THE JOURNAL OF Organic Chemistry

ห้องสมุด กรมวิทยาศาสตร์

NOTES

AUTHOR INDEX

In papers with more than one author the name of the author to whom inquiries about
the paper should be addressed is marked with an asterisk in the by-line.

NOTICE TO READERS AND CONTRIBUTORS

The Journal of Organic Chemistry will begin publishing Communications to the Editor in the August 11 issue. Communications are intended to provide rapid publication of important findings and will be handled as expeditiously as possible (publication within six to eight weeks of acceptance).

The maximum length will be 1000 words, including space required for structural formulas. A communication must have a one-sentence summary (informative, not simply indicative) placed at the beginning, and a longer abstract submitted on a separate sheet. The latter will not be printed in this journal but will be forwarded to "Chemical Abstracts" by the editor. The abstract is not counted in the 1000-word limit.

Inadequacy of experimental details has been a major objection to communications in their present format. Authors are encouraged to overcome this objection in one or both of the following ways: (a) inclusion of specific experimental procedures in the communication when appropriate; (b) submission of supplementary data along with the communication, for publication in the microfilm edition of the journal. {The supplementary material will appear in the microfilm edition immediately following the article with which it is associated. A footnote in the printed journal [for format, see footnote 15, *J. Org. Chem.*, **37**, 949 (1972)] will alert the reader to the microfilm supplement. See editorial in *ibid.*, **36**, No. 13, 2A (1971). See also J. A. Moore, *J. Chem. Doc.*, **12**, 75 (1972), and J. H. Kuney, *ibid.*, **12**, 78 (1972).} The supplementary sections will be available on request as soon as a journal issue appears.

Supplementary pages for the microfilm edition are not restricted to the presentation of experimental details but may be used for supporting data, spectral assignments, or other material that cannot be handled within the 1000-word limit. Page charges do not apply to supplementary sections in the microfilm edition.

Thus, contributions to the Communications section may be of two types: (a) preliminary announcements of findings of exceptional interest and utility; (b) concise accounts of significant work that is more comprehensive and broader in scope but which can be presented within the space limitation of 1000 words, amplified by a supplementary section for the microfilm edition. Contributions of the second type will, in some (perhaps many) instances, comprise a final account of the work. (The supplementary material will be indexed by *Chemical Abstracts*.)

It is the hope of the Editors and the Advisory Board that the Communications section, with the opportunity for supplementary data in the microfilm edition of the journal, will be a valuable addition to the scientific community.

Synthesis of Diacyl[3]ferrocenophanes.[1]
Heteroannular Directing Effects in Friedel–Crafts Acylations

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The Friedel–Crafts diacylation of [3]ferrocenophane (TMF) yielded four of the six theoretically possible heteroannular diacetyl isomers. The eclipsed isomers, 2,2' and 3,3', were not detected, but one homoannular isomer, 3,4-diacetyl TMF, was isolated. All possible acetyl–cinnamoyl TMF's were formed except the eclipsed ones, but only two of the dicinnamoyl isomers were produced in isolable quantities. Structure assignments of the acetyl–cinnamoyl and dicinnamoyl derivatives were based on the conversion to the diacetyl derivatives via a base-catalyzed reverse aldol type condensation (reverse Claisen–Schmidt). A significant directing effect of the acyl group of the monoacetyl derivative was noted. Using AlCl₃ as catalyst, the yield of the 2,3' isomer was six times that of the 2,4'. A 2,3'/2,4' isomer ratio of approximately 3 was obtained when BF₃ was used as the catalyst. A model based on BF₃ and AlCl₃ complexes with the carbonyl of the monoacyl derivative was used to explain the directing effects.

Recent investigations in our laboratories involving the synthesis of bridged ferrocenophanes required the synthesis, isolation, and purification of several of the isomeric heteroannular diacyl[3]ferrocenophanes. The diacylation of [3]ferrocenophane or 1,1'-trimethyleneferrocene (1) (TMF) may lead to six isomers exclusive of optical isomers. Except for the work of Rinehart, et al.,[2] and Schlögl, et al.,[3] attempts to synthesize and identify pure isomers of diacetylated [3]ferrocenophane have not been reported. Rinehart, et al.[2] identified a by-product from monoacetylation of 1 as 3,4'-diacetyl TMF (9) on the basis of the double ring closure of the dipropionic acid derived from 9 as well as the infrared and nmr spectra of 9.

Schlögl, et al.,[3] discussed the six isomeric compounds (4–9) which may in theory be obtained from the diacetylation of TMF (Figure 1). The acetyl chloride-aluminum chloride diacetylation of TMF and chromatography on alumina gave three fractions whose relative amounts, in order of elution, were 1:40:60. The general observation[2] that alkylferrocenes with α-acyl groups are eluted more quickly than β derivatives and the relative amounts of the fractions obtained led Schlögl to speculate that the smallest fraction might be a mixture of 5 and 6, the intermediate fraction a mixture of 4 and 7, and the largest fraction a mixture

of 8 and 9, though reliable structural assignments were not possible.

We have prepared, separated, and identified four of the six possible heteroannularly diacetylated [3]-ferrocenophanes and a number of cinnamoylated derivatives. Chemical interconversions and spectroscopic methods were used in determining the structural assignments. We have shown that Schlögl's tentative interpretation was in error. His smallest fraction was most probably 7, the intermediate fraction 5 and 6, and the largest fraction 9. If any 4 and 8 were present in Schlögl's mixture, they would probably be with 7 and 9, respectively. This elution sequence (αα', αβ', ββ') follows that previously suggested,[4] which can give mixtures such as 5 and 6 in the αβ' fraction.

Results and Discussion

Acetylation of [3]Ferrocenophane (1).—The Friedel–Crafts acetylation of [3]ferrocenophane (1) with an excess of acetyl chloride-aluminum chloride yielded four of the six theoretically obtainable heteroannularly disubstituted products. A fifth isomer, the homoannularly disubstituted 3,4-diacetyl[3]ferrocenophane (10), was also obtained in small yield (see Table I).

The major product, 3,4'-diacetyl[3]ferrocenophane (9), has been described previously.[2] The remaining three isomeric products were identified as 2,3'-diacetyl-[3]ferrocenophane (5), 2,4'-diacetyl[3]ferrocenophane (6), and 2,5'-diacetyl[3]ferrocenophane (7) by nmr

(1) Ferrocenophane nomenclature conforms to that suggested by B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964, pp 8–23. For a review, see W. E. Watts, *Organometal. Chem. Rev.*, **2**, 231 (1967).

(2) K. Rinehart, D. Bublitz, and D. Gustafson, *J. Amer. Chem. Soc.*, **85**, 970 (1963).

(3) K. Schlögl, M. Peterlik, and H. Seiler, *Monatsh. Chem.*, **93**, 1309 (1962).

(4) M. Rosenblum and R. B. Woodward, *J. Amer. Chem. Soc.*, **80**, 5443 (1958).
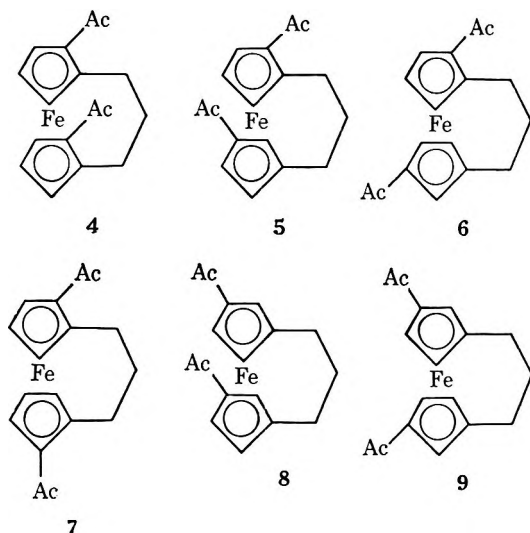
Figure 1.—Heteroannularly diacetylated [3]ferrocenophanes.
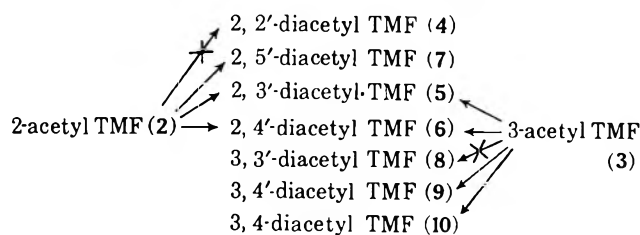
Figure 2.—Acetylation products of 2-acetyl TMF and 3-acetyl TMF.

Figure 3.—Structure correlation of 2,3'-diacetyl[3]ferrocenophane (5).

spectroscopy, by unambiguous synthesis from known starting materials, and by conversion of the 2,3'-diacetyl isomer 5 into a previously reported compound.[2] It should be noted that the two theoretical isomers not isolated from the reaction are the eclipsed products 2,2'-diacetyl[3]ferrocenophane (4) and 3,3'-diacetyl-[3]ferrocenophane (8).

Product Identification.—The acetylation of 2-acetyl-[3]ferrocenophane (2) and 3-acetyl[3]ferrocenophane (3) has provided evidence for the structures assigned to the unreported diacetyl isomers. Four heteroannularly diacetylated isomers are theoretically possible from the acetylation of each of these starting materials. Two of these four isomers are common to both reactions (see Figure 2). Again, the eclipsed isomers were not obtained.

The structures assigned to compounds 5 and 6 on the basis of their nmr spectra were supported by chemical evidence. Compound 5 was converted to 2,3'-[3]ferrocenophanyldipropionic acid (26), which was then cyclized and reduced to 2-[3][3]-1,3-ferrocenophanylpropionic acid (27). Attempts to cyclize and reduce 27 to the known [3][3][3]-1,2,3-ferrocenophane[2] were unsuccessful. Compound 27 was also synthesized by a known route[2] from 2-acetyl[3][3]-1,3-ferroceno-phane (28) and shown to be identical with the sample obtained from compound 5 (Figure 3).

The structural assignments for compounds 7 and 10 were made primarily on the basis of their very characteristic nmr spectra.[5] The 2,5'-diacetyl[3]ferrocenophane (7) shows a doublet of doublets at τ 6.11

for the 5 and 2' protons, a triplet at τ 5.70 for the 4 and 3' protons, and a doublet of doublets at τ 5.53 for the 3 and 4' protons. Compound 7 also shows two of the trimethylene bridge protons to be shifted downfield, indicating substitution α to the bridge.[5] The homoannularly disubstituted isomer, 3,4-diacetyl[3]-ferrocenophane (10), gives a singlet at τ 5.35 for the remaining protons on the substituted ring, i.e., the 2 and 5 protons, and a multiplet centered at τ 5.88 for the protons of the unsubstituted ring. This multiplet is superimposable with the multiplet produced by [3]ferrocenophane (1) itself. Compound 10 shows no downfield bridge protons. A homoannular diacetyl-ferrocene has been reported[6,7] to be 1,2-diacetylfer-rocene, which is also αα-substituted with respect to the two acetyl groups.

The identification of mixed acetyl-cinnamoyl and dicinnamoyl isomers was made by converting them to the corresponding diacetyl compounds (see Experimental Section).

Mechanism of Acetylation.—The acetylation of 2-acetyl[3]ferrocenophane (2) and 3-acetyl[3]ferro-cenophane (3) leads to product isomer ratios which cannot be explained by steric or electronic effects.[8] For example, the acetylation of 2-acetyl[3]ferroceno-phane with acetyl chloride–aluminum chloride gives 6.0 times as much of the 2,3'-diacetyl[3]ferrocenophane (5), expected to be a minor product on steric grounds, as of the 2,4'-diacetyl[3]ferrocenophane (6). Similarly, the acetylation of 3-acetyl[3]ferrocenophane gives 2.5 times as much of the more hindered 5 as of the less hindered 6. (Overall yields of diacetylated products for these reactions are 90 and 91%, respectively.)

The results of experiments designed to investigate this phenomenon are shown in Table II and can be briefly summarized as follows. Aluminum chloride gives high yields of diacetylated products with the site of substitution being relatively specific; boron trifluoride gives lower yields and is less specific; and boron trifluoride etherate gives no diacetylated products. This,

(5) An in-depth discussion of the nmr spectra for all the isomers 1–9 and 24 has been presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, and is in press.

(6) P. Carty and M. F. A. Dove, *J. Organometal. Chem.*, **21**, 195 (1970).

(7) J. H. Richards and T. J. Curphey, *Chem. Ind. (London)*, 1456 (1956).

(8) H. L. Lentzner and W. E. Watts, *Chem. Commun.*, 906 (1970).

TABLE I
NMR SPECTRA[a]

No.	Compd[b]	Ring protons[c]	Bridge protons[c]	Acetyl group[c]	Cinnamoyl group[c,e]
1	TMF	6.02 (m, 8 H)	8.05 (s, 5 H)		
2	2-ATMF	5.41 (t, 1 H), 5.71 (d, 2 H), 5.7–5.85 (m, 1 H), 5.9–6.15 (m, 2 H), 6.27 (m, 1 H)	7.0–7.4 (m, 1 H)[d] 7.8–8.2 (m, 5 H)	7.66 (s, 3 H)	
3	3-ATMF	5.41 (b, 2 H), 5.72 (t, 2 H), 5.75–5.85 (m, 1 H), 6.12 (m, 2 H)	7.9–8.2 (m, 6 H)	7.65 (s, 3 H)	
4	2,2'-AATMF	Not detected			
5	2,3'-AATMF	5.3–5.6 (m, 4 H), 5.75 (m, 2 H)	7.0–7.4 (m, 1 H)[d] 7.96 (m, 5 H)	7.61 (s, 3 H) 7.73 (s, 3 H)	
6	2,4'-AATMF	5.2 (m, 2 H), 5.42 (t, 1 H), 5.5 (q, 1 H), 5.85 (t, 1 H), 6.03 (q, 1 H)	7.1–7.5 (m, 1 H)[d] 7.95 (m, 5 H)	7.66 (s, 3 H) 7.68 (s, 3 H)	
7	2,5'-AATMF	5.38 (q, 2 H), 5.56 (t, 2 H), 6.05 (q, 2 H)	7.0–7.5 (m, 2 H)[d] 7.8–8.1 (m, 4 H)	7.75 (s, 6 H)	
8	3,3'-AATMF	Not detected			
9	3,4'-AATMF	5.4 (t, 2 H), 5.48 (d, 4 H)	8.01 (s, 6 H)	7.66 (s, 6 H)	
10	3,4-AATMF	5.21 (s, 2 H), 5.80 (m, 4 H)	7.9–8.2 (m, 6 H)	7.53 (s, 6 H)	
11	2A-2'-CTMF	Not detected			
12	2A-3'-CTMF	5.25 (q, 1 H), 5.4–5.55 (m, 3 H), 5.67 (q, 1 H), 5.79 (t, 1 H)	6.9–7.3 (m, 1 H)[d] 7.8–8.1 (m, 5 H)	7.76 (s, 3 H)	2.39 (m, 7 H)
13	2A-4'-CTMF	5.04 (q, 1 H), 5.1–5.23 (m, 2 H), 5.46 (q, 1 H), 5.83 (t, 1 H), 5.92 (q, 1 H)	7.1–7.4 (m, 1 H)[d] 7.7–8.1 (m, 5 H)	7.64 (s, 3 H)	2.62 (m, 7 H)
14	2A-5'-CTMF	5.25 (q, 1 H), 5.35 (q, 1 H) 5.47 (m, 2 H), 5.95 (m, 2 H)	7.0–7.4 (m, 2 H)[d] 7.8–8.0 (m, 4 H)	7.72 (s, 3 H)	2.63 (m, 7 H)
15	3A-2'-CTMF	5.25–5.6 (m, 4 H), 5.65–5.8 (m, 2 H)	7.0–7.4 (m, 1 H)[d] 7.8–8.1 (m, 5 H)	7.65 (s, 3 H)	2.64 (m, 7 H)
16	3A-3'-CTMF	Not detected			
17	3A-4'-CTMF	5.2–5.45 (m, 4 H), 5.49 (d, 2 H)	7.99 (s, 6 H)	7.67 (s, 3 H)	2.55 (m, 7 H)
18	3A-5'-CTMF	5.1 (s, 2 H), 5.4 (m, 2 H), 5.77 (t, 1 H), 5.98 (q, 1 H)	7.0–7.4 (m, 1 H)[d] 7.8–8.1 (m, 5 H)	7.67 (s, 3 H)	2.58 (m, 7 H)
19	2-CTMF	5.28 (t, 1 H), 5.62 (d, 2 H), 5.65–5.75 (m, 1 H), 5.9–6.15 (m, 2 H), 6.22 (m, 1 H)	6.9–7.3 (m, 1 H)[d] 7.7–8.1 (m, 5 H)		2.58 (m, 7 H)
20	3-CTMF	5.22 (d, 2 H), 5.59 (t, 1 H), 5.71 (m, 2 H), 6.03 (m, 2 H)	7.8–8.2 (m, 6 H)		2.56 (m, 7 H)
21	2,2'-CCTMF	Not detected			
22	2,3'-CCTMF	5.17 (q, 1 H), 5.25–5.5 (m, 3 H), 5.67 (m, 2 H)	6.85–7.3 (m, 1 H)[d] 7.6–8.1 (m, 5 H)		2.58 (m, 7 H) 2.67 (m, 7 H)
23	2,5'-CCTMF	Not detected			
24	3,3'-CCTMF	Not detected			
25	3,4'-CCTMF	5.18 (t, 2 H), 5.25–5.45 (m, 4 H)	7.95 (s, 6 H)		2.57 (m, 14 H)
27		6.12 (m, 4 H), 6.59 (s, 1 H)	7.23–8.55 (m, 16 H)[f]		

[a] Chemical shifts (τ) measured in CDCl$_3$ solution. [b] TMF = 1,1'-trimethyleneferrocene, A = acetyl, AA = diacetyl, C = cinnamoyl, CC = dicinnamoyl. [c] In order: chemical shift, multiplicity, number of protons. [d] These resonances indicate ring acylation α to the trimethylene bridge: G. J. Gauthier, J. A. Winstead, and A. D. Brown, Jr., *Tetrahedron Lett.*, 1593 (1970). [e] Includes phenyl group resonances. [f] Includes aliphatic protons of propionic acid side chain.

TABLE II
SUBSEQUENT ACYLATION OF ACYL[3]FERROCENOPHANE

Substrate	Catalyst	Moles of catalyst/ moles of substrate	Yield (overall) of acetylated product, %	Isomer distribution
2-acetyl TMF	AlCl$_3$	1	0	
	AlCl$_3$	2	90	**5:6:7** = 9.8:1.6:1.0
	BF$_3$	2	69	**5:6:7** = 6.7:2.4:1.0
	BF$_3$:O(C$_2$H$_5$)$_2$	2	0	
3-acetyl TMF	AlCl$_3$	1	0	
	AlCl$_3$	2	91	**9:5:6:10** = 39.0:11.4:4.5:1.0
2-cinnamoyl TMF	AlCl$_3$	2	60	**15:18:14** = 3.2:1.2:1.0
3-cinnamoyl TMF	AlCl$_3$	2	65	**17:12:13** = 8.6:2.0:1.0

along with the isomer distributions obtained from the acetylation of various acetyl and cinnamoyl [3]ferrocenophanes, indicates that the first acyl substituent directs the attacking group to a position on the second, unsubstituted ring as indicated in Figure 4 by arrows. A transition state such as that shown in Figure 4 would

account for all of the above observations. Such a complex[9] would be of approximately the right length to reach the positions on the unsubstituted ring, which are indicated by arrows and would be too short to reach

(9) Figure 4 is meant only to be indicative and no significance should be placed on coordinations shown for aluminum species.
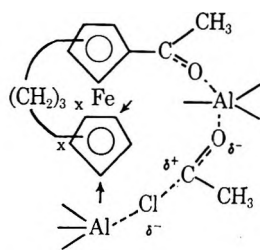
Figure 4.—Complex intermediate.
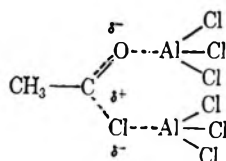
Figure 5.—Acetyl chloride–aluminum chloride 1:2 complex.

the positions indicated by x's. (It should be noted that the configurations of the rings are frozen with respect to each other by the presence of the trimethylene bridge.)

If the complex pictured in Figure 4 is plausible, the acetyl[3]ferrocenophane must be capable of complexing with aluminum chloride at the carbonyl oxygen and the acetyl chloride must be capable of complexing with two aluminum chloride molecules. That this is true can be seen by examining the infrared spectra summarized in Table III. The complexation of the carbonyl

TABLE III

CARBONYL STRETCHING FREQUENCIES OF $AlCl_3$ COMPLEXES

Compd	Molar ratio of $AlCl_3$	C=O, cm^{-1}
3-Acetyl TMF	0	1660[a]
3-Acetyl TMF	1	1510[a]
3-Acetyl TMF	2	1510[a]
Acetyl chloride	0	1805[b]
Acetyl chloride	1	1630,[b] 2200, 2300
Acetyl chloride	2	~1780[a]

[a] Measured in methylene chloride solution. [b] Data from D. Cassimatis, J. P. Bonnin, and T. Theophanides, *Can. J. Chem.*, 48, 3860 (1970), and references cited therein.

oxygen of 3-acetyl[3]ferrocenophane with aluminum chloride is shown by the strong bathochromic shift (150 cm^{-1}) of the carbonyl stretching band on addition of an equivalent amount of aluminum chloride. (The addition of a second equivalent of aluminum chloride does not affect this absorption.)

Cassimatis, *et al.*,[10] have shown that acetyl chloride forms a 1:1 complex with aluminum chloride that shows a strong hypsochromic shift corresponding to complexation by aluminum at the chlorine of acetyl chloride and a bathochromic shift (175 cm^{-1}) corresponding to complexation at the carbonyl oxygen. The infrared spectrum of an acetyl chloride–aluminum chloride 1:2 mixture shows only a broad absorption at ~1780 cm^{-1} for the carbonyl which would be indicative of a structure such as that shown in Figure 5, that is, a complexation by aluminum at both the chlorine and the carbonyl oxygen of acetyl chloride, giving a car-

bonyl stretching absorption between the two extremes previously cited.[10]

It can be seen from Table II that Lewis acids which are poorer complexing agents than aluminum chloride, *e.g.*, boron trifluoride[11] and boron trifluoride etherate, give poorer overall yields and less specificity than aluminum chloride. An investigation of this phenomenon has been undertaken by this laboratory. Results will be published in the near future.

Experimental Section

Methylene chloride (Baker Analyzed) was dried immediately prior to use in the acylation reactions by passing it through a column of activity I alumina. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian A-60 nmr spectrometer using tetramethylsilane as an internal standard and deuteriochloroform as a solvent. The nmr data is presented in Table I. Infrared spectra were obtained in methylene chloride solution in 1.0 mm solution cells with sodium chloride windows. Spectra were obtained on a Beckman IR-20 in double beam mode with solvent in the reference beam. All melting points were determined using a Reichert Austria melting point apparatus and are uncorrected. Analyses were performed at Galbraith Laboratories, Inc., Knoxville, Tenn., and at Huffman Laboratories, Inc., Wheatridge, Colo.

Acylation of [3]Ferrocenophane (1).—Monoacyl[3]ferrocenophanes were prepared by reacting equimolar amounts of acid chloride, aluminum chloride, and [3]ferrocenophane. Diacyl[3]ferrocenophanes required a 2:1 or greater molar ratio of the acid chloride and the aluminum chloride to [3]ferrocenophane. As a typical experiment, diacetyl[3]ferrocenophanes were prepared by adding a solution of 5.7 g (73 mmol) of acetyl chloride and 12.6 g (95 mmol) of $AlCl_3$ in 150 ml of methylene chloride to a solution of 6.0 g (26 mmol) of [3]ferrocenophane in 150 ml of methylene chloride. The reaction was allowed to proceed with stirring in a nitrogen atmosphere for 5 hr at 25° and then was quenched by pouring into 200 ml of ice water. The organic layer was separated and the aqueous solution was extracted with methylene chloride. The combined organic solutions were dried ($MgSO_4$) and concentrated *in vacuo* to an oily residue. The separation of isomers is described below.

Acylation of Acyl[3]ferrocenophane.—Acylation of an acyl[3]ferrocenophane required 1 mol of acid chloride and 2 mol of $AlCl_3$ to 1 mol of the acyl[3]ferrocenophane. The synthesis of the acetyl derivatives of 3-cinnamoyl[3]ferrocenophane illustrates a typical reaction. To a solution of 1.6 g (4.5 mmol) of 3-cinnamoyl[3]ferrocenophane (20) and 0.74 g (5.6 mmol) of $AlCl_3$ in 60 ml of dry methylene chloride was added dropwise, under nitrogen, a solution of 0.44 g (5.6 mmol) of acetyl chloride and 0.74 g (5.6 mmol) of $AlCl_3$ in 60 ml of methylene chloride. The reaction was allowed to proceed for 5 hr at 25° and was quenched by pouring into 100 ml of ice water. Acetylations of 2- and 3-acetyl[3]ferrocenophanes were run for 16 hr. The organic layer was combined with the methylene chloride extractions of the aqueous layer, dried ($MgSO_4$), and concentrated *in vacuo*.

Acetylation of 2-Acetyl[3]ferrocenophane with Acetic Anhydride and BF$_3$.—2-Acetyl[3]ferrocenophane (2) was acetylated using the acetic anhydride/BF$_3$ procedure of Carty and Dove[6] to determine the 2,3':2,4' isomer ratio. A stirred solution of 0.89 g (3.3 mmol) of 2 and 0.51 g (5 mmol) of acetic anhydride in 50 ml of dry, oxygen-free methylene chloride was saturated with purified BF$_3$ at 0°. The BF$_3$ was purified by bubbling through concentrated sulfuric acid saturated with boric oxide and then through a Dry Ice–acetone trap. The reaction mixture was stirred for 4 hr at 0° and then the excess boron trifluoride was expelled with nitrogen. Saturated sodium acetate was added and the methylene chloride layer was separated, washed with water, dried ($MgSO_4$), and evaporated to yield an oily residue.

The isomers were separated as described below to yield a trace of starting material, 0.07 g of the 2,5'-diacetyl isomer 7, 0.48 g

(10) D. Cassimatis, J. P. Bonnin, and T. Theophanides, *Can. J. Chem.*, 48, 3860 (1970).

(11) BF$_3$ has been shown to cause a bathochromic shift of carbonyl stretching frequencies on the order of 75 cm^{-1}: M. Rabinovitz and A. Grinvold, *Tetrahedron Lett.*, 641 (1971).

of the 2,3' isomer **5**, and 0.17 g of the 2,4'-diacetyl[3]ferrocenophane (**6**) for a 70% overall yield.

Separation of Isomers. Diacetyl Isomers of [3]Ferrocenophane.—The oily residue from the diacylation of 6.0 g (26.5 mmol) of **1** was chromatographed on deactivated neutral alumina. Six bands developed. The first band, eluted with petroleum ether (bp 20–40°)–diethyl ether (3:2), gave 1.6 g of starting material. The second band, also eluted with petroleum ether–diethyl ether, yielded 0.06 g (0.8%) of yellow-orange needles of 3-acetyl[3]ferrocenophane (**3**). The third band yielded 0.12 g (1.5%) of the 2,5'-diacetyl isomer **7**, which was recrystallized from hexane as red-orange plates, mp 144–146°. The fourth band contained a mixture of the 2,3' and 2,4' isomers (**5** and **6**, respectively). The 2,3'-diacetyl[3]ferrocenophane (**5**) crystallized from a hexane solution of the mixture to yield 1.16 g of orange plates, mp 113–114°. The fifth band was eluted with methylene chloride and yielded 0.024 g of 3,4-diacetyl[3]ferrocenophane (**10**), which crystallized from hexane as orange plates, mp 109–111°. The sixth band, also eluted with methylene chloride, yielded 1.6 g (19%) of 3,4'-diacetyl[3]ferrocenophane (**9**) as orange plates, mp 132–134°.

The supernatant from fraction four, after the fractional crystallization of **5**, was chromatographed on silica columns using methylene chloride–chloroform (1:1) and loading each column with a very small amount of the mixture. Combination of the first fraction from six 3 × 50 cm silica columns gave, after crystallization from petroleum ether (bp 60–110°), 0.29 g (3.5%) of the 2,4'-diacetyl[3]ferrocenophane (**6**) as red-orange blocks, mp 94–96°. The second fractions yielded an additional 0.14 g of **5** for a total yield of 1.3 g (16%) of 2,3'-diacetyl[3]ferrocenophane.

Anal. Calcd for $C_{17}H_{18}O_2Fe$: C, 65.85; H, 5.85; Fe, 18.01. Found—2,5' isomer (**7**): C, 65.97; H, 5.93; Fe, 17.85. 2,4' isomer (**6**): C, 65.74; H, 5.86; Fe, 17.83. 2,3' isomer (**5**): C, 65.69; H, 5.94; Fe, 18.05. 3,4 isomer (**10**): C, 65.96; H, 5.95; Fe, 17.52. 3,4' isomer (**9**): C, 65.95; H, 5.94; Fe, 17.83.

Diacetyl Isomers from Acetylation of 3-Acetyl[3]ferrocenophane.—The product mixture from the acetylation of 3.89 g (14.5 mmol) of **3** was first chromatographed on deactivated neutral alumina. Four bands developed. The first band, eluted with petroleum ether (bp 20–40°)–diethyl ether (3:2), gave a trace of starting material. The second band, eluted with the same solvent, was a mixture of **5** and **6**. The third band yielded 0.074 g of **10**. The fourth band, eluted with chloroform, yielded 2.87 g (64%) of **9**. After fractional crystallization of 0.68 g of **5** from fraction 2, the remaining mixture was rechromatographed on silica columns. The first band, eluted with methylene chloride–chloroform (1:1), yielded 0.33 g (7%) of **6**. The second band, eluted with chloroform, gave 0.16 g of **5** for a total yield of 0.84 g (19%) of **5**. Overall yield for the diacetyl isomers was 91%.

Diacetyl Isomers from Acetylation of 2-Acetyl[3]ferrocenophane.—The oily residue obtained from the acetylation of 1.68 g (6.3 mmol) of **2**, after work-up, was chromatographed on deactivated neutral alumina. The first band, eluted with petroleum ether–diethyl ether (2:1), yielded 0.14 g of **7**. The second band, eluted with methylene chloride, was a mixture of **5** and **6**. After fractional crystallization of 1.06 g of **5** from fraction 2, the remaining mixture was chromatographed on silica, as described above, to yield 0.23 g of **6** and an additional 0.32 g of **5**. Total yield of the diacetyl isomers was 90%.

Dicinnamoyl Isomers of [3]Ferrocenophane.—The mixture of isomers from the dicinnamoylation of 2.6 g (11.5 mmol) of **1** was chromatographed on neutral alumina employing mixtures of petroleum ether (bp 20–40°), methylene chloride, and chloroform as eluents. Two bands developed. The first band gave, after recrystallization from hexane, 0.8 g (14%) of 2,3'-dicinnamoyl[3]ferrocenophane (**22**) as red-orange needles, mp 138–140°. The second band yielded, after recrystallization from petroleum ether (bp 30–60°), 2.6 g (47%) of 3,4'-dicinnamoyl[3]ferrocenophane (**25**) as red blocks, mp 205–207°.

Anal. Calcd for $C_{31}H_{26}O_2Fe$: C, 76.55; H, 5.39; Fe, 11.48. Found—3,4' isomer (**25**): C, 76.59; H, 5.49; Fe, 11.39. 2,3' isomer (**22**): C, 76.57; H, 5.61; Fe, 11.51.

Cinnamoyl Isomers of [3]Ferrocenophane.—The oily residue from the monocinnamoylation of 4.0 g (17.6 mmol) of **1** was chromatographed on neutral alumina. Three bands developed. The first was eluted with petroleum ether (bp 20–40°)–ether (3:2) yielding 0.2 g of starting material. The second band,

eluted with ether, gave, after recrystallization from petroleum ether, 1.15 g (18%) of 2-cinnamoyl[3]ferrocenophane (**19**) as reddish-orange needles, mp 131–133°. The third band was eluted with a mixture of methylene chloride and chloroform. After recrystallization from low-boiling petroleum ether, the third band yielded 3.45 g (55%) of 3-cinnamoyl[3]ferrocenophane (**20**) as red plates, mp 145–146°.

Anal. Calcd for $C_{22}H_{20}OFe$: C, 74.17; H, 5.66; Fe, 15.68. Found—2 isomer (**19**): C, 73.95; H, 5.72; Fe, 15.70. 3 isomer (**20**): C, 74.12; H, 5.74; Fe, 15.43.

Acetyl Isomers of 3-Cinnamoyl[3]ferrocenophane.—The mixture of isomers from the acetylation of 1.6 g (4.5 mmol) of **20** was chromatographed on neutral alumina. Three bands developed. The first band was eluted with hexane–benzene (1:1) and yielded 0.10 g (5.5%) of 2-acetyl-4'-cinnamoyl[3]ferrocenophane (**13**) (or 3-cinnamoyl-5'-acetyl[3]ferrocenophane) which crystallized from petroleum ether (bp 30–60°) as orange plates, mp 58–60°. The second band, eluted with benzene, gave 0.20 g (11%) of 2-acetyl-3'-cinnamoyl[3]ferrocenophane (**12**). This isomer crystallized from cyclohexane as orange plates, mp 131–133°. Petroleum ether (bp 20–40°)–diethyl ether (3:2) eluted the first two bands in reverse order (*i.e.*, compound **12** before **13**). In both cases the separation was difficult. Methylene chloride eluted a third band which yielded 0.86 g (48%) of 3-acetyl-4'-cinnamoyl[3]ferrocenophane (**17**) (3-cinnamoyl-4'-acetyl[3]ferrocenophane) as orange plates, mp 163–165°.

Anal. Calcd for $C_{24}H_{22}O_2Fe$: C, 72.38; H, 5.57; Fe, 14.02. Found—2-Acetyl-3'-cinnamoyl isomer (**12**): C, 72.45; H, 5.60; Fe, 13.75. 2-Acetyl-4'-cinnamoyl isomer (**13**): C, 72.44; H, 5.60; Fe, 13.75. 3-Acetyl-4'-cinnamoyl isomer (**17**): C, 72.47; H, 5.62; Fe, 14.30.

Acetyl Isomers of 2-Cinnamoyl[3]ferrocenophane.—The mixture of isomers from the acetylation of 0.8 g (2.2 mmol) of **19** was chromatographed on neutral alumina employing mixtures of petroleum ether (bp 20–40°), diethyl ether, and methylene chloride as eluents. Four bands developed. The first band yielded 0.05 g of starting material. The second band gave, after recrystallization from hexane, 0.10 g (11%) of 2-acetyl-5'-cinnamoyl[3]ferrocenophane (**14**) as red plates, mp 155–157°. The third band yielded 0.12 g (13%) of 3-acetyl-5'-cinnamoyl-[3]ferrocenophane (**18**) which crystallized from hexane as rods, mp 180–181°. The fourth band gave 0.32 g (37%) of 3-acetyl-2'-cinnamoyl[3]ferrocenophane (**15**), mp 212–213.5°.

Anal. Calcd for $C_{24}H_{22}O_2Fe$: C, 72.38; H, 5.57; Fe, 14.02. Found—2-Acetyl-5'-cinnamoyl isomer (**14**): C, 72.49; H, 5.68; Fe, 13.90. 3-Acetyl-2'-cinnamoyl isomer (**15**): C, 72.44; H, 5.45; Fe, 14.30. 3-Acetyl-5'-cinnamoyl isomer (**18**): C, 72.49; H, 5.33; Fe, 14.19.

Interconversion of Acetyl and Cinnamoyl Derivatives of [3]Ferrocenophane.—The cinnamoyl derivatives of trimethyleneferrocene were converted to acetyl derivatives by heating them to 68° in aqueous ethanol under nitrogen in the presence of NaOH for 24 hr. As a typical experiment, 0.7 g (1.75 mmol) of 3-acetyl-4'-cinnamoyl[3]ferrocenophane (**17**) was dissolved in 100 ml of 95% ethanol, and 20 ml of aqueous 15% NaOH was added. The solution was then heated under nitrogen for 24 hr at 68°, diluted with two volumes of water, extracted with methylene chloride, and dried ($MgSO_4$). After concentrating, the residue from the work-up of the reaction mixture was chromatographed on neutral alumina employing petroleum ether (bp 20–40°)–diethyl ether (3:2). The major band yielded 0.36 g (66%) of 3,4'-diacetyl[3]ferrocenophane (**9**), mp 131–134°.

Acetyl derivatives were converted to cinnamoyl derivatives by addition of benzaldehyde to a solution of the acetyl derivative and NaOH in aqueous ethanol. For example, 0.24 g (2.4 mmol) of benzaldehyde was added to a solution of 0.5 g (1.6 mmol) of 3,4'-diacetyl[3]ferrocenophane (**9**) in 50 ml of 95% ethanol and 5 ml of aqueous 15% NaOH. The reaction mixture was stirred under nitrogen at 25° for 24 hr. The solution was diluted with 50 ml of water, extracted with methylene chloride, dried (MgSO₄), concentrated, and chromatographed on neutral alumina. The first band, eluted with petroleum ether–diethyl ether (3:2), gave 0.19 g (30%) of 3-acetyl-4'-cinnamoyl[3]ferrocenophane (**17**), mp 162–164°. The second band, eluted with diethyl ether, yielded 0.09 g of starting material. The third band, eluted with methylene chloride, yielded 0.2 g (25%) of 3,4'-dicinnamoyl[3]ferrocenophane (**25**), mp 203–207°. This reaction in the presence of excess benzaldehyde (10:1) yielded only the dicinnamoyl derivative **25**.

The results of a number of interconversions are summarized in Table IV. The melting points of the products are given and

Starting isomer	Product	Yield, %	Mp, °C
9 (9:PhCHO; 1:1.5)	17	30	162–164
	9	18	132–134
	25	25	203–207
9 (9:PhCHO; 1:10)	25	61	205–207
12	5	64	113–114
13	6	64	93–96
14	7	53	145–146
15	5	51	110–113
17	9	66	131–134
18	6	64	94–96
22	5	78	112–114
25	17	57	163–165
	9	Trace	

in all cases the nmr spectra of the products were identical with those of the isomer assigned.

Conversion of 2,3'-Diacetyl[3]ferrocenophane (5) to 2-[3][3]-1,3-ferrocenophanylpropionic Acid.—A mixture of 2.38 g (7.6 mmol) of 5 was converted to 1.56 g (55%) of 2,3'-[3]ferrocenophanyldipropionic acid (26), mp 158–162°, according to the procedure of Rinehart, et al.[2]

The diacid 26 (1.56 g, 4.2 mmol) was dissolved in 100 ml of dry methylene chloride and added slowly to a solution of 5 g (26 mmol) of trifluoroacetic anhydride in 50 ml of cold methylene chloride. The solution was maintained at 0° in a nitrogen atmosphere for 22 hr, then quenched by the addition of 100 ml of 5% sodium bicarbonate. The pH of the solution was adjusted to 6 so that the acid would remain in the organic layer. After separation of the organic layer and the extraction of the aqueous layer, the combined organic fractions were dried (MgSO₄) and concentrated. The material was chromatographed on a silica gel column packed in chloroform. Four bands developed. The first band, eluted with chloroform, and the second band,

eluted with chloroform–ethyl acetate (3:1), were unidentified. The third band, also eluted with the chloroform–ethyl acetate mixture, yielded 0.63 g (43%) of the crude yellow oily dibridged keto acid. The fourth band, eluted with methanol, was probably a mixture of decomposition products. The keto acid was dissolved in 50 ml of acetic acid and hydrogenated over 0.5 g of platinum oxide at 52 psi for 65 hr. After work-up, a yield of 0.57 g of oil was obtained. Repeated recrystallization from petroleum ether gave 0.28 g (46%) of 2-[3][3]-1,3-ferrocenophanylpropionic acid (27), mp 146–148°.

Anal. Calcd for $C_{19}H_{22}O_2Fe$: C, 67.47; H, 6.56; Fe, 16.51. Found: C, 67.63; H, 6.60; Fe, 16.41.

Preparation of 27 from 2-Acetyl[3][3]-1,3-ferrocenophane.—A solution of 3.0 g (11 mmol) of [3][3]-1,3-ferrocenophane (28, synthesized according to Rinehart, et al.[2]) and 2.75 ml of acetic anhydride in 50 ml of dry methylene chloride was cooled to 0° under nitrogen. BF₃ etherate (4 ml) was added and the solution was stirred at 0° for 30 min and then at 25° for 16 hr. The reaction was quenched by pouring into 50 ml of ice water. After work-up, the crude product was transferred to an alumina column and eluted with petroleum ether (bp 20–40°) to remove a trace of starting material and then 0.60 g (17%) of 2-acetyl[3][3]-1,3-ferrocenophane (28). Recrystallization of 28 from hexane yielded orange rods, mp 101–102° (lit.[2] mp 101–102.5°). A third band, eluted with petroleum ether–ether (4:1), yielded 1.9 g (55%) of 4-acetyl[3][3]-1,3-ferrocenophane, mp 148–149° (lit.[2] mp 148.5–149.5°).

A mixture of 0.5 g (1.6 mmol) of 28, 32 mmol of sodium hydride, and 0.6 g (4.8 mmol) of diethyl carbonate in 30 ml of dry benzene was heated at reflux for 48 hr in a nitrogen atmosphere. After the usual work-up, the crude keto acid was dissolved in 50 ml of acetic acid and hydrogenated over 0.3 g of platinum oxide at 52 psi for 48 hr. The reduced ester was isolated and saponified in refluxing ethanolic 2 N sodium hydroxide (1:1 ethanol–water). The crude acid obtained after work-up was purified on a silica gel column packed in chloroform. The first fraction, eluted with chloroform, was a mixture of nonacidic compounds. The acid was eluted with chloroform–ethyl acetate (3:1). Recrystallization from hexane yielded 0.25 g (46%) of yellow needles, mp 146.5–148°, whose nmr and infrared spectra were identical with those of 27 obtained from 5 described above.

Anal. Calcd for $C_{19}H_{22}O_2Fe$: C, 67.47; H, 6.56; Fe, 16.51. Found: C, 67.64; H, 6.59; Fe, 16.53.

The Base-Induced Rearrangement of Epoxides. IV.
Reaction of Cyclohexene Oxide with Various Lithium Alkylamides[1]

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The effect of variation of base structure in the reaction with cyclohexene oxide has been explored. The yields of the products 2-cyclohexenol, cyclohexanone, and amino alcohol (nucleophilic substitution) were determined for an extensive series of lithium alkylamides. The yield of 2-cyclohexenol is maximized with lithium di(primary alkyl)amide, being effectively quantitative with lithium di-*n*-propylamide and di-*n*-butylamide. Lithium monoalkylamides in general give low to moderate yields of the allylic alcohol, very little ketone, and extensive amino alcohol adduct formation. Bulky bases favor the formation of ketone at the expense of allylic alcohol. Certain bases cause the rearrangement of 2-cyclohexenol to 3-cyclohexenol, and the mechanism of this transformation has been briefly explored.

The reaction of epoxides with strong bases can occur by at least three major pathways, *viz.*, rearrangement to allylic alcohol, to ketone, or by direct nucleophilic substitution. Our earlier studies have been directed to the first process.[1b] The regiospecificity and stereospecificity exhibited in the reaction of a number of epoxides with lithium diethylamide to give allylic alcohol suggest the considerable synthetic potential

of this procedure. This paper describes the results of treating a single model system, cyclohexene oxide, with a wide range of lithium alkylamides, to test the effect of structural variation of the base on the yields of the various possible products.

Results and Discussion

The lithium alkylamide reagents were prepared by treating the appropriate amine in ether with *n*-butyllithium in hexane; 2.5 mol of base were used for each mole of epoxide. The excess of base was used because

(1) (a) Support by the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. (b) Part III: R. P. Thummel and B. Rickborn, *J. Org. Chem.*, **36**, 1365 (1971).

<div align="center">TABLE I</div>

Registry no.	Run	LiNHR, R =	Time, hr[a]	% 1	% 2	% 3	% 4
34566-51-3	1[b]	$C_6H_5CH_2$	24	26	0	0	70
34566-52-4	2[b]	$n\text{-}C_3H_7$	17	15	0.5	Trace	77
34566-53-5	3	$C_6H_5CH_2CH_2$	12	42	0	2	49
34566-54-6	4	$i\text{-}C_4H_9$	48	77	0	4	19
26372-63-4	5	$c\text{-}C_6H_{11}$	52	47	1	9	40
34566-56-8	6[c]	$C_6H_5CH_2(CH_3)CH$	21	53	0	4	39
34566-57-9	7	$i\text{-}C_3H_7$	41	75	0.5	5	10
34566-58-0	8	$sec\text{-}C_4H_9$	41	69	0	8	20
34566-59-1	9	$t\text{-}C_4H_9$	27[d]	60[d]	4	0	2

[a] The time required for loss of >93% of epoxide in all cases except run 9. Yields were determined by peak area measurement of vpc traces, using an inert internal standard as reference. [b] Cyclohexanol was also observed in some runs as follows: run 1, 3%; 2, 1.2%; 7, 0.6%. [c] *trans*-β-methylstyrene was formed in this reaction, presumably by base-induced elimination of either $LiNH_2$ or Li_2NH. [d] 66% of the epoxide was consumed in this time.

of a side reaction, the fragmentation of the ether solvent,[2] which consumes some of the amide reagent.

Lithium monoalkylamides provide a considerable range in yield of the 2-cyclohexenol product, with most of the remainder of the material balance appearing as amino alcohol adduct (these products were in most instances not specifically identified, but inferred from a relatively long retention time peak in the vpc trace). The data for the reaction shown in eq 1 are displayed in Table I. Several generalizations can be made. The primary alkylamides tend to give mostly adduct **4**, although the relatively bulky lithium isobutylamide does furnish 77% of the allylic alcohol **1**. The mono-

$$\text{(eq 1)}$$
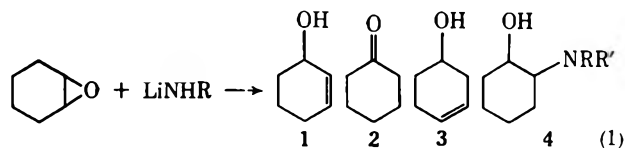
alkylamides, with one exception, do not give significant amounts of cyclohexanone. The exception is the only mono-*tert*-alkylamide examined (entry 9 in Table I). The rates of formation of adduct **4**, as judged from yields and the time required for reaction, vary in a manner consistent with a reaction having significant steric requirements. It appears that a major factor in the reaction of cyclohexene oxide with monoalkylamides is not the enhanced rate of formation of **4**, but rather the diminished rate (compared to lithium dialkylamide reactions) of the processes leading to **1** and **2**.

The relatively long times required for the reactions listed in Table I appear in part to be responsible for an interesting side reaction, the formation of homoallylic alcohol **3**. This process, described in greater detail later in this paper, occurs by further rearrangement of the initially formed 2-cyclohexenol.

The results obtained on treatment of cyclohexene oxide with a number of lithium dialkylamides are shown in Table II. In all instances the reactions are considerably faster than with the lithium monoalkylamides, requiring from 0.5 to 4 hr for complete consumption of the epoxide starting material.

The historically most widely used base, lithium diethylamide, gives a high yield of **1** (run 10), accompanied by a small amount of **2** and 10% of amino al-

cohol adduct. Although it might be thought difficult to improve on this already excellent yield, both lithium di-*n*-propylamide and di-*n*-butylamide furnish **1** in effectively quantitative yield. The significant advantage in the use of either of these bases over lithium diethylamide is not so much in diminished amino alcohol adduct formation (this material is easily separated from the allylic alcohol), but rather the absence of the isomeric products **2** and **3**, which in practice are difficult to separate from **1**. These two bases (runs 11 and 12) thus are the recommended reagents when a high yield of pure allylic alcohol is desired.

