M^+ - HCl$); ^{31}P absorption, $\delta -13.8$ (C_2H_5OH, from 85% H_3PO_4).

2,3,4,5-Tetrahydro-8-methyl-2-phenyl-1*H*-phosphorino[4,3-*b*]-indole (3b) and Formation of the Oxide 5b.—The compound **3b** was prepared from *p*-tolylhydrazine hydrochloride (2.55 g, 0.016 mol) and ketone **1** (3.08 g, 0.016 mol) by the above procedure. The crude product, on fractional recrystallization with aqueous ethanol, gave **3b**, 2.1 g (48%), mp 155–156°, *m/e* 279 (M^+), and **5b**, 0.4 g (10%), mp 203–204°, *m/e* 295 (M^+). Other data for **3b** are ir 3470 cm^{-1} (NH); nmr ($DCCl_3$) δ 2.09 (m, 2, CH_2), 2.45 (s, 3, CH_3), 2.60 (m, 2, CH_2), 3.11 (m, 2, CH_3), and 7.16 (m, 8, ArH and NH) (apparently oxidation of **3b** to **5b** occurred during recrystallization). The phosphine **3b** formed the phosphonium salt **6b** by the previously described method in quantitative yield, mp 299–301°, mass spectrum *m/e* 420 (for the cation part of the molecule, the molecular ion peak at 455 was absent), 419 ($M^+ -$ HCl).

2,3,4,5-Tetrahydro-8-hydroxy-2-phenyl-1*H*-phosphorino[4,3-*b*]-indole (3c) and Formation of the Oxide 5c.—The compound **3c** was prepared from *p*-methoxyphenylhydrazine hydrochloride (**2c**, 4.3 g, 0.024 mol) and ketone **1** (4.7 g, 0.024 mol) by the above procedure, except that the extraction of the reaction mixture was done with chloroform and recrystallization with chloroform–hexane to give **3c**: 2.5 g (36%); mp 100–102° (see footnote *a*, Table I); ir 3470 (NH), 3350 cm^{-1} (OH); nmr ($DCCl_3$) δ 2.4 (m, 2, CH_2), 2.72 (m, 2, CH_2), 3.06 (m, 2, CH_2), 4.80 (s, 1, OH), and 7.12 (m, 9, ArH and NH); *m/e* 281 (M^+).

The phosphine **3c** formed the phosphonium salt **6c** by the previously described method in 91% yield, mp 265–267°, mass spectrum *m/e* 422 (for the cation part of the molecule, the molecular ion peak at *m/e* 457 was absent), 421 ($M^+ -$ HCl).

The oxide **5c** was formed (by air oxidation) when **3c** was recrystallized using methanol–ether, mp 274–275°, *m/e* 297 (M^+).

2,3,4,5-Tetrahydro-8-fluoro-2-phenyl-1*H*-phosphorino[4,3-*b*]-indole (3d) and Formation of the Oxide 5d.—The compound **3d** was prepared from 4-fluorophenylhydrazine hydrochloride (**2d**, 5.42 g, 0.033 mol) and ketone **1** (6.4 g, 0.033 mol) by the above procedure. The crude product on fractional recrystallization from ether–hexane gave **3d**, 6.9 g (73%), mp 113–114°, *m/e* 283 (M^+), and **5d**, 0.3 g (3%), mp 184–186°, *m/e* 299 (M^+). Other data for **3d** are ir 3470 cm^{-1} (NH); nmr ($DCCl_3$) δ 1.96 (m, 2, CH_2), 2.48 (m, 2, CH_2), 2.93 (m, 2, CH_2), and 7.02 (m, 9, ArH and NH). The phosphine **3d** formed the phosphonium salt **6d** by the previously described method in quantitative yield, mp 276–278°, mass spectrum *m/e* 424 (for the cation part of the molecule, the molecular ion peak at *m/e* 459 was absent), 423 ($M^+ -$ HCl).

Attempted Preparation of 2,3,4,5-Tetrahydro-8-chloro-2-phenyl-1*H*-phosphorino[4,3-*b*]indole (3e). Formation of the Oxide 5e.—The reaction of 4-chlorophenylhydrazine hydrochloride (**2e**, 3.0 g, 0.017 mol) and ketone **1** (3.2 g, 0.017 mol) was done, as in the general procedure, except that the reaction mixture was extracted with chloroform. The product did *not* contain any indole **3e**, but only the oxide **5e**, 2.4 g (46%), mp 220–224°, *m/e* 315 (M^+). Recrystallization from chloroform–ether gave the analytical sample: mp 223–225°; ir 3470 cm^{-1} (NH); nmr (acetone-d_6) δ 2.62 (m, 2, CH_2), 3.09 (m, 2, CH_2), 3.62 (m, 2, CH_2), and 7.25 (m, 9, ArH and NH). Again apparently **3e** was oxidized during purification.