The further rearrangement of **1** to **3** fails to occur with a number of lithium dialkylamides, and in particular lithium diethylamide and di-*sec*-butylamide show negligible formation of **3** even on prolonged (>200 hr) treatment of **1**. Initially this observation led to the suspicion that an NH grouping was required in the lithium amide base to effect this rearrangement, but the data from runs 13, 14, 15, and 21 show that this is not the case. In fact, cyclic dialkylamides, exemplified best by *N*-lithiopyrrolidine (run 13), are the most effective of the bases examined in this work for carrying out the rearrangement of **1** to **3**, as well as the reverse reaction.

Although in some instances ketone may be formed by subsequent rearrangement of allylic alcohol under the basic reaction conditions,[3,4] this was not the case in the present study. The proportions of **1** and **2** shown in Table II remain constant through the course of the reactions, and in general the allylic alcohol is not converted to cyclohexanone even under extended treatment. The ketone is thus a primary product, presumably formed *via* the α-abstraction mechanism originally proposed by Cope[5] and more recently examined in detail by Crandall.[6] It is interesting that the competition between α- and β-proton abstraction increasingly favors the former process as the bulk of the lithium dialkylamide is increased. In the only di-*tert*-alkylamide examined (run 23), ketone formation clearly predominates. Although it is tempting to speculate that this effect is due to the greater steric requirements for β-proton abstraction (leading to allylic alcohol), this view is not supported by the relative rates as estimated from the reaction times shown in Table II. In other words, it does not appear that ketone

(2) Unpublished work of Brian H. Williams; ethanol has been identified as a product of this fragmentation. The longer times required for some reactions lead to the formation of lithium ethoxide, which appears as a white solid precipitate. The limited solubility of many lithium alkylamides mitigates against the use of hydrocarbon solvent alone. Recently we have found that THF can serve as an unreactive substitute for diethyl ether.

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

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

(5) A. C. Cope and B. D. Tiffany, *J. Amer. Chem. Soc.*, **73**, 4158 (1951).

(6) J. K. Crandall, L. C. Crawley, D. B. Banks, and L. C. Lin, *J. Org. Chem.*, **36**, 510 (1971).

TABLE II

Registry no.	Run	R$_2$NLi	Time, hr[a]	% 1[b]	% 2	% 3	% 4
25347-30-2	10	(C$_2$H$_5$)$_2$N	2	86	3	0	10
34566-61-5	11	(n-C$_3$H$_7$)$_2$N	2	>99	<0.5	<0.5	0
34566-62-6	12	(n-C$_4$H$_9$)$_2$N	4	97	0	<0.5	3
34566-63-7	13[c]	(pyrrolidino)N	1	63	0	17	15
24316-38-9	14	(azetidino)N	1	72	Trace	8	11
34566-65-9	15	(i-C$_4$H$_9$)$_2$N	2	68	10	5	18
34566-66-0	16[d]	C$_6$H$_5$CH$_2$CH(CH$_3$)N(CH$_3$)	4	79	0	0	20
26396-97-4	17[e]	(i-C$_3$H$_7$)$_2$N	3	38	33	0	28
34566-16-0	18[e]	(sec-C$_4$H$_9$)$_2$N	2	40	46	0	13
34566-17-1	19[c,e]	(c-C$_6$H$_{11}$)$_2$N	2	54	39	<1	3
34566-18-2	20[e]	(2,6-dimethylpiperidino)N	2	58	8	0	32
34566-19-3	21[e]	(azabicyclo)N	3	75	2	4	14
34566-20-6	22[c,e]	(c-C$_6$H$_{11}$)N(i-C$_3$H$_7$)	2	46	38	0	12
34566-21-7	23[e]	(2,2,6,6-tetramethylpiperidino)N	0.5	31	62	0	7

[a] The time required for loss of >97% of epoxide. [b] Yields as determined by vpc analysis using mesitylene as an internal standard. [c] A small amount of material with retention time identical with that of 2-cyclohexenone was observed in runs 13, 19, and 22. [d] *trans-β*-Methylstyrene was also formed in this run. [e] A small amount (0.5–2%) of cyclohexanol was formed in runs 17–23.

formation is associated with a lower rate of formation of allylic alcohol. The basis for the observed selectivity thus remains in doubt. It is also worth noting that even the most bulky bases still lead to some substitution product **4**; in fact, this process is minimized with the relatively unhindered lithium di-*n*-alkylamides.

Cyclohexylisopropylamide (run 22) was included in this study after seeing it recommended for a novel ester alkylation procedure by Rathke and Lindert.[7] In the present work it offers no particular advantage over other di-*sec*-alkylamides.

The mechanism of the rearrangement of **1** to **3** was examined in some detail, particularly because of our interest in determining the potential of the base-induced rearrangement of epoxides to generate optically active allylic alcohols by asymmetric induction. At least two reasonable pathways may be considered for the conversion of **1** to **3**. One would involve proton abstraction to give an allylic carbanion with subsequent reprotonation to give the rearranged material (eq 2). Alternatively, one might envision the lithium

$$(2)$$
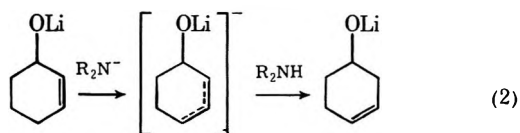
salt of **1** acting as a hydride donor for any available reducible species (*e.g.*, epoxide, ketone). The 2-cyclohexenone generated in this manner could undergo base-catalyzed equilibration to 3-cyclohexenone, which, acting in turn as a hydride acceptor, would lead to 3-cyclohexenol (eq 3). Rearrangement by this mechanism would necessarily involve loss of asymmetry. Several experiments were carried out to probe this mechanistic question.

$$(3)$$
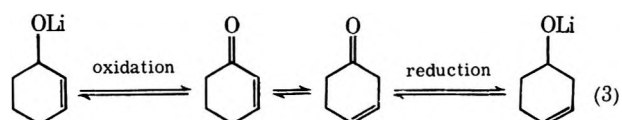
When the possible intermediate 2-cyclohexenone is added to a solution of lithium dialkylamide, it is consumed with formation of cyclohexanone and phenol. Although these are the products anticipated from a disproportionation of the enolate of 2-cyclohexenone, in fact such a process does not appear to be important. Substantial yields of phenol were formed with the several bases used, but the yields of cyclohexanone were variable, and always too low to be accounted for by this disproportionation. Furthermore, the saturated ketone was formed rapidly on mixing the reagents, while the yield of phenol increased with time. Finally, evidence was obtained for the formation of LiH (evolution of hydrogen on quenching); taken together these data suggest the following course for the reaction of 2-cyclohexenone with lithium dialkylamide (eq 4).[8]

$$(4)$$
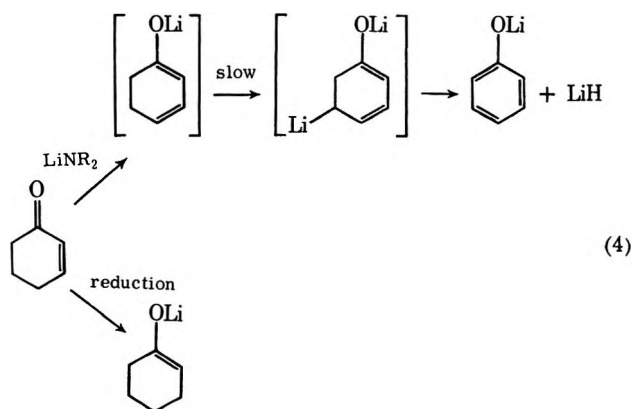
(7) M. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971).

(8) The aromatization of this system and others through the loss of LiH has been confirmed by Brian H. Williams (unpublished work).

Thus the cyclohexanone is formed *via* conjugate reduction of the enone, with lithium alkylamide providing the necessary hydride.[9] Very likely the traces of cyclohexanol observed in many of the reactions described in Tables I and II are formed in similar fashion by reduction of cyclohexene oxide. Of primary concern to the present mechanistic question, however, is the fact that in no instance did 2-cyclohexenone generate measurable quantities of either 2-cyclohexenol or 3-cyclohexenol under the basic reaction conditions. This clearly rules out the mechanism shown in eq 3 as a viable pathway for the rearrangement of 1 to 3, leaving eq 2 as the preferred depiction.

Two experiments were carried out in an attempt to establish the equilibrium concentrations of 1 and 3 (as their lithium salts). Treatment of 1 with 2.5 equiv of lithium *sec*-butylamide for 405 hr gave a mixture of 52% of 1 and 48% of 3. Similar treatment of 3 after 435 hr gave 19% of 1 and 81% of 3. While these data do not accurately establish the position of equilibrium, they suggest that 3 is slightly favored, probably comprising 70 ± 10% of the mixture at equilibrium.

Finally, some experiments were carried out to explore the effects of changing solvent, initial concentration of base, and other variables on the reaction with cyclohexene oxide. The data are shown in Table III. Com-

TABLE III

Run	Base (equiv)	Time, hr	% 1	% 2	% 4
24	LiN(C$_2$H$_5$)$_2$ (2.5) Ether solvent	10	83	0	15
25	LiN(C$_2$H$_5$)$_2$ (1.5)	3	95	0.5	4.5
26	LiN(*i*-C$_4$H$_9$)$_2$ (1.5)	5	83	4	11
27	LiN(*i*-C$_3$H$_7$)$_2$ (1.5)	3	75	23	0
28	LiN(*sec*-C$_4$H$_9$)$_2$ (1.5)	3	55	41	0.5
29	LiN(*sec*-C$_4$H$_9$)$_2$ (1.5) *n*-C$_4$H$_9$Li (1.5)	3	51	48	0.5
30	LiN(*sec*-C$_4$H$_9$)$_2$ (1.5) HN(C$_4$H$_9$)$_2$ (1.5)	3	64	34	2
31	*n*-C$_4$H$_9$Li (1.5)	4	89	11	

parison of run 24 with run 10 (Table I) shows that diethyl ether alone as solvent slows down the reaction somewhat, but does not greatly affect the product distribution relative to the reaction carried out in the usual ether–hexane mixture.

The effect of lower initial concentration of base (compare runs 25, 26, 27, and 28 with their counterpart runs 10, 15, 17, and 18) is to enhance the formation of 1 at the expense of both 2 and 4.

The last four entries in Table III examine the effects of excess amine or butyllithium on the reaction with cyclohexene oxide. Butyllithium alone (run 31) gives no measurable alkylation product under these reaction conditions; the proportion of ketone formed is somewhat larger than with lithium diethylamide, but less than that formed with the bulkier amides (*cf.* run 28). Excess free amine does not appreciably alter the rate of reaction, although a small change in product distribution occurs.[10]

Experimental Section

The cyclohexene oxide used in this study was prepared by the peracetic acid method[12] from the olefin in 87% distilled yield, bp 130–132°, and was shown by vpc and spectral analysis to be free of impurities.

With the exceptions noted below, all amines were commercial materials purified by distillation from KOH pellets before use. When this purification procedure was followed, all of the lithium alkylamides subsequently formed were completely soluble in the ether–hexane reaction mixtures.

Di-*sec*-Butylamine.—*sec*-Butylamine (40 mmol) and 40 mmol of 2-bromobutane were refluxed together without solvent for 24 hr. On cooling, a pale yellow, crystalline solid was obtained, which was carefully added to concentrated aqueous KOH solution. The organic layer was separated and distilled from KOH pellets at atmospheric pressure to give 5.0 g (97%) of di-*sec*-butylamine, bp 132–134° (lit.[13] bp 132–134°), picrate mp 107–109° (lit.[14] mp 111°).

Cyclohexylisopropylamine.—To a mixture of 1.0 mol of cyclohexylamine and 1.1 mol of acetone were added five drops of concentrated hydrochloric acid and 7 g of 4A molecular sieve. This mixture was stirred for 30 hr at ambient temperature; KOH pellets were added and the mixture was distilled to give 92 g (97%) of the imine, bp 96–100° (59 Torr).[15] A sample, 6.9 g (50 mmol), of the imine was reduced by adding it to a solution of 1.9 g (50 mmol) of sodium borohydride in 100 ml of isopropyl alcohol at 0°. After 10 min, 10 ml of concentrated aqueous sodium hydroxide was added, and the organic phase was separated and distilled to give 6.3 g (90%) of cyclohexylisopropylamine, bp 55–57° (9 Torr).[15]

Epoxide Rearrangements.—To a solution of 0.025 mol of the appropriate amine in 10 ml of anhydrous ether was added 15.5 ml of commercial 15% *n*-butyllithium in hexane. The epoxide (0.98 g, 0.01 mol) was then added and the mixture was refluxed; the course of the reaction was followed by removing aliquots, quenching with water (salt saturated), and vpc analysis of the organic phase, using a Carbowax 6M column. In several instances the amino alcohol adduct was isolated by preparative vpc; although not fully characterized, these materials exhibited the anticipated nmr and ir spectral features.

Registry No.—Cyclohexene oxide, 286-20-4.

(9) This is the nitrogen analog of the Meerwein–Ponndorf–Verley reduction; hydride transfer reduction processes involving lithium alkylamides have been described in the work of G. Wittig and A. Hesse, *Justus Liebigs Ann. Chem.*, **746**, 174 (1971).

(10) A complex composed of 1 mol of lithium diethylamide and 2 mol of diethylamine has recently been identified as the active species in the addition reaction to butadiene.[11]

(11) N. Imai, T. Narita, and T. Tsuruta, *Tetrahedron Lett.*, 3517 (1971).

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

(13) A. Fleury-Larsonneau, *Bull. Soc. Chim. Fr.*, **6**, 1567 (1939).

(14) J. Mitchell, Jr., and W. M. D. Bryant, *J. Amer. Chem. Soc.*, **65**, 128 (1943).

(15) D. G. Norton, V. E. Haury, F. C. Davis, L. J. Mitchell, and S. A. Ballard, *J. Org. Chem.*, **19**, 1054 (1954).

Syntheses and Reactions of Thiobenzophenone–Alkali Metal Complexes

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Received November 22, 1971

Deep-red unstable compounds were formed by the reaction of thiobenzophenone with alkali metals (Li, Na, K) in tetrahydrofuran (THF) under an atmosphere of nitrogen. It was found from the esr spectra that thiobenzophenone reacts with 1 equiv of an alkali metal to form the anion radical (thioketyl) and with 2 equiv of an alkali metal to form the dianion complex. The reactions of these complexes with carbon dioxide, acid, benzyl chloride, benzaldehyde, and benzonitrile were also carried out.

Unenolizable thioketones react with alkali metals to form colored complexes (thioketyls),[1] and, recently, Janzen, *et al.*,[2] have studied the electron spin resonance (esr) spectra of *p,p'*-dimethoxythiobenzophenone and *p,p'*-di(dimethyl)aminothiobenzophenone. Heller[3] has clarified from the esr spectra that thiobenzophenone forms the anion radical in alkali solution by irradiation.

Seman, *et al.*,[4] have studied the organic reactions of alkali metal complexes of diaryl ketone. They synthesized dialkali metal adducts of benzophenone derivatives and attempted the reaction of their complexes with many other organic compounds.

We have recently found that thiobenzophenone reacts with 1 equiv of an alkali metal to form the anion radical (thioketyl) and with 2 equiv of an alkali metal to form the dianion complex. The chemical properties of such complexes and their nucleophilic reactions to many organic compounds were examined. This paper describes the presumed nature of the alkali metal complexes of thiobenzophenone and discusses their structures and examples of the synthetic utility.

Results and Discussion

Esr Spectra.—Thiobenzophenone reacted with 1 equiv of alkali metals to form deep red thioketyls in tetrahydrofuran (THF). The esr spectrum of a THF solution of monosodium thiobenzophenone is shown in Figure 1. Its hyperfine spectrum, consisting of 70 lines, is very complex and the spectral width is about 25 G. Although it is difficult to analyze definitely, the formation of the radical anion I is suggested. The

$$M = Li, Na, K \qquad (1)$$
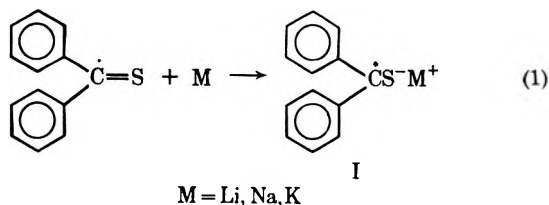
alkali metals used were lithium, sodium, and potassium and the reactivity of the alkali metal complexes increased in the order Li < Na < K. The colors of the thioketyls were all deep red.

In the reaction of thiobenzophenone with more than 2 equiv of an alkali metal, a deep red dianion complex II formed.

(1) E. Campaigne, *Chem. Rev.*, **39**, 1 (1964).
(2) E. G. Janzen and C. M. Dubose, *J. Phys. Chem.*, **70**, 3372 (1966).
(3) H. C. Heller, *J. Amer. Chem. Soc.*, **89**, 4288 (1967).
(4) S. Seman and J. F. Eastham, *J. Org. Chem.*, **30**, 3804 (1965).

$$(2)$$
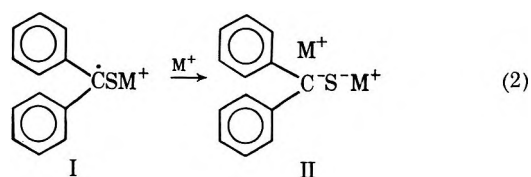
If the dianion complex has structure II, it is thought that its solution will not give an esr signal. However, the esr measurement of a THF solution of disodium thiobenzophenone gave the same hyperfine spectrum as that of thioketyl solution. From this fact, it is thought that the dianion complex II is partly in equilibrium with the anion radical I.

$$(3)$$
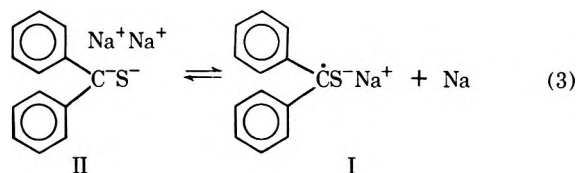
The solution of thiobenzophenone in THF exhibited a week esr signal at 3370 G (Figure 2) also. This will be explained by the existence of radical intermediates from the reaction of thiobenzophenone with small amounts of oxygen in the air, because the thiocarbonyl group easily forms a biradical.
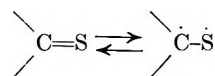
Visible Spectra.—A solution of thiobenzophenone in THF showed a strong absorption band at 500 mμ due to the thiocarbonyl group (Figure 3, I). Monosodium thiobenzophenone complex showed an absorption band at 530 mμ due to the excitation of an odd electron which transferred from the external orbital of a sodium atom to the lowest vacant orbital of a thiobenzophenone (Figure 3, II). The disodium thiobenzophenone complex showed an absorption band at 520 mμ. These thioketyls and dianions were all decolorized by air and moisture, and decomposed. The exchange of the visible spectrum of monosodium thiobenzophenone in air was measured and shown in Figure 4. In this figure, the 530-mμ band of the thioketyl disappears after 40 min and a new band appears at 600 mμ due to thiobenzophenone.

This is thought to show that the thioketyl decomposed slowly with oxygen and moisture in the air to form thiobenzophenone, since the surface of the solution of thioketyl was in contact with the air.

Carbonation.—The reaction of disodium thiobenzophenone with carbon dioxide was carried out by pouring a solution of the complex in THF into crushed
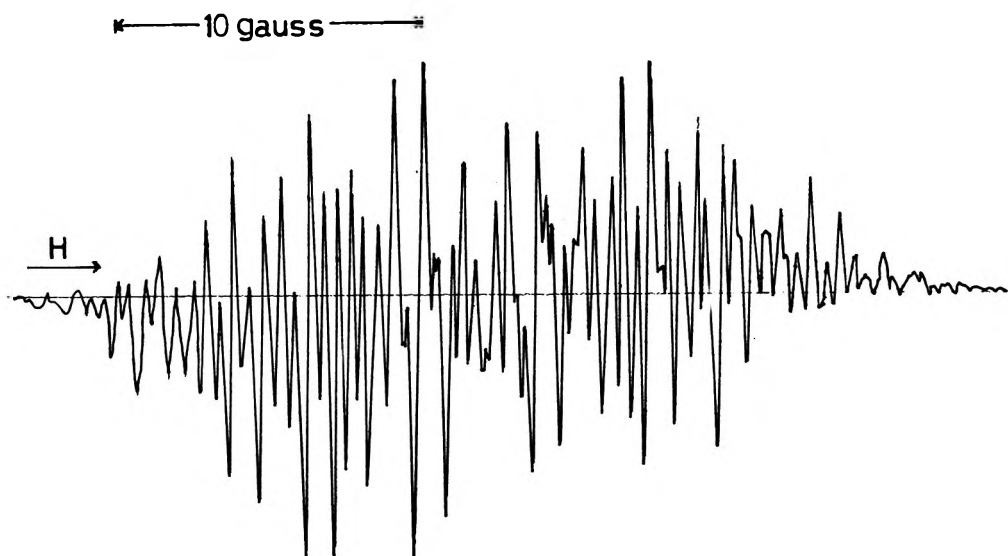
Figure 1.—Esr spectrum of monosodium thiobenzophenone in THF; c 0.19 mol/l.
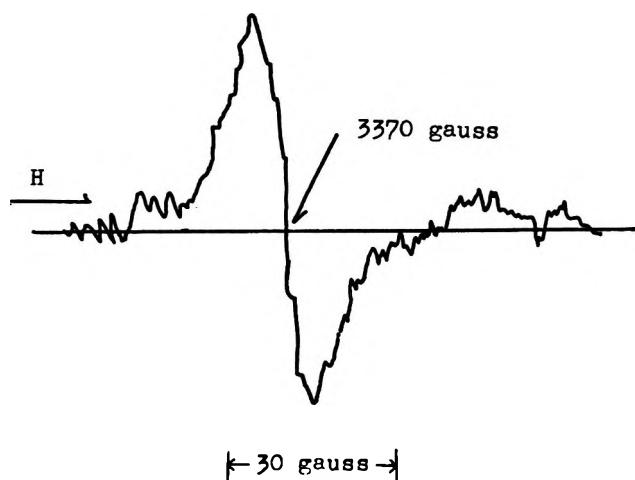
Figure 2.—Esr spectrum of thiobenzophenone in THF; c 0.19 mol/l.
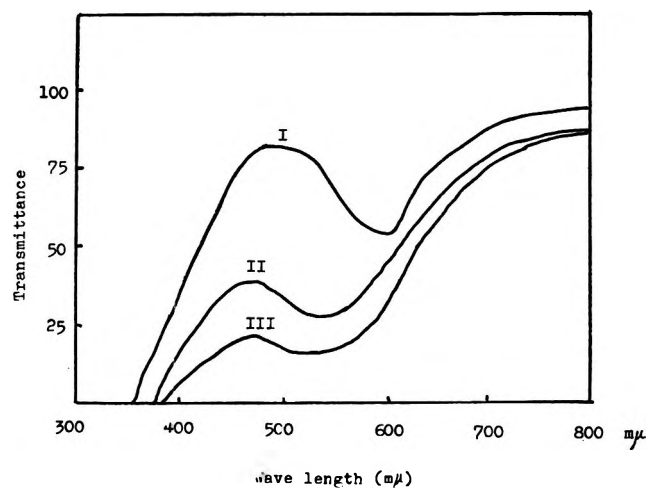
Figure 3.—The visible absorption spectra of alkali metal thiobenzophenone complexes: I, thiobenzophenone in THF; II, sodium thiobenzophenone in THF; III, disodium thiobenzophenone in THF; concentration in each case 3×10^{-3} mol/l.

Dry Ice. A white-yellow solid obtained from the acidic component was identified as thiobenzilic acid (III) by elemental analysis, melting point,[5] and infrared spectrum.

The formation of thiobenzilic acid (III) from disodium thiobenzophenone complex shows that this complex has the structure indicated by the structural formula II, which has a carbanion and a mercaptide ion, and the carbonation reaction is thought to have proceeded as shown in eq 4. Next, the carbonation
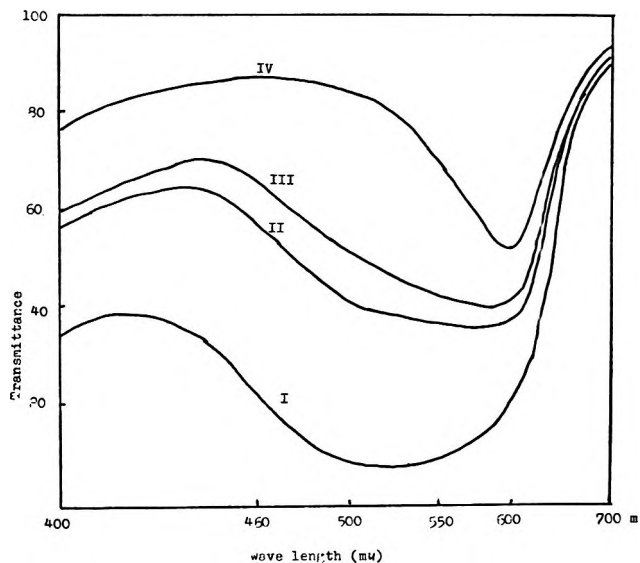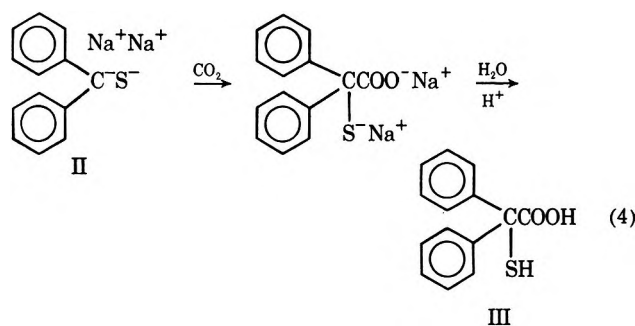
Figure 4.—Time changes in the visible absorption spectra of monosodium thiobenzophenone in THF under air: I, unchanged; II, after 15 min; III, after 20 min; IV, after 40 min; concentration is 3×10^{-3} mol/l.

(5) H. Becker and A. Bistrzycki, *Chem. Ber.*, **47**, 3152 (1914).

reaction of monosodium thiobenzophenone complex gave mostly thiobenzophenone and a small amount of thiobenzilic acid (III) (4.4% yield).

The fact that thiobenzilic acid was obtained is thought to indicate that the anion radical I partly disproportionates to the dianion II and thiobenzophenone, as shown in eq 5. Namely, it is thought

$$2\ \text{(structure I) } \rightleftharpoons \text{ (structure II) } + \text{ (structure C=S)} \qquad (5)$$
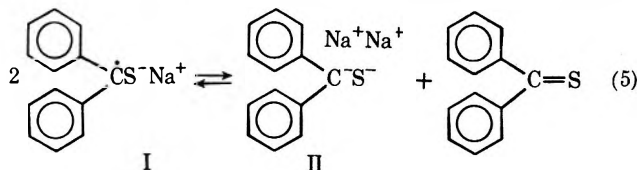
that an equilibrium exists between monoanion I and dianion II, the equilibrium being far on the side of I.

Acidic Hydrolysis.—When the THF solution of monosodium thiobenzophenone was poured into acidic ethanol, the solution became blue-violet and a large amount of sodium chloride precipitated. When the solvent was evaporated from the reaction mixture, a blue-violet solid, thought to be thiobenzophenone, was obtained. The formation of thiobenzophenone was confirmed by the fact that the reaction of this solid with 2,4-dinitrophenylhydrazine in ethanol gave thiobenzophenone 2,4-dinitrophenylhydrazone. Yet the coupling product IV of thioketyl I could not be ob-

$$\text{(structure I) } \rightleftharpoons \text{ (structure)} \qquad \not\rightarrow \qquad (6)$$

$$\text{HSC———CSH} \qquad (6)$$

IV
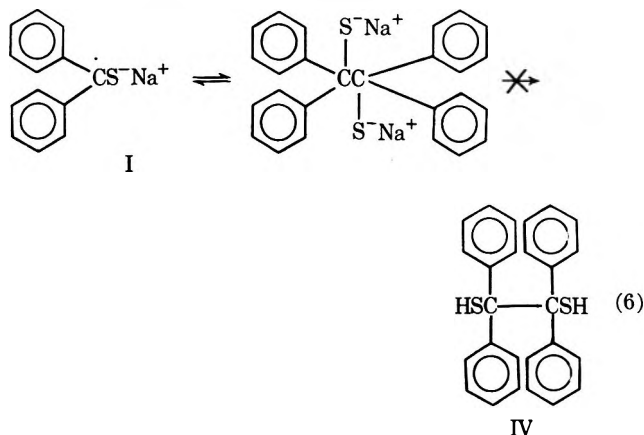
tained. This is thought to be due to two factors: (1) the resonance stabilization of the radical in the thioketyl with the two phenyl groups; (2) the steric hindrance of the four phenyl groups for the coupling of thioketyls.

Next disodium thiobenzophenone complex was decomposed with hydrochloric acid–methanol. When the product was oxidized by air in the presence of iodine, diphenylmethyl disulfide (V) was obtained. Therefore the reaction is thought to have proceeded as in eq 7, through the formation of benzhydryl mercaptan.

$$\text{(structure II) } \xrightarrow[-\text{NaCl}]{\text{HCl}} \text{ (structure CSH, H) } \xrightarrow[[\text{O}]]{\text{I}_2} \text{ (structure CSSC)} \qquad (7)$$

V
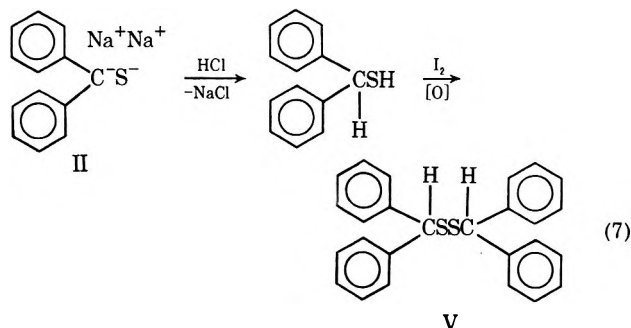
Reaction with Benzyl Chloride.—On the reaction of disodium thiobenzophenone complex (II) with benzyl chloride in THF under nitrogen, white, columnar crystals were obtained from the reaction mixture. It was found from infrared spectra, molecular weight, and elemental analysis that this product was a new compound, 1,1,2-triphenylethyl benzyl sulfide (VI).

This reaction may be represented by eq 8.

$$\text{(structure II) } + 2 \text{ (structure)}—\text{CH}_2\text{Cl} \rightarrow \text{ (structure)}—\text{CH}_2\text{CSCH}_2—\text{(structure)} + 2\text{NaCl} \qquad (8)$$

VI
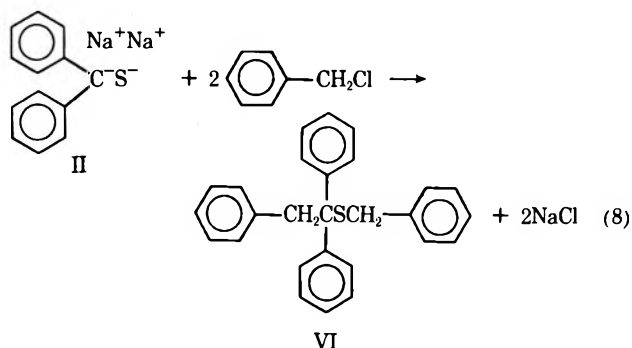
As well as the dianion complex II, monosodium thiobenzophenone complex (I) reacted with benzyl chloride, and sulfide VI was obtained in 12.6% yield.

The formation of this product can be explained by the following two mechanisms. One is the mechanism in which the dianion complex, which is possibly contained in the monosodium thiobenzophenone reaction mixture, reacts with benzyl chloride as shown in eq 8. The other is ionic reaction of thioketyl I with benzyl chloride, followed by the coupling of the resulting radical with the benzyl radical (eq 9). In addition to

$$\text{(structure I) } + \text{ClCH}_2—\text{(structure)} \xrightarrow{-\text{NaCl}}$$

$$\text{ (structure) }·\text{CSCH}_2—\text{(structure)} \xrightarrow[-·\text{Cl}]{\text{ClCH}_2—\text{(structure)}}$$

$$\text{ (structure)}—\text{CH}_2—\overset{}{\text{C}}—\text{SCH}_2—\text{(structure)} \qquad (9)$$

VI
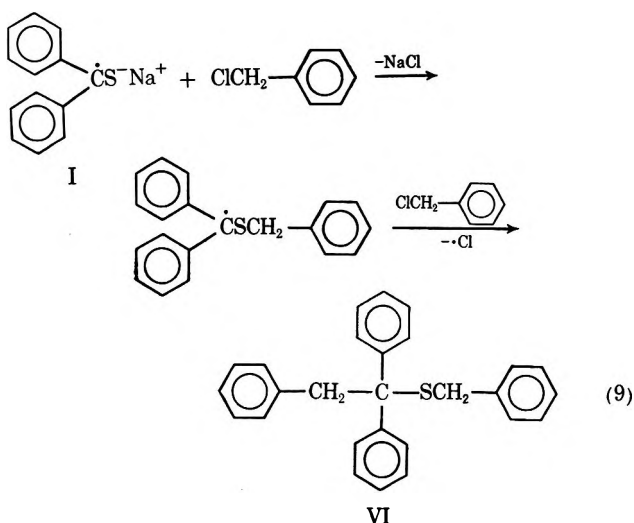
product VI, a blue-violet oil was obtained. After a few days in the air it became brown. When it was oxidized by hydrogen peroxide, white, needlelike crystals were obtained. These crystals are thought to be a mixture of sulfoxide and sulfone, but a clear identification was not established.

Reaction with *p*-Dichloroxylene.—The reaction of disodium thiobenzophenone complex (II) with *p*-dichloroxylene gave a polymerlike product, the structure of which was thought to be VII. Its molecular weight was found to be 2170. This product was yellow and spinnable.

$$\text{II} + \text{ClCH}_2\text{—C}_6\text{H}_4\text{—CH}_2\text{Cl} \xrightarrow{-\text{NaCl}} \text{VII} \quad (10)$$

$$\text{II} + \text{C}_6\text{H}_5\text{—C}\equiv\text{N} \longrightarrow$$

$$\overset{\cdot}{\text{C}}\text{S}^-\text{Na}^+ + \text{C}_6\text{H}_5\overset{\cdot}{\text{C}}=\text{N}^-\text{Na}^- \quad (12)$$

$$\text{C}_6\text{H}_5\overset{\cdot}{\text{C}}=\text{N}^-\text{Na}^+ \longrightarrow \text{X} \quad (13)$$
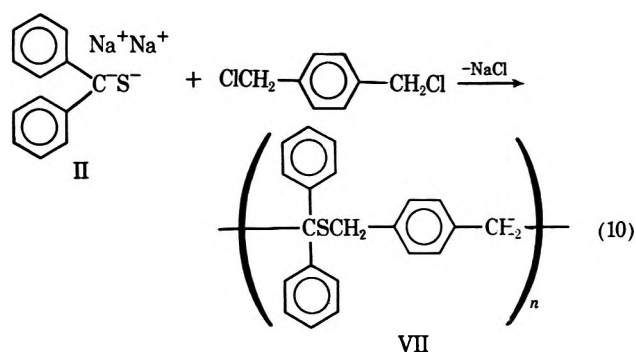
Reaction with Benzaldehyde.—On the reaction of disodium thiobenzophenone complex (II) with benzaldehyde, ω,ω'-diphenylacetophenone (IX)[6] was obtained. Therefore, this reaction is thought to have proceeded as shown in eq 11; first, compound VIII is formed and on neutralization this compound reacts with the acid to release hydrogen sulfide; and, next, by means of proton migration compound IX is formed.

$$\text{II} + \text{C}_6\text{H}_5\text{—CHO} \longrightarrow$$

$$\left[\text{VIII} \xrightarrow{\text{H}_2\text{O}} \xrightarrow{\text{H}^+}_{-\text{H}_2\text{S}} \right]$$

$$\xrightarrow{-\text{H}^+} \text{IX} \quad (11)$$
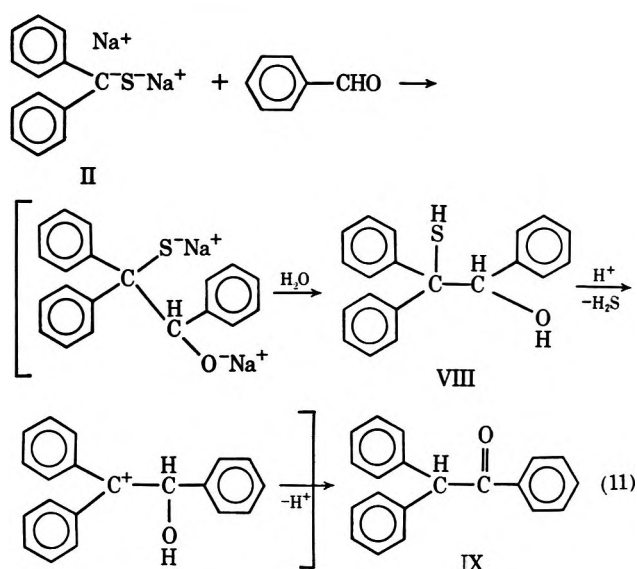
The presence of hydrogen sulfide was confirmed by the discoloration of lead acetate paper. In spite of the sufficiently careful neutralization, hydrogen sulfide was immediately produced and the product VIII was not obtained. On reaction of disodium benzophenone with benzaldehyde a compound corresponding to VIII was obtained,[4] but in the case of thiobenzophenone VIII was not obtained. Because of the weakness of the C–S bond compared to the C–O bond, the reaction indicated by eq 11 is thought to have taken place.

Next, in the case of the reaction of monosodium thiobenzophenone with benzaldehyde, a red-brown oil was obtained from the reaction mixture. This product was oxidized by hydrogen peroxide–acetic acid to white needles, which could not be clarified.

Reaction with Benzonitrile.—On reaction of disodium thiobenzophenone with benzonitrile, 2,4,6-triphenyl-1,3,5-triazine (X) and a yellow powder melting at 105–120° were obtained. The formation of the product X, known to be formed from the benzonitrile radical anion,[7] is thought likely to indicate the following reaction process: first, as shown in eq 12, a metal mi-

grates to benzonitrile from the dianion to form two anion radicals; and, next, as shown in eq 13, benzonitrile anion radical is oxidized to form the compound X. The yellow powder was polymeric (mol wt 892) and spinnable, but the structure was not clarified.
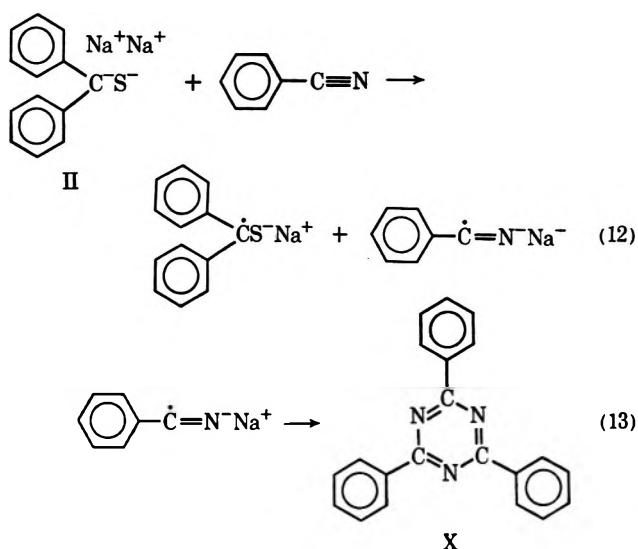
Next the reaction of monosodium thiobenzophenone with benzonitrile was attempted, but exchange did not occur and the starting material was recovered.

Summary.—As described above in the reactions of thiobenzophenone alkali metal complexes with organic compounds (benzyl chloride, *p*-dichloroxylene, benzaldehyde, and benzonitrile), the dianion complexes reacted easily with these compounds and results are summarized in Chart I, but the anion radical complexes

CHART I
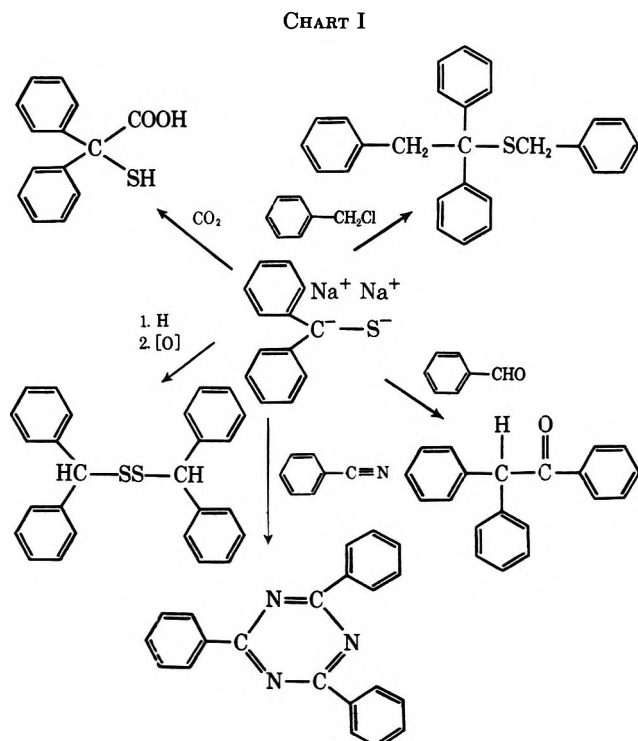
hardly reacted, so that the expected compounds were not obtained.

These results are thought to be due to the following reason: dianion complexes, having two anions localized on the carbon and sulfur of the thiocarbonyl group, are reactive, but anion radical complexes are not

(6) A. Werner, *Chem. Ber.*, **39**, 1286 (1906).
(7) G. Greber, *Makromol. Chem.*, **59**, 174 (1963).

so reactive because they are resonance stabilized by conjugation with the phenyl group. With the anion radical complexes, anionic reactions and radical reactions thus compete with each other, so that many products are formed.

Experimental Section

Alkali metals were added to reaction mixtures in small pieces. To remove moisture THF was refluxed with potassium hydroxide and redistilled from a mixture of sodium and benzophenone. Measurements of molecular weight were performed on a Knauer vapor pressure osmometer.

Synthesis of Thiobenzophenone.—Thiobenzophenone was prepared by the method described in the literature.[8]

Synthesis of Monosodium Thiobenzophenone (I).—Thiobenzophenone (2.0 g, 0.01 mol) was stirred with sodium (0.207 g, 0.009 g-atom) in THF (100 ml) for 24 hr under nitrogen at room temperature. After 1 hr the reaction mixture turned from blue-violet to deep red in color. After 6 hr the reaction mixture was filtered under a stream of nitrogen, and all the unreacted metal particles disappeared. This thioketyl solution was placed in a sealed bottle substituted with argon gas and it was stored in a cool and dark place. For use this thioketyl solution was taken with an injector under a stream of nitrogen.

Synthesis of Disodium Thiobenzophenone (II).—Thiobenzophenone (2.0 g, 0.01 mol) was stirred vigorously with sodium (0.92 g, 0.04 g-atom) in 100 ml of THF under nitrogen at room temperature. The reaction mixture turned gradually from blue-violet to dark red in color. After 24 hr the unreacted sodium (0.46 g, 0.02 g-atom) was recovered by the filtration of the reaction mixture and the formation of the dianion complex was confirmed. The method of use and storage was the same as that of the monosodium complex.

Measurement of Esr Spectra.—The THF solution of the monosodium complex, disodium complex, and thiobenzophenone (all 0.19 mol/l.) was placed in an quartz glass tube (i.d. 3 mm) by means of an injector. The quartz glass tube was sealed with a plastic film. Measurements of these samples were carried out on a Nipondenshi JES ME-3X esr spectrometer (100 MHz).

Carbonation Reaction.—The THF solution of monosodium thiobenzophenone (100 ml, 0.36 mol/l.) was added to an excess of crushed Dry Ice with stirring. After it was left to stand overnight, the solvent was evaporated and the residue was diluted with 300 ml of water. The red aqueous solution was washed with ether. The ether layer became blue-violet and exhibited an absorption spectra at 600 mμ, which was due to the thiocarbonyl group of thiobenzophenone. The ether was evaporated and the oily residue obtained (13.1 g) was thought to be thiobenzophenone. The aqueous solution was acidified with hydrochloric acid and the white-yellow solid precipitated and was recrystallized from 50% acetic acid to give 0.39 g (4.4%) of thiobenzilic acid (III), mp 145–147° (lit.[5] mp 146–148°).

Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 68.84; H, 5.02.

Next 100 ml of a THF solution of disodium thiobenzophenone (0.4 mol/l.) was added to an excess of crushed Dry Ice with stirring. After it was left to stand overnight, the solvent was evaporated and the residue was diluted with 300 ml of water. The red aqueous solution was washed with ether and acidified with hydrochloric acid. The precipitated crude thiobenzilic acid, 7.38 g (82.5%), mp 140–143°, was recrystallized from benzene to yield 4.1 g (42% yield) of thiobenzilic acid (III), mp 146–148.5° (lit.[5] m 146–148°).

Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 69.01; H, 5.05.

Acid-Decomposition Reaction.—The THF solution of monosodium thiobenzophenone (50 ml, 0.4 mol/l.) was poured into acidic ethanol (64 ml of ethanol and 16 ml of concentrated hydrochloric acid), and the solvent was evaporated. Ether was added to the residue, and the ether layer was washed with water and dried (Na_2SO_4). The ether was evaporated from the ether layer.

The residue, dissolved in 80 ml of ethanol, was treated with 2,4-dinitrophenylhydrazine (3.96 g, 0.02 mol), dissolved in 120 ml of ethanol containing a few drops of concentrated hydrochloric acid for 2 days at room temperature. From the solution hydro-

gen sulfide was evaporated. The solution was filtered to give 3.0 g (44.5% crude yield) of crude thiobenzophenone 2,4-dinitrophenylhydrazone, mp 216–230°.

This hydrazone was recrystallized from ethanol to give 1.2 g (16.6% yield) of a red-yellow powder: mp 230–235° (lit.[9] mp 238°, 229°); ir (KBr) 3100–3000 (NH), 1600 (benzene ring), 1500, 328 cm^{-1}.

Anal. Calcd for $C_{19}H_{14}N_4O_4$: C, 62.98; H, 3.89; N, 14.56. Found: C, 62.75; H, 3.72; N, 15.10.

Next 50 ml of THF solution of disodium thiobenzophenone (0.6 mol/l.) was poured into acidic methanol (150 ml of methanol and 50 ml of concentrated hydrochloric acid) and much sodium chloride precipitated. After removal of the solvent, the residue was extracted with benzene. The extracts were washed with water and dried ($CaCl_2$). Removal of the solvent left a light-yellow oil. To a solution of this oil in 50 ml of ethanol was added iodine dissolved in aqueous ethanol, until the color of iodine did not disappear. White crystals precipitated from the solution were separated and recrystallized from chloroform-ethanol (1:1) to afford 3.9 g (65.3%) of needle crystals of diphenyl methyl disulfide (V): mp 152–153° (lit.[10] mp 152°); ir (KBr) 3050, 1603, 1500, 1460, 760, 730, 710 cm^{-1}.

Anal. Calcd for $C_{26}H_{22}S_2$: C, 78.32; H, 5.58. Found: C, 78.13; H, 5.73.

Reaction with Benzyl Chloride.—To a solution of benzyl chloride (3.15 g, 0.025 mol) in 10 ml of THF was added 53 ml of a THF solution of monosodium thiobenzophenone (0.5 mol/l.). The mixture was refluxed under nitrogen for 3 hr. Removal of the solvent left a red-violet oil. It was extracted with ether, and the extracts were washed with water and dried (Na_2SO_4). Removal of solvent left a white crystal, which on recrystallization from ether gave 0.6 g (12.6%) of 1,1,2-triphenylethyl benzyl sulfide (VI), mp 126–128°. The filtrate was distilled to yield a first fraction (0.7 g), bp 148–160° (2 mm), and a second fraction (1.0 g), bp 160–165° (2 mm). Their infrared spectrum agreed with that of thiobenzophenone. These fractions changed in color from blue-violet to brown after 2 days in air. The first fraction (0.7 g) was added with stirring to a solution of 0.8 ml of 30% hydrogen peroxide and 4 ml of acetic acid at room temperature. The mixture was allowed to stand for 2 days. The white crystals were separated and recrystallized from ether to give 0.8 g of white needle crystals, mp 161–163°, mol wt 274.

Anal. Found: C, 74.44; H, 5.77.