Attempted Preparation of 2,3,4,5-Tetrahydro-8-bromo-2-phenyl-1*H*-phosphorino[4,3-*b*]indole (3f). Formation of the Oxide 5f.—The reaction of 4-bromophenylhydrazine hydrochloride (**2f**, 5.6 g, 0.025 mol) and ketone **1** (4.8 g, 0.025 mol) was done as in the general procedure. The product did not contain any indole **3f** but only the oxide **5f**, 4.7 g (52%), mp 229–230°, *m/e* 361 and 359 (M^+). Recrystallization from methanol–H_2O gave the analytical sample: mp 230–232°; ir 3470 cm^{-1} (NH); nmr ($DCCl_3$) δ 2.26 (m, 2, CH_3), 2.98 (m, 2, CH_2), 3.46 (m, 2, CH_2), 7.39 (m, 8, ArH), and 8.98 (s, 1, NH).

Attempted Preparation of 2,3,4,5-Tetrahydro-8-nitro-2-phenyl-1*H*-phosphorino[4,3-*b*]indole (3g). Formation of the Oxide 5g.—The reaction of 4-nitrophenylhydrazine (**2g**, 0.5 g, 0.003 mol) and ketone **1** (0.64 g, 0.003 mol) was done, as in the above procedure, except that the reaction mixture was extracted with chloroform. The product did not contain any indole **3g**, but only the oxide **5g**, 0.2 g (21%), *m/e* 326 (M^+). It was purified by chromatographing through neutral alumina column and eluting with chloroform, giving a deep orange solid: mp 220–222° dec; ir 3470 cm^{-1} (NH); nmr ($DCCl_3$) δ 1.78 (m, 2, CH_2), 2.50 (m, 2, CH_2), 2.98 (m, 2, CH_2), and 7.12 (m, 9, ArH and NH).

The 4-nitrophenylhydrazone **4** (R = NO_2) was isolated by boiling (6 hr) 4-nitrophenylhydrazine (0.6 g, 0.004 mol) and ketone **1** (0.64 g, 0.003 mol) in ethanol and diluting (H_2O). The solid product was collected by filtration: 0.72 g (66%, based on the amount of ketone); mp 150–151°; nmr ($DCCl_3$) δ 2.39 (m, 8, alicyclic H), 7.03 (d, 2, J = 9 Hz, ArH), 8.10 (d, 2, J = 9 Hz, ArH), 7.37 (m, 5, ArH), and 7.72 (s, 1, NH); *m/e* 327 (M^+). *Anal.* Calcd for $C_{17}H_{18}N_3O_2P$: N, 12.84. Found: N, 12.62.

Registry No.—**3a**, 36720-80-6; **3b**, 36720-81-7; **3c**, 36720-82-8; **3d**, 36720-83-9; **4** (R = NO_2), 36720-84-0; **5b**, 36720-85-1; **5c**, 36720-86-2; **5d**, 36720-87-3; **5e**, 36720-88-4; **5f**, 36720-89-5; **5g**, 36720-90-8; **6a**, 36720-91-9; **6b**, 36763-71-0; **6c**, 36720-92-0; **6d**, 36720-93-1.

2-Carbomethoxycyclopent-2-enone[1]

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Although many substituted cyclopentenones are known, no simple derivatives containing only an electron-withdrawing substituent in the 2 position seem to have been reported. Such compounds would be expected to be relatively unstable, since the substituent would polarize the enone system further, and probably enhance the tendency toward polymerization shown by cyclopentenone itself. An unsuccessful attempt to synthesize 2-acetylcyclopent-2-enone (Ia) has been reported.[3] A recently reported[4] method for synthesizing 3-alkyl-2-carboalkoxycyclopentenones failed for 3-methyl-2-carbethoxycyclopent-2-enone (Ib), the simplest case investigated, although Ib had been prepared by Yates[5] previously by a similar route.

We now report the synthesis of 2-carbomethoxycyclopent-2-enone (Ic), a compound of much potential value for natural products synthesis. The compound can be obtained in *ca.* 45% yield (nmr analysis) by oxidation of 2-carbomethoxycyclopentanone (IIa) with selenium dioxide in refluxing dioxane. Dichlorodicyanoquinone (DDQ) oxidation also gives the compound, but in low yield (5–10%), as it is polymerized under the reaction conditions. Ic is fairly stable in dioxane solution, but attempted purification by any of several methods leads to rapid polymerization. Fractions containing colored, moderately pure material (nmr analysis) were obtained by very rapid silica gel chromatography, but the material polymerized fairly rapidly. However, the compound could be trapped by adding dienes to the reaction mixture. 2,3-Dimethylbutadiene reacted smoothly at 100° to give the adduct III, and cyclopentadiene at 25° gave a 1:1 mixture of the endo and exo adducts IV, which were separated by silica gel chromatography. Pyrolysis of either isomer or

(1) Presented at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 31, 1972, Abstract ORGN 143.

(2) (a) Robert A. Welch Undergraduate Research Scholar; (b) NSF trainee.

(3) R. M. Acheson, *J. Chem. Soc.*, 4232 (1956).

(4) N. Finch, J. J. Fitt, and I. H. C. Hsu, *J. Org. Chem.*, **36**, 3191 (1971).

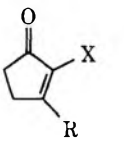
(5) P. Yates, N. J. Jorgenson, and P. Singh, *J. Amer. Chem. Soc.*, **91**, 4739 (1969).

the mixture of IV at 438° and trapping at −10° gave a pure sample of 2-carbomethoxycyclopent-2-enone (Ic). In contrast, adduct III was stable under these conditions.

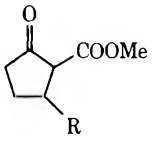
All spectral data on compound Ic are in accord with the assigned structure. The vinyl proton signal in the nmr spectrum appears as a triplet (J = 2.5 Hz) at δ 8.38. This is a very deshielded value for a vinyl proton and reflects the great polarity in the enone chromophore of the compound.

Pure 2-carbomethoxycyclopent-2-enone (Ic) polymerizes within several days at −10° but can be stored for prolonged periods in dilute solution at −10°. It polymerizes very readily with a variety of acidic and basic protic reagents (*e.g.*, anhydrous HBr,[6] diethylamine, NaOMe in MeOH, semicarbazide). Reaction with lithium dimethylcopper,[7] however, proceeds smoothly to give 3-methyl-2-carbomethoxycyclopentanone (IIb), whose semicarbazone was identical with an authenic sample.[5]

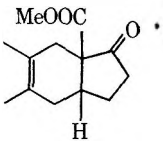
Some other attempts to obtain 2-carbomethoxycyclopent-2-enone (Ic) are of interest. Bromination of 2-carbomethoxycyclopentanone (IIa) in CCl_4 gave



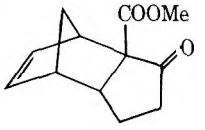
Ia, X = COOEt, R = Me
b, X = COMe, R = H
c, X = COOMe, R = H



IIa, R = H
b, R = Me



III



IV

exclusively the 5-bromo isomer. However, bromination of IIa in water containing $Cu(NO_3)_2$ gave the 2-bromo isomer in good yield, as suggested by a mechanistic study of the reaction.[8] However, on attempted dehydrobromination, rearrangement of the 2-bromo isomer to the 5-bromo isomer evidently occurred since either isomer gave only 5-carbomethoxycyclopent-2-enone and much polymer, but no Ic, under any dehydrobromination conditions investigated.

Experimental Section

2-Carbomethoxycyclopentenone–Cyclopentadiene Diels–Alder Adduct (IV).—To a solution of 14.2 g (0.10 mmol) of 2-carbomethoxycyclopentanone (IIa) in 25 ml of reagent grade dioxane was added 12.2 g (0.11 mol) of SeO_2. No oxidation occurred in dioxane which had been distilled from $LiAlH_4$. The mixture was refluxed for 25 min, and the black Se was removed by filtration. Then 66 g of cyclopentadiene was added and the dark brown solution stirred at room temperature overnight. Distillation of all volatile materials at 0.25 mm was followed by absorption of the residue on 25 g of silica gel and chromatography on 600 g of silica gel packed in petroleum ether (bp 40–60°). After elution with 3 l. of petroleum ether, a 1:1 mixture of the two stereoisomeric adducts IV (2.92 g) was obtained by elution with 10% ether in petroleum ether (2:1). More careful rechromatography of the combined fractions under the same conditions with 5% ether in petroleum ether gave, in early fractions, one pure stereoisomer of the adduct IV: ir (film) 3000, 1760, 1730 cm^{-1}; nmr (CCl_4) δ 0.9–3.4, complex absorption, 3.63 (3 H, s, COOMe) 6.28 (2 H, t, J = 2 Hz, vinyl); 2,4-dinitrophenylhydrazone, mp 164–166°. *Anal.* Calcd for $C_{18}H_{18}N_4O_6$: C, *55.96, H, 4.70. Found: C, 55.87; H, 4.65.*

Further elution with the same solvent mixture gave the same isomer contaminated with increasing amounts of its stereoisomer, which was obtained essentially pure in later fractions: ir (film) 3000, 1760, 1730 cm^{-1}; nmr (CCl_4) δ 0.8–3.4 (complex absorption), 3.70 (3 H, s, COOMe), 6.20 (2 H, t, J = 2 Hz, vinyl H's).