The second fraction (1.0 g) was added with stirring to a solution of 1.2 ml of 30% hydrogen peroxide and 5.7 ml of acetic acid at room temperature. The mixture was allowed to stand for 2 days. The white crystals were separated and recrystallized from ether to give 0.1 g of white needle crystals, mp 125–129°, mol wt 228.

Anal. Found: C, 70.19; H, 5.74.

To a solution of benzyl chloride (3.52 g, 0.028 mol) in 30 ml of THF was added 30 ml of a THF solution of disodium thiobenzophenone (0.46 mol/l.). The mixture was refluxed under nitrogen for 3 hr. The mixture was cooled, poured into an excess of crushed Dry Ice to remove any unreacted dianion complex, and diluted with 100 ml of water. After removal of solvent, the residue was extracted with ether and the extracts were washed with water and dried (Na_2SO_4). Removal of the solvent gave a white solid. Recrystallization of the crude product from ether yielded 3.0 g (56.6%) of white needle crystals of 1,1,2-triphenylethyl benzyl sulfide (VI): mp 126–127°; ir (KBr) 3070, 3040, 3020, 2925–2859 (CH_2), 1600 (benzene ring), 1490, 658 cm^{-1} (CS); nmr (CCl_4) δ 3.20 [s, 2, $C_6H_5CH_2[C_6H_5)_2]$, 3.57 (s, 2, $-SCH_2C_6H_5$), 6.4–7.15 [m, 10, $-C(C_6H_5)_2-$], 7.2 [s, 5, $C_6H_5CH_2C(C_6H_5)_2-$], and 7.23 (s, 5, $C_6H_5CH_2S-$).

Anal. Calcd for $C_{27}H_{24}S$: C, 85.22; H, 6.35; mol wt, 383. Found: C, 85.36; H, 6.29; mol wt, 380.6.

Reaction with p-Dichloroxylene.—To a solution of p-dichloroxylene (5.3 g, 0.0303 mol) in 30 ml of THF was added 60 ml of THF solution of disodium thiobenzophenone (0.5 mol/l.). Immediately the dark red of the dianion complex changed to dark yellow-green. The mixture was refluxed under nitrogen for 3 hr and cooled, and the solvent was evaporated. The residue was dissolved in benzene and precipitated from methanol. The precipitate was filtered, washed with methanol and with water and methanol, and dried to give 8.2 g of yellow powder, mp 105–120°, mol wt 1160. This powder was positive for the Beilstein

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(9) M. Busch and H. Kunder, *Chem. Ber.*, **49**, 328 (1916).

(10) E. Biilmann, *Justus Liebigs Ann. Chem.*, **364**, 325 (1909).

test, and it was spinnable. The reprecipitation of its benzene solution from methanol was repeated to give the yellow powder VII: mp 110–120°; mol wt 2170; ir (KBr) 3030, 3000, 2925–2840 (CH$_2$), 1600 (benzene ring), 1500, and 615 cm^{-1} (CS).

Anal. Calcd for C$_{21}$H$_{18}$S: C, 83.40; H, 6.00. Found: C, 83.06; H, 5.90.

Reaction with Benzaldehyde.—To a solution of benzaldehyde (1.33 g, 0.0125 mol) in 30 ml of THF was added 53 ml of THF solution of monosodium thiobenzophenone (0.5 mol/l.), and the mixture was refluxed under nitrogen. The deep red of the thioketyl was not changed and the viscosity of the mixture was increased. After 3 hr the mixture was cooled and 100 ml of water was added. After removal of the solvent, the residue was extracted with ether. The ether layer was washed with water. The water layer was acidified with hydrochloric acid to give a yellow-green precipitate. The precipitate was recrystallized from petroleum ether (bp 40–60°) to give 0.3 g of benzoic acid: mp 122–124° (sublimed at 100°); ir (KBr) 3100–3000, 2950–2500 (COOH), 1700 (C=O), 1600 cm^{-1} (benzene ring).

Removal of solvent from the ethereal layer gave a yellow oil. On distillation of this oil under nitrogen, 3 g of a blue-violet oil distilled, bp 150–165°. This oil changed from blue-violet to brown after 2 or 3 days in air. This brown oil (3 g) was stirred with a solution of 5 ml of acetic acid and 3.1 ml of 30% hydrogen peroxide at room temperature for 2 days. The white crystals were precipitated from the mixture. Recrystallization of the white precipitate from ether yielded 0.1 g of white needle crystals: mp 130–140°; mol wt 315; ir (KBr) 3100–3000, 1600 (benzene ring), 1500, 1350 (-SO$_2$), 1130 cm^{-1} (S=O).

To a solution of benzaldehyde (1.5 g, 0.014 mol) in 10 ml of THF was added 30 ml of THF solution of disodium thiobenzophenone (0.46 mol/l.). The mixture was refluxed under nitrogen for 3 hr. The dark red of the dianion complex gradually turned to yellow and sodium chloride was precipitated. After 3 hr the mixture was cooled, poured into crushed Dry Ice to remove any unreacted dianion complex, and diluted with 100 ml of water. After removal of the solvent, the residue was extracted with ether and the extracts were washed with water and dried (Na$_2$SO$_4$). Removal of the solvent left a white powder which on recrystallization from ether gave 1.3 g (33.4%) of white needle crystals of ω,ω′-diphenylacetophenone (IX): mp 136–137° (lit.[6] mp 137°); ir (KBr) 3070, 3050, 3010, 1680 (C=O), 1600 cm^{-1} (benzene ring).

Anal. Calcd for C$_{20}$H$_{16}$O: C, 88.20; H, 5.92; mol wt, 272. Found: C, 88.21; H, 6.05; mol wt, 276.

Reaction with Benzonitrile.—To a solution of benzonitrile (2.58 g, 0.025 mol) in 30 ml of THF was added 50 ml of a THF solution of monosodium thiobenzophenone (0.5 mol/l.). The mixture was refluxed under nitrogen. After 3 hr the mixture was cooled and poured into acidic ethanol (10 ml of concentrated hydrochloric acid and 100 ml of ethanol), and it turned blue-violet in color. After removal of the solvent the residue was distilled under nitrogen to give 1.0 g (39% recovered yield) of benzonitrile, bp 75–76° (9 mm), and 1.4 g (28% recovered yield) of thiobenzophenone, bp 138–140° (3 mm).

Next the reaction of a THF solution of disodium thiobenzophenone (26 ml, 0.5 mol/l.) with benzonitrile (2.58 g, 0.025 mol) was made by the same method as described above. When the dianion complex was added to benzonitrile, immediately the color of the mixture turned from deep red to red-violet. After 3 hr the mixture was poured into aqueous methanol. After removal of the solvent, the residue was extracted with ether. A pink powder (0.2 g), which was insoluble in ether, was recrystallized from chloroform to give 0.12 g of white needle crystals, 2,4,6-triphenyl-1,3,5-triazine (X), mp 234–236°. The ethereal extract was partially evaporated to induce crystallization and 0.45 g (22.1%) of 2,4,6-triphenyl-1,3,5-triazine (X) was obtained: mp 234–236° (lit.[11] mp 233–233.5°); ir (KBr) 3000–3050, 1590 (benzene ring), 1520, 1460 cm^{-1}.

Anal. Calcd for C$_{21}$H$_{15}$N$_3$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.41; H, 5.00; N, 13.62.

The ether was evaporated from the filtrate to give 1.3 g of polymeric precipitate which was spinnable. It was dissolved in benzene and precipitated from petroleum ether (bp 42–55°) to give 0.4 g of a yellow powder: mp 105–120°; ir (KBr) 3080, 3040, 1660, 1640, 1600, 1495 cm^{-1}; mol wt 892. *Anal.* Found: C, 84.25; H, 6.49.

Registry No.—I, 19495-83-1; II, 21129-36-2; VI, 34519-98-7; VII (copolymer), 9036-08-2; VII (repeating unit), 34521-12-5; benzyl chloride, 100-44-7; *p*-dichloroxylene, 623-25-6; benzaldehyde, 100-52-7; benzonitrile, 100-47-0; thiobenzophenone, 1450-31-3.

(11) P. Eitner and F. Krafft, *Chem. Ber.*, **25**, 2267 (1892).

Selectivity Differences of Some Cobalt Catalyst Systems in the Liquid Phase Oxidation of Alkyl Aromatics[1]

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A study of the products obtained in the oxidation of *p-tert*-butyltoluene and 2,2-bis(*p*-tolyl)propane at 182° and 200 psig O$_2$ in a mixed solvent consisting of chlorobenzene and acetic acid, and in the presence of cobaltous acetate–hydrochloric acid catalyst, has revealed some significant differences in oxidation products as compared with similar experiments using the cobalt–bromide and cobalt acetate-2-butanone catalyst systems at 182 and 138°, respectively. The use of the chloride catalyst results in carbon–carbon bond cleavage during the oxidation process and leads to significant amounts of products such as *p*-toluic acid, *p*-methylacetophenone, terephthalic acid, and *p*-acetylbenzoic acid in addition to the expected *p-tert*-butylbenzoic acid and 2,2-bis(*p*-carboxyphenyl)-propane. These results are most easily explained by a radical mechanism involving a chloride ion to chlorine atom chain.

Several important industrial processes for the liquid phase oxidation of toluene or xylenes to benzoic or phthalic acids are based on cobalt catalyst systems.[2]

The use of cobalt acetate and a ketone or aldehyde activator for the oxidation of xylenes or toluenes in acetic acid to carboxylic acids at 100° has been described

by Brill.[3] Cobalt or manganese salts and various bromide promoters have been used in acetic acid solvent for the oxidation of alkyl aromatics over a range of temperatures up to 200°.[4–9] The mechanism of such

(1) A limited preliminary account appeared in *Chem. Commun.*, 1166 (1971).

(2) The patent literature on these oxidations runs into hundreds of patents; literature references will be restricted mainly to publications dealing with mechanisms.

(3) W. F. Brill, *Ind. Eng. Chem.*, **52**, 837 (1960).

(4) D. A. S. Ravens, *Trans. Faraday Soc.*, **55**, 1768 (1959).

(5) A. S. Hay and H. S. Blanchard, *Can. J. Chem.*, **43**, 1306 (1965).

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(7) Y. Kamiya, T. Nakajima, and K. Sakoda, *ibid.*, **39**, 2211 (1966).

(8) C. E. H. Bawn and T. K. Wright, *Discuss. Faraday Soc.*, **46**, 164 (1968).

(9) E. K. Fields and S. Meyerson, *Advan. Chem. Ser.*, **76**, 395 (1968).

SCHEME I
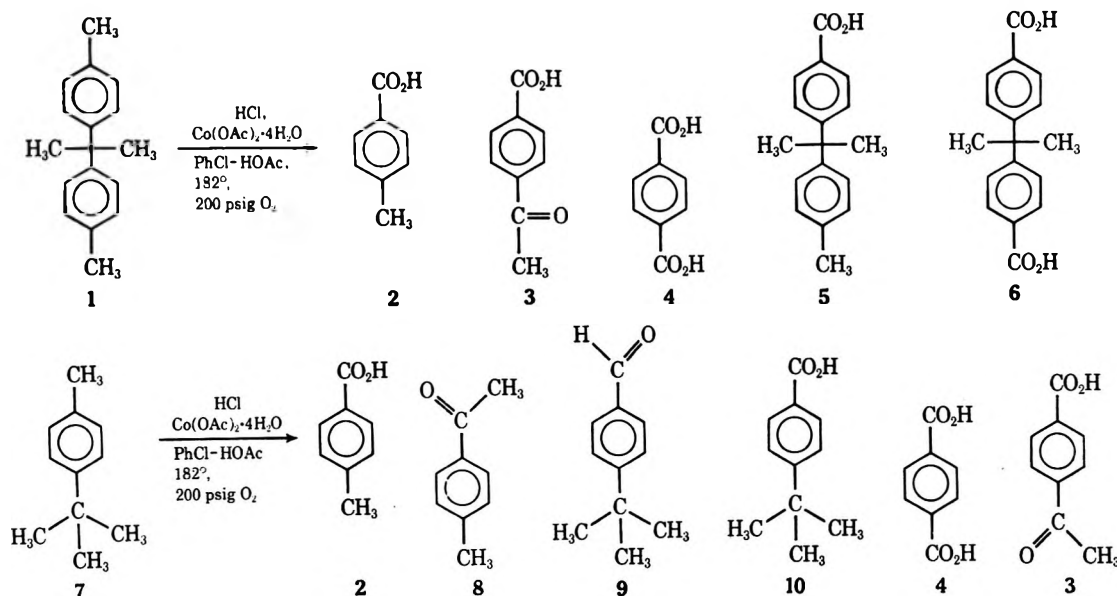
high-temperature (100–200°) metal-catalyzed oxidations is not yet well understood, as pointed out by Walling.[10] A system using chloride instead of bromide as promoter with cobalt for oxidation of p-xylene or p-toluic acid to terephthalic acid in high yields in the mixed solvent system acetic acid–chlorobenzene has recently been described.[1] Direct electron-transfer mechanisms have been suggested or implied for the oxidation of aromatic substrates by Co(III)[3,11−16] or Mn(III)[11,17,18] at low temperatures (<100°). Radical mechanisms have been suggested for the bromide-promoted cobalt[4,5,8] or manganese[19] catalyzed oxidations, and for cobalt or manganese acetate catalyzed oxidations of isopropyl benzenes at 130–150°.[20,21]

Heiba and coworkers[15] have suggested that the high-temperature (>100°) catalytic oxidation of alkylbenzenes at high concentration of catalyst proceeds predominantly via an electron-transfer process. It does not seem likely that mechanistic data obtained at low temperatures can be extrapolated to the high-temperature region, nor is it likely that kinetic data based on O_2 absorption rates obtained in the high-temperature region can serve to distinguish between radical and electron transfer mechanisms. In this study we demonstrate differences in selectivity toward attack at methyl vs. tert-butyl groups as a function of the catalyst system which may be useful in distinguishing between the two types of mechanism.

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(11) P. J. Andrulis, Jr., M. J. S. Dewar, R. Dietz, and R. L. Hunt, *ibid.*, **88**, 5473 (1966).

(12) T. Morimoto and Y. Ogata, *J. Chem. Soc. B*, 62 (1967).

(13) T. Morimoto and Y. Ogata, *ibid.*, 1353 (1967).

(14) K. Sakota, Y. Kamiya, and N. Ohta, *Can. J. Chem.*, **47**, 387 (1969).

(15) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **91**, 6830 (1969).

(16) A. Onopchenko, J. G. D. Schulz, and R. Seekircher, *Chem. Commun.*, 939 (1971).

(17) P. J. Andrulis, Jr., and M. J. S. Dewar, *J. Amer. Chem. Soc.*, **88**, 5483 (1966).

(18) T. Aratani and M. J. S. Dewar, *ibid.*, **88**, 5479 (1966).

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(21) R. Van Helden, A. F. Bickel, and E. C. Kooyman, *ibid.*, **80**, 1257 (1961).

Results

The Cobalt Chloride System.—The oxidation of 2,2-bis(p-tolyl)propane (1) and p-tert-butyltoluene (7) resulted in extensive carbon–carbon bond cleavage (see Scheme I).

Results for the oxidation of 1 and 7 are presented in Tables I and II.

TABLE I[a]

OXIDATION PRODUCTS OF 2,2-BIS(p-TOLYL)PROPANE (1)

Products, %[b]	Run no. 1	2
p-Toluic acid	5.3	4.8
Terephthalic acid p-Acetylbenzoic acid	28.7	27.2
Monoacid 5	10.8 (8.6)[c]	12.3
Diacid 6	47.6 (35.6)[c]	48.5
Unidentified	7.6	7.1
Carbon dioxide, l. (STP)	1.0	

[a] 1 (6.0 g, 26.7 mmol), Co(OAc)$_2$·4H$_2$O (0.25 g, 1 mmol), HCl (2 mmol), PhCl (45 ml), HOAc (30 ml), O$_2$ (200 psig, 5.1 l.), 2 hr at 182°. [b] Per cent of total peak area of methyl esters. [c] Actual yield of carboxylic acids using internal standard and predetermined response factors.

TABLE II[a]

OXIDATION PRODUCTS OF p-tert-BUTYLTOLUENE (7)

Products, %[b]	Run no. 1	2[c]	3[c]	4[d]	5[d]
p-Toluic acid	6.5	6.2	8.6	5.6	6.2
p-Methylacetophenone	10.1	9.8	10.1	11.9	12.8
p-tert-Butylbenzoic acid	29.7	30.6	30.3	31.2	31.8
Terephthalic acid	8.3	6.5	7.7	6.5	7.7
p-Acetylbenzoic acid	17.2	16.9	20.2	14.5	14.2
Carbon dioxide, l. (STP)	0.7	0.7	0.7	0.6	0.6

[a] p-tert-Butyltoluene (5.0 g, 33.7 mmol), Co(OAc)·4H$_2$O (0.25 g, 1 mmol), HCl (2 mmol), PhCl (45 ml), HOAc (30 ml), O$_2$ (200 psig, 5.1 l.), 2 hr at 182°. [b] Yields of the compounds calculated as acids (except for p-methylacetophenone) using internal standard. [c] Run in a glass liner in the titanium reactor, O$_2$ (200 psig, 4 l.). [d] Run for 5 min at 182°.

To demonstrate that p-methylacetophenone is one of the major intermediates in the oxidation of 7, several attempts were made to oxidize this ketone using the chloride system; no reaction occurred. However, in the presence of toluene, p-methylacetophenone is readily oxidized to p-toluic acid, terephthalic acid, and p-acetylbenzoic acid, the toluene being oxidized to benzoic acid (Table III)

TABLE III[a]
OXIDATION PRODUCTS OF TOLUENE AND
p-METHYLACETOPHENONE

	Run no. 1	2	3
Feed			
Toluene, g	3	3	5
p-Methylacetophenone, g	3	3	
Products, %[b]			
p-Toluic acid	9.4	9.4	
Recovered p-methyl-acetophenone	7.1	8.0	
Terephthalic acid	37.5	35.3	
p-Acetylbenzoic acid	24.6	26.3	
Benzoic acid	87.4	85.6	93.7
Carbon dioxide, l.	0.5	0.4	0.3

[a] $Co(OAc)_2 \cdot 4H_2O$ (0.25 g, 1 mmol), HCl (2 mmol), HOAc (30 ml), PhCl (45 ml), O_2 (200 psig, 5.1 l.), 2 hr at 182° [b] Yields calculated as acids (where applicable) using internal standard.

p-tert-Butylbenzoic acid can be oxidized alone or co-oxidized with toluene using the chloride system to give terephthalic acid, p-acetylbenzoic acid, and benzoic acid from toluene (Table IV).

TABLE IV[a]
OXIDATION PRODUCTS OF TOLUENE AND
p-tert-BUTYLBENZOIC ACID

	Run no. 1	2	3	4
Feed				
Toluene, g			3	3
p-Butylbenzoic acid, g	5	5	3	3
Products, %[b]				
Recovered p-tert-butylbenzoic acid	52.1	52.5	23.0	31.0
Terephthalic acid	8.6	8.6	17.8	19.6
p-Acetylbenzoic acid	23.2	22.1	32.1	26.8
Benzoic acid			76.7	66.9
Carbon dioxide (l.)	0.3	0.4	0.8	0.9

[a] $Co(OAc)_2 \cdot 4H_2O$ (0.25 g, 1 mmol), HCl (2 mmol), HOAc (30 ml), PhCl (45 ml), O_2 (200 psig, 5.1 l.), 2 hr at 182°. [b] Yields calculated as acids using internal standard.

The experiments described in Table V were carried out to illustrate the importance of both hydrochloric acid and the mixed solvent.

A benzylic methyl group need not be present for oxidation to occur, as illustrated by the oxidation of tert-butylbenzene to benzophenone and benzoic acid using the chloride system.[1]

The Cobalt Bromide System.—The oxidation of 1 was carried out as described for the chloride system except that NaBr (0.1 g, 1 mmol) was substituted for HCl. Products found by glc analysis of the methyl esters were 2,2-bis(p-carbomethoxyphenyl)propane (11, 98%), 2-(p-carbomethoxyphenyl)-2-(p-tolyl)propane (13, 0.7%) and dimethylterephthalate (1% of the total

TABLE V[a]
CONTROL EXPERIMENTS

	Run no. 1[a]	2[a]	3[c]	4[c]	5[d]
Products, %[b]					
p-Toluic acid	2.1	2.6	3.0	2.6	<0.1
p-Methylacetophenone	6.5	7.4	5.8	5.3	<0.1
p-tert-Butylbenzoic acid	31.4	35.6	42.1	40.9	27.0
Terephthalic acid	0.3	0.9	0.7	1.1	<0.1
p-Acetylbenzoic acid	1.1	2.7	2.7	3.4	<0.1
Carbon dioxide, l. (STP)	0.9	1.2	0.9	0.9	0.6

[a] p-tert-Butyltoluene (5.0 g, 33.7 mmol), $Co(OAc)_2 \cdot 4H_2O$ (0.25 g, 1 mmol), HOAc (30 ml), PhCl (45 ml), O_2 (200 psig, 5.1 l.), 2 hr at 182°. PhCl may provide some chloride under these conditions. [b] Yields calculated as acids (where applicable) using internal standard. [c] Same as b except solvent was HOAc only (75 ml) and HCl (2 mmol) also present. [d] Same as b except solvent was HOAc only (75 ml), no HCl.

peak area). Using an internal standard and response factors, the calculated yield of 6 was 86 mol %. p-tert-Butyltoluene was oxidized as above to give 10 in 94% yield. The yield of 4 was <1 mol %. tert-Butylbenzene was not oxidized under these conditions.[1]

The Cobalt Chloride–Bromide System.—Because of the very different results obtained in the oxidation of p-tert-butyltoluene using the CoCl and CoBr systems, some experiments were carried out in which both chloride and bromide were present. p-tert-Butyltoluene (5 g, 33.7 mmol), cobaltous acetate tetrahydrate (0.25 g, 1 mmol), hydrochloric acid (2 mmol), sodium bromide (1 mmol), chlorobenzene (45 ml), acetic acid (30 ml), and oxygen (200 psig, 5.1 l.) were allowed to react for 2 hr at 182°. The yields of products were as follows: p-tert-butylbenzoic acid, 72.7%; terephthalic acid, 13.4%; p-acetylbenzoic acid, 5.3%.

The experiment was repeated with tert-butylbenzene (5 g, 37.2 mmol) for 7 hr; 4.8 g of tert-butylbenzene was recovered; and no acetophenone was observed.

The Cobalt–2-Butanone System.[3,22]—Hydrocarbon 1 (4 g, 17.8 mmol) was oxidized with $Co(OAc)_2 \cdot 4H_2O$ (0.5 g, 2 mmol), 2-butanone (3 ml), water (3 ml), acetic acid (75 ml), and oxygen (200 psig, 5.1 l.) for 1 hr at 138°. Product analysis (glc) of the methyl esters gave diester 11 (95%) and monoester 13 (5% of the total peak area). The yield of 6 was 88.4% and of 5 was 5% as calculated using an internal standard and responses factors.

The oxidation was repeated using 7 (5 g, 33.7 mmol) instead of 1. The yield of 10 was 96%; no terephthalic acid was observed in the oxidation of 1 or 7.

Discussion

The oxidation behavior of most hydrocarbons in the liquid phase at low temperatures (<100°) is now well understood. A good recent review was published by Mayo.[23]

The autoxidation of alkyl aromatics has been studied[24,25] and the individual termination and propagation rate constants have been measured for the xylenes, toluene, ethylbenzene, cumene, and others. It is

(22) Oxidations using this system were found to have erratic induction periods.
(23) F. R. Mayo, *Accounts Chem. Res.*, 1, 193 (1968).
(24) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, 45, 793 (1967).
(25) L. Sajus, *Advan. Chem. Ser.*, 75, 59 (1968).

apparent that the relatively large termination rate constant for the termination reaction (eq 1) is responsible

$$2ROO\cdot \xrightarrow{k_t} \text{nonradical products} + O_2 \qquad (1)$$
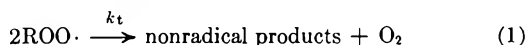
for the low $(2-3)^{25}$ chain length in the autoxidation of the primary benzylic hydrogens in alkyl benzenes. As a consequence, hydroperoxides are not accumulated in the reaction products of toluene or xylene autoxidations. The rate-accelerating effect in hydrocarbon autoxidations of transition metal ions is thought to be due to the ability of the ions to produce radicals from hydroperoxides by the following sequence of reactions[5,26]

$$ROOH + M^{2+} \longrightarrow RO\cdot + OH^- + M^{3+} \qquad (2)$$

$$ROOH + M^{3+} \longrightarrow ROO\cdot + H^+ + M^{2+} \qquad (3)$$
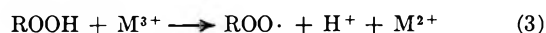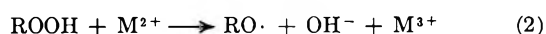
(eq 2, 3). The radicals produced can then initiate further chains. Walling[10] has recently pointed out that the rates of some commercial oxidations of alkyl aromatics are in excess of limiting rates predicted by a kinetic analysis. Under these conditions, the usual propagation step (eq 4) must be unimportant in the

$$ROO\cdot + RH \xrightarrow{k_p} ROOH + R\cdot \qquad (4)$$

consumption of RH and other reaction sequences must be invoked. Scott[27] has suggested eq 5, rather than eq 2, as a major path for the oxidation of Co(II) to Co(III).

$$RO_2\cdot + Co(II) \longrightarrow R'CHO + Co(III) + OH^- \qquad (5)$$

It is now well established[14,15,28] that Co(III) complexes in a variety of solvents (usually acetic acid) can oxidize alkyl aromatics such as toluene by direct electron transfer (from the aromatic to cobalt) in the absence of oxygen at temperatures below 100°.
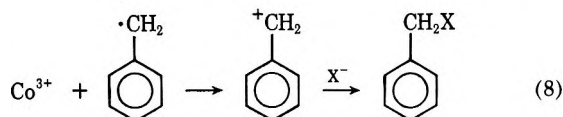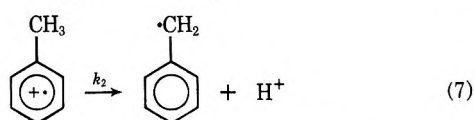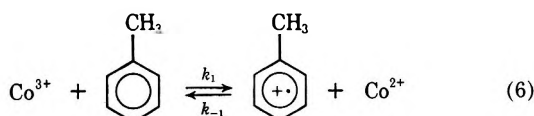
In the presence of oxygen, such a mechanism must include a sequence of reactions involving reaction of benzyl radicals with oxygen instead of eq 8. Such an electron-transfer mechanism in the presence of oxygen has indeed been suggested by Brill[3] for the oxidation of *p*-xylene to terephthalic acid using cobaltous acetate and 2-butanone in acetic acid at 100°. Dewar and coworkers[11] have suggested a similar mechanism involving the propagating steps after eq 7. In the Brill system,
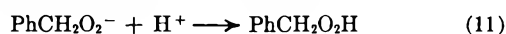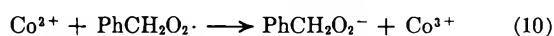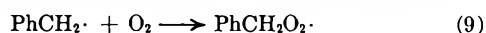
$$PhCH_2\cdot + O_2 \longrightarrow PhCH_2O_2\cdot \qquad (9)$$

$$Co^{2+} + PhCH_2O_2\cdot \longrightarrow PhCH_2O_2^- + Co^{3+} \qquad (10)$$

$$PhCH_2O_2^- + H^+ \longrightarrow PhCH_2O_2H \qquad (11)$$

Co^{3+} presumably arises from the reaction of Co^{2+} with peroxides derived from 2-butanone. Morimoto and Ogata[12,13] also suggest that cobalt acetate catalyzed toluene autoxidation at 90° proceeds, at least in part, *via* the direct electron transfer scheme. Finally, Heiba, *et al.*,[15] have suggested that all commercial oxidations of alkylbenzenes proceed predominantly *via* such a mechanism, and Onopchenko, *et al.*,[16] have shown recently that, in the Co(III)-catalyzed cooxidation of *p*-cymene and *n*-butane, *p*-isopropylbenzoic acid is the major product obtained, presumably by an electron transfer mechanism.

Free radical mechanisms have also been suggested. Such a mechanism would involve an initial abstraction of H from the alkyl aromatic by some species such as $Br\cdot$, $Cl\cdot$, $RO\cdot$, $ROO\cdot$, etc. (or their complexes with metal ions) and does not imply that no electron transfer takes place at all, since it must occur at some stage of the reaction if a Co(II)-Co(III) redox cycle is to be established. Such a mechanism, most likely in the bromide system and the chloride system, might be formulated as follows, to illustrate only how $X\cdot$ could

$$\text{Initiating radical} + HX \longrightarrow X\cdot \ (X = Br\cdot) \qquad (12)$$

$$X\cdot + RH \longrightarrow R\cdot + HX \qquad (13)$$

$$R\cdot + O_2 \longrightarrow RO_2\cdot \qquad (14)$$

$$RO_2\cdot + HX \longrightarrow RO_2H + X\cdot \qquad (15)$$

$$Co^{3+} + X^- \longrightarrow Co^{2+} + X\cdot \qquad (16)$$

$$HX + O_2 \longrightarrow X\cdot + HO_2\cdot \qquad (17)$$
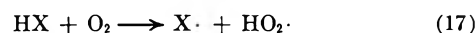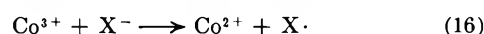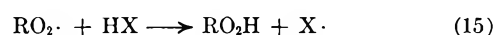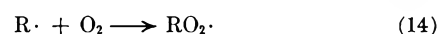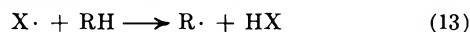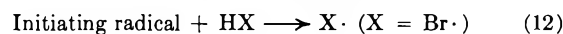
be involved in the chain reaction; other sequences such as eq 1-5, are probably involved too. Bromine atoms have been suggested as being involved in these oxidations[4,6,8,25] and reactions 16 and 17 have been proposed[4,6,8] for X = Br. Reaction 16 is known to occur in acetic acid solution for X = Cl.[15] Cooper and Waters[29] have observed that the oxidation of di-2-chloroethyl ether by Co^{3+} is autocatalytic and have proposed a chain reaction involving chlorine atoms and the oxidation of chloride to chlorine atoms by Co^{3+}.

Detailed mechanisms of metal-catalyzed autoxidations of alkylbenzenes under conditions of commercial processes (100–200°) are ill-defined and probably complex.[10] The results of this study, based on the unique differences in oxidation products of 1 and 7 as a function of catalyst, suggest a free-radical mechanism for the bromide and chloride systems. The observed products for the chloride and bromide systems are compatible in every respect with a mechanism involving initial abstraction of hydrogen by $Cl\cdot$, $Br\cdot$, or a cobalt complex involving $Cl\cdot$ or $Br\cdot$ (eq 18, 19).
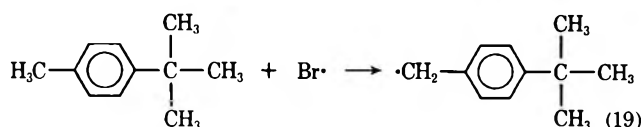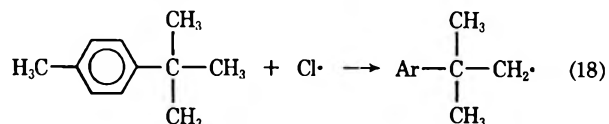
Using the data in Walling's book[30] for liquid phase chlorination at 80°, the relative reactivity per hydrogen

(26) A. E. Woodward and R. B. Mesrobian, *J. Amer. Chem. Soc.,* **75,** 6189 (1953).

(27) E. J. Y. Scott, *J. Phys. Chem.,* **74,** 1174 (1970).

(28) T. A. Cooper, A. A. Clifford, D. J. Mills, and W. A. Waters, *J. Chem. Soc. B,* 793 (1966).

(29) T. A. Cooper and W. A. Waters, *ibid.,* 464 (1967).

(30) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 360, 371.

in toluene is 1.0 *vs.* 0.22 for *tert*-butylbenzene. Accounting for all hydrogens, the reactivity is 3:2 for benzylic methyl *vs.* tertiary butyl. The additional 100° increase in temperature at which the oxidation is carried out would be expected to further decrease the selectivity in the abstraction reaction. In contrast to chlorination, *tert*-butylbenzene fails to undergo side-chain bromination under any conditions (see ref 30, p 371), whereas toluene is readily brominated to give benzyl bromide at 20°. Equations 20 and 21 illustrate

$$Ar-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2\cdot \ + \ O_2 \longrightarrow Ar-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_2}{|}}{C}}-CH_2OO\cdot \qquad (20)$$

$$Ar-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2OO\cdot \longrightarrow \ \longrightarrow \ Ar-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CO_2H \qquad (21)$$

$$Ar-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CO_2H \ + \ Co^{3+} \longrightarrow Ar-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}\cdot \ + \ CO_2 \ + \ Co^{2+} \qquad (22)$$

$$Ar-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}\cdot \ + \ O_2 \xrightarrow[Co^{3+}]{Co^{2+}} Ar-\overset{\overset{O}{\|}}{C}-CH_3 \longrightarrow ArCO_2H \qquad (23)$$
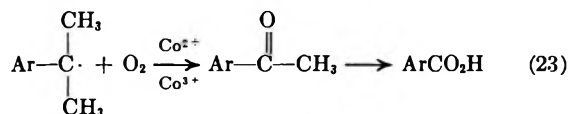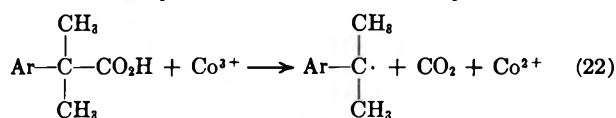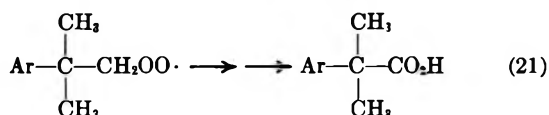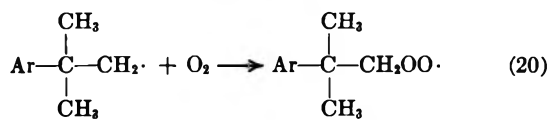
a reasonable and probable reaction sequence for converting the primary alkyl radical to carboxylic acid; others involving cobalt catalysis and free-radical rearrangements could be invoked. The reaction in eq 22 is well known[31] even at low temperature for carboxylic acids which can give relatively stable radicals. The reaction sequence shown in eq 23 has been demonstrated[20,21] for the cobalt-catalyzed autoxidation of isopropyl benzenes.

Additional evidence for an initial nonselective radical attack in the chloride system is the finding that appreciable amounts of *p*-toluic acid and *p*-methylacetophenone are obtained in the oxidation of *p-tert*-butyltoluene. These products are not observed in the oxidation of toluene; therefore, they cannot have arisen from addition of methyl or acetyl radicals to the aromatic ring followed by loss of the *tert*-butyl group.

Reported[32] oxidation potentials for Co^{2+}–Co^{3+} (−1.84 V), Mn^{2+}–Mn^{3+} (−1.5 V), Cl^-–Cl_2 (−1.36 V), and Br^-–Br_2 (−1.07 V) (in aqueous acidic solution) give support to the radical hypothesis, since we have found that Mn^{2+} is not effective as a catalyst for the chloride system, whereas it is known to be an effective catalyst in the bromide system.

The results obtained for the mixed bromide–chloride catalyst in the oxidation of *p-tert*-butyltoluene and *tert*-butylbenzene also suggest initial radical attack. In the reaction with *tert*-butylbenzene, bromide ion can act as an effective inhibitor until all the bromide is completely converted to bromine atoms.

In comparing the ratio of cleavage products to products with an intact carbon skeleton in the oxidation of 2,2-bis(*p*-tolyl)propane and *p-tert*-butyltoluene using the chloride system (Tables I and II), it is obvious that this ratio is >1 for **7** and <1 for **1**. This ob-

servation is consistent with the statistical distribution of aliphatic and benzylic hydrogens in the two compounds (3:1 for **7** and 1:1 for **1**) and their abstraction by $Cl\cdot$. It is inconsistent with an electron transfer mechanism such as that proposed by Heiba[8,15] for toluene oxidation in acetic acid by cobaltic acetate–lithium chloride. If cleavage products are to be explained by loss of either $\cdot CH_3$ or $^+CH_3$ from cation radicals A, A′, or B, B′, one should reasonably expect
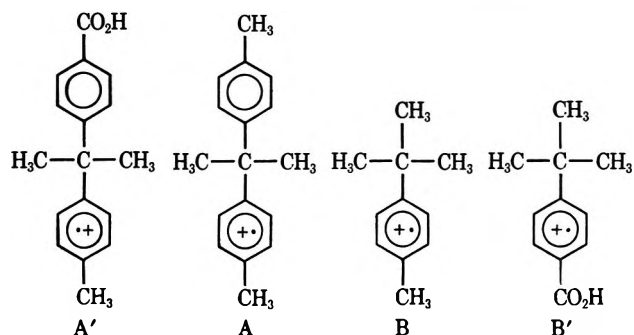
such a process to be favored in A or A′ relative to B or B′ if there is considerable bond breaking in the transition state leading to cleavage. The opposite result is observed, however, in agreement with the "Hammond postulate" as applied to the reaction of $Cl\cdot$ with RH. Appreciable C–C bond cleavage has not been observed by us in the Co–2-butanone system or by Onopchenko, *et al.*,[16] in the oxidation of *p*-cymene and *p-tert*-butyltoluene; however, Heiba, *et al.*,[15] have reported C–S bond cleavage in the oxidation of *p*-methoxybenzylphenyl sulfide by Co^{3+} in the presence of LiCl at room temperature; they have also reported a correlation between ionization potential and rates of oxidation of alkyl aromatics by cobaltic acetate–lithium chloride in acetic acid in support of the electron transfer mechanism. A plot of the data of Fields[33] for the autoxidation of the same alkyl aromatics in acetic acid using a cobalt acetate–bromide catalyst gives no such correlation, indicating that the mechanisms are probably not related.

In conclusion, although an electron transfer mechanism cannot be completely ruled out for the chloride system and the bromide system, the results obtained in this study are more compatible with a free-radical mechanism involving halogen radicals as the species involved in the initial attack on alkyl aromatic substrates.

Experimental Section

General Procedure.—All oxidations were carried out in a closed system consisting of a 500-ml Parr titanium rocking autoclave equipped with a silver gasket and dual silver rupture disks in a titanium rupture disk assembly.[34] All fittings in contact with reagents were titanium. Temperature was controlled remotely *via* a Hi-Lo control circuit using an Esterline Angus thermocouple controller. Agitation was by the rocking motion of the autoclave only. The autoclave was typically charged with the reactants, slowly raised to the operating temperature, kept there for a predetermined time, and then allowed to cool to room temperature. The gas was vented through a CO_2 trap and a wet test meter. The products were analyzed by esterification and glc analysis. All operations involving reactions under oxygen pressure were carried out in a barricade by remote control.

(31) A. A. Clifford and W. A. Waters, *J. Chem. Soc.*, 2796 (1965).

(32) W. M. Latimer, "The Oxidation States of the Elements and Their Potentials in Aqueous Solutions," 2nd ed, Prentice-Hall, Englewood Cliffs, N. J., 1952.

(33) E. K. Fields and S. Meyerson, *Advan. Chem. Ser.*, **76**, 395 (1968).

(34) A glass liner was used in control runs to establish that no significant results were due to the metal surfaces of the bomb.

Analyses.—In the oxidation of 2,2-bis(p-tolyl)propane (1) the dry product mixture including catalyst was obtained by removal of solvent and vacuum drying of the residue. The solid was homogenized and a 1-g sample was refluxed for 8 hr with CH_3OH (100 ml) and concentrated H_2SO_4 (2 ml). Methanol was removed and the residue was dissolved in ether (500 ml). The ether solution was washed with water (100 ml) and aqueous $NaHCO_3$ (100 ml), dried ($CaSO_4$), and filtered. Ether was evaporated from the filtrate and the residue was dissolved in a minimum of dry acetone; a known weight of internal standard (methyl tridecanoate) was added before glc analysis. The product mixture was analyzed on a 1 ft × 0.25 in. 16% CW 20 M on 60/80 mesh AW Chromosorb P column programmed at 130–260° in a Varian Aerograph A90P3 glc instrument with linear temperature programmer.

In the oxidation of p-tert-butyltoluene the products were expected to be more volatile than in the previously described system; it was decided not to attempt to dry them to constant weight. The total sample (after flashing the solvent) was esterified with 400 ml of absolute methanol and 3 ml of concentrated H_2SO_4 for 14 hr. On cooling, methanol was removed, the residue was taken into ether (500 ml), and the ether solution was washed with water (100 ml) and aqueous $NaHCO_3$ (100 ml). The solution was dried over $CaSO_4$ and filtered, and the ether was removed. The residue was dissolved in a minimum of acetone, and a known weight of methyl pentadecanoate was added as internal standard. The product mixture was analyzed on a 5 ft. × 0.25 in. Carbowax 20M column. Using the conditions described above, only methyl p-toluate and p-methylacetophenone were not completely separated. Known mixtures of the components were esterified in an identical manner (including the addition of cobaltous acetate, hydrochloric acid, acetic acid, and chlorobenzene, and flashing of the solvents to leave a residue) to determine correction factors for the acids relative to methyl pentadecanoate. Errors range from 5% of the reported values for large peaks to 10% for small peaks. All glc traces were obtained in duplicate. This procedure does not account for most of the unreacted p-tert-butyltoluene. The latter was not routinely determined; however, in some cases, the chlorobenzene–acetic acid mixture was analyzed for p-tert-butyltoluene after removal from the nonvolatile products. An aliquot was treated with excess cold aqueous potassium hydroxide and the neutral layer was extracted into ether and analyzed by glc using an internal standard.

The products were identified by comparing glc retention times, melting points, and ir and nmr spectra of the components as trapped from the glc effluent with authentic samples.

Instruments.—All ir spectra were obtained on a Perkin-Elmer Model 137 sodium chloride spectrophotometer. The nmr spectra were obtained on a Varian Model A-60 spectrometer.

Materials.—Starting materials were reagent grade materials and were routinely purified. $Co(OAc)_2 \cdot 4H_2O$ was Mallinckrodt reagent grade material. NaBr was reagent grade from B and A. In the chloride system, HCl was used as a solution of a weighed sample of concentrated aqueous HCl dissolved in 99% glacial acetic acid (Du Pont).

Syntheses. 2,2-Bis(p-tolyl)propane (1).—Hydrocarbon 1 was prepared from α,p-dimethylstyrene by reaction with hydrogen chloride and alkylation of toluene with the tertiary chloride and aluminum chloride–nitromethane complex in 64% yield by the method of Coscia, et al.,[35] mp 77–78° from methanol (lit.[35,36] mp 80, 78–79°). All melting points are uncorrected.

2,2-Bis(p-carboxyphenyl)propane (6).—Acid 6 was prepared by the method of Coscia, et al.,[35] by chromic acid oxidation of 1, mp 315–317° (lit.[35] mp 313–315°).

Acid 6 was also prepared by autoxidation; compound 1 (6 g, 26.7 mmol), $Co(OAc)_2 \cdot 4H_2O$ (0.25 g, 1 mmol), and NaBr (0.10 g, 1 mmol) in 75 ml of glacial acetic acid were allowed to react in a titanium Parr rocking autoclave for 90 min at 182° and 200 psig O_2 pressure (at room temperature). On cooling, the precipitate was filtered, washed with cold water (300 ml), and dried to constant weight under vacuum. A portion of the crude diacid 6 (6.71 g, 88.5%) was recrystallized twice from aqueous acetic acid, washed with water, and dried under vacuum. This sample

had mp 317–319°; neut equiv 400 mg KOH/g (calcd, 395); identical ir spectrum with that of 6 as prepared by chromic acid oxidation. *Anal.* Calcd for $C_{17}H_{16}O_4$: C, 71.8; H, 5.67. Found: C, 71.7; H, 5.74.

2,2-Bis(p-carbomethoxyphenyl)propane (11).—Diacid 6 (1 g) was refluxed for 8 hr with methanol (100 ml) and concentrated H_2SO_4 (2 ml). On cooling, methanol was removed and water was added to the residue. The precipitate was recrystallized three times from methanol to give 11: mp 106.5–108° (lit.[35,37] mp 107–107.5°, 101–102°); nmr ($CDCl_3$) δ 1.75 [s, 6, $(CH_3)_2$-$C(Ar)_2$], 3.9 (s, 6, CO_2CH_3), 7.2–8.1 (m, 8, aromatic A_2B_2).

2(p-Cyanophenyl)-2-(p-tolyl)propane (12).—p-Cyanoacetophenone (10 g, 0.069 mol) was dissolved in ether (300 ml) and the solution was cooled with Dry Ice–acetone. An ether solution of CH_3MgI (125 ml) prepared from Mg (1.7 g, 0.069 mol) and CH_3I (9.8 g, 0.069 mol) was added in portions under N_2 with stirring. The reaction mixture was allowed to come to room temperature and decomposed with 400 ml of saturated aqueous NH_4Cl solution. The ether layer was dried ($CaSO_4$) and filtered and ether was removed. The residue (9.2 g) exhibited the following functional groups (ir), 3400 (s, –OH), 2200 (–CN), and 1685 cm^{-1} (w, >C=O), indicating that it was probably a mixture of a little starting material and p-cyanocumyl alcohol. The alcohol was expected to be thermally unstable and was, therefore, not distilled but rather was converted directly to nitrile 12. The above residue (9.2 g), toluene (100 ml), and H_2SO_4 (250 ml, 80%) were stirred vigorously for 4 hr at room temperature. The mixture was poured on ice and extracted with ether (400 ml), the ether layer was washed with aqueous $NaHCO_3$, dried ($CaSO_4$), and filtered, and the ether was evaporated. The residue was distilled. The major fraction (5.0 g, 30.8%), bp 130–135° (0.25 mm), was recrystallized from methanol to give 12: mp 67.5–68°; nmr ($CDCl_3$) δ 1.6 [s, 6, $(CH_3)_2C(Ar)_2$], 2.25 (s, 3, CH_3Ar) and 7.05–7.6 (m, 8, aromatic); ir 2230 (s, –CN), 817 cm^{-1} (s, 1, 4-substituted aromatic). *Anal.* Calcd for $C_{17}H_{17}N$: C, 86.8; H, 7.28. Found: C, 86.9; H, 7.10.

2-(p-Carboxyphenyl)-2-(p-tolyl)propane (5).—Nitrile 12 (2 g, 0.85 × 10^{-2} mol) was refluxed for 16 hr with KOH (6 g) in 50 ml of 5:1 methanol–water. Methanol was removed under vacuum, and the residue was diluted with water (200 ml) and acidified with dilute HCl. The precipitate was filtered, recrystallized from aqueous acetic acid, and dried under vacuum to give 5 (2 g, 92.5%): mp 163–164°; nmr ($CDCl_3$) δ 1.67 [s, 6, $(CH_3)_2C(Ar)_2$], 2.3 (s, 3, CH_3Ar), 7.05–8.15 (m, 8, aromatic), 12.5 (s, 1 CO_2H). *Anal.* Calcd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.13. Found: C, 80.1; H, 7.08.

2(p-Carbomethoxyphenyl)-2-(p-tolyl)propane (13).—Acid 5 (1.0 g, 3.9 × 10^{-3} mol) was refluxed for 8 hr with absolute methanol (100 ml) and concentrated H_2SO_4 (2 ml). Methanol was removed and the residue was dissolved in ether (500 ml). The ether solution was washed with water (10 ml) and aqueous $NaHCO_3$ (100 ml), dried ($CaSO_4$), and filtered, and the ether was evaporated to give residue 13 (1.0 g, 94.8%): bp 136–140° (0.3 mm); nmr ($CDCl_3$) δ 1.65 [s, 6, $(CH_3)_2C(Ar)_2$], 2.28, (s, 3, CH_3Ar), 3.8 (s, 3, CO_2CH_3), 7.05–8.1 (m, 8, aromatic). *Anal.* Calcd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.51. Found: C, 80.8; H, 7.28.