2-Carbomethoxycyclopentenone–2,3-Dimethylbutadiene Adduct (III).—To a total SeO_2 oxidation mixture from 1.42 g of 2-carbomethoxycyclopentanone as described above was added 0.74 g of 2,3-dimethylbutadiene and the mixture heated in a sealed tube for 6 hr at 100°. The adduct III was isolated (256 mg) as the only monomeric product by chromatography over silica gel: ir (CCl_4) 1760, 1730 cm^{-1}; nmr (CCl_4) δ 1.65 (6 H, broadened s, Me's), 1.8–2.5 (mult), 3.70 (3 H, s, COOMe); simicarbazone, mp 207–208° (ethanol). *Anal.* Calcd for $C_{14}H_{21}N_3O_3$: *C, 60.20; H, 7.58. Found: C, 60.45; H, 7.95.* This compound was recovered unchanged upon attempted pyrolysis at 438°.

Pyrolysis of Adduct IV. 2-Carbomethoxycyclopent-2-enone (Ic).—A 1:1 mixture of the two isomeric adducts IV (676 mg, 3.3 mmol) was heated at 60–65° and carried by a slow stream (2 ml/min) of N_2 through a heated inlet system into a 50-ml pyrolysis chamber heated to 438° with a lead bath (contact time 20–30 sec). The exit gases were condensed in a U-tube cooled in an ice–salt bath, conditions which allowed the cyclopentadiene to escape. After 3 days, the tube contained 263 mg (57%) of pure 2-carbomethoxycyclopent-2-enone (Ic): λ_{max}^{EtOH} 220 nm (ϵ >8000); nmr ($CDCl_3$) δ 2.70 (4 H, mult), 3.92 (3 H, s, Me), 8.38 (1 H, t, J = 2.5 Hz, vinyl H). The compound polymerized on standing a few hours neat at room temperature or after several days in a refrigerator but can be kept for extended periods in dry ether solution in a refrigerator. It also polymerized during attempts to form a crystalline derivative or to effect reaction with a number of nucleophiles in protic media, as mentioned in the text.

2-Carbomethoxy-3-methylcyclopentanone (IIb).—To a suspension of 114 mg (0.50 mmol) of pure dry CuI in 10 ml of dry ether was added by syringe 26 mg (1.2 mmol) of methyllithium (0.67 ml of 1.8 M ethereal solution). The resulting pale yellow solution was cooled to −78° (Dry Ice–acetone) and 150 mg (1.06 mmol) of 2-carbomethoxycyclopent-2-enone in 10 ml of ether was added dropwise. The mixture was allowed to warm to room temperature during 1.5 hr, then poured into a saturated NH_4Cl solution. Concentrated NH_4OH was added until solution was complete. Then the ether layer was washed and dried ($MgSO_4$) and the ether evaporated to give an oil (100 mg) showing one spot on tlc and one peak on vpc: ir (CCl_4) 1765 and 1735 cm^{-1} (ketone and ester of keto form) and 1665 and 1630 (ester and double bond of enol form); nmr (CCl_4) δ 1.22, 1.24 (3 H total, d, J = 6 Hz, C-3 Me's of enol and keto form), 2.3–2.9 (complex absorption), 3.81 (3 H, s, COOMe); semicarbazone, mp 168–169.5° (H_2O), no depression on admixture with a sample kindly supplied by Professor Yates;[5] 2,4-dinitrophenylhydrazone (EtOH–H_2O), mp 127.5–128.5°. *Anal.* Calcd for $C_{14}H_{16}N_4O_6$: C, 50.00; H, 4.80. Found: C, 50.05; H, 4.48.