(35) A. T. Coscia, et al., *J. Org. Chem.*, **26**, 1398 (1961).
(36) R. R. Hiatt, U. S. Patent 2,719,871 (1955).
(37) C. E. Schweitzer, U. S. Patent 2,794,822 (1957).

Preparation, Stereochemistry, and Rearrangement of Mercurials in the Norbornenyl–Nortricyclyl System

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Acetoxymercuration of norbornadiene under the conditions of Winstein and Pande affords a 2:1 mixture of _exo,exo_-3-acetoxynortricyclyl-5-mercuric chloride (IIa) and the exo,endo isomer IIIa. An independent synthesis of IIIa is described, starting from the palladium analog IV. The stereochemistry of IIa and IIIa is proved by chlorinolysis to _exo_-3-acetoxy-_exo_-5-chloronortricyclene (Va) and _exo_-3-acetoxy-_endo_-5-chloronortricyclene (Vb), respectively. The rearrangement of _exo,exo_-2-acetoxynorborn-5-enyl-3-mercuric chloride (Ia) into a tricyclic isomer as described by Winstein and Pande is shown to be stereospecific in dimethyl sulfoxide (HgCl$_2$ catalysis) and to afford IIa. Treatment of the bicyclic palladium complex VIII with mercury affords _exo,endo_-2-acetoxy-norborn-5-enyl-3-mercuric chloride (IX). The latter also rearranges to IIa. although seven times more slowly than does Ia.

Winstein and Pande have shown that acetoxymercuration of norbornadiene under kinetic conditions leads to bicyclic mercurial I, which rearranges slowly to a tricyclic isomer II.[3] The rearrangement was also observed when purified Ia was treated with mercuric chloride in dimethyl sulfoxide. The original communication by Winstein and Pande established the exo,cis stereochemistry of I, but no stereochemical assignment has been made for the tricyclic isomer, although the exo,exo stereochemistry appears to have been assumed without proof by some workers. This paper describes stereospecific preparation and structure proof of both possible tricyclic mercurials IIa and IIIa, and presents evidence pertaining to the mechanism of rearrangement of Ia.

Synthesis of _exo,endo_-**3-Acetoxynortricyclyl-5-mercuric Chloride (IIa) and** _exo,endo_-**2-Acetoxynorborn-5-enyl-3-mercuric Chloride (IX).**—We have found that metal exchange occurs between arylmercuric salts and σ-bonded organopalladium complexes, analogously to the exchange reactions between palladium(II) chloride or acetate and phenylmercuric salts reported by Heck.[4] Treatment of the tricyclic palladium complex IV[5] with excess phenylmercuric acetate affords a mixture of products, including biphenyl (54%), _exo,exo_-3,5-diacetoxynortricyclene (20%), and a compound C$_9$H$_{11}$-HgO$_2$Cl (57%), assigned the structure IIIa. The absence of olefinic protons in the nmr spectrum strongly suggests a tricyclic carbon skeleton. Reaction of IIIa with chlorine in pyridine at −40° results in the formation of two acetoxy chlorides in a ratio of 96:4. The minor isomer is identical with authentic Va,[6] while the major isomer Vb is also formed upon chlorination of IV. Since the stereochemistry of IV is known,[5,7] and halogen cleavage of carbon–palladium bonds in closely analogous compounds occurs with retention,[8] Vb must be _exo_-3-acetoxy-_endo_-5-chloronortricyclene. The conditions used for chlorination of IIIa are known to cleave carbon–mercury bonds

Ia, X = Cl
b, X = OAc

IIa, b

IV → IIIa, b
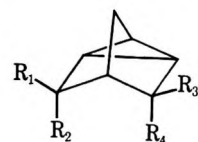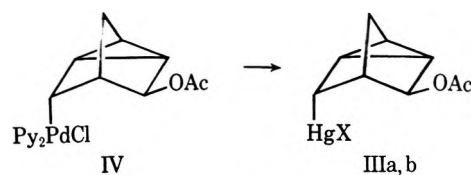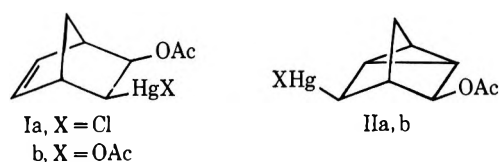
Va, R$_1$ = Cl; R$_3$ = OAc; R$_2$ = R$_4$ = H
b, R$_2$ = Cl; R$_3$ = OAc; R$_1$ = R$_4$ = H
c, R$_1$ = Cl; R$_4$ = OAc; R$_2$ = R$_3$ = H
d, R$_2$ = Cl; R$_4$ = OAc; R$_1$ = R$_3$ = H

VI → VII

VIII → IX
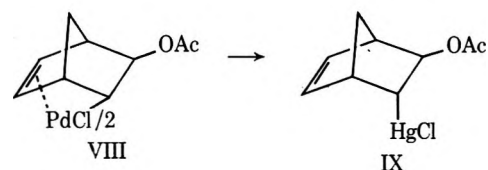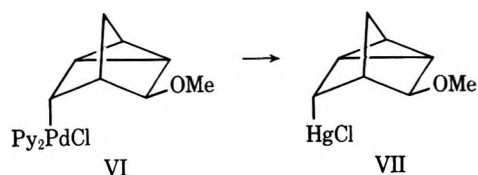
with retention of stereochemistry;[9] so III is assigned the _exo,endo_-3-acetoxynortricyclyl-5-mercuric chloride structure.

Metal exchange is likewise observed upon treatment of the methoxy analog VI with phenylmercuric salts to give biphenyl and _exo,endo_-3-methoxynortricyclyl-5-mercuric chloride (VII). Chlorination of VII as before results in the formation of the known _exo_-3-methoxy-_endo_-5-chloronortricyclene[8] as the major product. Metal exchange also takes place between IV and mercury metal or mercuric chloride, but the products are more difficult to purify.

(1) We thank the donors of the Petroleum Research Fund of the American Chemical Society for support of this work. We also acknowledge support from the National Institutes of Health in the form of a predoctoral fellowship to M. F. S., 1970–1971.

(2) Alfred P. Sloan Fellow, 1971–1973.

(3) K. C. Pande and S. Winstein, _Tetrahedron Lett._, 3393 (1964).

(4) R. F. Heck, _J. Amer. Chem. Soc._, **91**, 6707 (1969), and references cited therein.

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(6) G. M. Whitesides and J. SanFilippo, Jr., _ibid._, **92**, 6611 (1970).

(7) E. Forsellini, G. Bombieri, B. Crociani, and T. Boschi, _Chem. Commun._ 1203 (1970).

(8) D. R. Coulson, _J. Amer. Chem. Soc._, **91**, 200 (1969).

(9) F. R. Jensen. L. D. Whipple, D. K. Wedegaertner, and J. A. Landgrebe, _ibid._, **82**, 2466 (1960).

Attempted preparation of the bicyclic mercurial IX by exchange of the bicyclic palladium complex VIII with phenylmercuric salts results in the formation of tricyclic mercurial III. However, exchange with mercury metal affords the desired IX in 30% yield. Analogous exchange between allylpalladium complexes and mercury metal has been reported.[10]

Identification of IX rests on elemental analysis, molecular weight determination, and the characteristic nmr spectrum. In particular, the coupling constant $J_{2,3}$ = 2.8 Hz is characteristic of trans 2,3-disubstituted norbornene derivatives. Selective chlorinolysis of the carbon–mercury bond is not possible in this system, and the volatile products (obtained in 99% yield) consist of tricyclic Va (95%) and Vb (5%).

Stereochemistry of Acetoxymercuration of Norbornadiene, *exo,exo*-3-Acetoxynortricyclyl-5-mercuric Chloride (IIa).—Acetoxymercuration of norbornadiene (excess diene, 3 days in acetic acid at 25°) affords 3-acetoxynortricyclyl-5-mercuric chlorides in high yield.[3] The crude solid product (collected with 95% ethanol) melts over a wide range and is not homogenous by nmr, with two distinct methine hydrogen signals appearing at δ 4.55 (0.73 H) and 4.81 (0.27 H). The lower intensity signal corresponds exactly in chemical shift to the C_3 methine hydrogen of *exo,endo*-3-acetoxynortricyclyl-5-mercuric chloride (IIIa).

Chlorination of the crude solid in pyridine at −40° results in a 3:1 mixture of Va and Vb as sole products. Similar treatment of the mother liquors (ethanol filtrate) affords relatively more Vb and the corrected Va:Vb ratio is 2:1 (93% overall yield based on starting mercuric acetate). Two minor components are also present in the mother liquor chlorination mixture. One of these is identified as Vc[6] (3% overall yield) while the other minor chlorination product is also tricyclic and must therefore be the endo,endo isomer Vd. This assignment is supported by the chemical shifts of the C_3 and C_5 methine protons of Vd, which are similar to the corresponding chemical shifts of Va owing to the absence of "nearest neighbor" deshielding effects.[8,11]

The major tricyclic product from acetoxymercuration of norbornadiene can be purified by recrystallization from 95% ethanol, mp 150–151°. The nmr spectrum of pure material displays a signal for the C_3 methine proton at δ 4.55 (t, J = 1.2 Hz). This substance is assigned the *exo,exo*-3-acetoxynortricyclyl-5-mercuric chloride structure IIa on the basis of chlorination to Va and Vb in a ratio of 93:7.

Purified IIa or IIIa (or IIb and IIIb) are both stable in acetic acid and do not interconvert, with or without added mercuric acetate. However, addition of freshly distilled norbornadiene causes interconversion of IIb and IIIb at 25°. Loss of stereochemistry does not occur if hydroquinone is added along with the norbornadiene; so the formation of IIIb during acetoxymercuration is probably due to some free radical process initiated by trace impurities in the norbornadiene.[12]

Mercuric Chloride Catalyzed Rearrangement of Ia and IX.—*exo,exo*-2-Acetoxynorborn-5-enyl-3-mercuric chloride (Ia) is available from norbornadiene by acetoxymercuration under kinetic conditions.[3] The reaction is exothermic, and cooling is necessary in order to avoid further rearrangement.[12] Attempted characterization of Ia by chlorinolysis affords only *exo*-3-acetoxy-*exo*-5-chloronortricyclene (Va, 99% yield), as expected from the similar behavior of IX. That formation of Va is not the result of prior isomerization of Ia to IIa is proved by recovery of unrearranged Ia in addition to Va from an experiment with a deficiency of chlorine. In a similar experiment, an equimolar mixture of Ia and IX affords, upon treatment with 0.4 equiv of chlorine, Va (36%), recovered Ia (21%), and recovered IX (43%). This experiment shows that both Ia and IX do not rearrange under the reaction conditions, and that Ia is *ca.* two times more reactive than IX.

As reported by Winstein and Pande,[3] Ia rearranges in dimethyl sulfoxide solution in the presence of mercuric chloride. No rearrangement occurs under similar conditions in the absence of mercuric chloride. The sole product observed by nmr is IIa, a finding which is confirmed by preparative scale experiments. Similarly, the isomer IX (endo mercury) rearranges to IIa, although more slowly than does Ia by a factor of seven at 35.8°. Within the limits of nmr analysis, IX does not rearrange initially to Ia. Both of the tricyclic mercurials IIa and IIIa are stable under the reaction conditions and do not interconvert detectably; so the appearance of IIa is clearly a kinetically controlled process.

Discussion

Our structural assignments depend on the assertion that stereochemistry is retained during metal exchange of the palladium complexes IV and VIII, and also during cleavage of II and III by chlorine. According to Jensen, *et al.*, the chlorine–pyridine reagent cleaves carbon–mercury bonds at −40° with predominant retention.[9] We have found that this reagent converts 3-phenylnortricyclyl-5-mercuric chloride (known to be endo at the phenyl substituent) into *endo,endo*-3-chloro-5-phenylnortricyclene as the major (>90%) product.[13] This result provides strong evidence in favor of a cyclic chlorinolysis mechanism resulting in retention of stereochemistry. No other mechanism is likely to produce the highly hindered endo,endo product in the *endo*-3-phenyl-5-nortricyclyl system. There can be little doubt that chlorinolysis of the analogous (but less demanding) *exo*-3-acetoxy-5-nortricyclyl mercurials II and III likewise occurs with retention, and that metal exchange of IV and related complexes must therefore occur with retention. Similar results are observed in metal exchange between mercuric salts and numerous main groups element–carbon bonds.[14] Retention has also been observed in the only previous example of exchange between mercuric chloride and a transition metal–carbon bond of known stereochemistry.[15] Tentatively, the reaction of IV with phenylmercuric

(10) A. N. Nesmeyanov, A. Z. Rubezhov, L. A. Leites, and S. P. Gubin, *J. Organometal. Chem.*, **12**, 187 (1968).

(11) A. D. Cross and I. T. Harrison, *J. Amer. Chem. Soc.*, **85**, 3223 (1963).

(12) Under typical acetoxymercuration conditions, the rearrangement of Ib is complete after several hours according to nmr analysis. The initial product IIb is converted more slowly into the 2:1 mixture of IIb and IIIb, as judged by the appearance of the appropriate methine signals in the nmr spectrum. Highly purified norbornadiene, obtained by preparative glpc, does not induce interconversion of II and III.

(13) E. Vedejs and M. F. Salomon, *Chem. Commun.*, 1582 (1971).

(14) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N. Y., 1968, Chapter 5.

(15) G. M. Whitesides and D. J. Boschetto, *J. Amer. Chem. Soc.*, **93**, 1529 (1971).

salts is regarded as a four-center process, resulting in IIIa and a phenylpalladium derivative which decomposes to biphenyl and inorganic side products.[4,16] Nothing is known regarding the mechanism of exchange between VIII and mercury metal, although analogous exchange of allylpalladium chloride dimer with mercury metal has been rationalized via the intermediate $C_3H_7Pd-HgCl$ which presumably eliminates palladium metal.[10]

The catalyzed rearrangement of Ia and IX to IIa can be explained by formation of a mercuric chloride-olefin complex X or XI, followed by transannular displacement of $ClHg^+$. The final step involves electrophilic substitution at the C-3 mercury bond with inversion in the case of X and retention in the case of XI. A similar mechanism has been proposed by Matteson and coworkers for the mercuric chloride induced conversion of exo- and endo-5-norbornene-2-boronic acid into nortricyclylmercuric chloride.[17]

Both Ia and IX rearrange at 35.8° according to first-order kinetics by nmr analysis (80–90% conversion) with apparent first-order rate constants proportional to the concentration of mercuric chloride. Assuming a low concentration of an intermediate such as X or XI, the steady-state approximation leads to a first-order rate expression (eq 1) which is compatible

$$\frac{-d[\text{Ia}]}{dt} = k_{ap}[\text{Ia}] \qquad k_{ap} \sim [\text{HgCl}_2]k_1\left(1 - \frac{k_2}{k_1 + k_3}\right) \quad (1)$$

with the experimental data. Under identical conditions (35.8°), Ia rearranges faster than IX by a factor of seven, a fact which corresponds qualitatively to the greater reactivity of exo-5-norbornene-2-boronic acid compared to the endo isomer in the analogous reaction with mercuric chloride. However, the exo/endo rate ratio for the isomeric boronic acids varies from 270 at 45° to 420 at 25°[17] and indicates a greater preference for electrophilic substitution with inversion at the carbon–boron bond.

Stereospecific rearrangement of both Ia and IX to the same product IIa could conceivably be a consequence of initial conversion of one bicyclic isomer into the other. This definitely does not occur in the direction Ia → IX, since the latter would accumulate owing to its slower rate of conversion into IIa, and would have been detected. The alternate possibility IX → Ia cannot be excluded rigorously, since accumulation of less than 5% of Ia could not have been detected. However, ionic or radical mechanisms for the hypothetical conversion IX to Ia are unlikely, since nonstereospecific rearrangement to IIa and IIIa would accompany any such process.[6,13,18] More remote possibilities involve back-side displacement at the endo mercury bond by some mercury species. A concerted displacement lacks any precedent and is ruled out, while a two-step deacetoxymercuration-exo,cis acetoxymercuration sequence is unlikely since deacetoxymercuration generally requires acid catalysis.

The chlorination of Ia can be explained by initial formation of a chloronium ion, followed by transannular elimination of $HgCl^+$ to form Va. Again, IX

$$\text{HgCl}_2 + \text{Ia} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{X} \xrightarrow{k_3} \text{IIa} + \text{HgCl}_2$$
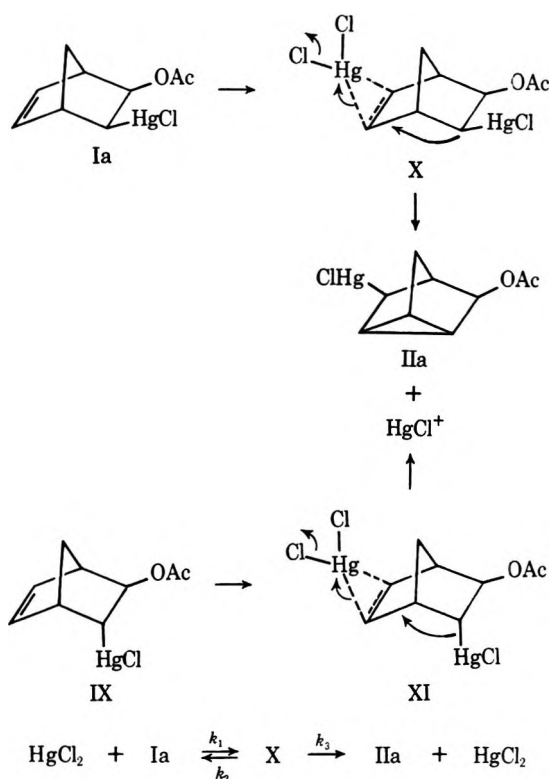
reacts more slowly than Ia, although by a factor of only two. The formation of a small amount of Vb from IX indicates some contribution from other chlorination mechanisms. In the related bromination of 5-bicyclo[2.2.2]octene-2-mercuric chloride, Matteson and Talbot reported only bicyclic bromide, although the bicyclic boronic acid afforded tricyclic mercurial by the transannular elimination process.[17]

The greater reactivity of Ia compared to IX in both the mercuric chloride catalyzed rearrangement and the reaction with chlorine is unusual, since all previously studied examples of electrophilic substitution of organomercury compounds take place with preferred retention of stereochemistry.[14] However, such reactions are believed to involve four-center transition states or similar cyclic mechanisms which are geometrically impossible for either of the proposed intermediates X or XI. The exo/endo rate difference may be due to unknown stereoelectronic factors which selectively favor the exo isomer Ia by increasing k_3 in eq 1. Alternatively, the ease of attack by the electrophile upon the double bond of Ia compared to IX may influence the relative rates (k_1 in eq 1).

Electrophilic cleavage of carbon–metal bonds most frequently occurs with retention, but predominant inversion of stereochemistry has been observed in halogenolysis of tri-exo-2-norbornylborane,[19] exo-2-norbornyllithium,[20] 4-tert-butylcyclohexyllithium and menthyllithium,[21] a π-bonded alkyliron complex,[15] sec-butyltrineopentyltin,[22] and sec-butyl- or cis-4-bromocyclohexylcobaloxime.[23] Contradictory stereochemical preferences have also been observed in related 1,3-elimination reactions, implying that orientation of the elec-

(16) K. Graves, *J. Org. Chem.*, **35**, 3273 (1970); P. M. Henry, *ibid.*, **36**, 1886 (1971).

(17) D. S. Matteson and M. L. Talbot, *J. Amer. Chem. Soc.*, **89**, 1119, 1123 (1967); D. S. Matteson and J. O. Waldbillig, *ibid.*, **86**, 3778 (1964).

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(19) H. C. Brown and C. F. Lane, *Chem. Commun.*, 521 (1971).

(20) D. E. Applequist and G. N. Chmurny, *J. Amer. Chem. Soc.*, **89**, 875 (1967).

(21) W. H. Glaze *J. Org. Chem.*, **34**, 641 (1969).

(22) F. R. Jensen and D. D. Davis, *J. Amer. Chem. Soc.*, **93**, 4048 (1971).

(23) F. R. Jensen, V. Madan, and D. H. Buchanan, *ibid.*, **93**, 5283 (1971).

TABLE I
NMR SPECTRA IN CDCl$_3$ (δ)
Tricyclic Products

	H$_3$	H$_4$	H$_5$	CH$_3$	H$_1$, H$_2$, H$_6$, H$_7$
IIa	4.55 (t, J = 1.2 Hz)	2.37 (br s)	2.59 (br s)	2.03 (s)	1.21–1.76 (4 H, m), 1.97 (1 H, br d, J = 10 Hz)
IIIa	4.81 (t, J = 1.5 Hz)	2.38 (br s)	2.38 (br s)	2.03 (s)	1.17–1.68 (4 H, m), 1.95 (1 H, br d, J = 10 Hz)
Va	4.62 (t, J = 1.2 Hz)	2.27 (br s)	3.99 (t, J = 1.2 Hz)	2.00 (s)	1.58 (3 H, br s), 1.87–2.03 (2 H, m)
Vb	5.30 (t, J = 1.3 Hz)	2.20 (br s)	3.95 (t, J = 1.3 Hz)	2.05 (s)	1.33–1.67 (4 H, m), 1.90 (1 H, br d, J = 9 Hz)
VII	3.69 (t, J = 1.5 Hz)	2.33 (br s)	2.42 (br s)	3.33 (s)	1.1–1.6 (4 H, m), 1.95 (1 H, br d, J = 10 Hz)

Bicyclic Products

	CH$_3$	H$_1$, H$_4$	H$_2$	H$_3$	H$_5$, H$_6$	H$_7$
Ia	2.10 (s)	3.1 and 3.3 (2 br s)	5.0 (d, $J_{2,3}$ = 7 Hz)	2.7 (br d, J = 7 Hz)	5.9–6.4 (m)	1.8 (br s)
IX	2.02 (s)	2.95 and 3.25 (2 br s)	5.04 (m, $J_{2,3}$ = 2.8 Hz)	2.12 (t, J = 2.8 Hz)	6.0–6.4 (m)	1.7 (br q, J_{AB} = 8.5 Hz)
VIII	2.0 (s)	3.07 and 3.35 (2 br s)	5.44 (br, d, J = 2 Hz)	2.85 (dd, J = 2, 4 Hz)	5.9–6.3 (m)	1.81 (br q, J_{AB} = 10 Hz)

tron-rich carbon–metal bond with respect to the electrophilic bond is not critical.[17,24] In the mercuric chloride induced rearrangement of Ia, inversion at C-3 is dictated by molecular geometry. The factors which render Ia more reactive than IX have not been identified, nor is it clear why inversion at the carbon–metal bond is preferred in certain electrophilic substitution reactions as outlined above. Substantial differences exist among the various studied examples with respect to bond lengths, bond angles, skeletal flexibility, degree of aggregation, and nature of the electrophile and leaving group, differences which preclude meaningful comparisons at this time.

Experimental Section

General.—Melting points were determined on a hot stage microscope apparatus and are corrected. Molecular weights were determined with a Mechrolab vapor pressure osmometer[25] calibrated with known mercurials. Nmr spectra were obtained using Varian HA-100 or A60-A spectrometers.[26] Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Volatile products were analyzed using a Varian Aerograph 90-P3 gas chromatograph. Commercial reagents were used without purification unless specified otherwise.

Di-μ-chlorobis(exo-6-acetoxy-2-norbornene-endo-5σ,2π)dipalladium (VIII).—A suspension of norbornadienepalladium dichloride (7.2 g, 0.027 mol), silver acetate (4.4 g, 0.026 mol), and dry chloroform (400 ml, distilled over P$_2$O$_5$) was stirred vigorously for 1 hr under nitrogen. The mixture was filtered and the filtrate was evaporated under the aspirator. The oily product solidified upon standing and was collected with ether, yielding VIII (7.5 g, 97%) as a pale yellow powder. This material was used without further purification. (See Table I for spectral data.)

trans-Chloro(exo-5-acetoxy-endo-3-nortricyclyl)dipyridinepalladium (IV).[5]—Finely ground VIII (16.7 g, 0.029 mol) was

(24) S. J. Cristol, A. R. Dahl, and W. Y. Lim, *J. Amer. Chem. Soc.*, **92**, 5670 (1970); B. M. Trost, W. L. Schinski, and I. B. Mantz, *ibid.*, **91**, 4320 (1969); A. Nickon and N. H. Werstiuk, *ibid.*, **89**, 3914, 3915, 3917 (1967).

(25) We are grateful to Professor P. M. Treichel for making this instrument available.

(26) Provided by a departmental grant from the National Science Foundation.

stirred vigorously with anhydrous ether (250 ml) under nitrogen. Dry pyridine (23.3 ml) was added dropwise over 10 min and stirring was continued for 2 hr. The crude IV was filtered (24.1 g, 95%), and stored in a freezer to avoid decomposition. Chlorination of IV in dry CH$_2$Cl$_2$ at $-78°$ using a twofold excess of chlorine in CCl$_4$ followed by the usual work-up and glpc analysis resulted in the formation of Vb (78%) and Va (22%).

exo,endo-3-Acetoxynortricyclyl-5-mercuric Chloride (IIIa).—A mixture of IV (0.24 g, 0.00054 mol), phenylmercuric acetate (0.37 g, 0.0011 mol), and dry acetonitrile (10 ml) was stirred for 20 hr in a flame-dried flask under nitrogen. The solution blackened immediately upon mixing the reactants. Acetonitrile was removed under vacuum and the residue was separated by preparative layer chromatography (plc) on silica gel with 2:1 CHCl$_3$-hexane, two developments. The following fractions were collected: R_f 0.6–0.7, biphenyl (0.045 g, 54%); R_f 0.2–0.25, *exo,exo*-3,5-diacetoxynortricyclene (0.020 g, 20%); R_f 0.1–0.2, IIb (0.12 g, 57%). Recrystallization of IIb from methanol afforded pure material: mp 136–137°; ir (KBr) 3.26 (w), 5.85 (s), 8.00 (s), 9.6 (s), 12.4 μ (s). *Anal.* Calcd for C$_9$H$_{11}$ClHgO$_2$: C, 27.92; H, 2.86; Cl, 9.15; Hg, 51.80. Found: C, 27.80; H, 2.85; Cl, 9.25; Hg, 51.76. Chlorination of IIb by the usual method (see below) affords Vb (96%) and Va (4%). Vb was collected by glpc as a colorless liquid: ir (neat) 3.25 (w), 5.85 (vs), 8.07 (vs), 12.25 μ (s).

General Procedure for Chlorination of Mercurials.—The reagent was prepared by adding 1.2 mmol of a titrated solution of chlorine in carbon tetrachloride to twice the volume of dry pyridine (distilled from CaH). A solution of the mercurial (1 mmol) in dry pyridine (10 ml) was cooled to $-44°$ (Dry Ice–Cl$_2$CHCHCl$_2$) and the chlorination reagent was added dropwise over 5 min. After 1 hr at $-44°$, the mixture was allowed to warm to 25° and pyridine was removed under vacuum below 50°. The residue was extracted with several small portions of pentane, the pentane was evaporated, and the products were analyzed by glpc and nmr, 80–100% yield of volatile products.

exo,endo-2-Acetoxynorborn-5-enyl-3-mercuric Chloride (IX).—The acetoxynorbornenylpalladium complex VIII (300 mg, 0.51 mmol) in dry benzene (10 ml, distilled from CaH$_2$) was stirred with a large excess of mercury (2 g) for 24 hr. The solution slowly deposited black palladium metal. The mixture was filtered through Celite and the Celite was washed with chloroform (2 × 10 ml). The combined filtrates were evaporated, the residue was purified by plc on silica gel with 2:1 chloroform–hexane (two developments), and the main band was extracted with chloroform to yield IX (106 mg, 30%). Two recrystallizations of IX from methanol afforded pure product: mp 105.5–

106°; ir (KBr) 3.27 (m), 3.33 (m), 3.36 (m), 3.39 (m), 3.49 (w), 5.8 (s), 5.86 (s), 6.95 (m), 8.05 (s), 12.95 (m), 13.2 (m), 13.8 (s), 14.05 μ (s). *Anal.* Calcd for $C_9H_{11}ClHgO_2$: C, 27.92; H, 2.86; Cl, 9.15; Hg, 51.80. Found: C, 27.90; H, 2.85; Cl, 9.27; Hg, 51.90.

Chlorination of IX with 1.0 equiv of the chlorine–pyridine reagent afforded Va (95%) and Vb (5%). Treatment of IX with 0.3 equiv of chlorine afforded IX and Va in a ratio of 8:3. No other compounds were present according to nmr analysis (5% of Ia would have been detected).

exo,endo-3-Methoxynortricyclyl-5-mercuric Chloride (VII).— A suspension of the methoxy complex VI[5] (0.21 g, 0.0005 mol) and phenylmercuric acetate (0.17 g, 0.0005 mol) in methanol (8 ml) was stirred for 24 hr under nitrogen. After filtration through Celite and evaporation, the product was chromatographed as before to yield biphenyl (23%) and VII (41%): mp 134–137° (recrystallized from methanol); ir (KBr) 3.28 (w), 3.54 (w), 9.1 (s), 12.5 μ (s). *Anal.* Calcd for $C_8H_{11}ClHgO$: C, 26.75; H, 3.09. Found: C, 26.84; H, 3.16. Chlorination of VII followed by glpc analysis on a 4 ft × 0.375 in 20% FFAP at 90° yielded 96% *exo*-3-methoxy-*endo*-5-chloronortricyclene and 4% of the exo,exo isomer.

Acetoxymercuration of Norbornadiene. *exo,exo*-3-Acetoxynortricyclyl-5-mercuric Chloride (IIa).—A stirred suspension of mercuric acetate (25 g, 0.078 mol) in glacial acetic acid (90 ml) was combined with freshly distilled norbornadiene (10 g, 0.11 mol) in acetic acid (10 ml). The mixture was stirred at 25° for 60 hr and 10% aqueous NaCl (100 ml) was then added. The resulting oil was separated, dissolved in hot ethanol (70 ml), and allowed to cool. A white solid precipitated and was collected with ethanol, yielding a mixture of IIa and IIIa (19 g, 64%), mp 114–124°, estimated to contain 73% of IIa and 27% of IIIa by nmr. Evaporation of the mother liquors afforded a brown oil (9.7 g, 32%). Recrystallization from 95% ethanol afforded pure IIa, mp 150–151°.

Chlorination of the Acetoxymercuration Products.—The solid mixture II and III from above was chlorinated according to the general method. Analysis of the products on a 10 ft × 0.375 in. 20% DEGS/Chromosorb P at 170° indicated the presence of 75% Va and 25% Vb. Similar treatment of the oily product from the mother liquors from above resulted in quantitative conversion to four products. In order of increasing retention time, these were Vc (11.4%), Va (47.4%), Vb (34%), and Vd (7.2%). The purified material IIa was chlorinated, yielding Va (93%) and Vb (7%).

exo,exo-2-Acetoxynorborn-5-enyl-3-mercuric Chloride (Ia).— According to the method of Winstein and Pande,[3] solid mercuric acetate (15.8 g, 50 mmol) was added in small portions to a stirred solution of freshly distilled norbornadiene (10 g, 108 mmol) in acetic acid (50 ml) cooled to 13°. The addition was maintained at a rate such that the reaction temperature did not rise above 15° (total addition time 15 min). After the addition was complete, the reaction mixture was immediately poured with stirring into distilled water (300 ml) containing sodium chloride (6 g, 100 mmol). An oil appeared immediately which solidified after stirring for 5 min. The crude product (15.6 g, 82%) was filtered and washed with methanol (2 × 25 ml) and pentane (2 × 50 ml). Mercurial Ia can be purified by plc or recrystallization without rearrangement. The melting point after two recrystallizations from methanol was 155–156° dec (reported[3] mp 152–153°).

Treatment of Ia with 1 equiv of chlorine in the usual way gave a 99% yield of Va. Treatment of Ia with 0.5 equiv of chlorine afforded a 1:1 mixture of Ia and Va with no detectable IIa or IX by nmr.

A competitive reaction between equal amounts of Ia and IX with 0.4 equiv of chlorine afforded a mixture of Ia, IX, and Va in a relative ratio of 4.7:9.3:8 respectively by nmr of the crude product.

Rearrangement of Compound Ib under Acetoxymercuration Conditions.—The crude acetoxymercuration mixture containing Ib was allowed to stand at room temperature without work-up. Rearrangement of Ib to IIb occurred (disappearance of olefinic nmr signals) and was complete within 6 hr. The characteristic methine signal of IIIb appeared more slowly.

A purified sample of Ib (0.2 g) in acetic acid and freshly distilled norbornadiene (0.02 g) rearranged to IIb within 5 hr at 25°. Rearrangement of IIb to IIIb was detectable after 24 hr and reached a steady state of ca. 5:3 of IIb:IIIb after standing for 30 days. Addition of hydroquinone (0.015 g) or use of glpc-purified norbornadiene had no effect on the rearrangement of Ib to IIb but prevented the rearrangement to IIIb.

Mercuric Chloride Catalyzed Rearrangement of Ia and IX in Dimethyl Sulfoxide.—The bicyclic mercurials Ia or IX (0.15 g) were dissolved in 0.50 ml of purified dimethyl sulfoxide (distilled under vacuum from CaH_2, stored over molecular sieves) containing the appropriate concentration of mercuric chloride catalyst. The solutions were transferred into nmr tubes and sealed under nitrogen. The samples were immersed in a water bath at 35.8 ± 0.02° and analyzed periodically by nmr. Progress of the rearrangement was monitored by integration of the olefinic signals of Ia or IX, and also by the disappearance of the methine signals due to C-2 hydrogen of Ia or IX and the appearance of the corresponding signal of IIa. No signals other than those of IIa appeared during any of the rearrangements. Linear plots of log [Ia] or log [IX] *vs.* time were obtained over 2–3 half-lives, but at greater conversion the sensitivity of integration was too low for reproducible measurements. The rate of rearrangement increased with mercuric chloride concentration, and the following apparent first-order rate constants were calculated (Table II).

TABLE II

Starting mercurial	$HgCl_2$ concn in DMSO, M	Rate constant k_{ap}, sec^{-1}
Ia	0.0257	3.0×10^{-5}
Ia	0.0184	2.1×10^{-6}
IX	0.0184	3.1×10^{-6}
Ia	0.0129	1.3×10^{-6}
Ia	0.0055	3.8×10^{-6}

Upon completion of the rearrangement of a typical run using Ia or IX, the DMSO solution was diluted with water and filtered. The solid precipitate was crystallized from methanol to yield IIa (0.14 g), in two crops.

Registry No.—Ia, 1077-98-1; IIa, 32737-75-0; IIIa, 34454-50-7; Va, 31002-62-7; Vb, 34493-26-0; VII, 34493-27-1; VIII, 11096-74-5; IX, 34454-52-9.

The Structure and Stereochemistry of the Products Derived from the Reaction of Halosulfenes with 1-(Morpholino)cyclohexene

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Received December 6, 1971

The reaction of 1-(morpholino)cyclohexene with chloro- and bromomethanesulfonyl chloride is described, and the nature and stereochemistry of the products are discussed.   Detailed nmr analyses of the cycloadducts arising *via* halosulfene intermediates are presented.

Recently the chemistry of sulfenes has received considerable attention, and several reviews have appeared.[1,2] Halogen-substituted sulfenes have, however, received only brief attention, the most detailed study being that of chlorosulfene by Paquette.[3] The present study deals with the nature and the stereochemistry of the products obtained by the reaction of halomethanesulfonyl chlorides with 1-(morpholino)cyclohexene (1) in the presence of triethylamine.

The reaction of 1 with bromomethanesulfonyl chloride[4] in the presence of triethylamine (benzene) afforded four isolable products (eq 1).   The salts 2 and 3 were
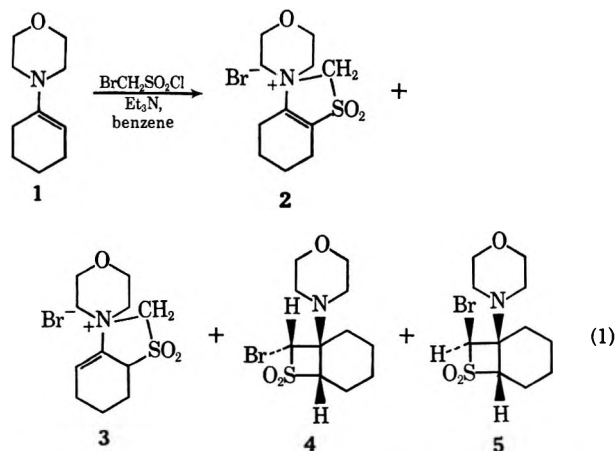
isolated as a 50:50 mixture of white, water-soluble crystals which could not be separated.   These products are believed to arise *via* sulfonation of 1, equilibration of the sulfonyl enamines 6 and 7, and finally, intramolecular displacement by the tertiary nitrogen on the bromomethylsulfonyl group (eq 2).[5] The final displacement step in the formation of 2 and 3 represents the first known example of the displacement of a halogen α to a sulfonyl group by a "neutral" nitrogen nucleophile.[6]

The cycloadducts 4 and 5 were isolated by fractional crystallization from ethanol, and arise *via* the cycloaddition of bromosulfene (8) to 1 (eq 3).[7]

$$BrCH_2SO_2Cl \xrightarrow{Et_3N}$$

$$[BrCH=SO_2 \overset{8}{\longleftrightarrow} Br\overset{-}{C}H\overset{+}{S}O_2] \xrightarrow{1} 4 + 5 \quad (3)$$
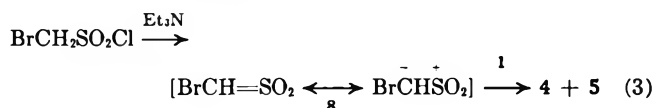
The reaction of chloromethanesulfonyl chloride[8] with 1 was also investigated.   In contrast to the results previously reported by Paquette,[3] 1 was found to react with chloromethanesulfonyl chloride to give both isomers of the sulfene cycloaddition product, 9 and 10 (eq 4).[9]
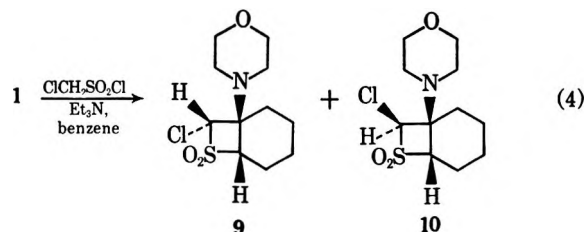
The structures of 2–5, 9, and 10 were established by nmr and mass spectroscopy.   The nmr spectrum (60 MHz, CF_3CO_2H) of the mixture of 2 and 3 displays singlets at δ 5.32 and 5.46 for the $-SO_2CH_2N^+$ protons of the two isomers, and a multiplet centered at δ 7.08 for the vinyl proton of 3.   The $-SO_2CH_2N^+$ protons of 2 and 3, as well as the methine proton α to the sulfonyl

(1) T. J. Wallace, *Quart. Rev., Chem. Soc.,* **20**, 67 (1966).

(2) P. N. Son, Ph.D. Thesis, Purdue University, 1967.

(3) L. A. Paquette, *J. Org. Chem.,* **29**, 2854 (1964).

(4) W. E. Truce, D. J. Abraham, and P. Son, *J. Org. Chem.,* **32**, 990 (1967).

(5) The mechanisms proposed for the reaction of 1 with cyanosulfene [M. P. Sammes, C. M. Wylie, and J. G. Hoggett, *J. Chem. Soc. C,* 2151 (1971)] might account for the formation of 3, but not 2.
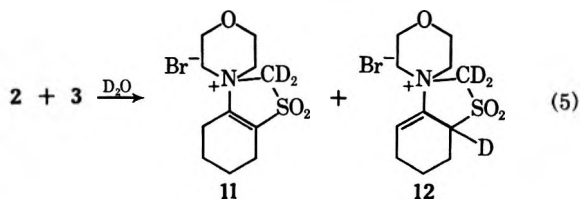
(6) Displacement of halogen α to a sulfonyl group by nitrogen anions has been reported in the base-catalyzed decomposition of halomethanesulfonamides: T. B. Johnson and I. B. Douglass, *J. Amer. Chem. Soc.,* **63**, 1571 (1941); F. G. Bordwell and G. D. Cooper, *ibid.,* **73**, 5187 (1951); W. V. Farrar, *J. Chem. Soc.,* 3058 (1960).

(7) It has been established that products such as 4 and 5 do, in fact, arise *via* sulfene intermediates: I. J. Borowitz, *J. Amer. Chem. Soc.,* **86**, 1146 (1964).

(8) H. Brintzinger, H. Koddebusch, K. Kling, and G. Jung, *Chem. Ber.,* **85**, 455 (1952).

(9) Although the chloro analogs of 2 and 3 were not isolated from this reaction, their formation cannot be precluded, since a detailed material balance was not carried out.
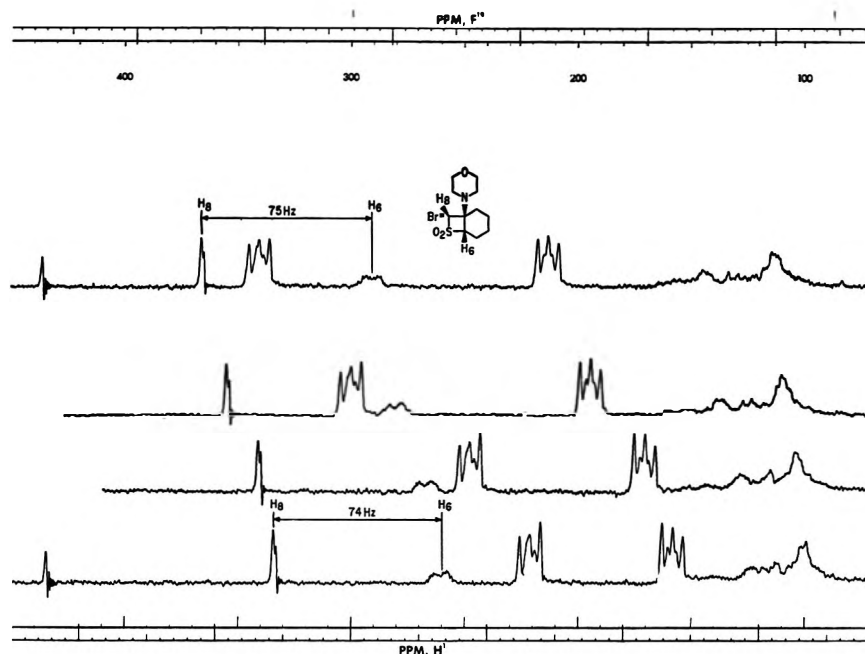
Figure 1.—Successive scans displaying the effect of the addition of incremental amounts of Eu(fod)₃ on the 60-MHz nmr spectrum of **4**.
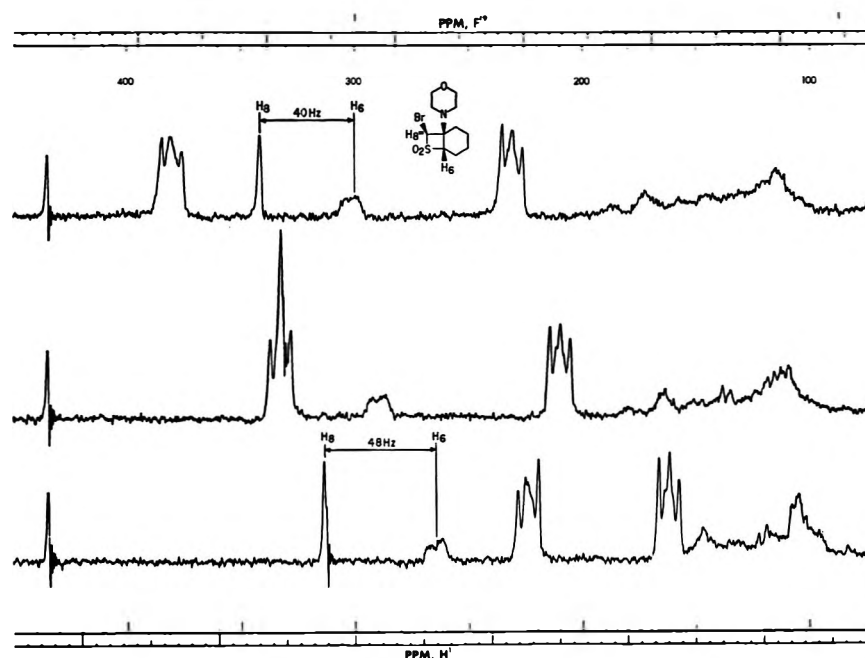
Figure 2.—Successive scans displaying the effect of the addition of incremental amounts of Eu(fod)₃ on the 60-MHz nmr spectrum of **5**.

group in **3**, are readily exchangeable, and are not seen when the nmr spectrum is run in D_2O (eq 5).

The exchange of **2** and **3** with D_2O to give **11** and **12** was confirmed by mass spectroscopy. The mass spectrum of the mixture of **2** and **3** gave a parent peak at *m/e* 323. The mass spectrum of the crystalline solid obtained by treatment of **2** and **3** with D_2O displayed parent peaks at *m/e* 325 and 326, corresponding to **11** and **12**.

The stereochemistry of compounds such as **4, 5, 9**, and **10** has not previously been determined in a definitive manner. Consideration of the nmr chemical shifts induced upon complexation with Eu(fod)₃, however, permits an unambiguous assignment of the stereochemistry. The results of the complexation studies

are shown in Figures 1, 2, and 3 for **4, 5**, and the unhalogenated analog, **13**, respectively.[10] The primary

13
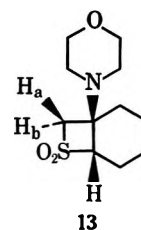
site of complexation in each case is the oxygen of the morpholine ring, since the largest shifts are induced

(10) Similar studies were carried out with the chloro analogs. **9** and **10**, with similar results.
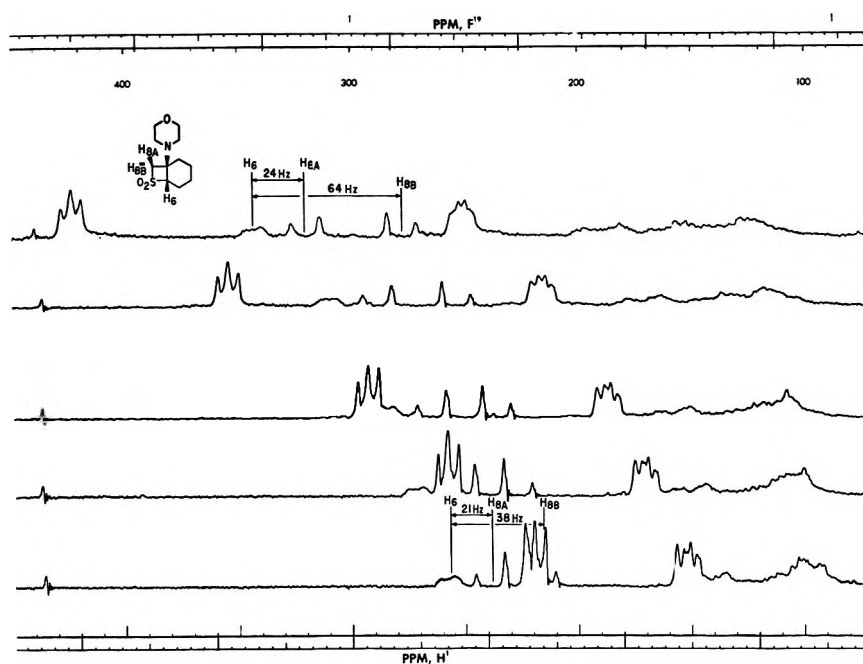
Figure 3.—Successive scans displaying the effect of the addition of incremental amounts of Eu(fod)₃ on the 60-MHz nmr spectrum of 13.

in the protons vicinal to the oxygen. The Eu(fod)₃ was added in several small quantities, and the spectrum was recorded after each addition so that spectral bands could be assigned even if two adjacent bands crossed.

In Figure 1, the difference in chemical shift between H₆ and H₈ remains essentially constant (within approximately 2%), whereas in Figure 2 the same chemical shift difference has decreased by approximately 20% at a comparable ratio of complex to substrate. Thus, in 5 H₈ is deshielded less than H₆, whereas in 4 H₈ and H₆ are deshielded to approximately the same extent. Similar behavior is observed in 13 (Figure 3); i.e., one of the H₈ protons is deshielded at approximately the same rate as H₆, whereas the other H₈ proton is deshielded more slowly.

An examination of Dreiding models of 4, 5, and 13 indicates that for a complexation site near the morpholine oxygen, H₆ and H₈ (in 4 and 5) and H₆, H₈ₐ, and H₈ᵦ (in 13) all have about the same angular dependence with respect to the paramagnetic chelate. Thus, the only reasonable explanation for the observed differences in induced shifts must lie in the distance from the chelate to the protons,[11] establishing that H₆ and H₈ are cis to each other in 4 and trans to each other in 5. This distance dependence also permits the unambiguous assignment of the downfield signal of the AB pattern in 13 to H₈ₐ, and the upfield signal to H₈ᵦ (see Table I for a summary).

Since the signal for H₈ of 9 had previously been reported to be a triplet ($J = 1.5$ Hz)[3] and no reasonable explanation had been proposed, the signals due to H₆ and H₈ in 4, 5, 9, and 10 were studied in detail. The signal due to H₈ is a doublet in each case, and the coupling constants are summarized in Table I. That

(11) An examination of Dreiding models also shows that if complexation occurred at the sulfonyl group, H₆ and H₈ (in 4 and 5) and H₆, H₈ₐ, and H₈ᵦ (in 13) are symmetrically disposed with respect to the complexation site. Consequently, complexation at the sulfonyl group cannot account for the differential shifts which are observed.

TABLE I

100-MHz NMR SPECTRAL DATA FOR THIETANE DIOXIDES (CDCl₃)

Compd	H₆, δ	H₈, δ	$J_{6,8}$, Hz
4	4.35	5.59	1.1
5	4.42	5.26	0.9
9	4.28	5.49	1.1
10	4.42	5.12	0.9
13	4.36	a	b

ᵃ The signals for the geminal protons H₈ₐ (δ 4.04) and H₈ᵦ (δ 3.73) appear as the AB portion of an ABX pattern with $J_{a,b} = -12.6$ Hz. ᵇ $J_{6,8a} = 0.8$ Hz and $J_{6,8b} = 0.9$–1.0 Hz.

the large coupling to H₈ was, in fact, due to H₆ was established in each case by selective decoupling.[12]

Similar studies of the couplings to H₈ₐ and H₈ᵦ in 13 were also conducted. An INDOR experiment demonstrated that $J_{6,8a}$ and $J_{6,8b}$ are of opposite sign, but the signs could not be related to the sign of the geminal coupling constant, $J_{8a,8b}$, since the H₆ signal is very broad owing to strong coupling of H₆ with protons of the carbocyclic ring.

Experimental Section

All reactions were run in a nitrogen atmosphere. The nmr spectra were recorded on a Varian HA-100 spectrometer with an internal lock on tetramethylsilane (TMS = 0) unless otherwise indicated. The infrared spectra were recorded on a Perkin-Elmer Infracord. All melting points and boiling points are uncorrected.

Reaction of 1 with Bromomethanesulfonyl Chloride.—In a 250-ml, three-neck flask equipped with a magnetic stirrer, a nitrogen inlet, a thermometer, a calcium chloride drying tube, and an addition funnel were placed 16.72 g (0.10 mol) of 1-(morpholino)cyclohexene, 10.0 g (0.10 mol) of triethylamine, and 100 ml of dry benzene. The flask was flushed with nitrogen, and the contents were cooled to 2°. To the cooled solution, a solution of 19.3 g (0.10 mol) of bromomethanesulfonyl chloride in 20 ml of benzene was added dropwise, with stirring, over 1.25 hr. After the addition was complete, the reaction mixture was

(12) Any further coupling to H₈ was not resolved, and would be estimated to be less than 0.2 Hz.

stirred at 2–5° for an additional 0.5 hr. The reaction mixture was filtered to remove the triethylamine hydrochloride produced. The triethylamine hydrochloride was washed with several portions of benzene. The benzene was removed *in vacuo* from the combined filtrates, leaving a heavy, orange oil. A small amount of absolute ethanol was added to the oil, and after standing for 3 days, orange-brown crystals separated. The crystals were filtered, washed with acetone, and vacuum dried to give 9.30 g (29% yield) of crude 2 and 3, mp 165–166°. The solid was recrystallized from aqueous ethanol to give 7.03 g of a mixture of 4,5,6,7-tetrahydrospiro[benzothiazoline-3,4'-morpholinium] bromide 1,1-dioxide (2) and 5,6,7,7a-tetrahydrospiro-[benzothiazoline-3,4'-morpholinium] bromide 1,1-dioxide (3), mp 175–177°.

Anal. Calcd for $C_{11}H_{18}BrNO_3S$: C, 40.75; H, 5.59; Br, 24.65; N, 4.32; S, 9.89. Found: C, 40.90; H, 5.51; Br, 24.65; N, 4.42; S, 10.25. Mass spectrum (intense ions): *m/e* 325, 323 (molecular ion), 261, 259 (1 Br), 180, 136, 136, 109, 95, 87.

The combined filtrate and acetone washings from the isolation of 2 and 3 were treated with 25 ml of 10% sodium hydroxide solution and then extracted with methylene chloride. The methylene chloride extracts were washed with water and dried, and the methylene chloride was removed *in vacuo*, leaving 13.85 g of a viscous, yellow-brown oil. The oil was treated with approximately 50 ml of absolute ethanol, and a crystalline solid separated. The solid was filtered and vacuum dried to give 5.44 g (17% yield) of crude 4, mp 166–168°. The solid was recrystallized from approximately 150 ml of aqueous ethanol to give 3.81 g of 4-(*trans*-8-bromo-7-thiabicyclo[4.2.0]oct-1-yl)-morpholine *S,S*-dioxide (4) as fine, white crystals, mp 172–174°.

Anal. Calcd for $C_{11}H_{18}BrNO_3S$: C, 40.75; H, 5.59; Br, 24.65; N, 4.32; S, 9.89. Found: C, 41.06; H, 5.57; Br, 24.81; N, 4.28; S, 9.81. Mass spectrum (intense ions): *m/e* 325, 323 (molecular ion), 244, 180, 167, 166, 152, 139, 138, 137, 136, 124, 123, 122, 110, 109, 108, 95, 94, 93, 91, 86, 81, 79, 77, 67, 66, 65, 56, 55, 54, 53, 42, 41, 39, 30, 29, 27.

The filtrate from the isolation of 4 was refrigerated and, after standing for 30 days, yielded 3.20 g (10% yield) of crude 5 as a slightly orange solid, mp 120–129°. The solid was recrystallized from approximately 50 ml of ethanol (with decolorization) to give 1.20 g of 4-(*cis*-8-bromo-7-thiabicyclo[4.2.0]oct-1-yl)-morpholine *S,S*-dioxide (5) as white needles, mp 129.5–131.5°.

Anal. Calcd for $C_{11}H_{18}BrNO_3S$: C, 40.75; H, 5.59; Br, 24.65; N, 4.32; S, 9.89. Found: C, 40.67; H, 5.46; Br, 24.60; N, 4.44; S, 10.00.

Reaction of 1 with Chloromethanesulfonyl Chloride.—In a 250-ml, three-neck flask equipped with a magnetic stirrer, a nitrogen inlet, a thermometer, a calcium chloride drying tube, and an addition funnel were placed 12.00 g (0.072 mol) of 1-(morpholino)cyclohexene, 7.30 g (0.072 mol) of triethylamine, and 150 ml of benzene. The flask was swept with nitrogen and cooled in an ice bath. To the cooled solution, a solution of 10.96 g (0.072 mol) of chloromethanesulfonyl chloride in 20 ml of benzene was added dropwise, with stirring, over a period of 50 min. After the addition was complete, the reaction mixture was stirred with ice-bath cooling for an additional 0.5 hr. The reaction mixture was filtered to remove the triethylamine

hydrochloride produced. The triethylamine hydrochloride was washed with several portions of benzene. The benzene was removed *in vacuo* from the combined filtrates, leaving a yellow oil. The oil was mixed with a small amount of absolute ethanol and allowed to stand at room temperature. After 3 days some small crystals formed. The crystals were filtered to give 0.65 g of crude 9. The solid was recrystallized from 15 ml of absolute ethanol to give 0.35 g of 4-(*trans*-8-chloro-7-thiabicyclo[4.2.0]oct-1-yl)morpholine *S,S*-dioxide (9) as colorless crystals, mp 139–140.5° (lit.[3] mp 155–157°). This material is apparently a different crystalline modification of 9 than that isolated by Paquette,[3] since it has the same nmr spectrum as a sample of 9 with mp 155–157° which we later isolated (*vide infra*).

Anal. Calcd for $C_{11}H_{18}ClNO_3S$: C, 47.23; H, 6.48; Cl, 12.67; N, 5.00; S, 11.46. Found: C, 47.26; H, 6.50; Cl, 12.69; N, 4.90; S, 11.66. Mass spectrum (intense ions): *m/e* 279 (molecular ion), 244, 180, 168, 167, 166, 152, 139, 138, 137, 136, 124, 123, 122, 110, 109, 108, 96, 95, 94, 93, 91, 86, 82, 81, 80, 79, 78, 77, 68, 67, 66, 65, 64, 58, 57, 56, 55, 54, 53, 52, 49, 46, 45, 44, 43, 42, 41, 40, 37, 33, 31, 30, 29, 28, 27.

The filtrate was refrigerated to give another crop of 1.26 g of crude 9. This solid was recrystallized from approximately 25 ml of ethanol to give 0.67 g of 9 as fine, white crystals, mp 155–157° (the same as that reported by Paquette[3]). The ethanol was removed *in vacuo* from the filtrate from the isolation of crude 9, leaving an orange oil. The oil was treated with 100 ml of ether. Not all of the oil dissolved in the ether. The ether solution was separated and the ether was removed *in vacuo*, leaving another orange oil. The oil was diluted with a small amount of absolute ethanol, seeded with a crystal of 9, and refrigerated to give an additional 0.44 g of 9. The ethanol was again removed from the crystallization liquor, leaving an orange oil. A 4.50-g sample of this oil was placed on a silica gel column (neutral, 100–200 mesh) and eluted with ether. In this manner we obtained three fractions (total 1.95 g) of a pale yellow oil consisting of approximately 84% 10 and 16% 9. The yellow oil slowly crystallized under refrigeration, but several attempts to get a pure (isomerically) sample of 10 were unsuccessful, the recrystallizations always leading again to a yellow oil.

4-(7-Thiabicyclo[4.2.0]oct-1-yl)morpholine *S,S*-Dioxide (13).—This compound was prepared by a modification of the procedure described by Borowitz (see ref 7) in which benzene was substituted for dioxane as solvent. Small, white prisms were obtained after recrystallization, mp 137–139° (lit. mp 139–140°).

Photoadditions of 2-Cyclohexenone Derivatives to Cyclopentene. An Investigation of Stereochemistry

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The photoaddition reactions of 4,4-dimethyl-2-cyclohexenone, 3-methyl-2-cyclohexenone, and 3-phenyl-2-cyclohexenone with cyclopentene have been studied. Trans-fused cyclobutanes are formed by the methylcyclohexenones but not by the phenyl derivative. The major product (47%) from 4,4-dimethyl-2-cyclohexenone and cyclopentene is the cis–anti–cis ketone. The latter was reduced by $LiAlH_4$ to the exo alcohol 6, shown to have the anti configuration by an X-ray study. The details of the structure are described. The second product (38%) is a trans-fused cyclobutane 4 which equilibrates with base to a cis-fused isomer 7 assigned as the syn compound. The syn ketone 7 is reduced by $LiAlH_4$ to two isomeric alcohols. The addition of 3-methyl-2-cyclohexenone and cyclopentene appears to parallel the 4,4-dimethyl-2-cyclohexenone reaction. In contrast, 3-phenyl-2-cyclohexenone adds to afford only cis-fused compounds, the major one (93%) being tentatively assigned the cis–anti–cis structure. The factors controlling stereochemistry in the reactions are discussed. The excited state geometry, the nature of metastable and biradical intermediates, and the polarity of the substrate all appear to play a role. The timing of the bond formation is also considered, and it is concluded that trans-fused adducts may be formed by initial bonding of the olefin to C_2 of the cyclohexenone.

The stereochemistry of photocycloadditions of 2-cyclohexenones with alkenes,[1-3] and the factors controlling it, are among the most intriguing of stereochemical problems. Thus, while the triplet state additions of many cyclic unsaturated compounds, including cycloalkenes,[3] 2-cyclopentenone,[1,2] and aromatic compounds,[3] occur to afford cyclobutanes having cis ring fusions and anti stereochemistry, e.g., 1, simple 2-cyclohexenones can afford strained, trans-fused cyclobutanes.[1,2] Indeed, cycloaddition of 4,4-dimethyl-2-cyclohexenone and tetramethylethylene gives only trans-fused cyclobutane 2, no cis-fused compound being detected.[4]

1   2

The picture is further complicated in the cyclohexenone case by the observation that the trans-fused cyclobutanes are, in general, only formed whenever an electron-rich substrate is used.[2] Thus, the dimerization of cyclohexenone,[5,6] its reaction with acrylonitrile,[7,8] and the addition of 3-methyl-2-cyclohexenone and ethylene[9] all give little or no trans-fused compounds.[10] However, despite these synthetically im-

portant[11] and inherently interesting problems associated with enone photoannelation, very few careful studies of stereochemistry[12,13] have been reported, and these involved cyclopentenone. We are now describing our results on the reactions of cyclopentene with 4,4-dimethyl-2-cyclohexenone, 3-methyl-3-cyclohexenone, and 3-phenyl-2-cyclohexenone in this paper. This report includes the isolation of products, the assignment of their structures and stereochemistry, and a discussion of implications of the stereochemistry.

Results

Cyclopentene and 4,4-Dimethyl-2-cyclohexenone.— Irradiation of 4,4-dimethyl-2-cyclohexenone and 0.8 *M* cyclopentene in alcoholic solution, with a Hanovia 450 W, type L mercury vapor lamp using a Pyrex filter, resulted in disappearance of the enone carbonyl band at 6.00 μ and the formation of products giving two peaks on vpc (ratio 6:4), having two carbonyl bands at 5.83 and 5.91 μ. The nmr spectrum of the reaction mixture showed that three products were formed, since three pairs of methyl resonances in addition to that of the enone were observed. The per cent ratio of these three products was estimated to be 47:38:15 from the nmr spectrum, and the products will subsequently be referred to as **3**, **4**, and **5**, respectively. Samples of **3** and **4** were isolated by distillation and preparative vpc respectively and were identified as follows (Chart I).

Identification of 3.—The compound showed a molecular ion at *m/e* 192, showing that it was a 1:1 adduct of the enone and cyclopentene. The methyl resonances occurred at δ 0.87 and 0.88, and the carbonyl infrared absorption was at 5.91 μ, suggesting a cis-fused cyclobutane structure.[7] The adduct was unchanged by treatment with base, also suggesting that **3** is not a trans-fused adduct.[7] Further, this ketone readily formed a thiosemicarbazone, indicating that the carbonyl function is relatively unhindered. These observations all pointed to the cis–anti–cis structure for **3**

(1) For a recent and particularly lucid review which covers the many facets of enone photoannelation, see P. de Mayo, *Accounts Chem. Res.*, **4**, 41 (1971).

(2) Earlier work was reviewed by P. E. Eaton, *ibid.*, **1**, 50 (1968).

(3) For a number of examples, see R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, Chapters 5, 6.

(4) P. J. Nelson, D. Ostrem, J. D. Lassila, and O. L. Chapman, *J. Org. Chem.*, **34**, 811 (1969).

(5) E. Y. Y. Lam, D. Valentine, and G. S. Hammond, *J. Amer. Chem. Soc.*, **89**, 3482 (1967).

(6) (a) G. Mark, F. Mark, and O. E. Polansky, *Justus Liebigs Ann. Chem.*, **719**, 151 (1969); (b) P. J. Wagner and D. J. Bucheck, *J. Amer. Chem. Soc.*, **91**, 5090 (1969).

(7) E. J. Corey, J. D. Bass, R. Le Mahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964).

(8) T. S. Cantrell, W. S. Haller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969).

(9) Y. Yamada, H. Uda, and K. Nakanishi, *Chem. Commun.*, 423 (1966).

(10) See, however, P. Boyle, J. A. Edwards, and J. H. Fried, *J. Org. Chem.*, **35**, 2560 (1970). Note also ref 6b.

(11) P. G. Sammes, *Quart. Rev., Chem. Soc.*, **24**, 37 (1970), gives many examples of application in synthesis; see also ref 1.

(12) L. Duc, R. A. Mateer, L. Brassier, and G. W. Griffin, *Tetrahedron Lett.*, 6175 (1968).

(13) W. L. Dilling, T. E. Tabor, T. P. Boer, and P. P. North, *J. Amer. Chem. Soc.*, **92**, 1399 (1970).

CHART I

3 (47%) 4 (38%)

$\downarrow$ Al$_2$O$_3$

5 (15%) 7

Figure 1.—Molecular structure of *p*-bromophenylurethane of 6; numbering agrees with that used in Tables II and III.
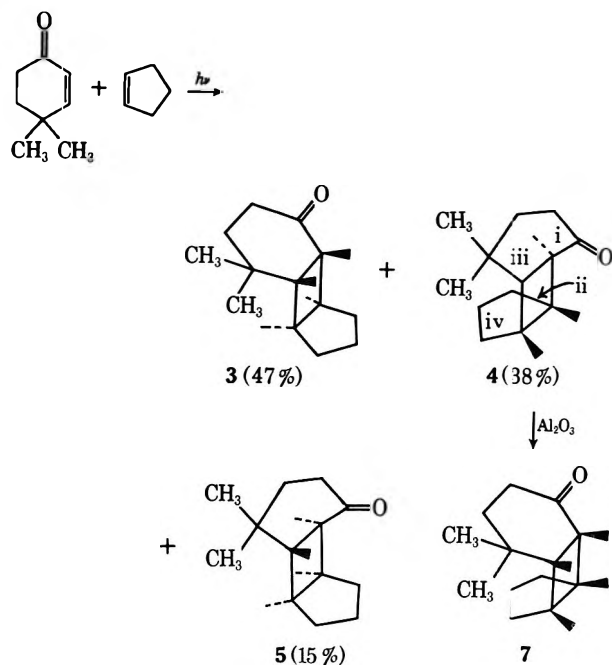
(Chart I), and there is ample precedent for this assignment.[14-16]

However, it was hoped to use **3** as a reference in assigning the stereochemistry to **4** and **5**, and X-ray work was undertaken to establish its structure. We were unable to obtain single crystals of the thiosemicarbazone of **3**. Therefore, the ketone was reduced with LiAlH$_4$ to an alcohol **6**, mp 51–56°, which reverted to **3** on chromic acid oxidation. This alcohol afforded a *p*-bromophenylurethane in good yield and this gave crystals suitable for an X-ray structure determination. The X-ray work is described in the Experimental Section. The structure of the *p*-bromophenylurethane is shown in Figure 1. It can be seen that the five- and six-membered rings have the anti relationship, and the two ring junctions are cis.

Also of interest is the exo configuration of the hydroxy group, a feature which would not have been predicted (see below).

Identification of 4.—This adduct had a molecular ion of *m/e* 192, and methyl group resonances at δ 0.98 and 1.19 in the nmr. The carbonyl band in the infrared was at 5.83 μ, and the compound isomerized on treatment with base to **7**, a ketone having the infrared absorption at 5.91 μ. This points to a trans-fused junction of the four- and six-membered rings, and its structure follows from that assigned to **7**.

(14) The stereochemistry of the adducts is designated by α and β, as in steroid nomenclature; α or β refers to hydrogen, methyl, or phenyl substituents at the bridgehead positions. Thus, the cis–syn–cis compound **4** is the 1β,7β,2β,6β isomer.

(15) Some of these are as follows. (a) Cyclopentenone additions: P. E. Eaton, *J. Amer. Chem. Soc.*, **84**, 2344, 2454 (1962); see also ref 2. (b) Dimerization of coumarin: G. O. Schenck, I. von Wilucki, and C. H. Krauch, *Chem. Ber.*, **95**, 1409 (1962). (c) Dimerization of cyclohexenones: P. Yates, S. N. Ege, G. Buchi, and D. Knutsen, *Can. J. Chem.*, **45**, 2927 (1967); S. N. Ege and P. Yates, *ibid.*, 2933 (1967). See also ref 5 and 6.

(16) The closest analogy to our reactions is the photolysis of 3-methyl-2-cyclohexenone and 4,4-dimethylcyclopentene, used by Corey and Nozoe[17] in the synthesis of α-caryophyllene alcohol. The adduct used had to be cis–anti–cis to afford the required alcohol, whose geometry is known from X-ray work.[18]

(17) E. J. Corey and S. Nozoe, *J. Amer. Chem. Soc.*, **87**, 5733 (1965).

(18) K. W. Gemmell, W. Parker, J. S. Roberts, and G. A. Sim, *ibid.*, **86**, 1438 (1964).
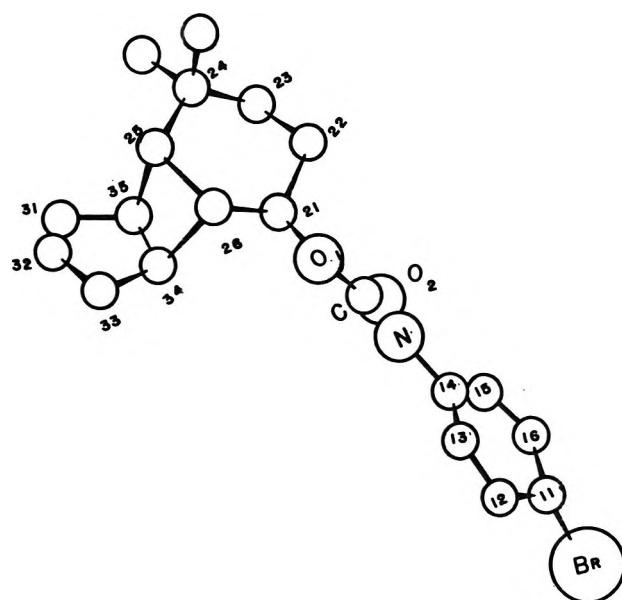
Identification of 7.—This had carbonyl absorption typical[7] of cis-fused six-four ring junctions (5.91 μ). However, the compound was distinctly different from **3**, as shown by vpc and nmr (methyl group resonances at δ 0.95 and 1.02) and by the failure of attempts to prepare the thiosemicarbazone (*cf.* **3**, above). This indicates a hindered carbonyl group. Also, reduction of **7** with LiAlH$_4$ gave rise to two alcohols, **8** and **9**, quite different from **6**. Therefore, since **3** was shown to be the cis–anti–cis compound, **7** must have the cis–syn–cis configuration, and the compound is assigned the structure 1β,7β,2β,6β-11,11-dimethyltricyclo[5.4.0.0^{2,6}]-undecan-8-one.[19] It follows that **4** must be 1β,7α,-2β,6β,11,11-dimethyltricyclo[5.4.0.0^{2,6}]undecan-8-one,[19] since the latter would be converted to **7** and not to **3** on equilibration with base.

Probable Identity of 5.—The unstable nature of this adduct precluded its isolation. Equilibration of the photolysis mixture, which shows three pairs of methyl group resonances, gives rise to a mixture of **3** and **7**, showing only two pairs of methyl resonances. Since **4** gives **7** on equilibration, **5** (15%, by nmr) should afford **3** when equilibrated and is assigned the 1α,7β,2β,-6β stereochemistry.[14]

The photoreaction and the equilibration are summarized in Chart I.

LiAlH$_4$ Reduction of Ketones 3 and 7.—The reductions of **3** and **7** are shown in Chart II. Ketone **3** gave a single alcohol **6** on LiAlH$_4$ reduction, as described above.

Ketone **7** was reduced with LiAlH$_4$ to afford two alcohols, **8** and **9**, which were separated by column chromatography. They both gave ketone **7** on chromic acid oxidation. They must be the exo and endo compounds, but we do not know which is which. Attempts to prepare crystalline derivatives were, as in the case of ketone **7**, unsuccessful.

(19) Implicit in these assignments is the assumption that the four- and five-membered rings are cis fused, as in **1**. While at least one case of trans fusion is known in photochemistry [H. D. Scharf, *Tetrahedron Lett.*, 4231 (1967)], enone additions have not been reported to give trans 5,4 ring junctions (*cf.* ref 12). If **3** and **5** were trans at the 5,4 junction, the adducts would be trans fused at *both* ring junctions, an extremely unlikely situation.

CHART II
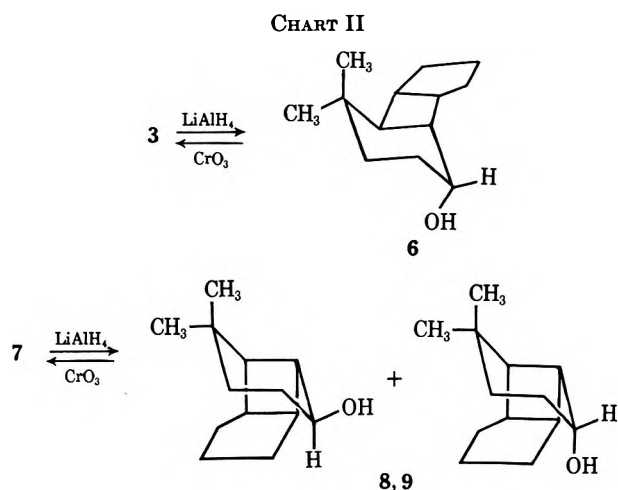
The formation of the exo alcohol from **3** is somewhat surprising. It is presumably the product of kinetically controlled reduction, in which the hydride approached along an equatorial path. In the reduction of **7**, this path may be hindered by the syn cyclopentane ring, and axial, exo approach apparently becomes competitive.

Cyclopentene and 3-Methyl-2-cyclohexenone.—This addition was studied to determine if an alkyl substituent at C_3 of the enone affects the stereochemistry of the addition.

The photolysis of 3-methyl-2-cyclohexenone and cyclopentene as described above gave rise to three mixed addition products, **10**, **11**, and **12**, separated by vpc. The reaction is shown in Chart III.

CHART III
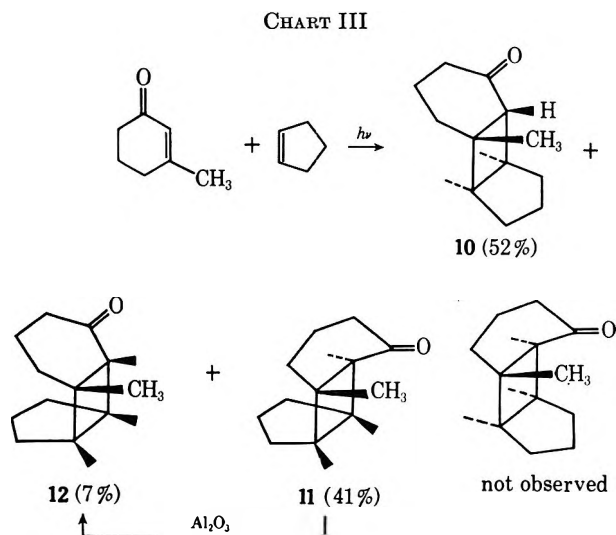
The major adduct **10** (52%) had carbonyl absorption at 5.91 μ and was stable to base treatment, indicating a cis six–four ring fusion. Note that the major adduct in the photoaddition of Corey and Nozoe[17] had the cis–anti–cis configuration,[16] and, by analogy with this, and with the 4,4-dimethyl-2-cyclohexenone addition described above, **10** is assigned the structure 1β-methyl-7β,2α,6α-tricyclo[5.4.0.0^{2,6}]undecan-8-one.

Isomer **11**, second in abundance (41%), had the carbonyl band at 5.82 μ, isomerized on base treatment, and was therefore a trans-fused cyclohexanone. The product of equilibration was not **10**, but **12**, the minor (7%) product of the photolysis. The latter had the

carbonyl band at 5.91 μ and is assigned the cis–syn–cis structure, 1β-methyl-7β,2β,6β-tricyclo[5.4.0.0^{2,6}]undecan-8-one, by the same reasoning used above for **4** and **7**. Adduct **11** would therefore be 1β-methyl-7α,2β,6β-tricyclo[5.4.0.0^{2,6}]undecan-8-one. These findings agree with those of Cantrell, *et al.*,[8] whose results appeared while our work was in progress.

Cyclopentene and 3-Phenyl-2-cyclohexenone.—This reaction was also studied by Cantrell, *et al.*[8] Photolysis of 3-phenyl-2-cyclohexenone and cyclopentene in *tert*-butyl alcohol gave two mixed addition products, **13** and **14**, in the ratio of 90:7, respectively, by vpc. The reaction is shown in Chart IV.

CHART IV
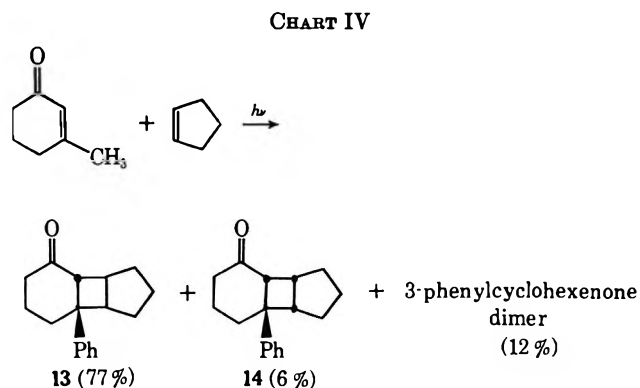
These were separated by column chromatography and preparative vpc, and gave molecular ions of m/e 240, with base peaks at m/e 173.

The major adduct **13** had mp 59.5–61°, was stable to base treatment, and had the carbonyl band at 5.91 μ. A cis-fused cyclohexanone system was indicated. The cis–anti–cis stereochemistry was tentatively assigned to **13** by analogy with the dimer of 3-phenyl-2-cyclohexenone.[15c] The minor adduct formed in this addition should therefore be the cis–syn–cis isomer.

2-Phenyl-2-cyclohexenone and Cyclopentene.—Irradiation of 2-phenyl-2-cyclohexenone and cyclopentene in the usual way for 45 hr resulted in no appreciable adduct formation, as indicated by vpc analysis and recovery of starting enone. The reason for this lack of reactivity is not apparent, but it should be noted that methyl substitution at C_2 of 2-cyclohexenone considerably retards the rate of addition.[7]

Multiplicity of 4,4-Dimethyl-2-cyclohexenone–Cyclopentene Addition.—While it is now well known that simple cyclic enone additions involve triplet states,[1] our method of establishing this in the case of 4,4-dimethylcyclohexenone differs from the standard methods. This enone[20] is known to undergo the "type A rearrangement"[21] on photolysis, to afford **15** together with the cyclopentenone **16**.[20]
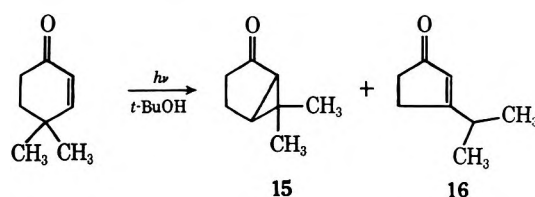
(20) O. L. Chapman, T. A. Rettig, A. A. Griswold, A. I. Dutton, and P. Fitton, *Tetrahedron Lett.*, 2049 (1963).

(21) H. E. Zimmerman, R. G. Lewis, J. J. McCullough, A. Padwa, S. W. Staley, and M. Semmelback, *J. Amer. Chem. Soc.*, **88**, 1965 (1966).

The "type A" enone rearrangement has been shown to be a triplet state reaction,[21] as also has the formation of **16**.[22] In the presence of a suitable concentration of cyclopentene, photolysis of 4,4-dimethyl-2-cyclohexenone gave a conveniently· measurable ratio of rearrangement products (**15** and **16**) to adducts (**3, 4, 5**). It was found that this ratio was virtually unchanged by quenching with naphthalene, although a threefold retardation in rate was observed. The results of these experiments are given in Table I. The observation

TABLE I
PHOTOREARRANGEMENT AND ADDITION OF
4,4-DIMETHYL-2-CYCLOHEXENONE AND CYCLOPENTENE

Naphthalene, M^b	Conversion of enone, %	Rearrangement products 15	16	Addition products 3, 4, 5
	73	11	8[c]	81
	83	10	6	84
	76	10	7	83
0.050	80	10	11	79
0.050	74	11	11	79
0.050	83	11	11	78

[a] Analysis by vpc on a 10 ft × 0.125 in. 12% QF-1 at 175°. [b] Methanol as solvent. Molar concentrations were 0.0143 and 0.0858 for 4,4-dimethylcyclohexenone and cyclopentene, respectively. [c] Estimated maximum error ±4%.

that the rearrangement product to adduct ratio does not change on quenching is good evidence that a triplet state of the enone adds to cyclopentene, and the following simple kinetic scheme can be used to describe the processes.

$$\text{enone } T_1 \xrightarrow{k_r} \text{rearrangement}$$

$$\text{enone } T_1 + \text{cyclopentene} \xrightarrow{k_a} \text{adducts}$$

$$\text{enone } T_1 + \text{naphthalene} \xrightarrow{k_q} \text{enone} + \text{naphthalene } T_1$$
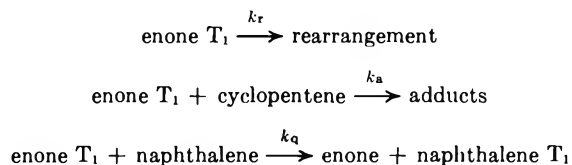
The "type A" addition ratio is therefore given by the expression

$$\text{rearrangement/addition} = k_r/k_a[\text{cyclopentene}]$$

Since k_r for this rearrangement (in a different enone) was found[21] to have a value of $2.9 \times 10^5 \text{ sec}^{-1}$, the above expression allows an estimate of k_a to be made. A cyclopentene concentration of 0.086 M gives a product ratio of 1/8, and from this a value of 2.7×10^7 l. mol^{-1} sec^{-1} for k_a is derived, which is similar to the rate constants for 2-cyclohexenone–cyclohexene additions.[1]

The additions of 3-phenyl-2-cyclohexenone and alkenes may occur *via* the singlet or triplet states to afford the same products in both cases. Our work on the multiplicity of this reaction will be described elsewhere.

Discussion

In general, the formation of cyclobutanes by addition of triplets is sensitive to steric effects, and the adduct with cis–anti–cis stereochemistry predominates in a number of structurally different cases.[5,3,15,16] Therefore, the assignment of the cis–anti–cis configuration to **3** is no surprise, but does show that mixed additions of 2-cyclohexenones conform to the above general rule.

The trans-fused adducts formed in these 2-cyclohexenone additions are particularly interesting. The structure of the major, trans-fused compound **4** can be rationalized in terms of a mechanism comprising the following steps: (a) attack by a nonplanar triplet T_1 of the enone on ground state alkene (it is proposed that initial bonding occurs at C_2 of the enone), and (b) rapid formation of the second bond of the cyclobutane ring, before the enone residue can relax to its equilibrium configuration. This sequence has been considered previously, notably by de Mayo,[1] and can be used to explain the stereochemistry of **4**.

There is now ample evidence[1] that additions of cyclic enones occur from the triplet manifold, generally T_1, and our experiments confirm this in the case of 4,4-dimethyl-2-cyclohexenone. There are also strong indications that unconstrained enones should resemble ethylene in being twisted about the carbon–carbon double bond in state T_1. This inference derives from spectroscopic studies on model compounds,[23] and from calculations.[24] Thus, in general, the trans-fused adducts could arise from a twisted cyclohexenone, if the geometry of the latter can be preserved throughout the reaction.

Consider now the geometry of adduct **4**. It can be seen that the bonds of the five- and six-membered rings are mutually anti in the region of the carbonyl group (bonds i and ii are anti and bonds iii and iv are syn). This could mean that initial bonding to cyclopentene occurs close to the carbonyl group in the enone triplet state, and steric interactions are causing a preference for anti attack in this bonding process. That steric effects are generally important in this type of addition is evidenced by the predominance of cis–anti–cis adducts in many cases.[5,6,15,16] Once the steric relationship of bonds i and ii has been fixed, then the shape of the trans-fused molecule is determined (assuming only cis fusion at the 5–4 ring junction).[19]

As pointed out above, it is difficult to see why an equilibrated 1,4 biradical should close to give adducts, e.g., **5**, which are considerably less stable than other possible products. Since it is probable that biradicals are intermediates in this type of cyclobutane formation,[7,25] it is therefore necessary to propose that the second bond-forming step is a rapid one. This is reasonable in the case of 2-cyclohexenones and cyclopentene, since the radical centers are not effectively stabilized. One might therefore envisage the formation of **4** as follows.

triplet–olefin complex   slow   rapid ↓

4

(22) O. L. Chapman, Abstracts, 20th National Organic Symposium, Burlington, Vt., June 18–22, 1967, p 133.
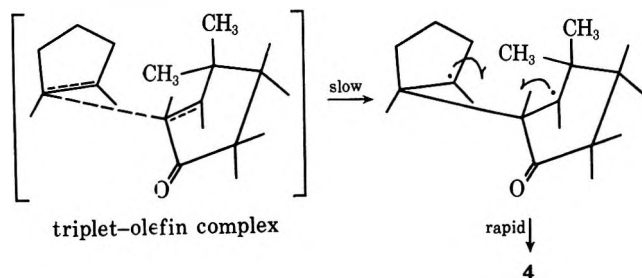
(23) R. L. Cargill, P. de Mayo, A. C. Miller, K. R. Neuberger, D. M. Pond, J. Saltiel, and M. F. Tchir, *Mol. Photochem.*, **1**, 301 (1969).

(24) (a) J. J. McCullough, H. O. Ohorodnyk, and D. P. Santry, *Chem. Commun.*, 570 (1969); (b) A. Devaquet and L. Salem, *Can. J. Chem.*, **49**, 977 (1971); (c) also work by Professor N. C. Baird and by Dr. J. S. Wasson, cited in footnote 19 of ref 1.

(25) J. J. McCullough, J. M. Kelly, and P. W. Rasmussen, *J. Org. Chem.*, **34**, 2933 (1969).

While this sequence is reasonable and explains the trans-fused structures, it is certainly not a complete picture. First of all it does not explain why the only cyclobutane found in the addition of 4,4-dimethyl-2-cyclohexenone and tetramethylethylene is trans fused. Second, it does not account for the absence of these strained systems from additions of 2-cyclohexenones and electron-deficient substrates (see, however, ref 6b, 10). These last two facts may be related and could be due to charge-transfer interactions in the triplet olefin encounter complex. There is evidence that the latter are intermediates[26,27] in these additions and selective quenching of cis- and trans-fused product formation can be ascribed to them.[23] It is possible that the twisted geometry of the cyclohexenone triplet is generally only preserved, to give trans-fused products, if the cyclohexenone reacts with an electron-rich substrate, e.g., tetramethylethylene,[4] 1,1-dimethoxyethylene,[7,8] and norbornadiene,[25] but not when the substrate is acrylonitrile,[7,8] 2-cyclohexenone,[6b] or even ethylene.[9] It seems that oxetane formation frequently parallels that of trans-fused cyclobutanes[4,28] and this suggests that the latter are formed by attack near the carbonyl group of the enone triplet (*cf.* formation of 2).

These processes are summarized in Chart V, where

CHART V

$$E^3 + O \longrightarrow \overset{\delta^+}{E}---\overset{\delta^-}{O^3} \text{ and/or } \overset{\delta^-}{E}---\overset{\delta^+}{O^3}$$

complex 1   complex 2

↓   ↓

biradicals   biradicals

↓   ↓

cis-fused   trans-fused
adducts   adducts
                    (+ oxetane)
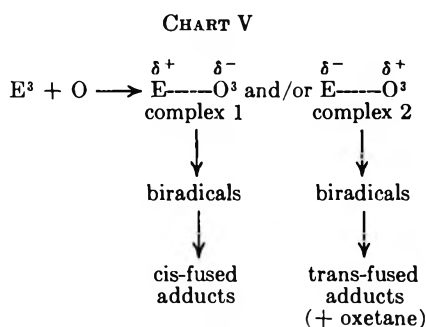
E^3 = enone triplet and O = unsaturated substrate. It is clear that the polarity of complex 1 should be favored by electron-deficient substrates, while complex 2 will be more important with those which are electron rich.

A second factor which must be important in determining stereochemistry is the stability of the proposed biradical intermediates. If these possessed considerable stability, then formation of trans-fused systems might be precluded by the relatively long lifetimes of the biradicals. In the case of 3-phenyl-2-cyclohexenone additions, both Cantrell[8] and the authors found no evidence for trans-fused products. This may be due to radical stability. However, the tendency for twisting about the C=C double bond in the excited states of this enone is probably considerably less than in simple enones.[29] Both these factors could be important. It should be mentioned that the above considerations do not counter the results of Dilling[13] on 2-cyclopentenone and 1,2-dichloroethylene, and their interpretation. Obviously, restrictions are imposed on

the geometry of T_1 by the five-membered ring. Also, the biradicals formed in this case should be more stable owing to the chloro substituents. Therefore, the situation is rather different from 2-cyclohexenone–olefin reactions.

Finally, we would point out that an explanation of the trans-fused compounds cannot be derived from the arguments of Stephenson and Brauman.[30] They attributed the stereospecificity of 1,4-biradical ring closures to an energetic biradical, resulting in very rapid closure. This situation obtains when the biradicals are formed, for example, by loss of nitrogen from an azo compound.[31] However, the 1,4 biradicals from enone–olefin additions have about 17 kcal of excess energy.[32,33] This would not be sufficient to provide the strain energy of even cis-fused cyclobutanes (26.4 kcal), and an alternative explanation must be sought.

Experimental Section

(26) P. de Mayo, A. A. Nicholson, and M. F. Tchir, *Can. J. Chem.*, **47**, 711 (1969).

(27) P. J. Wagner and D. J. Buchek, *ibid.*, **47**, 713 (1969).

(28) O. L. Chapman, T. H. Koch, F. Klein, P. J. Nelson, and E. L. Brown, *J. Amer. Chem. Soc.*, **90**, 1657 (1968).

(29) (a) H. Ohorodnyk and D. P. Santry, unpublished calculations on cinnamaldehyde; (b) A. Devaquet and L. Salem, *J. Amer. Chem. Soc.*, **91**, 1347 (1969).

(30) L. M. Stephenson and J. I. Brauman, *ibid.*, **93**, 1988 (1971).

(31) P. D. Bartlett and N. A. Porter, *ibid.*, **90**, 5317 (1968); C. J. Overberger and J. W. Stoddard, *ibid.*, **92**, 4922 (1970).

(32) This assumes an excitation energy of 60 kcal/mol for enone T_1: B. S. Kirkiacharian, P. de Mayo, and A. A. Nicholson, *Mol. Photochem.*, **2**, 145 (1970).

(33) Thermochemical data was taken from J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1965, pp 77, 112.

(34) T. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 1347 (1963).

(35) W. F. Gannon and H. O. House, *Org. Syn.*, **40**, 148 (1960).

(36) G. F. Woods and I. W. Tucker, *J. Amer. Chem. Soc.*, **70**, 2174 (1948).

(37) C. F. H. Allen and S. Converse, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 226.

(38) L. Meites and T. Meites, *Anal. Chem.*, **20**, 984 (1948).

Melting points were taken on a Reichert hot stage and are reported uncorrected. Elemental analyses were by Spang Microanalytical Laboratory, Ann Arbor, Mich., or by A. B. Gygli, Toronto.

Synthesis of 2-Phenyl-2-cyclohexenone.—A modification of the method of Warnhoff, Martin, and Johnson[39] was used in the synthesis of 2-phenyl-2-cyclohexenone. To 15.50 g (0.089 mol) of 2-phenylcyclohexanone, mp 50–52° (Aldrich reagent) in dry carbon tetrachloride (100 ml), with 1 drop of concentrated HCl, was added during 90 min sulfuryl chloride (12.03 g, 0.0891 mol) in dry CCl₄ (15 ml). The reaction was stirred for an additional 3 hr and maintained at 25° throughout. After successive washings with 2 × 25 ml of distilled water, 2 × 20 ml of saturated NaHCO₃ solution, and 25 ml of saturated sodium chloride solution, the solution was dried (MgSO₄) and the ether was distilled.

To this residue, *N*,*N*-dimethylformamide (25 ml) and lithium chloride (2.34 g) was added. After flushing with nitrogen, the reaction flask was heated to 100° for 40 min with stirring. The mixture was then cooled, ether (100 ml) and 3% H₂SO₄ (100 ml) were added, and the mixture was stirred for 4 hr. The aqueous layer was separated and extracted with 2 × 50 ml of ether. The combined ether fractions were washed with 40 ml of saturated NaCl solution and 40 ml of saturated NaHCO₃ solution, and dried (MgSO₄). Crystallization of the residue after solvent removal from hexane gave 2-phenyl-2-cyclohexenone (6.78 g, 44%) as pale yellow needles, mp 91–94° (lit.[39] mp 94–94.5°).

Photoaddition of 4,4-Dimethyl-2-cyclohexenone and Cyclopentene.—4,4-Dimethyl-2-cyclohexenone (7.300 g, 0.059 mol) and cyclopentene (22.1 g, 0.324 mol) in methanol (400 ml) were irradiated with the Hanovia lamp fitted with a Pyrex sleeve under nitrogen for 4 hr. Monitoring by vpc (5 ft × 0.125 in. of 5% QF-1 on 60–70 Chromosorb W at 160°) showed products of retention times of 4 and 5 min, and that 85% of the enone had reacted. The solution was evaporated to afford 11.0 g of yellow oil showing carbonyl bonds in the infrared at 5.84 and 5.91 μ. The oil was distilled without fractionation to yield 9.948 g of ketone mixture, bp 115–120° (4.0 mm), consisting of ketones **3** and **4**, according to vpc, infrared, and nmr spectra. A sample of this mixture was distilled in a Nester-Faust Auto-annular spinning band column (Teflon band), at a reflux ratio of 30:1. From 8.6 g of mixture, 4.0 g of **3** was obtained, bp 124° (8 mm). This had infrared absorption at 5.91 μ, and methyl resonances at δ 0.87 and 0.88. It showed one peak on columns of QF-1, Carbowax, and FFAP. It is assigned the cis–anti–cis structure **3**, 1α,7α,-2β,6β-11,11-dimethyltricyclo[5.4.0.0.²,⁶]undecan-8-one, on the basis of the X-ray work described below. *Anal.* Calcd for C₁₃H₂₀O: C, 81.25; H, 10.42. Found: C, 81.02; H, 10.40.

On treatment with thiosemicarbazide, sodium acetate, and HCl in aqueous methanol, **3** readily formed a thiosemicarbazone, mp 160–162°. *Anal.* Calcd for C₁₄H₂₃N₃S: C, 63.37; H, 8.74; N, 15.84; S, 12.06. Found: C, 63.11; H, 8.94; N, 16.01; S, 12.00. The other fractions (total 4.0 g) from the spinning band distillation were mixtures of **3** and **4**. These were separated by preparative vpc on 10 ft × 0.375 in. of 20% QF-1 on 45–60 Chromosorb W at 215°. By making several injections, 300 mg of **3** and 200 mg of **4** were obtained from 1.0 g of mixture (recovery 50%). **4** was homogeneous by VPC (QF-1 and FFAP columns) and had carbonyl absorption at 5.84 μ and methyl resonances at δ 0.98 and 1.19. It is assigned the structure 1β,7α,2β,6β,11,11-dimethyltricyclo[5.4.0.0.²,⁶]undecan-8-one.

Base-Catalyzed Equilibration of 4.—The trans-fused cyclobutane adduct (**4**, ca. 50 mg) isolated from the photolysis was stirred at ambient temperature with Fisher basic alumina (10 g), in ether (50 ml), until the infrared spectrum showed complete disappearance of the carbonyl band at 5.83 μ, with appearance of a new band at 5.91 μ. The alumina was filtered and the ether was evaporated to yield a compound (ca. 50 mg) identical by vpc, nmr, and infrared spectra with the 1β,7β,2β,6β isomer **7** isolated from the equilibrated photolysis product.