2-Bromo-2-carbomethoxycyclopentanone.—To an aqueous solution (250 ml) which was 0.10 M in KBr, 0.15 M in HNO_3, and 0.10 M in $Cu(NO_3)_2$ was added 14.2 g of 2-carbomethoxycyclopentanone (0.10 mol). An aqueous solution containing 16.0 g of Br_2 (0.10 mol) was added during 0.5 hr. Ether extraction gave 20.8 g (94%) of 2-bromo-2-carbomethoxycyclopentanone, homogeneous by tlc: nmr (CCl_4) δ 2.31 (6 H, mult), 3.86 (3 H, s, COOMe), absence of absorption at 2.8–3.2 due to the C-2 H of starting material.

5-Bromo-2-carbomethoxycyclopentanone.—Treatment of 1.42 g of 2-carbomethoxycyclopentanone in 10 ml of CCl_4 with 1.60 g of Br_2 in 10 ml of CCl_4 by dropwise addition with stirring and then washing and drying ($MgSO_4$) gave a quantitative yield of the 5-bromo isomer, homogeneous by tlc: nmr (CCl_4) δ 2.50 (5 H, mult), 3.89 (3 H, s, COOMe), 4.88 (1 H, mult, C-5 H).

5-Carbomethoxycyclopent-2-enone.—To 1.1 g of 5-bromo-2-carbomethoxycyclopentanone in 10 ml of DMF under N_2 was added 3 g of powdered $CaCO_3$, and the mixture was refluxed 10 min. The cooled mixture was filtered, diluted with water, and

(6) J. N. Marx, *Tetrahedron Lett.*, 4957 (1971).
(7) *Cf.* H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).
(8) K. J. Pederson, *Acta. Chem. Scand.*, **2**, 385 (1948).

extracted with ether. After washing, drying, and removal of the ether, 460 mg of oily 5-carbomethoxycyclopent-2-enone was obtained: nmr (CCl_4) δ 2.0–3.6 (mult), 3.82 (3 H, s, COOMe), 6.45 (1 H, mult, C-2 H), 8.17 (1 H, mult, C-3 H). No carbonyl derivative could be obtained.

Substitution of 1.2 g of 2-bromo-2-carbomethoxycyclopentanone for the 5-bromo isomer in the above procedure gave (nmr analysis) 0.4 g of an oil containing mostly 5-carbomethoxycyclopent-2-enone and some 2-carbomethoxycyclopentanone (contaminant in the starting material), but no 2-carbomethoxycyclopent-2-enone (Ic), since the signal at δ 8.38 was absent.

Other dehydrobromination reagents whose action on the above compounds was investigated include Li_2CO_3–LiBr–DMF; 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU); 5-ethyl-2-methylpyridine; and KOBu-*t*. These reagents gave only polymeric material.

Registry No.—Ic, 36601-73-7; IIb, 18067-33-9; IIb DNP, 36601-75-9; III, 36601-76-0; exo-IV, 36601-77-1; *endo*-IV, 36622-61-4; IV DNP, 36596-59-5; 2-bromo-2-carbomethoxy cyclopentanone, 36596-60-8; 5-bromo-2-carbomethoxycyclopentanone, 36596-61-9; 5-carbomethoxycyclopent-2-enone, 36596-62-0.

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Carbon Tetrachloride Dimerization of 2-Nitropropane Anion. An Electron-Transfer Process

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Received June 27, 1972

The lithium or potassium salts of 2-nitropropane react exothermically with carbon tetrachloride in DMSO saturated with nitrogen to yield 2,3-dinitro-2,3-dimethylbutane in approximately 50% yield. Although a variety of procedures[1,2] are available for producing the synthetically useful vicinal dinitroalkanes[2] in high yields, the carbon tetrachloride oxidative dimerization of nitroalkyl anions reported in this note may prove to be a synthetically useful reaction because of its greater simplicity and speed, especially with *in situ* preparation of the anion by use of commercial potassium *tert*-butoxide.

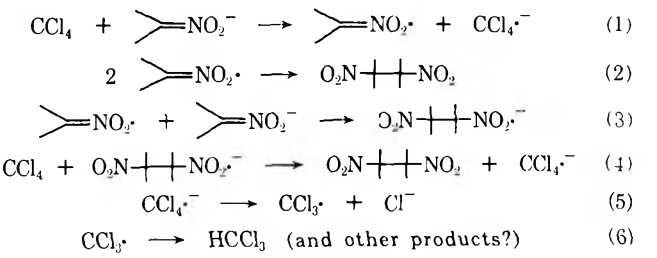
Table I lists the yields of products obtained under several reaction conditions. Since both carbon tetrachloride and the 2-nitropropyl anion are stable to oxygen, the reduction in dimer yield and the formation of acetone when the reaction solution is saturated with oxygen instead of nitrogen suggest that the reaction proceeds *via* 2-nitropropyl radicals which are trapped by oxygen.[3] Quenching the reaction with 6 *N* HNO_3 and Volhard titration of the liberated chloride indicated that the reaction is complete within 1–2 min with DMSO or 2:1 DMSO–cyclohexene as solvent. No detectable reaction occurs in 1 hr with ether, cyclohexene, carbon tetrachloride, ethanol, or 10:2 *tert*-butyl alcohol–water as solvent. Because CCl_4 undergoes nucleophilic substitution with carbanions[4] and is also a good acceptor of electrons, with the intermediate carbon tetrachloride radical anion exothermically decomposing to trichloromethyl radical and chloride anion,[5] two mechanisms for the reaction are immediately conceivable: mechanism A, consisting of nucleophilic substitution on carbon tetrachloride by 2-nitropropyl anion to form trichloromethyl carbanion and 2-chloro-2-nitropropane, which reacts with 2-nitropropyl anion by a radical anion process to form the dimer,[3] and mechanism B (eq 1–6).