Equilibration of the Photolysis Mixture of 3 and 4.—A sample of distilled photolysis mixture consisting of ketones **3** and **4** (9.257 g) was heated under reflux for 3 hr with a 5% solution of potassium hydroxide in aqueous methanol, 1:1 (100 ml). The mixture was poured into water and worked up with ether. The residue which remained on evaporation of the ether was distilled to afford 5.55 g of ketone mixture. This mixture showed

only one carbonyl band at 5.91 μ, and one peak on vpc (10 ft × 0.125 in. of 12% QF-1 on 60–70 Chromosorb W at 218°). Also, the methyl resonances at δ 0.98 and 1.19 were replaced by resonances at δ 0.95 and 1.10. On columns of FFAP or Carbowax (5 ft × 0.125 in. at 180°) the mixture showed two peaks, ratio 6:4. The compounds were separated by preparative vpc on 10 ft × 0.375 in. of 10% Carbowax on 60–80 Chromosorb W at 210°. By making repeated injections, 2.8 g of mixture was resolved to yield 933 mg of **3** and 329 mg of **5** (46% recovery). The latter ketone had infrared absorption at 5.91 μ and methyl singlets at δ 0.95 and 1.02, and gave one peak on vpc (columns FFAP, QF-1 and Carbowax). It is assigned the cis–syn–cis configuration **7** and is 1β,7β,2β,6β,11,11-dimethyltricyclo[5.4.0.0.²,⁶]undecan-8-one.

Reduction of Ketone 3 with LiAlH₄.—Ketone **3**, from the above fractional distillation (2.177 g, 0.011 mol) in ether (20 ml) was added dropwise to a stirred slurry of lithium aluminum hydride (0.50 g, 0.013 mol) in ether (40 ml), and the mixture was refluxed for 5 hr. The residual hydride was decomposed with water and the aluminum compounds were filtered. The ether was dried (Na₂SO₄) and evaporated to afford 1.794 g (80α) of alcohol as an oil which solidified on standing. Sublimation at 50° (1 mm) gave waxy crystals, mp 51–56°. *Anal.* Calcd for C₁₃H₂₂O: C, 80.35; H, 11.41. Found: C, 80.00; H, 11.39. The alcohol readily formed a *p*-bromophenylurethane on treatment with *p*-bromophenylisocyanate in refluxing cyclohexane. The derivative was formed in 71% yield, mp 130–132° (from ethanol). *Anal.* Calcd for C₂₀H₂₆O₂NBr: C, 61.22; H, 6.68; N, 3.56; Br, 20.37. Found: C, 61.37; H, 6.57; N, 3.69; Br, 20.26. The X-ray structure determination described below was performed on this derivative, showing the alcohol **6** to be *exo*-1α,7α,2β,6β-11,11-dimethyltricyclo[5.4.0.0.²,⁶]undecan-8-ol.

Description of X-Ray Work.—The *p*-bromophenylurethane derivative of **6** crystallized from aqueous ethanol as needles. The crystals had surface irregularities which caused them to be translucent rather than transparent. The lattice parameters were determined from a least squares refinement of 15 values of 2 θ measured with monochromatic Mo Kα radiation utilizing a Syntex automatic diffractometer. The values obtained were *a* = 13.00(1), *b* = 5.597(5), *c* = 27.20(3) Å and β = 109.46(5)°. The space group was established as *P*2₁/*c* since Weissenberg photographs indicated that *l* odd and *k* odd reflections were extinct for the *h0l* and *0k0* sets, respectively. The calculated density is 1.36 g/cm³ for *z* = 4, while the value measured using a solution of potassium tartrate in water is 1.40 g/cm³.

A crystal with dimensions of 0.03 × 0.03 × 0.05 mm was used to record data. Graphite monochromatized Mo Kα radiation was used in conjunction with a Syntex automatic diffractometer. All the data in a hemisphere with a maximum radius defined by 2θ ≤ 35° were recorded using a θ–2θ scan with a scan rate determined by the intensity at the peak and a scan range dependent upon the value of θ. Backgrounds were recorded on either side of the peak and used to determine the integrated intensity together with an estimated standard deviation based upon counting statistics. Those reflections whose intensity were less than 3σ were regarded as unobserved with the maximum possible intensity set at 3σ. Reflections whose intensity calculated < 0 were left out of the refinement. Of the total 1025 reflections in the data set, 610 had observable intensities. The data were corrected for Lorentz and polarization but not absorption.

The bromine atom position was determined from the Patterson function. The signs determined from the subsequent structure factor calculation were used to calculate an electron density map from which the remaining atoms were found. The structure was refined utilizing a full matrix least squares program written by Stephens for the CDC-6400. The atomic scattering curves, dispersion corrected where necessary, were taken from the International Tables for X-Ray Crystallography.[40] Weights, *w*, were chosen so that *w*|*F*ₒ − *F*ₒ|² would locally be independent of the *F*ₒ, observed structure factor, and the function obtained was

$$W = [25 + 0.2|F_o| + 0.04 F_o|^2]^{-1}$$

Unobserved reflections whose calculated structure factor was less than the minimum observable value were given zero weight in the refinement. The final *R* value is 0.10, while the least squares residual is 0.13. The refinement was terminated when

(39) E. W. Warnhoff, D. G., Martin, and W. S. Johnson, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 162.

(40) "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1962.

TABLE II

BOND DISTANCES AND ANGLES IN *p*-BROMOPHENYLURETHANE WITH ESTIMATED STANDARD DEVIATIONS IN PARENTHESES

Atoms	Bond length, Å	Atoms	Bond angle, deg	Atoms	Bond angle, deg
Br–C11	1.90 (3)			C13–C14–C15	117 (4)
C11–C12	1.51 (4)	C16–C11–C12	112 (2)	C14–C15–C16	115 (4)
C12–C13	1.39 (5)	C11–C12–C13	113 (2)	C15–C16–C11	136 (4)
C13–C14	1.36 (5)	C12–C13–C14	123 (4)	Br–C11–C16	136 (4)
C14–C15	1.43 (5)	Br–C11–C12	110 (2)	N–C14–C15	122 (4)
C15–C16	1.27 (5)	N–C14–C13	121 (4)		
C16–C11	1.24 (6)				
C14–N	1.40 (4)	C14–N–C	117 (3)	C21–O1–C	102 (2)
N–C	1.57 (5)	N–C–O1	92 (3)	O1–C21–C22	113 (4)
C–O2	1.04 (4)	N–C–O2	133 (4)	O1–C21–C26	97 (4)
C–O1	1.48 (4)	O1–C–O2	134 (3)		
O1–C21	1.51 (4)				
C21–C22	1.58 (5)	C26–C21–C22	109 (4)	C23–C24–C25	112 (4)
C22–C23	1.62 (6)	C21–C22–C23	102 (4)	C24–C25–C26	116 (4)
C23–C24	1.53 (4)	C22–C23–C24	106 (4)	C25–C26–C21	107 (3)
C24–C25	1.52 (4)	C23–C24–C24a	101 (3)	C23–C24–C24b	117 (3)
C25–C26	1.64 (5)	C25–C24–C24a	106 (3)	C25–C24–C24b	113 (3)
C26–C21	1.66 (5)				
C24–C24a	1.71 (6)	C24a–C24–C24b	107 (3)		
C24–C24b	1.46 (6)				
C25–C35	1.54 (6)	C35–C25–C24	127 (4)	C34–C26–C21	105 (4)
C26–C34	1.64 (5)	C35–C25–C26	88 (4)		
C31–C32	1.44 (6)	C31–C32–C33	113 (4)	C33–C26–C21	109 (3)
C32–C33	1.60 (6)	C32–C33–C34	99 (4)	C34–C35–C31	109 (3)
C33–C34	1.67 (5)	C35–C31–C32	104 (4)		
C34–C35	1.48 (5)				

the calculated shifts were less than $^1/_3$ of the estimated standard deviations. A final difference synthesis showed no missing structural features, although peaks as high as $^1/_4$ of a carbon atom were noted.

Table II contains a list of pertinent bond lengths and angles. Tables III, containing the parameters, and Table IV, comparing the observed and calculated structure factors, will appear in the microfilm edition.[41] The structure is shown in Figure 1.

Reduction of Ketone 7 with LiAlH₄.—Ketone 7 (201 mg, 0.0011 mol) in ether (10 ml) was added to a stirred suspension of lithium aluminum hydride (51.0 mg, 0.0013 mol) in ether (5.0 ml). The mixture was heated at reflux for 6 hr, and the excess hydride was decomposed with water (20 ml). The alumina was filtered and the ether layer was separated and dried (Na₂SO₄). The residue on evaporation of the ether was an oil (123 mg, 58%) which showed two peaks on vpc (5 ft × 0.125 in. 5% QF-1 on 60–80 Chromosorb W at 150°) in the ratio of about 2:1. The mixture was chromatographed on 80 g of silica gel for tlc (E. Merck, A. G.; grain size, 10–40) packed in a column 2.5 × 50 cm. Elution was with benzene–ether (4:1) and 20-ml fractions were collected. A pressure of 5 psi was applied to obtain a reasonable flow rate. Fractions 1–6 contained fast-moving material (vpc), 38 mg; fractions 7–9 contained 36 mg of alcohol 8, mp 74–78°, obtained as needles from pentane, mp 78–79°. *Anal.* Calcd for C₁₃H₂₂O: C, 80.35; H, 11.41. Found: C, 80.47; H, 11.27. Fractions 10–13 contained 56 mg of alcohol 9, mp 89–91°, recrystallized from pentane, mp 90–91°. *Anal.* Calcd for C₁₃H₂₂O: C, 80.35; H, 11.41. Found: C. 80.44; H, 11.38.

Oxidation of Alcohols 6, 8, and 9 to the Corresponding Ketones.—The alcohol (20 mg) in ether (5 ml) was stirred at ambient temperature for 5 hr with 1.5 ml of a solution containing 1.19 g of sodium dichromate dihydrate and 1.31 g of H₂SO₄ in 98 ml of water. The ether layer was separated and dried (MgSO₄) and the ketonic product was subjected to vpc analysis (5 ft × 0.125 in. 10% QF-1 at 140°). When oxidized in this way alcohol 6 gave product of identical retention time with that of 3.

(41) Listings of structure factors, coordinates, and anisotropic tempera-ture factors 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-72-2084. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Alcohols 8 and 9 were oxidized to a compound with the same retention time as 7.

Quenching of the Addition of 4,4-Dimethyl-2-cyclohexenone and Cyclopentene.—Six solutions (80 ml) of 4,4-dimethyl-2-cyclohexenone (0.0143 *M*) and cyclopentene (0.0858 *M*), three of which contained naphthalene (0.050 *M*), were cooled in Dry Ice–acetone, flushed with purified nitrogen for 0.5 hr, and irradiated. The unquenched solutions were photolyzed for 190 min; those containing naphthalene for 570 min. The products (rearrangement and 1:1 addition products) were analyzed by vpc (10 ft × 0.125 in. 12% QF-1 on 60–70 Chromosorb W at 175°) without removal of the solvent. The products ratios obtained are given in Table I. The vpc was calibrated for this work with prepared mixtures of purified adduct and rearrangement product.

Photoaddition of 3-Methyl-2-cyclohexenone and Cyclopentene.—Irradiation of 3-methyl-2-cyclohexenone (2.374 g, 0.0133 mol) and cyclopentene (24.52 g, 0.360 mol) in *tert*-butyl alcohol (375 ml) and methanol (20 ml) for 5.5 hr resulted in reaction of about 99% of the enone. The solvent was distilled *in vacuo* at 30° into a receiver at −78°. Infrared bands in the residual oil (2.50 g) at 5.82 (trans 6–4 ring fusion) and 5.91 μ (cis 6–4 ring fusion) indicated a near equimolar ratio of cis and trans 6–4 fused rings. A flash distillation afforded 2.05 g of liquid, bp 110° (5 mm) (10 ft × 0.125 in. 12% QF-1 at 194°). Analysis of the photolysis mixture by vpc showed three products with retention times of 8.3, 9.5, and 10.5 min.

The nmr of the photolysis mixture showed the disappearance of the methyl signal at δ 1.97 of 3-methyl-2-cyclohexenone and the appearance of three methyl singlets. By measuring the area of the methyl peaks, product ratios were established and are given following the chemical shift: δ 0.95, 51.6% (10); 1.06, 41.3% (11); 1.31, 7.1% (12). The isomers were separated by preparative vpc on 10 ft × 0.375 in. of 20% QF-1 at 183°. Recovery from this separation was poor owing to the similar retention times of the products.

The following fractions were collected. (a) A peak, retention time 38 min, had carbonyl absorption at 5.91 μ (cis-fused 6–4 junction) and a methyl singlet at δ 0.95. This, the major product, is assigned the cis–anti–cis configuration 10. *Anal.* Calcd for C₁₂H₁₈O: C, 80.84; H, 10.18. Found: C, 80.84; H, 10.14. (b) A sample of the product of retention time 42 min had carbonyl absorption at 5.82 μ (trans 6–4 ring fusion) and a methyl singlet at δ 1.06. On the basis of this data and of the equilibration of the compound to 12 with base, it is assigned structure 11.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.18. Found: C, 80.64; H, 10.11. (c) A fraction at 33 min had carbonyl absorption at 5.91 μ (cis 6–4 fusion) and a methyl singlet at δ 1.31. It was the minor compound, and was identical with the product of equilibrium of 11. It is assigned the cis–syn–cis structure 12. *Anal.* Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.18. Found: C, 80.97; H, 10.20.

Equilibration of 11.—The photoadduct 11 (30 mg) was dissolved in 30 ml of ether, basic alumina was (2.0 g) added, and the solution was stirred for 3.5 hr. After filtration and evaporation of the ether, the infrared showed a band at 5.91 μ and the nmr had a methyl singlet at δ 1.30, characteristic of isomer 12 (see below). Analysis on a 10 ft × 0.125 in. 12% QF-1 at 194° showed the disappearance of a peak of retention time 10.5 min and the appearance of a peak at 8.3 min corresponding to 12.

Photolyses with 2-Phenyl-2-cyclohexenone.—Irradiation of 2-phenyl-2-cyclohexenone (1.779 g, 0.0103 mol) and cyclopentene (16.87 g, 0.248 mol) for 45 hr in *tert*-butyl alcohol (380 ml) and methanol (20 ml) gave less than 5% cross-addition products as indicated by vpc and recovery of starting enone.

Photoaddition of 3-Phenyl-2-cyclohexenone and Cyclopentene.—Irradiation of 3-phenyl-2-cyclohexenone (1.663 g, 0.0097 mol) and cyclopentene (11.06 g, 0.163 mol) in *tert*-butyl alcohol (375 ml) and methanol (20 ml) for 7 hr resulted in reaction of 97% of 3-phenyl-2-cyclohexenone, determined by vpc analysis on 3 ft × 0.125 in. of 10% FFAP at 245°. The vpc analysis showed that two products were formed having retention times of 7.4 (13) and 12.3 min (14), in the ratio 90:7 as measured from vpc peak areas. After removing the solvent by distillation, the residue (1.873 g) was chromatographed on a 3 × 28 cm column of silica gel slurry packed in benzene, and 200-ml fractions were collected. Fractions 1–5 were eluted with benzene, 6–10 with

0.5% ethyl acetate–benzene, 11–20 with 1%, 21–25 with 2%, 26 and 27 with 4%, 28 with 8%, and 29–30 with 15% ethyl acetate–benzene. Fractions 14–16 contained the major photoadduct 13 (959 mg). This gave colorless prisms, mp 59.5–61°, from aqueous ethanol. *Anal.* Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.93 Found: C, 84.99; H, 8.30. The compound had infrared absorption at 5.91 μ and was stable to base, strongly suggesting cis fusion of the cyclohexanone ring. It is assigned the cis–syn–cis structure 13.

Fractions 29–30 contained the photodimer of 3-phenyl-2-cyclohexanone (500 mg), which had mp 199–200° from ether–light petroleum (lit.[15c] mp 204–205°).

Registry No.—3, 34404-88-1; 3 thiosemicarbazone, 34404-89-2; 4, 34404-90-5; 6, 34404-91-6; 6 *p*-bromophenylurethane, 34404-92-7; 7, 34404-93-8; 8, 34404-94-9; 9, 34404-95-0; 10, 34404-96-1; 11, 34404-97-2; 12, 34404-98-3; 13, 34404-99-4; cyclopentene, 142-29-0; 4,4-dimethyl-2-cyclohexenone, 1073-13-8; 3-methyl-2-cyclohexenone, 1193-18-6; 2-phenyl-2-cyclohexenone, 4556-09-6; 3-phenyl-2-cyclohexenone, 10345-87-6.

Stereochemistry and Mechanism of Thermal and Base-Catalyzed Rearrangements of α-Hydroxy Ketones

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A pair of diastereomeric α-hydroxy ketones, *exo*-2-benzoyl-*endo*-2-hydroxybicyclo[2.2.1]heptane (1) and *endo*-2-benzoyl-*exo*-2-hydroxybicyclo[2.2.1]heptane (2), were prepared starting from 2-benzoylbicyclo[2.2.1]heptane (3). Rearrangement of these hydroxy ketones under pyrolytic conditions yielded products predicted by a cyclic concerted mechanism, 1 giving exclusively *endo*-2-hydroxy-*exo*-2-phenyl-3-bicyclo[3.2.1]octanone (8) and 2 yielding an equilibrium mixture of *exo*-3-hydroxy-*endo*-3-phenyl-2-bicyclo[3.2.1]octanone (9) and *exo*-2-hydroxy-*endo*-2-phenyl-3-bicyclo[3.2.1]octanone (10). On the other hand, treatment of hydroxy ketone 1 with sodium hydroxide in a water–dioxane system yielded 10 while compound 2 rearranged to give 8 under more severe alkaline conditions. The proof of structure for all the rearrangement products is presented and mechanisms are discussed for the transformations.

The rearrangements of 17-hydroxy-20-keto steroids have been studied extensively as a method for D-homoannulation.[2] Outside the steroidal field, the only investigation in this area appears to be that of Elphimoff-Felkin and coworkers, who extended this reaction for the preparation of a few cyclic acyloins.[3] The present work was undertaken to investigate the stereochem-

istry of this rearrangement in simpler systems where diastereomeric hydroxy ketones (1 and 2) could be prepared. The norbornane ring system was chosen, as it has the additional advantage of undergoing carbon skeletal rearrangements with great facility.

Results

Hydroxy ketone 1 was prepared by a series of reactions starting from the known 2-benzoylbicyclo[2.2.1]-heptane[4] (3). Treatment of 3 with bromine in CCl_4 at room temperature yielded a single crystalline bromo ketone, *exo*-2-bromo-*endo*-2-benzoylbicyclo[2.2.1]heptane (4). That the bromine and benzoyl groups were attached to the same carbon in 4 was indicated by the nmr spectrum, which showed no downfield protons characteristic of hydrogen on a carbon bearing a bromine or a benzoyl group. The exo configuration of

1   2
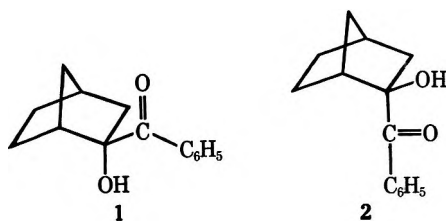
(1) Taken in part from the Ph.D. Dissertation of T. A. Treat, Wayne State University, 1969; Ethyl Corporation Fellow, 1968–1969.

(2) For a review, see N. L. Wendler in "Molecular Rearrangements," Part II, P. de Mayo, Ed., Interscience, New York, N. Y., 1964, p 1114.

(3) I. Elphimoff-Felkin, G. LeNy, and B. Tchoubar, *Bull. Soc. Chim. Fr.*, 522, 581 (1958).

(4) N. K. Kochetkov and A. Y. Khorlin, *Zh. Obshch. Khim.*, 27, 3182 (1957); *Chem. Abstr.*, 52, 8984g (1958).

bromine was expected on the basis that bromine would attack the enol of 4 from the less hindered side.[5] Bromo ketone 4 was converted to a crystalline epoxy ether, 5, by the general method involving the use of sodium methoxide on an α-bromo ketone.[6] Hydroxy ketone 1 was prepared by the acid hydrolysis of epoxy ether 5. As the formation and hydrolysis of epoxy ethers are known to be stereospecific[7] and to yield hydroxy ketones with inversion at the α position, endo configuration for the hydroxyl group in the product was expected. That the hydroxy ketone 1 was indeed 2-hydroxy-2-benzoylnorbornane was shown by its reduction to a mixture of two vicinal diols with sodium borohydride followed by the cleavage of the mixture with sodium periodate to give benzaldehyde and norcamphor, which were isolated and characterized as their 2,4-dinitrophenylhydrazones.
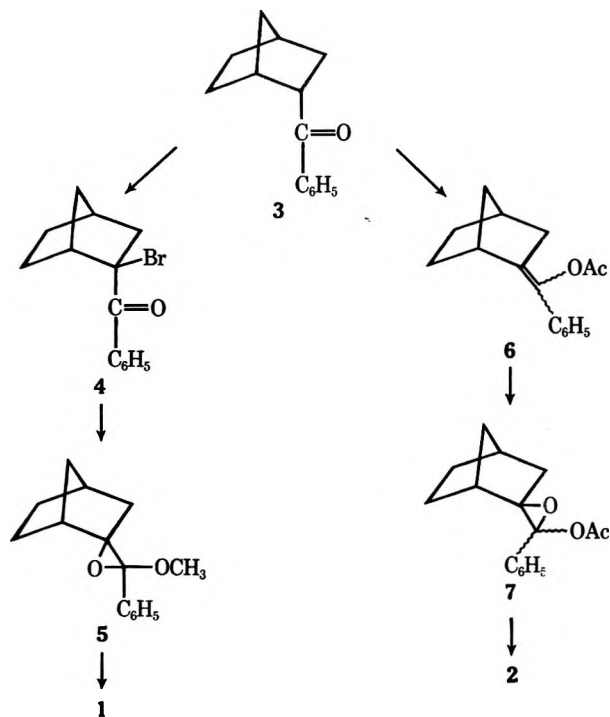
As the epimer of bromo ketone 4 was not available, the synthesis of hydroxy ketone 2 was accomplished by a different route. The most successful approach was through the enol acetate 6, which was prepared[8] as a diastereomeric mixture by the action of hot acetic anhydride on ketone 3 in the presence of p-toluenesulfonic acid as a catalyst. The enol acetate 6 was easily epoxidized on treatment with pure m-chloroperbenzoic acid at $-20°$ to give the epoxy acetate 7. Assignment of the exo configuration for the epoxide ring is based on the known stereospecificity of peracid attack on the double bond from the less hindered side,[9] in this case from the exo side.[5] The epoxy acetate 7 was thermally unstable and was found to rearrange to the corresponding acetoxy ketone under a variety of gas phase chromatographic conditions.[10] Although 7 could be hydrolyzed to 2 under acidic and basic conditions, the best results were obtained when methylamine was used for this reaction. The crystalline hydroxy ketone 2 thus prepared was different from 1, but had the same gross structure as shown by its reduction with sodium borohydride followed by cleavage with sodium metaperiodate to benzaldehyde and norcamphor, which were isolated and characterized as their 2,4-dinitrophenylhydrazones.

Rearrangements.—Hydroxy ketones 1 and 2 behaved very differently under rearrangement conditions. Compound 1 was converted completely to 8 when pyrolyzed neat at 175° for 2 hr. Rearrangement of 2 involved a more complex equilibrium and it required 14 hr at 214° for 2 to reach its lowest concentration, 7%. At this point, the major component in the reaction mixture was 9 (65%) and the remainder (28%) was another hydroxy ketone, 10. However, on prolonged heating, 10, which is perhaps the thermodynamic product, began to increase and was the major product (60%) after about 50 hr. The fact that 10 was produced more rapidly when pure 9 was rearranged under the same conditions and that the reaction mixture eventually reached the same equilibrium concentrations indicates that most, if not all, of 10 was formed from 9 by phenyl migration. However, a part of 10 being formed from 2 by C-1 migration cannot completely be ruled out.
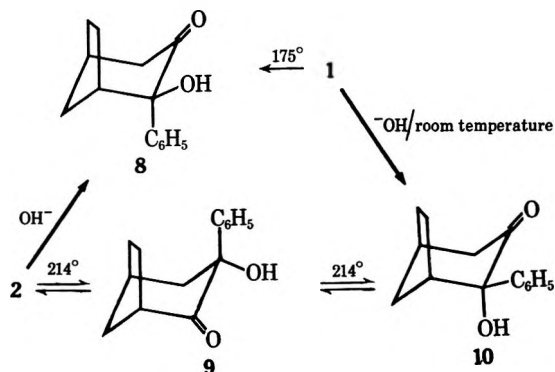
Hydroxy ketones 1 and 2 were also rearranged under basic conditions. Thus 1 was converted to 10 in over 90% yield when rearranged in the presence of sodium hydroxide in a water–dioxane solution at room temperature for 24 hr. A small amount of hydroxy ketone 8 was also formed in this reaction. Compound 2 rearranged extremely slowly under the same conditions and, when 2 was treated with sodium hydroxide in a water–dioxane solution at 62° for 6 days, only 10% of 8 was formed. Periodic examination of the reaction mixture by gas chromatography showed that no detectable amount of hydroxy ketone 10 was generated in this reaction. The absence of the formation of 10 indicated that it is not an intermediate in the base-catalyzed conversion of 2 to 8. Further, the formation of hydroxy ketone 1 can also be ruled out in this reaction because, if 1 were formed, it would have been converted to 10 under the same conditions. Rearrangement of 2 to 8 in 75% yield was accomplished by heating a water–dioxane solution of 2 under reflux for 8 hr in the presence of sodium hydroxide. The mother liquor from this reac-

(5) Electrophiles are known to attack similar olefins from the exo (less hindered) side. *Cf.* H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1963); H. C. Brown and W. J. Hammer, *J. Amer. Chem. Soc.*, **89**, 1524 (1967).

(6) See, for example, C. L. Stevens and E. Farkas, *J. Amer. Chem. Soc.*, **74**, 618 (1952).

(7) H. Patel and G. Hite, *J. Org. Chem.*, **30**, 4337 (1965).

(8) H. O. House and H. W. Thomson, *ibid.*, **26**, 3729 (1961).

(9) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 114.

(10) Epoxy acetates, in general, rearrange to acetoxy ketones easily. See, for example, ref 9, p 121.

tion did not show the presence of **10** but contained only **2** and **8** in the ratio 2:3 as indicated by gas chromatography.

Slow conversion of **10** to **8** was also observed under basic conditions. Thus treatment of **10** with sodium hydroxide in a water–dioxane solution at 62° for 6 days produced a mixture containing 8% of **8** and 92% of **10** as shown by gas chromatography. Although an infrared spectrum of the reaction mixture did not reveal the presence of **1** (as a carbonyl conjugated to a phenyl group), the formation of **1** in small quantities as an intermediate in this transformation cannot be ruled out. Hydroxy ketone **8**, which is apparently the thermodynamic product in base-catalyzed rearrangements, was also the major product when **1** was treated with sodium hydroxide in boiling ethanol. It may be noted here that no evidence was obtained for the interconversion of hydroxy ketones **1** and **2** under any rearrangement conditions. Also treatment of **8** with sodium hydroxide in a water–dioxane solution at 62° for 6 days did not produce any other hydroxy ketone, **1, 2, 9,** or **10**.

The structures of hydroxy ketones **8, 9,** and **10** were established by a combination of degradative, synthetic, and spectral data. Compounds **8** and **10** were shown to be α-hydroxy 3 ketones by their incorporation of three deuterium atoms on treatment with deuterium oxide in the presence of sodium deuteroxide. Only 3-keto compounds in this series are enolizable and therefore capable of deuterium exchange at the α carbon. This uptake of deuterium was easily observed by a comparison of the nmr spectra of the compounds before and after deuterations.

Hydroxy ketones **8** and **10** were shown to differ only in their configuration at C-2 by conversion to a common keto nitrile, **13**. Each hydroxy ketone was converted to its oxime (**11** and **12**), which underwent a second-order Beckmann rearrangement when treated with p-toluenesulfonyl chloride and base.[11] The resulting keto nitriles **13** were identical in all respects, including their crystalline semicarbazones.
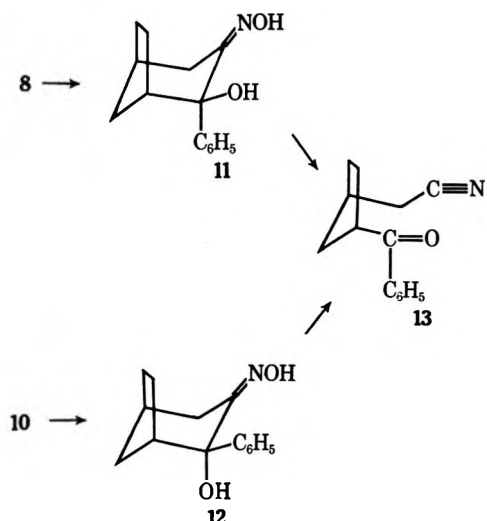
The exo configuration of the C-2 hydroxyl of **10** was established by its conversion to epoxide **19**. Hydroxy ketone **10**, when heated with methylamine, gave hydroxy imine **14**, which was reduced with sodium boro-

hydride to yield a crystalline amino alcohol,[12] **15**. Compound **15** was methylated under Clark–Eshweiler reaction conditions[13] and converted to the quaternary ammonium iodide **16**. Treatment of **16** with freshly prepared wet silver oxide in methanol at 25° yielded the
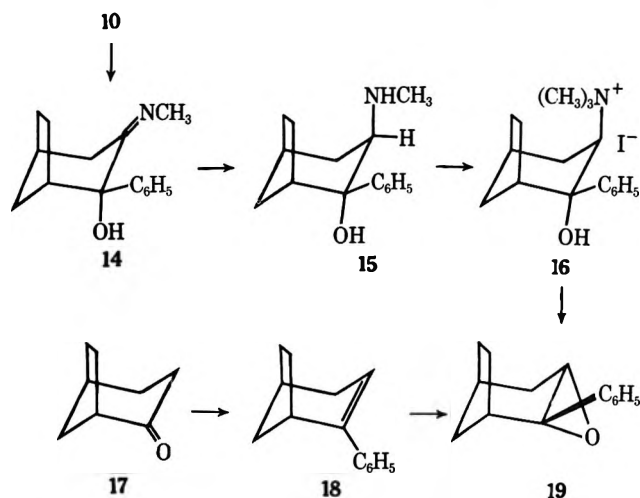
crystalline epoxide **19**. The structure of **19** was established by synthesizing it from 2-bicyclo[3.2.1]octanone[14] (**17**) by an unequivocal route. Ketone **17** was converted to olefin **18** by addition of phenyllithium followed by dehydration of the resultant alcohol. Epoxidation of **18** with m-chloroperbenzoic acid yielded **19** in 80% yield. The exo epoxide is expected in this reaction, as the peracid is known to attack similar olefins from the less hindered side.[9,15]

As the structure of **10** has now been assigned as exo-2-hydroxy-endo-2-phenyl-2-bicyclo[3.2.1]octanone, the structure of **8** must be endo-2-hydroxy-exo-2-phenyl-3-bicyclo[3.2.1]octanone, because it was established earlier that the two compounds are C-2 epimers. Further evidence to this effect was obtained by a comparison of their infrared spectra. Hydroxy ketone **10** exhibited both a sharp (free OH) absorption at 3583 cm⁻¹ and a broad (H-bonded OH) absorption at 3455 cm⁻¹, the relative intensity of the latter decreasing on dilution with carbon tetrachloride. This was indicative that the H bonding in **10** was intermolecular.[16] On the other hand, **8** exhibited only a broad OH absorption (intramolecular H bonding) that remained unchanged on dilution with carbon tetrachloride. This is in agreement with the fact that the hydroxyl group in **10** is held far away from the carbonyl preventing intramolecular H bonding, whereas the two groups in **8** are thrust close together, a perfect setting for a strong intramolecular H bonding.

In order to establish the structure of hydroxy ketone **9**, it was converted to the Schiff base **20** by treating it with methylamine. The hydroxy imine **20** was reduced with sodium borohydride to a crystalline amino alcohol,[12] **21**. Conversion of **21** to the quaternary am-

(11) For abnormal Beckman rearrangements of this type, see R. K. Hill, *J. Org. Chem.*, **27**, 29 (1962).

(12) Trans configuration is expected for this amino alcohol on the basis of previous findings in cyclohexane ring systems. See C. L. Stevens, H. T. Hanson, and K. G. Taylor, *J. Amer. Chem. Soc.*, **88**, 2769 (1966).

(13) R. N. Icke and B. B. Wisegarver, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 723.

(14) Available from Aldrich Chemical Co., Milwaukee, Wis.

(15) R. R. Saners, H. M. Howard, and H. Feilich [*Tetrahedron*, **21**, 983 (1965)] obtained 95% of exo epoxide by the reaction of peracetic acid on 2-bicyclo[3.2.1]octene.

(16) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 40.

monium iodide **22** followed by treatment with silver oxide yielded a quaternary ammonium hydroxide which on heating under vacuum gave a crystalline epoxide, **25**. This epoxide was also prepared by a different route as follows. Treatment of 3-bicyclo[3.2.1]octanone[17]
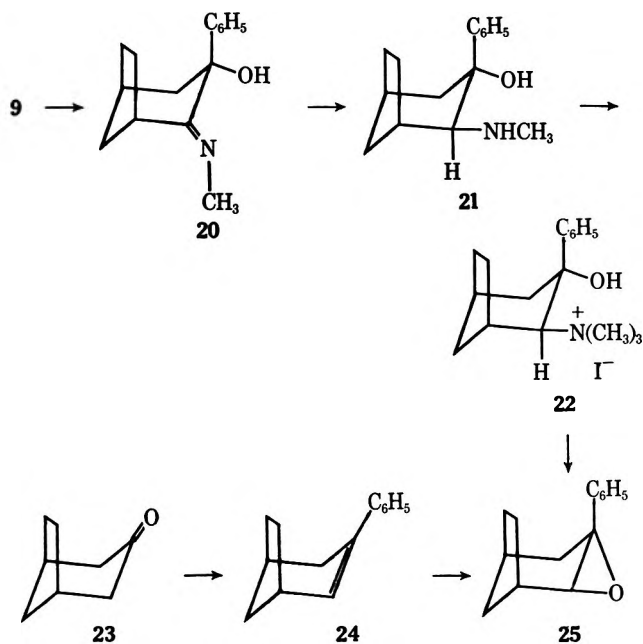
(23) with phenyllithium followed by dehydration gave olefin **24**. Reaction of **24** with *m*-chloroperbenzoic acid gave compound **25**. This indicates that the epoxide in **25** and hence the hydroxyl group in **9** have exo configuration.[15]

Discussion

The thermal rearrangements of **1** and **2** are stereo-specific and yield products predicted by a cyclic concerted mechanism. The configuration of the hydroxyl group is reversed when the rearrangement condition is switched from pyrolysis to base catalysis. Turner has explained similar findings in steroids on the basis of reagent control of carbonyl orientation in the transition state.[18] Thus in the thermal rearrangement, the carbonyl and hydroxyl groups are cisoid (**1a**) due to H bonding and the transfer of hydrogen and alkyl migration take place in a concerted fashion. On the other
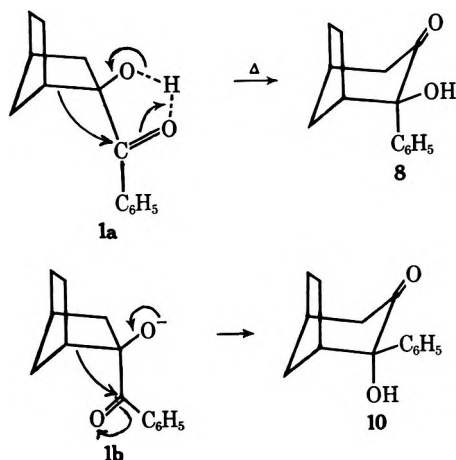
hand, alkali produces a negative charge on the hydroxyl oxygen and the charge–dipole repulsion causes the hydroxyl and carbonyl to be transoid in the active species **1b**, so that the rearrangement product has an inverted hydroxyl group. Because the carbonyl group is not held rigidly in the trans configuration, a small amount of **8** can be expected and was, in fact, detected in the base-catalyzed rearrangement of **1**.[19] In all the cases, at least part of the driving force for the rearrangement is derived from the strain relief realized in going from the [2.2.1] system to a [3.2.1] system.

In the thermal rearrangement of **1** and in the base-catalyzed rearrangement of both **1** and **2**, it is the 1,2 bond that migrates. In fact, electronic considerations should lead one to predict that the 1,2 bond should migrate in all the cases, since the more substituted carbon should be more effective in stabilizing the charge deficiency created at the carbonyl center. An immediate rationale for the migration of the 3,2 bond in the thermal rearrangement of **2** would be that this rearrangement is conformationally controlled and that the transition state which resembles a bridged chair (**2a**) leads to the product.[20] However, this argument fails to explain the fact that it is the 1,2 bond that migrates in the base-catalyzed rearrangement of **2**. If the answer was indeed conformational control, the migrating group should be C-3 in this rearrangement as well. In other words, the product (**8**) in the base-catalyzed rearrangement of **2** is formed through a bridged cyclohexane boat transition state (**2b**). However, a close examination of the boat conformation (**8a**) of **8** and the transition state (**2b**) leading to it reveals that the non-bonded interaction between the bulky phenyl group and the 2-carbon bridgehead is at a minimum in these structures. In the thermal rearrangement of **2**, this nonbonded interaction would be very high if C-1 was to migrate and the transition state would resemble a bridged cyclohexane boat (**10a**). It is probably to pre-

(17) Prepared according to a briefly outlined procedure in L. F. Fieser and M. Fieser, "Reagents in Organic Synthesis," Wiley, New York, N. Y., 1967, p 758.

(18) R. B. Turner, *J. Amer. Chem. Soc.*, **75**, 3484 (1953).
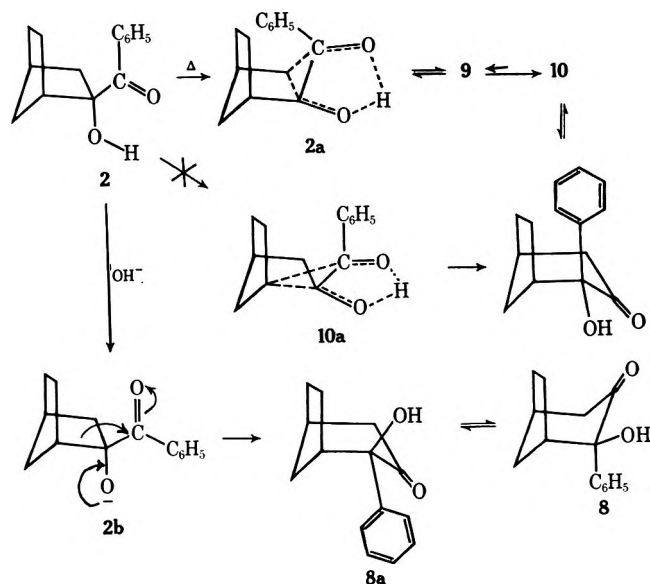
(19) *Cf.* D. K. Fukushima, S. Dobriner, M. S. Haffler, T. H. Kritchevsky, F. Herling, and G. Roberts, *J. Amer. Chem. Soc.*, **77**, 6585 (1955).

(20) N. L. Wendler, D. Taub, and R. Firestone [*Experientia*, **15**, 237 (1959)] first advanced a similar argument for explaining rearrangements in steroidal acyloins, but later came to the conclusion that conformational argument is less definitive and the rearrangement is more diverse in character. See N. L. Wendler, D. Taub, and R. W. Walker, *Tetrahedron*, **11**, 163 (1960), and also ref 1, p 1121.

vent this energetically unfavorable transition state that the less substituted C-3 migrates to form **9** under very strenuous conditions. The small amount of **10** obtained in this reaction is probably formed from **9** by phenyl migration. In conclusion, then, the more substituted C-1 migrates in all rearrangements where the steric interactions are not prohibitive. In the thermal rearrangement of **2**, the interaction between the phenyl and hydrogens of the 2-carbon bridgehead is so severe that C-3 migrates in preference to C-1.

This view is in agreement with the fact that, as expected for a higher energy process, the thermal rearrangement of **2** requires a higher temperature compared to the thermal rearrangement of **1**.

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Thin layer chromatography was performed using silica gel H from Brinkman Instruments on 5 × 15 cm plates. Gas chromatographic analyses were performed on an F & M Model 810 instrument with a flame ionization detector. Preparative gc was accomplished on an F & M Model 775 preparative gas chromatograph using a 0.75 in. × 8 ft, 4% ethylene glycol succinate column. Infrared spectra were obtained with a Perkin-Elmer 237B grating spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Varian A-60 spectrometer. All pK_a's were obtained in 50% methanol. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

exo-2-Bromo-*endo*-2-benzoylbicyclo[2.2.1]heptane (4).—A solution of 4.0 g (0.025 mol) of bromine in 10 ml of CCl₄ was added dropwise to a stirred solution of 5.0 g (0.025 mol) of 2-benzoylbicyclo[2.2.1]heptane[4] (3). After the addition was complete, the solvent was removed and the residue was crystallized from hexane to yield 6.10 g (90%) of **4**, mp 21–21.5°, ir (neat) 1670 cm⁻¹ (C=O).

Anal. Calcd for C₁₄H₁₅BrO: C, 60.23; H, 5.37; Br, 28.66. Found: C, 60.46; H, 5.50; Br, 28.38.

3'-Methoxy-3'-phenylspiro[norbornane-*endo*-1'-O-2,2'-oxirane] (5).—Fresh sodium (0.52 g, 0.0226 g-atom) was weighed under toluene and added to 30 ml of dry methanol. After the reaction of the sodium with methanol was complete and the solution had cooled to room temperature, bromo ketone 4 (3.72 g, 0.0133 mol) was added. The homogeneous solution was stirred at room temperature for 2 hr and then heated to reflux for 5 min. The solution was cooled and poured into a separatory funnel containing 150 ml of petroleum ether (bp 30–60°) and 100 g of ice. The separatory funnel was shaken until the ice melted, and the petroleum ether layer was separated and dried with anhydrous K₂CO₃. Removal of the petroleum ether gave a crystalline solid which was recrystallized from hexane to yield 2.7 g (88%) of **5**, mp 45–47°, ir (KBr) 1060 and 1080 cm⁻¹, no C=O or OH. A sample was recrystallized from hexane for analysis, mp 52.5–53.5°.

Anal. Calcd for C₁₅H₁₈O₂: C, 78.26; H, 7.83. Found: C, 78.54; H, 7.64.

exo-2-Benzoyl-*endo*-2-hydroxybicyclo[2.2.1]heptane (1).— Epoxy ether 5 (0.698 g, 0.003 mol) was dissolved in a mixture of 20 ml of methanol and 1 ml of water. One drop of concentrated HCl was added and the solution was allowed to stand at room temperature for 12 hr. Most of the methanol was removed and the product was extracted with ether after dilution with water. The ether solution was dried (Na₂SO₄) and evaporated to dryness and the residue was recrystallized from hexane to give 0.490 g (71%) of **1**, mp 59–60°, ir (CCl₄) 1685 cm⁻¹ (C=O).

Anal. Calcd for C₁₄H₁₆O₂: C, 77.78; H, 7.41. Found: C, 77.78; H, 7.34.

The structure of **1** was established as follows. The hydroxy ketone 1 (0.509 g, 0.0024 mol) was dissolved in methanol, and NaBH₄ (250 mg) was added in portions over a 6-hr period. The solution was allowed to stir at room temperature for 24 hr. The methanol was removed *in vacuo*, water was added, and the product was extracted with ether. Removal of ether yielded 0.499 g (96%) of a mixture of diols, mp 137–148°. The mixture (122

mg, 0.00065 mol) was cleaved with NaIO₄ (140 mg, 0.00065 mol) by refluxing in 10 ml of water for 3 hr. The reaction mixture was then distilled into a solution containing 2 equiv of 2,4-dinitrophenylhydrazine in ethanol. The mixture of 2,4-dinitrophenylhydrazones was filtered and separated by preparative tlc (ether–hexane, 1:1 system) to give 74 mg (68%) of norcamphor 2,4-DNP, mp 127–128°, and 61 mg (58%) of benzaldehyde 2,4-DNP, mp 237–239°. The identities of the DNPs were established by mixture melting point determinations with authentic samples.

2-Benzoylbicyclo[2.2.1]heptane Enol Acetate (6).—A mixture of 10.0 g (0.05 mol) of **3**, 100 ml of acetic anhydride, and 1.0 g *p*-toluenesulfonic acid was heated at 140° for 2 days, during which time 50 ml of a mixture of acetic acid and acetic anhydride was distilled off. Potassium acetate (1.0 g) was added to the cooled reaction mixture and the mixture was poured into 200 ml of water. The product was extracted with hexane and dried (Na₂SO₄) and the solvent was removed. The residue was distilled at 115–121° (0.5 mm) to give 10.9 g of 6, ir (neat) 1750 cm⁻¹ (C=O). Glc of this material showed that it was a mixture of two diastereomeric enol acetates and 9% starting ketone. An analytical sample was obtained by preparative glc.

Anal. Calcd for C₁₆H₁₈O₂: C, 78.90; H, 7.49. Found: C, 79.05; H, 7.43.

endo-2-Benzoyl-*exo*-2-hydroxybicyclo[2.2.1]heptane (2).—The impure enol acetate mixture, 6 (8.60 g, 0.0355 mol), was dissolved in 30 ml of chloroform and cooled to −5° in an ice–salt bath. *m*-Chloroperbenzoic acid (6.30 g, 0.0356 mol), which had been purified by washing with a phosphate buffer solution, was dissolved in 130 ml of chloroform and added dropwise to a stirred solution of the enol acetates. Addition was conducted at such a rate that the temperature did not exceed 0°. After addition was complete, the solution was placed in a freezer at −20° for 60 hr. The *m*-chlorobenzoic acid which had precipitated by this time was filtered from the chloroform solution and the filtrate was stirred with saturated bicarbonate solution for 2 hr at 0°. The chloroform layer was separated and dried (K₂CO₃), and the CHCl₃ was removed *in vacuo* to yield epoxy ester 7 as an oil (8.90 g, 98%), 90% pure by gc. This impure compound 7 (7.87 g, 0.0305 mol) was cleaved with methylamine in a sealed tube at 25° for 8 hr. After the reaction was complete, the methylamine was removed, and the residue was dissolved in ether, washed with water, dried (K₂CO₃), and evaporated to dryness. The product was crystallized from hexane to give 6.20 g (74%) of 2, mp 73.5–74.5°, ir (CCl₄) 1675 cm⁻¹ (C=O). A mixture melting point with hydroxy ketone 1 was depressed to 45–51°.

Anal. Calcd for C₁₄H₁₆O₂: C, 77.78; H, 7.41. Found: C, 77.68; H, 7.40.

Hydroxy ketone 2 (82 mg) was reduced with NaBH₄ in methanol to yield 70 mg (85%) of *exo*-2-hydroxy-*endo*-2-(α-hydroxybenzyl)bicyclo[2.2.1]heptane, mp 136.5–137.5°. *Anal.* Calcd for C₁₄H₁₈O₂: C, 77.03; H, 8.31. Found: C, 76.93; H, 8.34. This diol (105 mg, 0.00048 mol) was oxidized with 273 mg (0.00128 mol) of NaIO₄ in water and the products were isolated as their 2,4-dinitrophenylhydrazones as previously described. The yield of norcamphor 2,4-DNP was 88 mg (84%), mp 127–129°, and that of benzaldehyde 2,4-DNP was 80 mg (74%), mp 236–239°.

endo-2-Hydroxy-*exo*-2-phenyl-3-bicyclo[3.2.1]octanone (8). Thermal Rearrangement of 1.—Hydroxy ketone 1 (3.02 g, 0.014 mol) was heated neat at 175° under a N₂ atmosphere. The rearrangement was followed by ir and was found to be complete after 2 hr. The product was crystallized from hexane to give 2.20 g (73%) of 8, mp 58–59°, ir (CCl₄) 1712 (C=O), 3475 cm⁻¹ (OH). Gc analysis of the mother liquor using a 4 ft, 3% diglycerol on Chromosorb W column which cleanly separated hydroxy ketones 2, 8, 9, and 10 at 150° showed the presence of only 8 and no other hydroxy ketone.