Table I

Reaction of CCl_4 with 2-Nitropropyl Anion in DMSO

[CCl_4], *M*	[2-Nitropropane], *M*	[*t*-BuOK], *M*	Gas	Products, mol %: Dimer	Cl^-	Other
1.8	0.3 (Li salt)		N_2	50	70	60 ($CHCl_3$)
1.8	0.3 (Li salt)		O_2	30	40	$CHCl_3$, acetone
1.8[a]	0.3 (Li salt)		N_2	40	70	50 ($CHCl_3$)
0.4	0.22	0.22	N_2	50	80	
0.22	0.22	0.22	N_2	50	80	
0.4	0.22	0.22	O_2	30	40	

[a] Solvent: 2:1 DMSO–cyclohexene.



We tentatively favor mechanism B as the mechanism of the reaction for the following reasons. (a) Mechanism A involves the formation of trichloromethyl carbanion, which should rapidly decompose to dichlorocarbene which is trappable by cyclohexene.[4] When the reaction was conducted in 2:1 DMSO–cyclohexene solvent no dichloronorcarane was detectable. (b) The yield of dimer in the carbon tetrachloride reaction was reduced from 50 to 30% when the reaction was carried out in the presence of oxygen instead of nitrogen (Table I). In mechanism A dimer is formed *via* the reaction of 2-nitropropyl anion with 2-chloro-2-nitropropane. When this reaction was conducted in oxygen- instead of nitrogen-saturated DMSO solutions, the yield of dimer decreased from 65 to ≤5% at 22° and from 80 to 10% at 60° (Table II) (see also ref 3). It therefore appears unlikely that 2-chloro-2-nitropropane is an intermediate in the carbon tetrachloride mediated dimerization of 2-nitropropyl anion as required by mechanism A. (c) The dimerization of 2-nitropropyl

(1) (a) N. Kornblum, S. D. Boyd, and F. W. Stuchal, *J. Amer. Chem. Soc.*, **92**, 5783, 5784 (1970); (b) W. S. Lindsay and R. J. Hardy, *Chem. Abstr.*, **63**, 13075*h* (1965); (c) H. Schechter and R. B. Kaplan, *J. Amer. Chem. Soc.*, **75**, 3980 (1953); (d) A. H. Pagano and H. Schechter, *J. Org. Chem.*, **35**, 295 (1970); (e) G. A. Russell, R. K. Norris, and E. J. Panek, *J. Amer. Chem. Soc.*, **93**, 5839 (1971).

(2) N. Kornblum, S. D. Boyd, H. W. Pinnide, and R. G. Smith, *ibid.*, **93**, 4316 (1971).

(3) G. A. Russell, *ibid.*, **76**, 1595 (1954); G. A. Russell and W. C. Danen, *ibid.*, **88**, 5663 (1966); G. A. Russell and W. C. Danen, *ibid.*, **90**, 347 (1968).

(4) C. Y. Meyers, S. D. Boyd, H. W. Pinnide, and R. G. Smith, *ibid.*, **91**, 7510 (1969).

(5) R. E. Fox and R. K. Curran, *J. Chem. Phys.*, **34**, 1595 (1961); W. E. Wentworth, R. S. Becker, and R. Tang, *J. Phys. Chem.*, **71**, 1652 (1967).

TABLE II

REACTION OF 0.1 *M* 2-CHLORO-2-NITROPROPANE WITH 0.1 *M* LITHIUM SALT OF 2-NITROPROPANE IN DMSO

Temp, °C	Gas	Products, mol % Dimer	Cl⁻
22	N_2	65	80
22	O_2	≤5	15
60	N_2	80	95
60	O_2	10	50

anion has been effected by a variety of oxidants,[1c,d] *1,1,1-trinitroethane*,[6] and several electrophilic aromatics.[1e] The latter reactions were considered to proceed *via* electron transfer reactions similar to mechanism B.[1e,6]

Because carbon tetrachloride is a common chemical, its electron transfer chemistry with anions is deserving of considerable further investigation.

Experimental Section

Reaction of CCl_4 with the Lithium Salt of 2-Nitropropane.—Nitrogen gas was bubbled through a stirred solution of 2 g of the powdered lithium salt of 2-nitropropane[2] in 30 ml of anhydrous DMSO for at least 15 min. Carbon tetrachloride (5 ml) was then added to the solution. The solution rapidly turned from a frothy suspension of some undissolved lithium salt into a clear, yellowish-orange solution. The reaction was exothermic with the temperature rising as high as 60° within 1–3 min. After 15–30 min, 50 ml of water was added and the reaction mixture was extracted with three 150-ml portions of ether. The ether extracts were combined, washed with 100 ml of water, and dried with anhydrous $MgSO_4$. Evaporation of the ether solution yielded 2,3-dinitro-2,3-dimethylbutane in 50% yield, mp 209–212° on recrystallization from absolute ethanol, mp 212° on sublimation (lit.[1e] mp 216°). The nmr spectrum, a singlet at δ 1.8 in CH_2Cl_2, the elemental analysis, and the mass spectrum[7] all confirmed the structure of the product.

Analysis for Other Products.—The dried ether extract of the reaction mixture was carefully distilled until most of the ether had been removed. Gas chromatographic analysis of the remaining solution on a 6-ft column of 5% SF-96 on Chromosorb W at 80 and 150° showed the presence of chloroform and 2,3-dinitro-2,3-dimethylbutane. The nmr spectrum of the solution showed the presence of chloroform and the dimer. The addition of a known weight of chloroform to a known fraction of the concentrated ether solution and measurement of the increase in the area of the chloroform signal permitted an estimation of the yield of chloroform. When the reaction was conducted in a solution saturated with oxygen, 5 ml of the 55–60° distillate of the dried ether extract of the reaction mixture was collected. The nmr spectrum of this distillate showed the presence of chloroform and acetone. The acetone was further confirmed by precipitating its 2,4-dinitrophenylhydrazone from the solution, mp 124–125° (lit.[8] mp 126°). Chloride was determined by the Volhard method[9] on 1-ml aliquots of the reaction solution.

Potassium *tert*-Butoxide System.—After nitrogen gas was passed through 200 ml of DMSO containing 6.3 g (0.22 mol) of potassium *tert*-butoxide and 5 g (0.22 mol) of 2-nitropropane for at least 15 min, 10 ml (0.41 mol) of CCl_4 was added. The frothy solution rapidly became a clear yellowish-orange with the evolution of heat. Water (200 ml) was added to the reaction mixture. This solution was extracted with three 150-ml portions of ether. The combined ether extracts were dried over $MgSO_4$ and distilled, and the residue was recrystallized from absoluted ethanol. The yield was 2.5 g of dimer, mp 212°.

Registry No.—Carbon tetrachloride, 56-23-5; 2-nitropropane anion, 20846-00-8; lithium salt of 2-nitropropane, 28273-55-4; 2,3-dinitro-2,3-dimethylbutane, 3964-18-9.

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(7) J. T. Larkins, F. E. Saalfeld, and L. Kaplan, *Org. Mass Spectrom.*, **2**, 213 (1969).

(8) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 126.

(9) A. I. Vogel, "Inorganic Quantitative Analysis," 3rd ed, Wiley, New York, N. Y., 1961, p 266.

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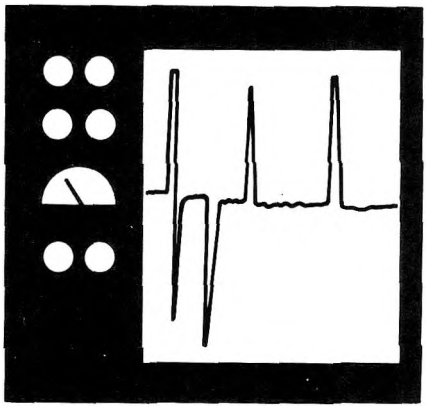