Anal. Calcd for C₁₄H₁₆O₂: C, 77.78; H, 7.41. Found: C, 77.63; H, 7.47.

Treatment of 8 with D₂O in the presence of NaOD in dioxane provided evidence that three deuterium atoms were incorporated, as shown by nmr.

Thermal Rearrangement of *endo*-2-Benzoyl-*exo*-2-hydroxybicyclo[2.2.1]heptane (2).—A solution of 31 mg of 2 in 2 ml of tridecane was heated at 214° under a N₂ atmosphere. The rearrangement was followed by gc using a 4 ft 3% diglycerol column at 150°. After 14 hr, 2 reached its lowest concentration (7%), hydroxy ketone 9 was at its maximum (65%) and the remainder

was hydroxy ketone **10** (28%). On prolonged heating **10** increased and at 50 hr reached its maximum value (60%).

exo-3-Hydroxy-*endo*-3-phenyl-2-bicyclo[3.2.1]octanone (**9**).—A solution of 2.0 g (0.0092 mol) of hydroxy ketone **2** was heated at 225° in 30 ml of tridecane for 17 hr. The tridecane was removed *in vacuo* and the hydroxy ketones **9** and **10** were separated by preparative tlc (ether–hexane–benzene–MeOH, 10:10:10:1). The yield of **9** was 0.905 g (45%), ir (CCl₄) 1712 cm⁻¹ (C=O).

Anal. Calcd for C₁₄H₁₆O₂: C, 77.78; H, 7.41. Found: C, 77.68; H, 7.57.

Thermal Rearrangement of *exo*-3-Hydroxy-*endo*-3-phenyl-2-bicyclo[3.2.1]octanone (9).—A solution of 31 mg of **9** in 2 ml of tridecane was heated at 214° under a N₂ atmosphere. The rearrangement was followed by gc. Hydroxy ketone **10** began building up immediately. Equilibrium was reached after 25 hr. The equilibrium mixture consisted of 60% of **10**, 7% of **2**, and 23% of **9**.

exo-2-Hydroxy-*endo*-2-phenyl-3-bicyclo[3.2.1]octanone (**10**). Base-Catalyzed Rearrangement of **1**.—Hydroxy ketone **1** (5.20 g, 0.024 mol) was dissolved in 310 ml of freshly distilled dioxane and 2.8 g of NaOH in 170 ml of water was added. The homogeneous solution was stirred at room temperature for 30 hr. The dioxane was removed *in vacuo*, the product was extracted with ether, washed with water, and dried (K₂CO₃) and the solvent was removed to give 4.90 g (94%) of **10**.²¹ Recrystallization from hexane yielded 4.31 g (83%) of **10**, mp 100–101°, ir (CCl₄) 1712 (C=O), 3585 and 3455 cm⁻¹ (OH).

Anal. Calcd for C₁₄H₁₆O₂: C, 77.78; H, 7.41. Found: C, 77.78; H, 7.52.

Deuterium exchange with D₂O in the presence of NaOD showed that three deuterium atoms were incorporated in the molecule, as shown by nmr.

Base-Catalyzed Rearrangement of *endo*-2-Benzoyl-*exo*-2-hydroxybicyclo[2.2.1]heptane (2).—A solution of 2.0 g (0.0092 mol) of **2** in 75 ml of dioxane was mixed with 1.0 g of NaOH in 50 ml of water and the homogeneous solution was stirred at room temperature for 5 hr. As the ir spectrum indicated no reaction, the solution was heated under reflux. In about 8 hr, 90% of the starting material had disappeared and no more reaction was observed in another 2 hr. Most of the dioxane was removed *in vacuo* and the product was extracted with ether, washed with water, dried (K₂CO₃), and removed from the solvent. The residue was crystallized from hexane to give 1.53 g (75%) of **8**, mp 56–57°. Analysis of the mother liquor by gc showed that it consisted of hydroxy ketones **2** and **8** in the ratio 2:3.

A solution of 101 mg of **2** in 5 ml of dioxane was treated with a solution of 30 mg of NaOH in 2 ml of water at 62°. The slow rearrangement was followed by gc. After 6 days, the mixture showed 10% of **8** and 90% of **2**. No other hydroxy ketone was detected.

Base-Catalyzed Rearrangement of 10 to 8.—A solution of 101 mg of **10** in 5 ml of dioxane was treated with a solution of 30 mg of NaOH in 2 ml of H₂O at 62° and the rearrangement was followed by gc. After 6 days the mixture contained 92% of **10** and 8% of **8**. The solvents were evaporated and the residue was extracted with ether. An ir spectrum (CCl₄) did not show any peak at 1675 cm⁻¹, indicating that **1** was not present in any significant amount.

Base-Catalyzed Rearrangement of 1 in Boiling Ethanol.—A solution of 3.4 g (0.016 mol) of **1** in 50 ml of 95% EtOH was refluxed with 2.5 ml of a saturated solution of NaOH in EtOH for 2 days. The alcohol was removed *in vacuo*, the residue was extracted with ether, and the ether solution was decolorized by passing through a short column of fluorisil. The solution was evaporated to dryness and the residue was crystallized from hexane to give 1.0 g (30%) of **8**, mp 58–59°. The low yield in this reaction is probably due to base cleavage of the hydroxy ketones. The mother liquor contained **8** and **10** as shown by gc, and an ir spectrum (CCl₄) did not show any absorption at 1675 cm⁻¹.

Attempted Rearrangement of 8 under Base Catalysis.—A solution of 102 mg of **8** in 5 ml of dioxane was treated with 30 mg of NaOH in 2 ml of water at 62° and the reaction was followed by gc. No new product was formed for 6 days. Work-up of the mixture provided 81 mg (80%) of **8**, mp 57–58° after recrystallization from hexane.

endo-2-Hydroxy-*exo*-2-phenyl-3-bicyclo[3.2.1]octanone Oxime (**11**).—A mixture of 1.015 g (0.0047 mol) of **8**, 1.0 g of hydroxyl-

amine hydrochloride, 10 ml of absolute ethanol, and 10 ml of pyridine was heated on a steam bath for 3 hr. The solvents were removed *in vacuo*, the product was dissolved in ether, washed with 1.5 N HCl followed by water, and dried (K₂CO₃), and the solvent was evaporated. The residue was evaporatively distilled to give 0.752 g (69.3%) of **11**, which crystallized on standing, mp 82–88°.

Anal. Calcd for C₁₄H₁₇NO₂: C, 72.70; H, 7.41; N, 6.06. Found: C, 73.00; H, 7.40; N, 5.93.

exo-2-Hydroxy-*endo*-2-phenyl-3-bicyclo[3.2.1]octanone Oxime (**12**).—Hydroxy ketone **10** (1.465 g, 0.0067 mol) was mixed with 1.53 g of hydroxylamine hydrochloride, 10 ml of pyridine, and 10 ml of ethanol and heated on a steam bath for 3 hr. After removal of the solvents the residue was dissolved in ether, washed with dilute HCl, dried (K₂CO₃), and evaporated to dryness. The oily residue was crystallized from acetonitrile to give 0.79 g (50.5%) of **12**, mp 163–165°.

Anal. Calcd for C₁₄H₁₇NO₂: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.50; H, 7.49; N, 6.24.

3-Cyanomethylcyclopentyl Phenyl Ketone (13).—Oxime **11** (438 mg, 0.0019 mol) was shaken vigorously with 800 mg of *p*-toluenesulfonyl chloride and 400 mg of sodium hydroxide in 40 ml of water for 2 hr. The product was extracted with ether, dried (K₂CO₃), removed from the solvent, and evaporatively distilled to give 299 mg (73.8%) of **13** as a colorless oil, ir (neat) 1678 (C=O) and 2250 cm⁻¹ (C≡N).

Anal. Calcd for C₁₄H₁₅NO: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.77; H, 7.03; N, 6.50.

A small portion of **13** was converted to its semicarbazone, mp 122–124°.

Anal. Calcd for C₁₅H₁₈N₄O: C, 66.65; H, 6.71; N, 20.03. Found: C, 66.90; H, 6.80; N, 20.67.

Oxime **12** (204 mg, 0.00089 mol) was also converted to 151 mg (80%) of ketonitrile **13** under the above conditions. The ir spectra of the two samples of **13** were superimposable and their semicarbazones were identical in all respects.

exo-2-Hydroxy-*endo*-2-phenyl-3-bicyclo[3.2.1]octanone-*N*-methylimine (**14**).—A mixture of 414 mg (0.0019 mol) of hydroxy ketone **10**, 15 ml of anhydrous methylamine, and 3.0 g of K₂CO₃ was heated in a sealed tube at 110° for 45 hr. Filtration followed by evaporation of excess methylamine from the reaction mixture yielded 420 mg (95%) of **14** as an oil, ir (neat) 1645 (C=N), 3400 cm⁻¹ (OH). It was converted to a crystalline HCl salt, mp 160–162°, ir (KBr) 1680 cm⁻¹ (C=N), pKₐ 6.68.

Anal. Calcd for C₁₅H₂₀ClNO: C, 67.78; H, 7.57; N, 5.27. Found: C, 67.85; H, 7.53; N, 5.51.

exo-2-Hydroxy-*endo*-2-phenyl-*endo*-3-*N*-methylaminobicyclo[3.2.1]octane (**15**).—A solution of 420 mg (0.0018 mol) of **14** in 40 ml of methanol was reduced with 500 mg of NaBH₄ over an 18-hr period. Water was added and the mixture was heated at 60° for 30 min. Most of the methanol was removed *in vacuo*, and the product was extracted with ether and dried (K₂CO₃) and the ether removed. The residue was recrystallized from hexane to yield 306 mg (73%) of **15**, mp 78–79°.

Anal. Calcd for C₁₅H₂₁NO: C, 77.88; H, 9.15; N, 6.05. Found: 77.84; H, 9.23; N, 6.23.

A small portion of **15** was converted to the HCl salt, mp 228–230°, pKₐ 8.37.

Anal. Calcd for C₁₅H₂₂ClNO: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.15; H, 8.36; N, 5.34.

exo-2-Hydroxy-*endo*-2-phenyl-*endo*-3-*N,N,N*-trimethylammoniumbicyclo[3.2.1]octane Iodide (**16**).—A mixture of 221 mg (0.001 mol) of **15**, 220 mg of a 40% solution of formaldehyde, and 230 mg of a 90% solution of formic acid was heated on a steam bath for 12 hr. The excess formaldehyde and formic acid were removed and the product was extracted with ether after treatment with NaHCO₃ solution. The ether solution was dried (K₂CO₃) and the solvent was removed to give 199 mg of the dimethylamino alcohol, which was refluxed with 2 ml of methyl iodide in 5 ml of acetonitrile for 1 hr. After removal of the solvent *in vacuo*, the residue was crystallized from ethanol–ether to yield 236 mg (74%) of **16**, mp 215–216°.

Anal. Calcd for C₁₇H₂₆INO: C, 52.72; H, 6.77; N, 3.62. Found: C, 52.97; H, 6.63; N, 3.86.

endo-2-Phenyl-2-bicyclo[3.2.1]octene Oxide (**19**). A. From Quaternary Salt 16.—A solution of 150 mg (0.000388 mol) of **16** in 5 ml of MeOH was treated with 44 mg (0.0002 mol) of freshly prepared NaOH-free silver oxide at room temperature for 12 hr. The AgI was filtered off and the methanol was evap-

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(21) The mother liquor showed the presence of **8** by gc and did not show the presence of **1** or **2** by an ir spectrum.

orated to dryness to give 47 mg (61%) of epoxide **19**, mp 59.5–60.5°.

Anal. Calcd for $C_{14}H_{16}O$: 83.96; H, 8.05. Found C, 83.95; H, 8.06.

B. From 2-Phenyl-2-bicyclo[3.2.1]octene (18).—A solution of phenyllithium (10 ml, 0.02 mol) was added with stirring to an ethereal solution of 1.192 g (0.0096 mol) of 2-bicyclo[3.2.1]-octanone[14] (**17**) at −78° under a nitrogen atmosphere. After stirring for 1 hr, the mixture was warmed to room temperature, water was added, and the product was extracted with ether. After removal of the solvent, the residue was evaporatively distilled to give 1.260 g (65%) of 2-hydroxy-2-phenylbicyclo[3.2.1]-octane, which was dehydrated by azeotroping with toluene in the presence of *p*-toluenesulfonic acid to yield 860 mg (74.8%) of 2-phenyl-2-bicyclo[3.2.1]octene (**18**).

A solution of 860 mg of **18** in 50 ml of $CHCl_3$ was epoxidized using 850 mg of *m*-chloroperbenzoic acid. After refluxing for 14 hr the mixture was cooled and filtered, and the filtrate was washed with $NaHCO_3$ solution and dried (K_2CO_3). Removal of chloroform yielded 850 mg of an oil, 500 mg of which was purified by preparative tlc to give 140 mg of the epoxide **19**, mp 60–61°, identical in all respects with the epoxide obtained from **16**.

exo-3-Hydroxy-*endo*-3-phenyl-2-bicyclo[3.2.1]octanone-*N*-methylimine (**20**).—A mixture of 625 mg (0.00287 mol) of hydroxy ketone **9** and 10 ml of methylamine was heated at 110° in a sealed tube for 4 days. The excess methylamine was removed to give 650 mg (98%) of **20** as an oil, ir 3300 (OH) and 1660 cm⁻¹ (C=N). This material was converted to its HCl salt, 605 mg (85%), mp 259–260° dec, ir (KBr) 1675 cm⁻¹ (C=N), pK_a 7.70.

Anal. Calcd for $C_{15}H_{20}ClNO$: C, 67.78; H, 7.57; Cl, 13.34; N, 5.27. Found: C, 68.05; H, 7.74; Cl, 13.57; N, 5.33.

endo-2-*N*-Methylamino-*exo*-3-hydroxy-*endo*-3-phenylbicyclo-[3.2.1]octane (**21**).—A solution of 605 mg (0.00227 mol) of the HCl salt of **20** in 50 ml of anhydrous methanol was reduced with 1.0 g of $NaBH_4$ for 12 hr. Water (20 ml) was added to the reaction mixture, most of the methanol was removed *in vacuo*, and the amino alcohol was extracted with 1 *N* HCl. The acid solution was basified with NaOH, extracted with ether, dried (K_2CO_3) and removed from the solvent. The residue was recrystallized from hexane to give 500 mg (95%) of **21**, mp 106–107°.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.97; H, 8.99; N, 6.06.

endo-2-*N,N,N*-Trimethylammonium-*exo*-3-hydroxy-*endo*-3-phenylbicyclo[3.2.1]octane Iodide (**22**).—The conversion of 403 mg (0.00174 mol) of amino alcohol **21** to the quaternary salt **22** was accomplished under the same conditions as for the synthesis of **16**. The yield of **22** was 540 mg (80%), mp 190–191°.

Anal. Calcd for $C_{17}H_{26}INO$: C, 52.72; H, 6.77; I, 32.51; N, 3.62. Found: C, 52.47; H, 6.87; I, 32.77; N, 3.46.

endo-3-Phenyl-2-bicyclo[3.2.1]octene Oxide (**25**). A. From Compound 22.—A solution of 104 mg (0.00029 mol) of **22** in 5 ml of methanol was treated with 100 mg of freshly prepared wet silver oxide at room temperature for 5 hr. The precipitated AgI was removed by filtration and the filtrate was evaporated to dryness. The resultant quaternary hydroxide was sublimed at 60° (0.1 mm) to yield 44 mg (83%) of **25**, mp 28–29°.

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.70; H, 8.04.

B. From 3-Phenyl-2-bicyclo[3.2.1]octene (24).—3-Phenyl-2-bicyclo[3.2.1]octene (**24**) was prepared from 3-bicyclo[3.2.1]-octanone[17] (**23**) using essentially the same conditions for the synthesis of 2-phenyl-2-bicyclo[3.2.1]octene (**18**). A solution of 0.78 g (0.0042 mol) of **24** in 25 ml of $CHCl_3$ was refluxed with 0.90 g (0.0052 mol) of *m*-chloroperbenzoic acid for 90 min. The mixture was allowed to stand at room temperature for 12 hr and then cooled at −20° for 2 hr. The precipitated *m*-chlorobenzoic acid was removed by filtration and the filtrate was washed with $NaHCO_3$ solution. After drying (K_2CO_3), the $CHCl_3$ was removed to yield 655 mg (89%) of **25** as an oil which could be crystallized from hexane, mp 27–28°. The epoxide **25** obtained by both the routes were identical in all respects.

Registry No.—**1**, 34546-64-0; **2**, 34546-65-1; **4**, 34546-66-2; **5**, 34546-67-3; **6**, 34546-68-4; **8**, 34546-69-5; **9**, 34546-70-8; **10**, 34546-71-9; **11**, 34546-72-0; **12**, 34546-73-1; **13**, 34546-74-2; **13** semicarbazone, 34546-75-3; **14**, 34546-76-4; **15**, 34546-77-5; **15** HCl, 34546-78-6; **16**, 34546-79-7; **19**, 34546-80-0; **20** HCl, 34546-81-1; **21**, 34546-82-2; **22**, 34546-83-3; **25**, 34546-84-4.

Synthesis, Resolution, and Stereochemistry of 5-Hydroxy-10-alkyl-Δ¹(⁹)-2-octalones[1]

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Received October 14, 1971

The 5-hydroxy-10-methyl- (ethyl- and isopropyl-) Δ¹(⁹)-2-octalones (2) have been prepared and the corresponding phthalate half esters have been resolved by means of their brucine salts. From the ORD and CD data, (+)-5β-hydroxy-10β-alkyl-Δ¹(⁹)-2-octalones and (−)-5α-hydroxy-10α-alkyl-Δ¹(⁹)-2-octalones have been assigned the 5S,10S and 5R,10R configurations, respectively.

In connection with a current project dealing with the synthesis of optically active cyclic olefins,[1b] it became necessary to synthesize, resolve, and determine the absolute configuration of the title compounds before proceeding with this project. Syntheses of chiral steroid synthetic intermediates, such as 1 and 2, have been accomplished by resolution,[3–6] microbiological reductions,[7] and most recently by "chiral induction.[8]" In view of the various diversified routes of resolution, it was deemed desirable to find a simple, suitable chemical resolution of 2 and to attempt their structural correlation *via* ORD and CD.

The starting 2-methyl-[9] and 2-ethyl-[10]-1,3-cyclohexanediones were prepared by the previously outlined routes. The 2-isopropyl-1,3-cyclohexanedione was synthesized by an improved five-step sequence of Bhattacharyya[11] in an overall 30% yield (Scheme I). The application of this scheme for the synthesis of 2-*tert*-butyl-1,3-cyclohexanedione was successful until the terminal cyclization stage. None of the desired product was isolated; the details of this reaction course will be published elsewhere.

(1) (a) Part 1. Chiral Cyclic Olefins. (b) Presented in part at the Southwest Regional Meeting of the American Chemical Society, Tulsa, Okla., Dec 1969, ORGN 30; and 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, ORGN 33.

(2) To whom correspondence should be addressed.

(3) L. Velluz, G. Nominé, G. Amiard, V. Torelli, and J. Cérède, *C.R. Acad. Sci.*, **257**, 3086 (1963).

(4) Z. G. Hojos, D. R. Parrish, and E. P. Oliveto [*Tetrahedron*, **24**, 2039 (1968)] have recently resolved the related 7,7a-dihydro-1-hydroxy-7a-methyl-5(6H)-indanone (i).

(5) W. R. Adams, O. L. Chapman, J. B. Sieja, and W. J. Welstead, Jr., *J. Amer. Chem. Soc.*, **82**, 162 (1966), partially resolved 10-methyl-Δ¹(⁹)-2-octalone (ii) by fractional recrystallization of the *d*-camphor-10-sulfonic acid salt of the pyrrolidine enamine of ii.

i   ii
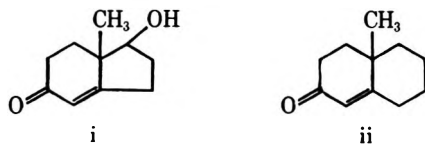
(6) Also see A. J. Speziale, J. A. Stevens, and Q. E. Thompson, *ibid.*, **76**, 5011 (1954).

(7) (a) V. Prelog and W. Acklin, *Helv. Chim. Acta*, **39**, 748 (1956); (b) W. Acklin, V. Prelog, and D. Zäch, *ibid.*, **41**, 1416, 1424, 1428 (1958); (c) V. Prelog, U. S. Patent 2,833,694 (1959); *Chem. Abstr.*, **53**, 3179d (1959); (d) V. Prelog, Swiss Patent 366,530 (1964); *Chem. Abstr.*, **60**, 431c (1964); (e) H. H. Weston, *Helv. Chim. Acta*, **47**, 575 (1964).

(8) U. Eder, G. Sauer, and R. Weichert, *Angew. Chem., Int. Ed. Engl.*, **10**, 496 (1971).

(9) (a) H. Schick, G. Lehmann, and G. Hilgetag, *ibid.*, **6**, 80 (1967); (b) H. Schick and G. Lehmann, *J. Prakt. Chem.*, [4] **38**, 361 (1968); (c) A. B. Mekler, S. Ramachanchan, S. Swaninathan, and M. S. Newman, *Org. Syn.*, **41**, 56 (1961).

(10) N. Stetter and W. Diericks, *Ber.*, **85**, 61 (1952).

(11) P. C. Bhattacharyya, *J. Indian Chem. Soc.*, **42**, 467 (1965).

SCHEME I
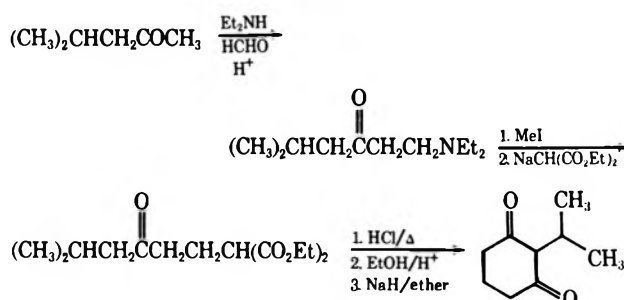
The Robinson annelation sequence, that is, the Michael addition of methyl vinyl ketone to 2-methyl-1,3-cyclohexanedione followed by dehydration, gave (50%) the known (±)-methyl bicyclic diketone **1a**.[12] An alternate route utilizing the intermediate pyrrolidine enamine was used for the synthesis of racemic **1b** and **1c**. This latter route seems to be preferable for the bulkier 2-alkyl substituted 1,3-cyclohexanediones in order to increase the activity of the carbonyl compound toward the initial Michael-type addition.

The saturated carbonyl group **1a** has been stereoselectively reduced with either sodium borohydride[13] or lithium tri-*tert*-butoxyaluminum hydride to afford the α,β-unsaturated keto alcohol **2a** (Scheme II). Although **2a** is an oil,[14] both **2b** and **2c** are crystalline solids. The stereochemistry of the hydroxyl group in **2a** has been adequately established, since the attacking hydride will approach the 1-keto group from the less hindered α side; therefore, the β-equatorial configuration of the hydroxyl function in **2b** and **2c** seems justifiable. The nmr spectra of **2** also showed a doublet of doublets (J = 7 and 7 Hz) for the >CHOH proton. These data correspond to the β-equatorial assignment of the hydroxyl group and are in rather good agreement with nmr data reported for steroids.[15]

The resolution of **2** can be accomplished by their initial conversion to the corresponding hydrogen phthalates by standard procedures, and then subsequent reso-

(12) (a) S. Swaminathan and M. S. Newman, *Org. Syn.*, **41**, 38 (1961); (b) M. S. Newman and A. B. Mekler, *J. Amer. Chem. Soc.*, **82**, 4039 (1960); (c) S. Swaminathan and M. S. Newman, *Tetrahedron*, **2**, 88 (1958); (d) P. Wieland and K. Miescher, *Helv. Chem. Acta*, **33**, 2215 (1950).

(13) (a) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2680 (1960); (b) J. D. Cocker and T. G. Halsall, *ibid.*, 3441 (1957).

(14) The anhydrous oil solidified on exposure to moisture; the hydrate can be recrystallized with difficulty from ether,[13a] mp 58–59°.

(15) D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, **86**, 2742 (1964).

lution as a typical carboxylic acid.[16] Although Pasteur's method of resolution is commonly employed, the use of chiral amines, *e.g.*, (+)-1-phenylethylamine, (+)-1-(1-naphthyl)ethylamine, and dehydroabietyl amine,[17] failed in our hands to afford separable diastereoisomeric salts. The successful resolution of **3** was accomplished with the use of brucine in acetone, or less preferably benzene. After several recrystallizations, nearly pure specimens of the diastereoisomeric salts of **3a** can be achieved, although after one recrystallization *ca.* 50% optical purity is obtained. No attempts were made herein to prepare pure samples of these salts. Simple extraction of the alkaloid with cold dilute hydrochloric acid regenerated the chiral phthalate half esters (+)- or (−)-**3**.

SCHEME II

a, R = CH₃
b, R = CH₃CH₂
c, R = (CH₃)₂CH
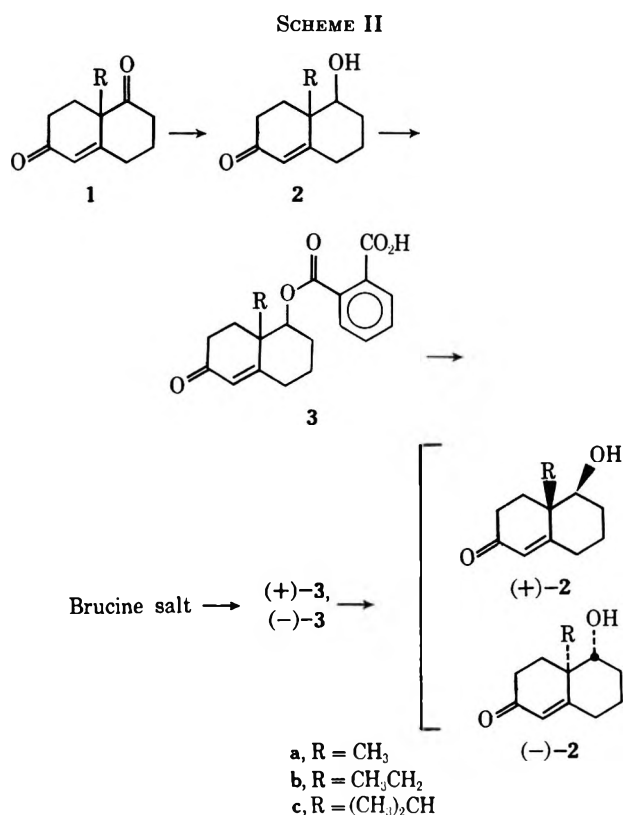
The removal of the phthalate group is a facile process *via* treatment with dilute aqueous base. It was found, however, that on prolonged contact with base the freed chiral **2** easily rearranged to 1-hydroxy-4-alkyl-5,6,7,8-tetrahydronaphthalene, which is the product of a diene–phenol-type rearrangement.[18] To avoid this unwanted side reaction, a heterogeneous mixture of dilute aqueous base containing **3** and ether was rapidly stirred at 0–10° with constant addition and removal of the product contained in the ether extract. After several minutes of such continuous extraction, the product was isolated in high yield and contaminated with little or no rearranged material.

Structural Correlations.—As alluded to earlier,[19] the characteristic shapes of ORD, as well as CD, curve of a given α,β-unsaturated ketone should be governed predominantly by the unsaturated chromophore rather than by any additional substituents unless certain conformational factors interfere. Since the structure of (+)-**2a** appears to be substantiated[7a,20] as (5S,10S)-5-hydroxy-10-methyl-Δ¹⁽⁹⁾-2-octalone and the ORD curve measured,[20] it could serve as an excellent standard for the assignment of the configurations of the angular alkyl function in **2b** and **2c**.
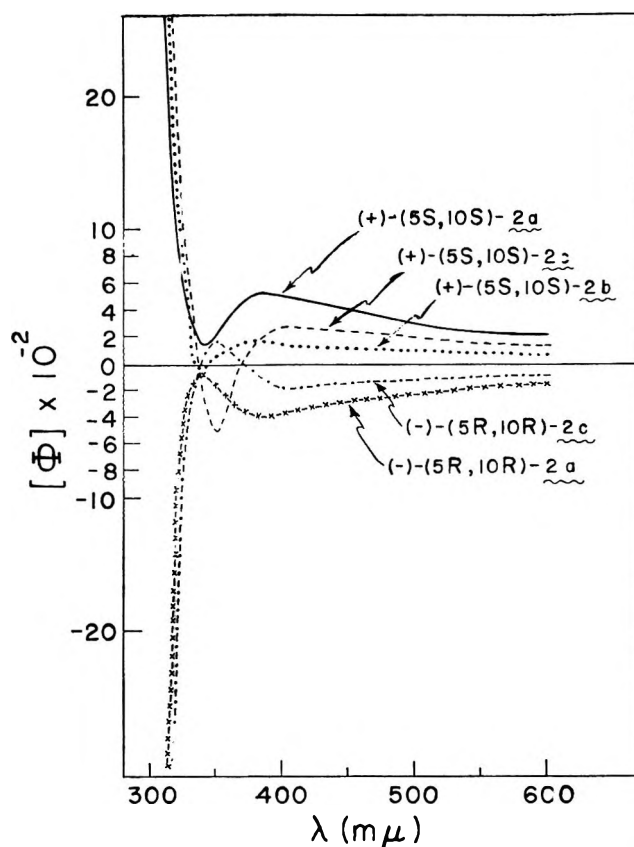
Figure 1.—Optical rotatory dispersion curves of 5-hydroxy-10-alkyl-Δ¹⁽⁹⁾-2-octalones (methanol).

In Figures 1 and 2 are reproduced the ORD and CD curves, respectively, of (+)-**2** and (−)-**2**. Since (+)-**2b** and (+)-**2c** differ only in the size of the angular alkyl substituent, it is evident that except for some amplitude changes, the ORD and CD curves are nearly identical with those of (+)-**2a**, thus establishing the congeneric absolute configurations. Similarly, the dispersion curves of (−)-**2** are of a mirror image relationship to that of (+)-**2a** and, therefore, possess the opposite configuration.

From the ORD and CD curves, (+)-**2** and (−)-**2** are assigned the (5S,10S) and (5R,10R) configurations, respectively.

(16) For a recent review concerning the methods of optical resolution, see P. H. Boyle, *Quart. Rev., Chem. Soc.*, **25**, 323 (1971).

(17) W. J. Gottstein and L. C. Cheney, *J. Org. Chem.*, **30**, 2072 (1965), described the isolation of dehydroabietyl amine from Amine D, which was generously supplied by Hercules Powder Co.

(18) J. B. Jones, J. D. Leman, and P. W. Marr, *Can. J. Chem.*, **49**, 1604 (1971), and references cited therein.

(19) See (a) C. Djerassi, *Bull. Soc. Chim. Fr.*, 741 (1957); (b) C. Djerassi, "Optical Rotatory Dispersion: Application to Organic Chemistry," McGraw-Hill, New York, N. Y., 1960, p 83; (c) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 191.

(20) C. Djerassi, J. Osiecki, and W. Herz, *J. Org. Chem.*, **22**, 1361 (1957).
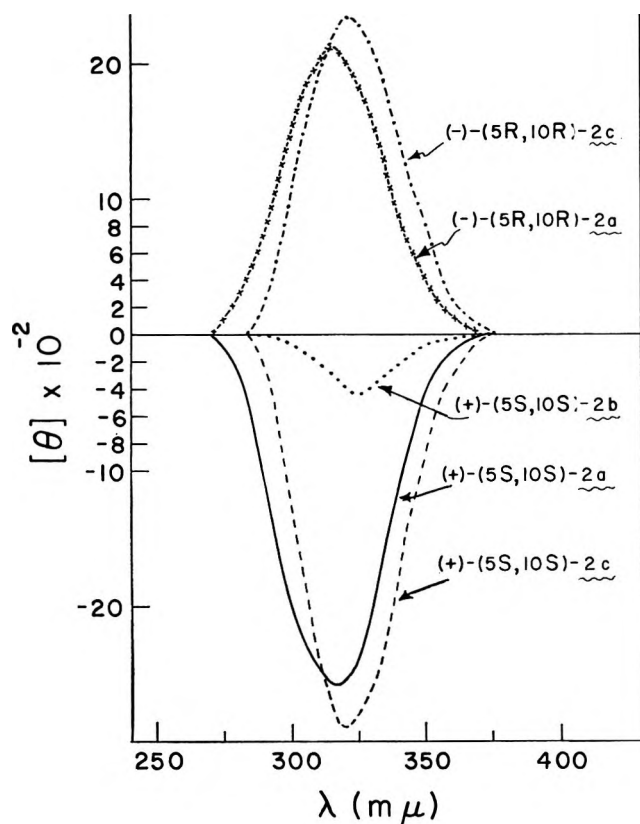
Figure 2.—Circular dichroism curves of 5-hydroxy-10-alkyl-$\Delta^{1(9)}$-2-octalones (methanol).

Experimental Section[21]

1,6-Dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (1a) was prepared from 2-methyl-1,3-cyclohexanedione,[9] mp 204–206° (lit.[9b] mp 204–206°), as previously outlined,[11] mp 49–50° (lit.[12a] mp 47–50°).

(±)-5-Hydroxy-10-methyl-$\Delta^{1(9)}$-2-octalone (2a) was prepared (89%) by the method of Boyce and Whitehurst,[13a] bp 135–136° (0.05 mm) [lit.[13] bp 140° (0.25 mm)].

2-Ethyl-1,3-cyclohexanedione was prepared[10] (31%) by alkylation of 1,3-cyclohexanedione with ethyl iodide, mp 172–175° (lit.[10] mp 178°).

1,6-Dioxo-8a-ethyl-1,2,3,4,6,7,8,8a-octahydronaphthalene.—A solution of 20 g (0.143 mol) of 2-ethylcyclohexanedione, 12 g (0.169 mol) of pyrrolidine, and 100 ml of benzene was refluxed for 12 hr using a Dean–Stark trap. The benzene and excess pyrrolidine were then removed under reduced pressure. To the crude air-sensitive enamine was added 15 g (0.212 mol) of methyl vinyl ketone in 100 ml of benzene followed by a solution of 20 ml of acetic acid, 20 ml of water, and 10 g of sodium acetate. The mixture was refluxed with stirring for 6 hr under nitrogen. The reaction mixture was cooled and extracted with benzene. The extract was washed with four 10-ml portions of 10% aqueous hydrochloric acid, then once with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated to give 14 g of an orange oil. The oily crude product was chromatographed on 200 g of Merck alumina eluting with 10% ether in petroleum ether (bp 30–60°) and upon *in vacuo* concentration gave a semisolid, which was vacuum distilled giving (52%) a colorless, crystalline diketone, mp 58–62°. Recrystallization from ether–petroleum ether (bp 30–60°) gave an analytical sample of **1b**, mp 66–67° (lit.[22] mp 67.5–68.5°).

(21) Melting points were recorded in sealed capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 137-B spectrophotometer. Nmr spectra were determined on a Varian Associates Model A-60A spectrometer; chemical shifts are given in parts per million relative to TMS as an internal standard. Optical rotatory dispersion (ORD) and circular dichroism (CD) spectra were determined on a Durrum-Jasco spectropolarimeter, Model J-20. Analyses were performed by Mr. R. Seab in these laboratories.

(22) M. Los, U. S. Patent 3,321,489 (1967); *Chem. Abstr.*, **68**, 195442c (1968).

(±)-5-Hydroxy-10-ethyl-$\Delta^{1(9)}$-2-octalone (2b) was prepared (92%) by the ethanolic sodium borohydride reduction of the diketone **1b** following the procedure of Boyce and Whitehurst:[13a] bp 140–144° (0.05 mm); mp 87–88° [lit.[22] bp 165° (0.8 mm); mp 88.0–89.5°]; ir (neat) 1670 (C=O), 1625 (C=C), and 3450 cm⁻¹ (OH); nmr (CCl₄) δ 0.96 (CH₃CH₂–, t, J = 7 Hz, 3 H), 3.7 (CH₃CH₂–, q, J = 7 Hz, 2 H), 5.99 (–CH=C<, s, 1 H), and 3.8 (CHOH, dd, J = 7.7 Hz, 1 H).

Preparation of 2-Isopropyl-1,3-cyclohexanedione. A.—A solution of 4-methyl-2-pentanone (75 g, 0.75 mol), diethylamine hydrochloride (106 g), paraformaldehyde (29 g), concentrated hydrochloric acid (1.5 ml), and absolute ethanol (600 ml) was refluxed for 6 hr with stirring under nitrogen. The yellow solution was diluted with water (500 ml) and extracted with ether (2 × 250 ml); then the aqueous solution was neutralized with sodium hydroxide (200 ml, 5 N) and extracted with ether (3 × 25 ml each). The ethereal extract was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*, and distillation afforded (60%) the pungent-smelling 1-diethylamino-5-methylhexan-3-one, bp 69–76° (1–2 mm) [lit.[11] bp 93–94° (6 mm)].

B.—An ethereal solution of the above 1-diethylamino-5-methylhexan-3-one and excess methyl iodide was stirred for 7 hr at room temperature. The crude quaternary iodide was separated and dried *in vacuo*, yield 195 g. Further purification was not attempted nor necessary.

C.—The above crude methiodide (195 g, 0.595 mol) dissolved in 100 ml of anhydrous ethanol was added dropwise to diethyl sodiomalonate, prepared from diethyl malonate (105.6 g, 0.66 mol) and sodium (15.8 g) in 400 ml of absolute ethanol. After the addition, the mixture was heated with stirring for 10 hr. The reaction mixture was poured into ice water and extracted with chloroform, dried over anhydrous magnesium sulfate, and concentrated, giving (62%) an yellow oil, which was vacuum distilled to afford the keto diester: bp 143–152° (1–2 mm) [lit.[11] by 145–150° (4 mm)]; nmr (CCl₄) δ 0.92 (Me₂CH, d, J = 7 Hz, 6 H), 1.25 (CH₃CH₂O–, t, J = 7 Hz, 6 H), 3.52 (Me₂CH–, t, J = 7 Hz, 1 H), and 4.16 (CH₃CH₂O, q, J = 7 Hz, 4 H).

D.—A solution of the above keto diester (100 g, 0.37 mol), 200 ml of concentrated hydrochloric acid, and 200 ml of water was refluxed for 48 hr under nitrogen. The reaction mixture was extracted with methylene chloride; then the organic layer was extracted with a 10% sodium hydroxide solution. The aqueous extract was acidified with concentrated hydrochloric acid and extraction with methylene chloride to give the crude keto acid, nmr (CDCl₃) δ 0.88 (Me₂CH–, d, J = 7 Hz, 6 H) and 11.25 (CO₂H, s, 1 H). After concentration, the crude keto acid was dissolved in 500 ml of absolute ethanol with 1 g of *p*-toluenesulfonic acid, and then refluxed for 24 hr. After removal of the excess ethanol, the oily residue was vacuum distilled, affording (92%) ethyl 5-keto-7-methyloctanoate: bp 93–97° (1.0–1.5 mm) [lit.[11] bp 120–122° (5 mm)]; nmr (CDCl₃) δ 0.90 (Me₂CH–, d, J = 7 Hz, 6 H), 1.21 (CH₃CH₂O–, t, J = 7 Hz, 3 H), and 4.15 (CH₃CH₂O, q, J = 7 Hz, 2 H).

E.—An ethereal solution of ethyl 5-keto-7-methyloctanoate (90 g, 0.5 mol) was added dropwise to a stirred suspension of 30 g (50% oil dispersion, 0.75 mol) of sodium hydride in anhydrous diethyl ether (400 ml). The stirred mixture was refluxed for 8 hr under nitrogen. The reaction mixture was cooled to 5° and acidified with dilute hydrochloric acid. The ethereal layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated to give (80%) a white solid, which was recrystallized from benzene giving analytically pure 2-isopropyl-1,3-cyclohexanedione: mp 150–151° (lit.[11] mp 140–143°); nmr (D₂O) δ 0.75 and 1.1 (Me₂CH, d, J = 7 Hz, 6 H).

Anal. Calcd for C₉H₁₄O₂: C, 70.13; H, 9.09. Found: C, 70.19; H, 9.04.

1,6-Dioxo-8a-isopropyl-1,2,3,4,6,7,8,8a-octahydronaphthalene.—The procedure used for **1b** was followed giving (58%) the crude diketone, which was vacuum distilled affording a pale yellow oil, bp 140–150° (0.5 mm). Recrystallization from anhydrous diethyl ether gave analytically pure diketone: mp 64–65°; nmr (CDCl₃) δ 0.85 and 0.99 (Me₂CH, J = 7 Hz, d, 6 H), 5.97 (–CH=C<, s, 1 H), and 1.5–3.0 (m, 11 H); ir (CHCl₃) 1720, 1670, and 1620 cm⁻¹.

Anal. Calcd for C₁₃H₁₈O₂: C, 75.73; H, 8.76. Found: C, 75.53; H, 8.59.

(±)-5-Hydroxy-10-isopropyl-$\Delta^{1(9)}$-2-octalone was prepared (93%) in a manner similar to that for the reduction of **1b**: bp

162–166° (1.3 mm); mp 85–87° from ether–petroleum ether; nmr (CDCl₃) δ 0.85 and 1.22 (Me₂CH, d, J = 7 Hz, 6 H), 3.0 (–OH, s, 1 H), 3.82 (>CHOH, dd, J = 7.5 Hz, each, 1 H), and 5.91 (HC=C<, s, 1 H); ir (neat) 3500, 1665 cm⁻¹.

Anal. Calcd for C₁₃H₂₀O₂: C, 75.01; H, 9.68. Found: C, 75.01; H, 9.54.

(±)-5-Hydroxy-10-methyl-Δ¹(⁹)-2-octalone Hydrogen Phthalate.—A solution of phthalic anhydride (68.8 g, 0.46 mol), (±)-5-hydroxy-10-methyl-Δ¹(⁹)-2-octalone (80 g, 0.445 mol), and anhydrous pyridine (160 ml) was stirred under nitrogen at room temperature for 24 hr. The solution was poured onto ice and acidified with 6 N hydrochloric acid. The white precipitate was filtered, dried *in vacuo* overnight, and recrystallized from acetone, affording the crystalline hydrogen phthalate: 109.2 g; mp 205–206°; nmr (CDCl₃) δ 1.31 (CH₃–, s, 3 H), 4.9 (>CHO, dd, J = 6, 6 Hz, 1 H), 5.88 (HC=C<, s, 1 H), 7.5–8.0 (Cₐᵣₒₘₐₜᵢc H, m, 4 H), and 9.04 (–CO₂H, s, 1 H).

Concentration of the mother liquor gave an additional 7.9 g, mp 189–206°, of the half ester. The fractions were combined (82%) and used without further purification.

Anal. Calcd for C₁₉H₂₀O₅: C, 69.50; H, 6.15. Found: C, 69.84; H, 6.58.

(±)-5-Hydroxyl-10-ethyl-Δ¹(⁹)-2-octalone hydrogen phthalate was prepared in a similar manner: mp²³ 196–206°; nmr (CDCl₃) δ 0.89 (CH₃CH₂–, t, J = 7 Hz, 3 H), 3.8 (CH₃CH₂–, m, 2 H), 5.13 (>CHO, dd, J = 7, 7 Hz, 1 H), 6.00 (HC=C<, s, 1 H), and 7.3–8.0 (Cₐᵣₒₘₐₜᵢc H, m, 4 H).

(±)-5-Hydroxy-10-isopropyl-Δ¹(⁹)-2-octalone hydrogen phthalate was prepared in a similar manner: mp²³ 204–208°; nmr (CDCl₃) δ 0.85 and 1.08 (Me₂CH–, d, J = 7 Hz, 6 H), 5.29 (>CHO–, dd, J = 7, 7 Hz, 1 H), 6.00 (HC=C<, s, 1 H), and 7.5–8.0 (Cₐᵣₒₘₐₜᵢc H, m, 4 H).

Resolution of (±)-5-Hydroxy-10-methyl-Δ¹(⁹)-2-octalone Hydrogen Phthalate with Brucine.—A solution of brucine (204 g) in 2 l. of hot acetone was added to a solution of (±)-methyl half ester [(±]-3a, 116 g] in hot acetone (1 l.). The solution was concentrated to 1 l. and allowed to slowly cool overnight to ambient temperature. The resultant white solid was filtered and dried *in vacuo*, giving (49%) the brucine salt of the (±)-methyl phthalate, mp 124–126° dec. Further recrystallization from benzene did not appreciably increase the melting point, but from acetone the melting point was increased, mp 146–148° dec.

The combined mother liquors from the recrystallization of the brucine salt of the (+)-methyl half ester were concentrated *in vacuo*, affording the crude brucine salt of the enantiomeric methyl half ester, as a semicrystalline solid. Further recrystallization was not attempted.

A. (+)-(5S,10S)-5β-Hydroxy-10β-methyl-Δ¹(⁹)-2-octalone Hydrogen Phthalate [(+)-3a].—The brucine salt of the (+)-methyl hydrogen phthalate (135 g) dissolved in acetone (1.2 l.) at 20°. The acetone was removed *in vacuo*, affording an aqueous suspension, which was filtered, washed with water, and dried. The crude solid was recrystallized from acetone to give (+)-5β-hydroxy-10β-methyl-Δ¹(⁹)-2-octalone hydrogen phthalate, 92% recovery, mp 192–196°, [α]²⁵₆₀₀ +17° (MeOH). Recrystallization from acetonitrile, instead of acetone, gave poor results.

(+)-(5S,10S)-5β-Hydroxy-10β-methyl-Δ¹(⁹)-2-octalone [(+)-2a].—A mixture of 47 g (0.143 mol) of (+)-methyl hydrogen phthalate dissolved in 5 N sodium hydroxide and ether (25 ml) was rapidly agitated at 15–20°. After several minutes, the ether was removed and additional ether was added to the basic solution. The ethereal extracts were stirred over 0.1 N hydrochloric acid until extraction procedure was complete; this extraction was continued every 5 min for 1 hr. The combined extracts were washed with a dilute sodium bicarbonate solution, water, and a saturated salt solution and then dried over an-

hydrous magnesium sulfate. After concentration, the residual oil was vacuum distilled to give the (+)-methyl hydroxy ketone: yield 14.0 g (0.078 mol); bp 128–131° (0.04 mm); [α]²⁵₆₀₀ +115° (MeOH); optical purity²⁴ 55%; ORD data, see Figure 1; CD data, see Figure 2.

B. (–)-(5R,10R)-5α-Hydroxy-10α-methyl-Δ¹(⁹)-2-octalone hydrogen phthalate [(–)-3a] was recovered in an identical manner to the corresponding levorotary brucine salt: 83% recovery; mp 200–208° (acetone); [α]²⁵₆₀₀ –105° (MeOH).

(–)-(5R,10R)-5α-Hydroxy-10α-methyl-Δ¹(⁹)-2-octalone [(–)-2a] was recovered from the corresponding phthalate as outlined for the (+) isomer: yield 16 g; bp 120–130° (0.075 mm); [α]²⁵₆₀₀ –84° (MeOH); optical purity²⁴ 41%; ORD data, see Figure 1; CD data, see Figure 2.

Resolution of (±)-5-Hydroxy-10-ethyl-Δ¹(⁹)-2-octalone Hydrogen Phthalate with Brucine.—The general procedure used for the resolution of 3a was followed using acetone solvent. No resolution could be effected if benzene was used as solvent.

(+)-(5S,10S)-5β-Hydroxy-10β-ethyl-Δ¹(⁹)-2-octalone hydrogen phthalate was isolated as previously described, mp 196–206° (acetone), [α]²⁵₆₀₀ +27.2° (MeOH).