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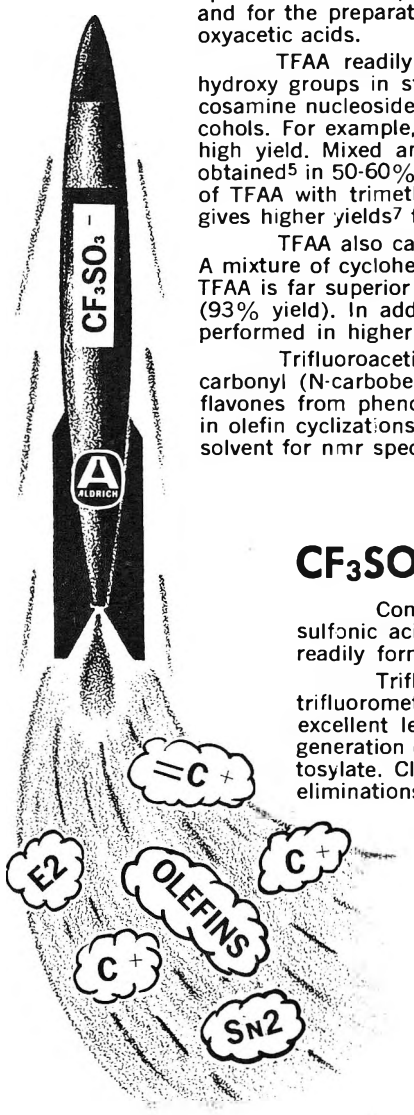
Trifluoroacetic Anhydride Trifluoroacetic Acid

One of the most important uses of trifluoroacetic anhydride (TFAA) is in the preparation[1] of peroxytrifluoroacetic acid, a remarkable oxidizing agent. Peroxytrifluoroacetic acid, readily prepared by mixing 90% hydrogen peroxide with an appropriate amount of TFAA in methylene chloride,[1] is the reagent of choice for Baeyer-Villiger oxidations,[2] for hydroxylation of an olefin,[3] for epoxidation in the presence of sodium carbonate,[3] for the oxidation of anilines[4] to nitrobenzenes and for the preparation of pyridine N-oxides which cannot be formed with peroxybenzoic and peroxyacetic acids.

TFAA readily acylates primary and secondary alcohols and has been used to protect 11-hydroxy groups in steroids,[5] 1-halosugar hydroxyls,[5] and an amine[5] in the synthesis of a D-glucosamine nucleoside. In addition TFAA enables the esterification of highly hindered acids and alcohols. For example, a mixture of mesitoic acid and mesitol in TFAA yielded mesityl mesitoate[6] in high yield. Mixed anhydrides useful in preparing malonic anhydrides for pyrolysis to ketenes are obtained[5] in 50-60% yield simply by refluxing a mixture of TFAA and a carboxylic acid. The reaction of TFAA with trimethylamine N-oxide forms N,N-dimethylformaldiimmonium trifluoroacetate which gives higher yields[7] than classical Mannich conditions.

TFAA also catalyzes the acylation of activated aromatic compounds, olefins and acetylenes. A mixture of cyclohexene, acetic acid and TFAA yields cyclohexenyl methyl ketone[5] in 48% yield. TFAA is far superior to phosphorus pentoxide[5] for the cyclization of a phenothiazinecarboxylic acid (93% yield). In addition, Beckmann rearrangements which give water-soluble amides[5] have been performed in higher yield, using TFAA, because of a much simpler isolation.

Trifluoroacetic acid (TFA) itself is highly useful[8] as a solvent for cleaving N-benzyloxycarbonyl (N-carbobenzoxy), t-butoxy and benzyl groups. TFA also enables a one-step synthesis of flavones from phenols and malonic acid,[9] efficiently catalyzes thioketal formation[10] and is useful in olefin cyclizations[8,11] for steroid total synthesis developed by Johnson. In addition TFA is a good solvent for nmr spectroscopy and for HBr cleavage of protective groups[8] in place of acetic acid.



A Better LEAVING Group

CF_3SO_3H CF_3SO_3Ag $(CF_3SO_2)_2O$ CF_3SO_2Cl

Conductivity measurements in acetic acid have established that trifluoromethanesulfonic acid, a stable non-oxidizing liquid, is the strongest proton acid known. The acid readily forms oxonium compounds from oxygen-containing materials.

Trifluoromethanesulfonic anhydride, trifluoromethanesulfonyl chloride and silver trifluoromethanesulfonate are useful for preparing trifluoromethanesulfonate esters. The excellent leaving ability of the $CF_3SO_3^-$ group is evident from the 41,500 times faster[12] generation of vinyl cations from the trifluoromethanesulfonyl ester than from the analogous tosylate. Clearly trifluoromethanesulfonate esters are potentially very useful for difficult eliminations, for nucleophilic displacements and for mechanistic kinetic studies.

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