(+)-(5S,10S)-5β-Hydroxy-10β-ethyl-Δ¹(⁹)-2-octalone [(+)-2b] was obtained by careful saponification of the phthalate: bp 140–147° (0.06 mm); mp 74–78° (ether–petroleum ether); [α]²⁵₆₀₀ +8.6° (MeOH); ORD data, see Figure 1; CD data, see Figure 2.

Resolution of (±)-5-Hydroxyl-10-isopropyl-Δ¹(⁹)-2-octalone Hydrogen Phthalate with Brucine.—The general procedure outlined above was followed using acetone. The brucine salt of 3c crystallized, mp 145–155° dec (acetone).

A. (–)-(5S,10R)-5β-Hydroxy-10β-isopropyl-Δ¹(⁹)-2-octalone hydrogen phthalate was isolated from the brucine salt of 3c as above described. mp 200–210° (acetone), [α]²⁵₆₀₀ –55.3° (MeOH).

(+)-(5S,10R)-5β-Hydroxy-10β-isopropyl-Δ¹(⁹)-2-octalone [(+)-2c] was isolated from (–)-3c: bp 60–61° (ether); [α]²⁵₆₀₀ +73° (MeOH); ORD data, see Figure 1; CD data, see Figure 2.

B. (+)-(5R,10S)-5α-Hydroxy-10α-isopropyl-Δ¹(⁹)-2-octalone hydrogen phthalate was obtained by saponification of the brucine salt of 3c as previously described, mp 188–198°, [α]²⁵₆₀₀ +45° (MeOH).

(–)-(5R,10S)-5α-Hydroxy-10α-isopropyl-Δ¹(⁹)-2-octalone [(–)-2c] was isolated from (+)-3c: mp 60–62° (MeOH); [α]²⁵₆₀₀ –53° (MeOH); ORD data, see Figure 1; CD data, see Figure 2.

Registry No.—1c, 34996-04-8; (+)-2a, 34996-05-9; (–)-2a, 34996-06-0; (±)-2b, 17506-54-6; (+)-2b, 34996-08-2; (±)-2c, 34996-09-3; (+)-2c, 34996-10-6; (–)-2c, 34996-11-7; (±)-3a, 34996-12-8; (±)-3a brucine salt, 34969-17-0; (+)-3a, 34996-13-9; (–)-3a, 34996-14-0; (±)-3b, 34996-15-1; (+)-3b, 34996-16-2; (±)-3c, 34996-17-3; (±)-3c brucine salt, 34996-18-4; (+)-3c, 34996-19-5; (–)-3c, 34996-20-8; 2-isopropyl-1,3-cyclohexanedione, 3401-01-2; keto diester of bp 143–152°, 3400-99-5; ethyl 5-keto-7-methyloctanoate, 3401-00-1.

(23) No attempt was made to purify this sample or to obtain the analytical datum at this intermediary stage.

(24) The optical purity can be easily calculated, since Prelog and Acklin⁷ᵃ determined the absolute rotation of (+)-5β-hydroxy-10β-methyl-Δ¹(⁹)-2-octalone to be +203° by enzymatic reduction of (±)-1,6-dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene with *Curvularia falcata*.

Photoreduction and α Cleavage of Aryl Alkyl Ketones[1]

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The photochemical α cleavage and reduction reactions of several aryl alkyl ketones have been investigated. Electron-releasing aromatic substituents decrease the excited state reactivity of *tert*-alkyl aryl ketones toward both primary photoprocesses to a similar extent. The aromatic carbonyl $^3(n,\pi^*)$ state is concluded to be responsible for α cleavage as well as hydrogen abstraction reactions. The rate constant for intermolecular hydrogen abstraction by the carbonyl triplet state decreases with α-methyl substitution. Pinacol and carbinol products are formed *via* the combination and disproportionation of ketyl radicals. A primary deuterium isotope effect on isobutyrophenone ketyl radical disproportionation of 2.7 is observed. α-Methyl substituents increase the percentage of carbinol products due to steric hindrance of free-radical combination.

Synthetic[3,4] and mechanistic[5-7] aspects of aryl alkyl ketone photoreduction have been extensively investigated. A number of α-substituted acetophenones form pinacols upon irradiation in 2-propanol or other suitable hydrogen-donor solvents;[3,4] however, quantitative data on such ketones was unavailable prior to our investigation.[7] The elegant studies of Yang and coworkers[5] on aryl-substituted acetophenones established that the carbonyl $^3(n,\pi^*)$ excited state is responsible for the primary photochemical process, intermolecular hydrogen abstraction. The reactivity of the n,π^* state toward inter- or intramolecular hydrogen abstraction is generally attributed to the half-vacant nonbonding orbital on oxygen, which gives the excited state properties similar to those of alkoxy radicals.[8] The half-vacant nonbonding orbital on oxygen also has been postulated to be responsible for α cleavage;[9,10] however experimental evidence on this point has been lacking. In fact the α-cleavage reactions of aryl alkyl ketones remain largely uninvestigated. Aside from *tert*-alkyl phenyl ketones,[11-14] only several deoxybenzoins[15] have been reported to undergo α cleavage.

Results

α **Cleavage.**—Irradiation of pivalophenone (1) and *p*-methoxypivalophenone (2) in degassed benzene solution gives benzaldehyde and *p*-methoxybenzaldehyde, respectively, along with isobutane and isobutylene (eq 1). No other products are formed in amounts >5% of benzaldehyde formation. *p*-Phenylpivalophenone (3) remains unchanged after prolonged irradia-

$$\underset{\substack{\text{1, Ar} = \text{C}_6\text{H}_5 \\ \text{2, Ar} = p\text{-CH}_3\text{OC}_6\text{H}_4}}{\text{ArCC(CH}_3)_3} \overset{h\nu}{\longrightarrow} \text{Ar}\overset{\text{O}}{\text{C}}\cdot + \dot{\text{C}}(\text{CH}_3)_3 \longrightarrow \text{ArCH} + \\ \text{HC(CH}_3)_3 + \text{H}_2\text{C}{=}\text{C(CH}_3)_2 \quad (1)$$
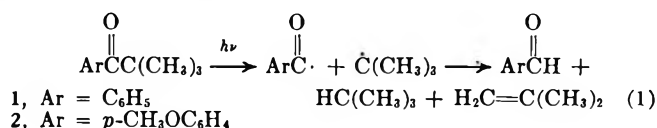
tion in degassed benzene or 2-propanol solution. Photolysis of ketones 1 and 2 in nondegassed solution results in more complex product mixtures, presumably due to reaction of the intermediate free radicals with oxygen.[12,15]

Quantum yields for benzaldehyde formation were determined for 0.05 *M* ketone solutions in benzene or benzene containing 3×10^{-3} *M* 1-dodecanethiol using 313-nm irradiation (Table I). Light intensities were

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, the Research Corporation, and the Merck Foundation for support of this research.

(2) NDEA Fellow, 1970–present.

(3) A. Schönberg, "Preparative Organic Photochemistry," Springer-Verlag, New York, N. Y., 1968, p 204.

(4) (a) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **33**, 1271 (1968); (b) *ibid.*, **36**, 1095 (1971); (c) *Chem. Commun.*, 204 (1969); (d) A. Padwa, E. Alexander, and M. Niemcyzk, *J. Amer. Chem. Soc.*, **91**, 456 (1969).

(5) (a) N. C. Yang, D. S. McClure, S. L. Murov, J. J. Houser, and R. Dusenbery, *ibid.*, **89**, 5466 (1967); (b) N. C. Yang and R. L. Dusenbery, *ibid.*, **90**, 5899 (1968); (c) N. C. Yang and R. L. Dusenbery, *Mol. Photochem.*, **1**, 159 (1969).

(6) F. D. Lewis, *J. Phys. Chem.*, **74**, 3332 (1970), and references cited therein.

(7) For a preliminary report of a portion of this work, see F. D. Lewis, *Tetrahedron Lett.*, 1373 (1970).

(8) C. Walling and M. J. Gibian, *J. Amer. Chem. Soc.*, **87**, 3361 (1965).

(9) H. E. Zimmerman, *Advan. Photochem.*, **1**, 183 (1963).

(10) D. I. Schuster, R. G. Underwood, and T. P. Knudsen, *J. Amer. Chem. Soc.*, **93**, 4304 (1971).

(11) T. Matsuura and Y. Kitaura, *Tetrahedron*, **25**, 4487 (1969).

(12) H.-G. Heine, *Justus Liebigs Ann. Chem.*, **732**, 165 (1970).

(13) F. D. Lewis and T. A. Hillard, *J. Amer. Chem. Soc.*, **92**, 6672 (1970).

(14) F. D. Lewis and T. A. Hillard, *ibid.*, **94**, 3852 (1972).

(15) J. Kenyon, A. Rassoul, and G. Soliman, *J. Chem. Soc.*, 1774 (1956).

Ketone	$\Phi_{\text{C}_6\text{H}_6}{}^a$	$\Phi_{\text{C}_6\text{H}_6}{}^b$ RSH	$k_q\tau^c$	$1/\tau \times 10^{-6}$, sec^{-1}
PhCOC(CH₃)₃ (1)	0.163	0.300	447	110
p-MeOPhCOC(CH₃)₃ (2)	0.081	0.174	7360	6.8
p-PhPhCOC(CH₃)₃ (3)	<0.001	<0.001		

^{a} Quantum yield for benzaldehyde formation in benzene solution. ^{b} Quantum yield for benzaldehyde formation in benzene containing 3×10^{-3} *M* 1-dodecanethiol. ^{c} Least-squares slopes of Stern–Volmer plots, limits of error ±10%.

measured by simultaneous irradiation of the ketone solutions and benzophenone–benzhydrol actinometer solutions[16] on a merry-go-round apparatus at 25°. Product yields were determined by analytical vpc after <2% conversion of starting ketone. Quantum yields diminished markedly at higher conversions, principally due to quenching by photoproducts.[17] Quantum yields for benzaldehyde formation increased with added 1-dodecanethiol. No increase was observed at concentrations greater than 10^{-3} *M*. Such low mercaptan concentrations did not lead to formation of photoreduction products.

The triplet lifetimes of ketones 1 and 2 were determined by the usual Stern–Volmer treatment. Quenching of benzaldehyde formation from 1 by 1,3-pentadiene gave a Stern–Volmer plot with upward curvature. Curved Stern–Volmer plots (Φ_0/Φ *vs.* quencher) were also observed for 1,3-pentadiene quenching of benzaldehyde formation from α,α-dimethyl-

(16) W. M. Moore and M. Ketchum, *J. Amer. Chem. Soc.*, **84**, 1368 (1962).

(17) F. D. Lewis and D. R. Kory, unpublished results.

butyrophenone and α,α-dimethylvalerophenone.[14] The curvature presumably is due to scavenging of benzoyl radicals by the diene. Imposition of a linear least-squares fit on the 1,3-pentadiene quenching data for ketone **1** gave a slope of 220, in reasonable agreement with that recently reported by Heine[12] ($k_q\tau$ = 160). Quenching of benzaldehyde formation from **1–3** with 2×10^{-4} to 3×10^{-3} M naphthalene ($E_T \cong 61$ kcal/mol[18]) using 365-nm irradiation to avoid competitive absorption led to the linear Stern–Volmer plots shown in Figure 1. The slopes of the Stern–Volmer plots are equal to $k_q\tau$ (Table I), where k_q is the rate constant for quenching of the ketone triplet state by naphthalene and τ is the ketone triplet lifetime. Assumption of the value 5×10^9 M^{-1} sec^{-1} for k_q[19] allows calculation of τ or $1/\tau$ (Table I).

Photoreduction.—Irradiation of ketones **1** and **2** in degassed 2-propanol–benzene solution results in formation of the corresponding carbinols and acetone (eq 2)

$$\text{ArCC(CH}_3)_3 + \text{(CH}_3)_2\text{CHOH} \xrightarrow{h\nu}$$
$$\text{ArCC(CH}_3)_3 + \text{(CH}_3)_2\text{C=O} \quad (2)$$
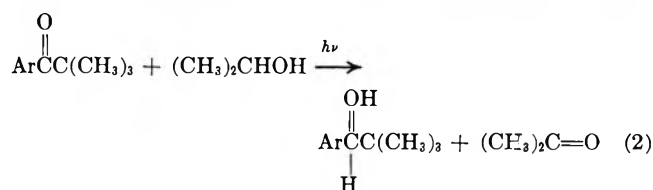
as well as the products of α cleavage (eq 1). The absence of pinacol formation from photoreduction of ketone **1** has previously been noted.[7,12] Irradiation of alkyl phenyl ketones **4–6** in 2-propanol solution under nitrogen resulted in the formation of acetone, a mixture of dl and meso pinacols, and the corresponding carbinol (eq 3). No mixed pinacols of the type observed by

$$\text{PhCOR} + \text{(CH}_3)_2\text{CHOH} \xrightarrow{h\nu}$$

4, R = CH$_3$
5, R = CH$_2$CH$_3$
6, R = CH(CH$_3$)$_2$

$$\text{PhC—CPh} + \text{PhCH} + \text{(CH}_3)_2\text{C=O} \quad (3)$$
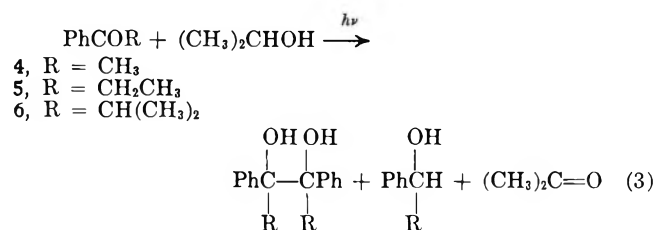
Weiner[20] for benzophenone photoreduction by 2-propanol were detected; however, the possibility of their presence in small amounts cannot be eliminated. Carbinol products were isolated by silica gel chromatography and were identical with authentic samples. In view of the small percentage of carbinol in the product mixture from acetophenone (4), it is not surprising that previous reports of acetophenone photoreduction[4–6] do not mention carbinol formation. Mixtures of the diastereomeric pinacols were obtained by fractional distillation of the photolysis products. No attempt was made to separate the dl and meso isomers; however the nmr and ir spectra of the mixtures were consistent with the assigned structures and literature reports.[5,21,22]

Irradiation of isobutyrophenone (**6**) in (CH$_3$)$_2$CHOD followed by silica gel chromatography gave a mixture of deuterated and undeuterated carbinols.

(18) P. S. Engel and B. M. Monroe, *Advan. Photochem.*, **8**, 245 (1971).

(19) P. J. Wagner and I. Kochevar, *J. Amer. Chem. Soc.*, **90**, 2332 (1968).

(20) S. A. Weiner, *ibid.*, **93**, 425 (1971).

(21) H. Agahigian, J. F. Moraveck, and H. Gauther, *Can. J. Chem.*, **41**, 194 (1963).

(22) W. A. Mosher and N. D. Heindel, *J. Org. Chem.*, **28**, 2154 (1963).
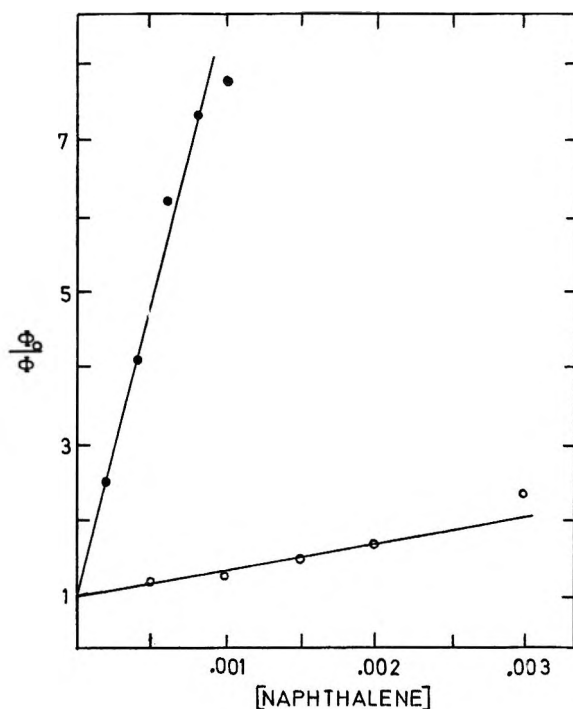
Figure 1.—Stern–Volmer plots for quenching of benzaldehyde formation from pivalophenone (O) and p-methoxypivalophenone (●).

Nmr analysis of this mixture showed $27 \pm 3\%$ C–D incorporation (eq 4).

$$\text{PhCOCH(CH}_3)_2 + \text{(CH}_3)_2\text{CHOD} \xrightarrow{h\nu}$$

6

$$\text{PhCH} + \text{PhCD} \quad (4)$$

$$73\% \qquad 27\%$$
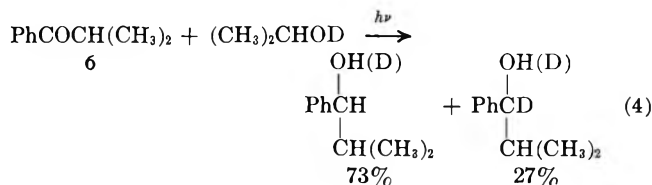
Quantum yields for product formation were determined for degassed 0.1 M solutions of ketones **4–6** in 2.0 M 2-propanol–benzene solution using 313-nm irradiation. Products were analyzed on calibrated vpc columns after <10% conversion of starting ketone.[23] The results are given in Table II. In all cases $\Phi_{\text{acetone}} \approx$

Table II
Quantum Yields for Photoreduction of Aryl Alkyl Ketones

Ketone	Solvent,[a] M	Φ_{pinacol}	Φ_{carbinol}
PhCOC(CH$_3$)$_3$ (1)	4.0	<0.001	0.0099
p-CH$_3$OPhCOC(CH$_3$)$_3$ (2)	4.0	<0.001	0.011
p-PhPhCOC(CH$_3$)$_3$ (3)	4.0	<0.001	<0.001
PhCOCH$_3$ (4)	2.0	0.37	0.007
PhCOCH$_2$CH$_3$ (5)	2.0	0.19	0.033
PhCOCH(CH$_3$)$_2$ (6)	2.0	0.071	0.049

[a] Concentration of 2-propanol in benzene.

$\Phi_{\text{pinacol}} + \Phi_{\text{carbinol}}$.[6,7] Quantum yields for carbinol formation from ketones **1** and **2** were measured as a function of 2-propanol concentration (0.5–4.0 M) in benzene solution. Values are given in Table II for 4.0 M 2-propanol–benzene solution. The low quantum yields combined with the necessity of analysis at low

(23) Quantum yields for acetophenone photoreduction decrease for conversions over 10%.[6]

conversion resulted in fairly large errors for these measurements ($\pm 20\%$).

Plots of $1/\Phi$ for carbinol formation from ketones **1** and **2** vs. $1/[$2-propanol$]$ had intercepts near unity and slopes equal to $(\tau k_r)^{-1}$, where k_r is the rate constant for intermolecular hydrogen abstraction. Values of $(\tau k_r)^{-1}$ are given in Table III along with k_r values

TABLE III

KINETIC DATA FOR PHOTOREDUCTION OF
ARYL ALKYL KETONES[a]

Ketone	$(\tau k_r)^{-1}$	$\tau \times 10^6$, sec	$k_d \times 10^5$, sec^{-1}	$k_r \times 10^5$, M^{-1} sec^{-1}
1	460	0.09		0.24
2	192	1.5		0.035
4[b]		2.4	3.4	6.8
5		2.7	3.2	4.4
6		2.9	3.4	0.9

[a] Limits of error for kinetic data = $\pm 10\%$ for **4**, $\pm 20\%$ for **1, 2, 5,** and **6**. [b] Values from ref 6.

calculated using the τ values from Table I. The rate constants for intermolecular hydrogen abstraction (k_r) and nonradiative decay (k_d) of the carbonyl triplet states of **4–6** in 0.1 M 2-propanol–benzene solvent[6] were determined by standard Stern–Volmer analysis of the variation of $1/\Phi$ for acetone formation with quencher (piperylene) concentration (eq 5). The values of

$$\frac{1}{\Phi} = \frac{k_r[\text{RH}] + k_d}{k_r[\text{RH}]} + \frac{k_q[\text{Q}]}{k_r[\text{RH}]} \quad (5)$$

k_r obtained from the slopes of linear Stern–Volmer plots assuming $k_q = 5 \times 10^9 \, M^{-1}$ sec^{-1} [19] decrease with increasing α substitution (Table III). The k_d values obtained from the intercepts of the Stern–Volmer plots in 0.1 M 2-propanol–benzene are the same for **4–6** within the experimental error and are in good agreement with values for acetophenone obtained by phosphorescence decay measurements.[24] The calculated values for τ, the triplet lifetime $[\tau = (k_r[\text{RH}] + k_d)^{-1}]$ increase slightly for the series **4–6**. Since the triplet lifetimes of **1** and **2** in benzene solution are determined by α cleavage as well as by nonradiative decay, no value of k_d for **1** or **2** is included in Table III.

Discussion

α Cleavage and Photoreduction.

—The yields and efficiencies of photochemical α-cleavage reactions of carbonyl compounds have frequently been observed to depend on the stability of the pair of radicals or biradical that is formed.[25] This dependence reflects the balance between the carbonyl excited state energy and the heat of reaction. The calculated heat of reaction for α cleavage of *tert*-alkyl phenyl ketones is comparable to the carbonyl triplet energy (73 ± 1 kcal/mol).[14] Thus it is not surprising that *tert*-alkyl[11-14] and benzyl phenyl ketones[15] undergo α cleavage, but primary and secondary alkyl phenyl ketones do so inefficiently, if at all.

The photochemical α-cleavage reactions of a *tert*-alkyl aryl ketone (A) can be described by the following

(24) (a) W. C. K. Clark, A. D. Litt, and C. Steel, *Chem. Commun.*, 1087 (1969); (b) H. Lutz and L. Lindquist, *ibid.*, 493 (1971).

(25) (a) J. C. Dalton and N. J. Turro, *Annu. Rev. Phys. Chem.*, **21**, 499 (1970); (b) J. E. Starr and R. H. Eastman, *J. Org. Chem.*, **31**, 1393 (1966); (c) H. Küntzel, H. Wolf, and K. Schaffner, *Helv. Chim. Acta*, **54**, 868 (1971).

simplified mechanism, where Q is the triplet quencher naphthalene and RSH is the radical scavenger 1-dodecanethiol. In benzene solution photoreduction

$$A \xrightarrow{h\nu} A^1 \xrightarrow{k_{ST}} A^3 \quad (6)$$

$$A^3 \xrightarrow{k_d} A \quad (7)$$

$$A^3 + Q \xrightarrow{k_q} A + Q^3 \quad (8)$$

$$A^3 \xrightarrow{k_\alpha} Ar\overset{O}{\overset{\|}{C}}\cdot + R\cdot \xrightarrow{RSH} Ar\overset{O}{\overset{\|}{C}}H + RH \quad (9)$$
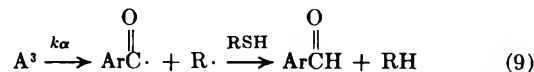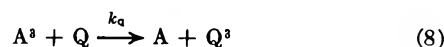
does not compete with α cleavage. Hence the quantum yield for benzaldehyde formation in the absence and presence of naphthalene is given by eq 10 and 11, respectively, where β is the probability that the initially

$$\Phi_0 = \left(\frac{k_\alpha}{k_\alpha + k_d}\right)\beta \quad (10)$$

$$\Phi = \left(\frac{k_\alpha}{k_\alpha + k_d + k_q[\text{Q}]}\right)\beta \quad (11)$$

formed benzoyl-*tert*-alkyl radical pair will lead to benzaldehyde formation. Addition of 1-dodecanethiol increases β (and Φ_0) by providing a source of readily abstractable hydrogens for the benzoyl radical.[26] Values of Φ_0 less than unity for ketones **1** and **2** are due at least in part to cage recombination of the initially formed radical pair.[27] Assuming that the triplet quencher naphthalene does not alter β,[29] the Stern–Volmer equation (eq 12) can be obtained from eq 10

$$\frac{\Phi_0}{\Phi} = 1 + \frac{k_q[\text{Q}]}{k_\alpha + k_d} = 1 + k_q\tau[\text{Q}] \quad (12)$$

and 11. The $1/\tau$ values in Table I equal the sum of the rate constants for α cleavage (k_α) and nonradiative decay (k_d). Values of $k_d \sim 3 \times 10^5$ sec^{-1} have been reported by ourselves[6,7] and others[24] for a number of aryl ketones, including **4–6**, in benzene solution. Such values are small compared to $1/\tau$ for ketone **1**, indicating that $k_\alpha \approx 1/\tau$. However, $1/\tau$ for ketone **2** is not much greater than k_d, so that $k_\alpha \leq 1/\tau$. Thus part of the inefficiency of benzaldehyde formation from ketone **2** may be due to competition of nonradiative decay with α cleavage.

In 2-propanol–benzene solution photoreduction (eq 13) competes with α cleavage. The quantum yield for formation of carbinol (Φ') in the absence of quencher is given by eq 14. From plots of $1/\Phi'$ vs. $1/[\text{RH}]$ (eq 15) and the values of $1/\tau$ in Table I, the rate constants

$$A^3 + R'H \xrightarrow{k_r} Ar\overset{\overset{OH}{|}}{\underset{\cdot}{C}}R + R'\cdot \longrightarrow \longrightarrow Ar\overset{\overset{OH}{|}}{\underset{|}{C}}R \quad (13)$$
$$\overset{}{\underset{H}{}}$$
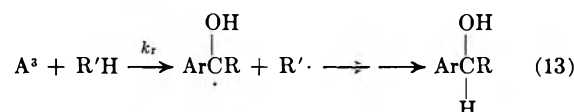
$$\Phi' = \frac{k_r[\text{RH}]}{k_r[\text{RH}] + k_\alpha + k_d} \quad (14)$$

$$\frac{1}{\Phi'} = 1 + \frac{k_\alpha + k_d}{k_r[\text{RH}]} = 1 + \frac{1}{\tau k_r[\text{RH}]} \quad (15)$$

(26) The resulting thiyl radicals do not react with benzaldehyde: R. M. Kellog, "Methods in Free Radical Chemistry," Vol. II, E. S. Huyser, Ed., Marcel Dekker, New York, N. Y., 1969, p 107.

(27) Fractions of cage recombination >0.2 have been observed for pairs of ketyl radicals.[28]

(28) S. A. Weiner, *J. Amer. Chem. Soc.*, **93**, 6978 (1971).

(29) Naphthalene is an inefficient scavenger even for reactive radicals such as methyl radical, which adds to dienes 300 times more rapidly than to naphthalene: W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 221.

for hydrogen abstraction (k_r) in Table III were obtained. The bimolecular rate constants for hydrogen abstraction (k_r) for ketones 1 and 2 are much smaller than the rate constants for α cleavage. However, both primary processes show similar substituent effects, with p-methoxy substitution (2) resulting in a large decrease in rate constant and p-phenyl substitution (3) resulting in total lack of reactivity. Similar substituent effects on the efficiency of phenyl ketone intra-[30,31] and inter-molecular[5] hydrogen abstraction have been observed. Decreased excited state reactivity results from lowered energy of the unreactive $^3(\pi,\pi^*)$ state relative to that of the reactive $^3(n,\pi^*)$ state upon substitution with electron-releasing groups. The residual reactivity of some such ketones has been attributed by Yang[5] to mixing of an upper $^3(n,\pi^*)$ state with a lowest $^3(\pi,\pi^*)$ state, and, recently, by Wagner[32] to abstraction from an equilibrium concentration of an upper $^3(n,\pi^*)$ state. In either case, the similarity of the substituent effects indicates that α cleavage, like hydrogen abstraction, occurs more efficiently from a $^3(n,\pi^*)$ state than from a $^3(\pi,\pi^*)$ state. The half-vacant nonbonding orbital on oxygen of the n,π^* excited state can overlap with the bond undergoing homolysis (eq 16).[9,10] No such overlap is possible for a π,π^* excited state.

$$\text{R} \cdot + \text{PhC}{=}\text{O} \cdot \longleftrightarrow \text{Ph}\overset{+}{\text{C}}{=}\text{O}{:} \qquad (16)$$
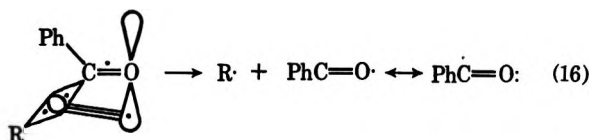
Steric Effects on Photoreduction.—With the measurement of the rate constant for intermolecular hydrogen abstraction (k_r) by pivalophenone (1), comparison of the complete series of α-methyl-substituted acetophenones (1, 4, 5, and 6, Table III) becomes possible. The rate constant for hydrogen abstraction by propiophenone (5) is only slightly smaller than that for acetophenone (4); however, much larger decreases are observed for isobutyrophenone (6) and pivalophenone (1). It is unlikely that the decrease in k_r with α-methyl substitution is due to a change in triplet energy or the n,π^* character of the lowest triplet state. Phosphorescence lifetime measurements indicate that the n,π^* triplet is of lower energy than the π,π^* triplet for ketones 1 and 4 in nonpolar media.[33] α-Methyl substituents cause no decrease in the rate constants for intramolecular γ-hydrogen abstraction by butyrophenone or valerophenone.[14] Furthermore, CNDO-2 calculations by Blanchi[34] show that there is no change in the excited state charge density on oxygen with α substitution for 4-6.

The observed effect of α-methyl substitution is consistent with increased steric hindrance of intramolecular hydrogen abstraction. Additional evidence for a steric requirement for hydrogen abstraction by alkyl

phenyl ketones has been provided by using 2,4-dimethyl-3-heptanol in place of 2-propanol as the hydrogen donor for ketones 4-6.[7] The increased steric requirements of the secondary alcohol resulted in decreased values of k_r.[7]

Two possible cases of a steric effect on benzophenone photoreduction by secondary alcohols have been reported;[35] however, in neither case have quantitative excited state reactivity data been presented. Steric effects are reported to be unimportant for hydrogen abstraction by excited uranyl ion from secondary alcohols.[36] However, the steric requirements for hydrogen abstraction *via* an intermolecular collision are clearly smaller for the uranyl ion than for aryl alkyl ketones. Steric hindrance of triplet energy transfer has been postulated in several instances.[37] Our results would at first seem to be in agreement with those of Hammond[37a] for triplet energy transfer from ortho alkyl benzophenones to stilbenes. However, photoenolization and possibly undetected competing reactions[11,38] greatly complicate interpretation of Hammond's results. Wagner[39] recently compared the rate constants for energy transfer from valerophenone and α,α-dimethylvalerophenone and found no evidence for steric hindrance. Since Wagner's system is quite similar to ours, it seems reasonable to conclude for aryl alkyl ketones that steric effects are considerably more important for intermolecular hydrogen transfer than for energy transfer.

The effects of substituents on photochemical reduction can be compared with results for ground-state reductions of alkyl phenyl ketones. Brown and Ichikawa[40] attributed the decrease in relative rates of sodium borohydride reduction for ketones 4 (1.0), 5 (0.56), and 6 (0.52) to a combination of inductive and steric effects. The large increase in relative rate for 1 (18.1) was attributed to partial deconjugation of the phenyl and carbonyl groups due to the interaction of the phenyl and *tert*-butyl groups.[40] The increase in relative rate of hydrogenation on palladium for ketones 4 (1.0), 5 (1.34), 6 (1.55), and 1 (2.84) was similarly attributed to acceleration of hydrogenation due to release of steric strain in a transition state with considerable tetrahedral character.[41] It seems likely that the transition state for photochemical hydrogen abstraction is more reactantlike, thus explaining the absence of steric acceleration for ketone 1.

Ketyl Radical Disproportionation and Combination. —In addition to their effect on the rate of intermolecular hydrogen abstraction, α-methyl substituents influence the quantum yields for pinacol and carbinol formation (Table II). Pinacol formation is known to occur by combination of two ketyl radicals (eq 17).

(30) E. J. Baum, J. K. S. Wan, and J. N. Pitts, Jr., *J. Amer. Chem. Soc.*, **88**, 2652 (1966).

(31) For a recent review, see P. J. Wagner, *Accounts Chem. Res.*, **4**, 168 (1971).

(32) P. J. Wagner and R. A. Leavitt, *J. Amer. Chem. Soc.*, **92**, 5806 (1970).

(33) P. J. Wagner, M. J. May, A. Haug, and D. R. Graber, *ibid.*, **92**, 5269 (1970).

(34) J. P. Blanchi, University of Grenoble, France, private communication.

(35) (a) D. C. Neckers and A. P. Schaap, 153rd National Meeting of the American Chemical Society, Miami, Fla., Apr 1967, No. O-138; (b) D. E. Pearson and M. Y. Moss, *Tetrahedron Lett.*, 3791 (1967).

(36) R. Matsushima and S. Sakuraba, *J. Amer. Chem. Soc.*, **93**, 5421 (1971).

(37) (a) G. S. Hammond and R. S. Cole, *ibid.*, **87**, 3256 (1965); (b) W. G. Herkstroeter, L. B. Jones, and G. S. Hammond, *ibid.*, **88**, 4777 (1966); (c) D. Bellus, D. R. Kearns, and K. Schaffner, *Helv. Chim. Acta*, **52**, 971 (1969); (d) P. S. Engel and P. D. Bartlett, *J. Amer. Chem. Soc.*, **92**, 5883 (1970).

(38) E. J. O'Connell, Jr., *ibid.*, **90**, 6550 (1968).

(39) P. J. Wagner and J. M. McGrath, *ibid.*, unpublished work.

(40) H. C. Brown and K. Ichikawa, *ibid.*, **84**, 373 (1962).

(41) H. Van Bekkum, A. Kieboom, and K. vande Putte, *Recl. Trav. Chim. Pays-Bas*, **88**, 52 (1969).

$$2 \underset{Ph}{\overset{OH}{\underset{R}{\bigwedge}}} \xrightarrow{k_{com}} PhC\underset{R}{\overset{OH}{\underset{|}{}}}\!\!-\!\!\underset{R}{\overset{OH}{\underset{|}{}}}CPh \quad (17)$$

$$2 \underset{Ph}{\overset{OH}{\underset{R}{\bigwedge}}} \xrightarrow{k_{dis}} Ph\underset{R}{\overset{OH}{\underset{|}{C}}}H + PhCOR \quad (18)$$

$$\underset{Ph}{\overset{OH}{\underset{R}{\bigwedge}}} + (CH_3)_2\dot{C}OH \xrightarrow{k'_{dis}} Ph\underset{R}{\overset{OH}{\underset{|}{C}}}H + (CH_3)_2CO \quad (19)$$

Carbinol formation could conceivably occur either by disproportionation of two ketyl radicals (eq 18) or by disproportionation of the nonsymmetrical radical pair (eq 19). The reduction of 6 in $(CH_3)_2CHOD$ was studied in order to differentiate between these possibilities (eq 20–23). Disproportionation of the non-

$$6^j + (CH_3)_2CHOD \xrightarrow{k_r} \underset{Ph}{\overset{OH}{\underset{R}{\bigwedge}}} + (CH_3)_2\dot{C}OD \quad (20)$$

$$6 + (CH_3)_2\dot{C}OD \xrightarrow{k_t} \underset{Ph}{\overset{OD}{\underset{R}{\bigwedge}}} + (CH_3)_2CO \quad (21)$$

$$\underset{Ph}{\overset{OH}{\underset{R}{\bigwedge}}} + \underset{Ph}{\overset{OD}{\underset{R}{\bigwedge}}} \xrightarrow{k_{dis}} \underset{Ph}{\overset{OH(D)}{\underset{\underset{H(D)}{|}}{\bigwedge}}}R + 6 \quad (22)$$

$$\underset{Ph}{\overset{OH}{\underset{R}{\bigwedge}}} + (CH_3)_2\dot{C}OD \xrightarrow{k'_{dis}} \underset{Ph}{\overset{OH}{\underset{\underset{D}{|}}{\bigwedge}}}R + (CH_3)_2CO \quad (23)$$
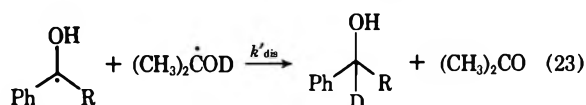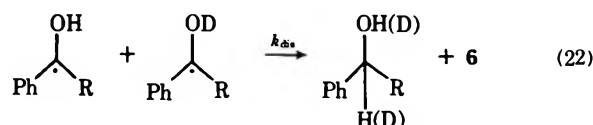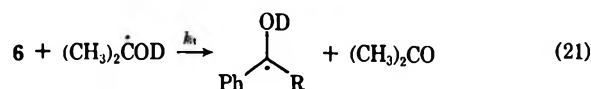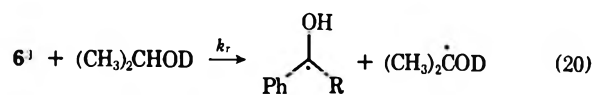
symmetrical radical pair (eq 23) requires carbinol formation with 100% C–D incorporation. Ketyl radical disproportionation (eq 21, 22) should lead to ≤50% C–D incorporation with the exact value depending on the size of the isotope effect on disproportionation. The experimental value was 27 ± 3% C–D incorporation. Although a small amount of nonsymmetric radical disproportionation (eq 23) cannot be ruled out, this result is in accord with ketyl radical disproportionation (eq 21, 22) having a primary kinetic isotope effect of $k_H/k_D = 2.7$. This isotope effect is somewhat larger than that obtained by Gibian and Corley[42] by comparing the disproportionation/combination ratios of $Ph\dot{C}HCH_3$ and $Ph\dot{C}HCD_3$ $[(k_{dis}/k_{com})(H)/(k_{dis}/k_{com}) \cdot (D) = 1.87]$. The isotope effect is indicative of a small activation energy for free-radical disproportionation in solution.[43]

Since pinacol and carbinol formation are the result of ketyl radical disproportionation and combination, the ratio of rate constants (k_{dis}/k_{com}) can be obtained from the quantum yields in Table II. The results are given in Table IV along with selected values for other free radicals. The value of k_{dis}/k_{com} for acetophenone ketyl radical is much lower than those for the hy-

TABLE IV
DISPROPORTIONATION/COMBINATION RATIOS FOR RADICAL PAIRS

Radical pair	k_{dis}/k_{com}	Ref
Ph—C(OH)—CH₃	0.02	*a*
Ph—C(OH)—CH₂CH₃	0.17	*a*
Ph—C(OH)—CH(CH₃)₂	0.69	*a*
Ph—C(OH)—C(CH₃)₃	>10	*a*
α-Hydroxyethyl	0.25	*b*
α-Hydroxycyclohexyl	2.0	*c*
Methyl + ethyl	0.036	*d*
Ethyl	0.134	*d*
1-Propyl	0.154	*d*
2-Propyl	0.694	*d*
2-Butyl	1.2	*e*
tert-Butyl	2.32	*d*
Cumyl	0.054	*f*
2-Phenyl-3-methyl-2-butyl	0.3	*g*

a This work. *b* Reference 44. *c* Reference 45. *d* Reference 48. *e* Reference 49. *f* Reference 46a. *g* Reference 46b.

droxyl radicals formed upon pulse radiolysis of ethanol[44] and cyclohexanol.[45] Low values of k_{dis}/k_{com} are characteristic of benzyl type radicals and apparently are the result of enhanced combination rate constants for radical pairs in which the odd electron is highly delocalized.[28,46] The k_{dis}/k_{com} ratio is observed to increase by over a factor of 500 in going from acetophenone ketyl radical to pivalophenone ketyl radical.[47] The effect of β substituents on acetophenone ketyl radicals is thus far greater than the effect of α-methyl substituents on simple alkyl radical gas phase k_{dis}/k_{com} ratios (Table II).[48–50] Whereas α-substituent effects on k_{dis}/k_{com} have been extensively studied for alkyl radicals, less is known about β-substituent effects. Small increases in k_{dis}/k_{com} are observed for ethyl *vs.* 1-propyl and 2-propyl *vs.* 2-butyl radicals (Table IV). The larger increase in k_{dis}/k_{com} for cumyl *vs.* 2-phenyl-3-methyl-2-butyl radical has been attributed with trepidation to simple steric hindrance.[46c] A comparable but larger increase is observed for acetophenone *vs.* isobutyrophenone ketyl radical. The very large increase in k_{dis}/k_{com} between isobutyrophenone and pivalophenone ketyl radicals is similar to that observed for S_{N2} rate constants for isobutyl and neo-

(42) M. J. Gibian and R. C. Corley, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, No. 0-140.

(43) (a) P. S. Dixon, A. P. Stefani, and M. Szwarc, *J. Amer. Chem. Soc.*, **85**, 2551 (1963); (b) R. Klein, M. D. Scheer, and R. Kelley, *J. Phys. Chem.*, **68**, 598 (1964); (c) R. S. Konar, *Int. J. Chem. Kinet.*, **2**, 419 (1970).

(44) I. D. Taub and L. M. Dorfman, *J. Amer. Chem. Soc.*, **84**, 4953 (1962).

(45) P. L. McCarthy and A. MacLachlan, *Trans. Faraday Soc.*, **57**, 1107 (1961).

(46) (a) S. F. Nelson and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 137 (1966); (b) P. D. Bartlett and J. M. McBride, *Pure Appl. Chem.*, **15**, 89 (1967); (c) S. A. Weiner and G. S. Hammond, *J. Amer. Chem. Soc.*, **91**, 986 (1969); (d) R. C. Neuman, Jr., and E. S. Alhadeff, *J. Org. Chem.*, **35**, 3401 (1970); (e) J. R. Shelton, C. K. Liang, and P. Kovacic, *J. Amer. Chem. Soc.*, **90**, 354 (1968); (f) G. S. Hammond and S. A. Weiner, *Intra-Sci. Chem. Rep.*, **3**, 241 (1969).

(47) Since disproportionation of ketyl radicals involves hydroxyl hydrogen transfer, there is no need to normalize these results for the number of abstractable β hydrogens.

(48) (a) J. O. Terry and J. H. Futrell, *Can. J. Chem.*, **45**, 2327 (1967); (b) *ibid.*, **46**, 664 (1968).

(49) S. W. Benson, *Annu. Rev. Phys. Chem.*, **16**, 397 (1965).

(50) The value of k_{dis}/k_{com} for ethyl radical is somewhat larger in solution (0.16 in isooctane at 25°) than in the gas phase (0.13). See ref 43a.

pentyl substrates.[51] The k_{dis}/k_{com} results for ketyl radicals are consistent with a steric hindrance argument. The magnitude of the β-substituent effect is clearly greater than would have been predicted on the basis of previous free-radical literature. Generalization of these results should be treated with caution in view of the complex nature of the interactions of such large and delocalized free radicals in solution.[46f]

Summary.—The rate constant for acetophenone photoreduction decreases with increasing α-methyl substitution. This trend is attributed to increasing steric hindrance of the primary photoprocess, intermolecular hydrogen abstraction. In contrast to the continuous decrease in rate constant for photoreduction with α-methyl substitution, photochemical α cleavage occurs efficiently only for *tert*-alkyl aryl ketones. Quantitative comparison of the competition between photoreduction and α cleavage requires kinetic data for both processes. The similar effects of aromatic substituents on the rate constants for photoreduction and α cleavage indicates that both processes occur from a $^3(n,\pi^*)$ state. Deuterium labeling establishes that carbinol formation is the result of ketyl radical disproportionation. The marked increase in the ratio of disproportionation to combination rate constants with methyl substitution is due to a large steric effect on ketyl radical termination.

Experimental Section

Materials and Solvents.—Acetophenone (Eastman) and propiophenone (MCB) were purified by recrystallization from ethanol–water and from petroleum ether (bp 30–60°) at 10° and then distilled. Isobutyrophenone (Aldrich) was distilled and the middle fraction was retained. The *tert*-butyl aryl ketones **1–3** were prepared by the method of Peterson.[52] The physical constants of **1**[52] and **2**[53] were in agreement with literature values. Ketone **3** was obtained as a colorless solid, mp 92–93°, nmr (CCl₄) δ 1.35 (s, 9 H), 7.2–7.8 (m, 9 H). The carbinols prepared by reduction of ketones **1–4**[54] and **5**[53] with lithium aluminum hydride all had physical constants in agreement with literature values. Benzaldehyde, anisaldehyde (Eastman), and 4-biphenylcar-

boxaldehyde (Aldrich) were commercial samples. Benzene and 2-propanol were purified as previously described. 2-Propanol-*O-d* was prepared by treatment of purified 2-propanol with a 50-fold excess of D₂O followed by extraction with benzene. *n*-Dodecanethiol (Aldrich) was used as received.

Product Studies.—Carbinol products from ketones **1, 2,** and **4–6** and aldehydes from **1** and **2** were isolated by chromatography of large-scale photolysis mixtures on silica gel with benzene–ethyl acetate solvent. The isolated carbinols and aldehydes had nmr and ir spectra and vpc retention times identical with those of authentic samples. The extent of C–D incorporation in the carbinol from irradiation of ketone **6** (0.8 g) in 20 ml of 3 *M* 2-propanol-*O-d*-benzene was determined by comparison of the integrated methine and hydroxyl regions of the nmr spectrum with those for an undeuterated authentic sample. Mixtures of *dl* and *meso* pinacols from ketones **4–6** were obtained by distillation of large-scale photolysis mixtures at 0.2 mm. The fractions with bp >120° were recrystallized from hexane and had melting points (for pinacols from **4**,[22] **5**,[22] and **6**[55]), ir spectra (pinacols from **4**[22] and **5**[22]), and nmr spectra (pinacol from **4**[21]) in accord with literature data. Propiophenone pinacol nmr follows (CCl₄): *dl*, δ 0.55 (t, $J = 7.5$ Hz, CH₃), 2.42 (s, OH); meso, δ 0.52 (t, $J = 7.5$ Hz, CH₃), 1.98 (s, OH). Isobutyrophenone pinacol nmr follows (CCl₄): *dl*, δ 0.77 (q$_{ab}$, $J = 6.5$ Hz, $\Delta_{ab} = 42$ Hz, CH₃), 1.75 (septet, $J = 6.5$ Hz, CH), 2.71 (s, OH); meso, δ 0.67 (d, $J = 6.9$ Hz, CH₃), 2.28 (septet, $J = 6.9$ Hz, CH), 2.08 (s, OH). Infrared spectra were recorded on a Beckman IR-10 spectrometer and nmr spectra on a Varian A-60 spectrometer.

Quantum Yields and Rate Constants.—The yields of benzaldehyde and/or carbinol from ketones **1** and **2** were determined by vpc analysis on a calibrated 7 ft × 0.125 in. column of 10% FFAP on DMSC-treated Chromosorb G. Yields of acetone, pinacol, and carbinol from ketones **4–6** were determined as previously described. Actinometry, isolation of 313-nm irradiation, and determination of rate constants were as previously described.[6,7] Corning filters 7-54 and 0-52 were used to isolate the 365-nm mercury line.

(51) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 13.

(52) D. E. Peterson, *J. Amer. Chem. Soc.*, **72**, 4169 (1950).

(53) A. C. Dachauer, B. Cocheo, M. G. Solomon, and D. J. Hennessy, *J. Agr. Food Chem.*, **11**, 47 (1963).

(54) I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, London, 1965.

(55) R. Claus, *J. Prakt. Chem.*, **46**, 481 (1892).

The Chemistry of a Diazo Ketone and Its Derivatives Obtained from Cholanic Acid

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Received December 8, 1971

Treatment of the steroidal diazo ketone **3** with hot acetic acid afforded, besides the expected ketol acetate **4**, the as yet unknown steroidal dioxane derivative **5**. The latter compound is the dimeric form of ketol **6**. The dimeric structure was inferred from physical data and from the high optical purity observed in the α-hydroxy acids, the tautomerized and oxidized products of steroidal ketols. The characteristic chemical behavior of the dimeric compound **5** and the operative factors determining its properties are reported.

The chemistry of diazo ketones and diazo compounds has been recently reviewed.[1,2]

Diazo ketone **3** was obtained in high yield by the well-known procedure[3] starting with cholanic acid (**1**). In boiling acetic acid the diazo ketone **3** was converted into two products, the expected ketol acetate **4** and the hitherto unknown dioxane derivative **5**, which can be regarded as the dimer of ketol **6** (Scheme I).

SCHEME I
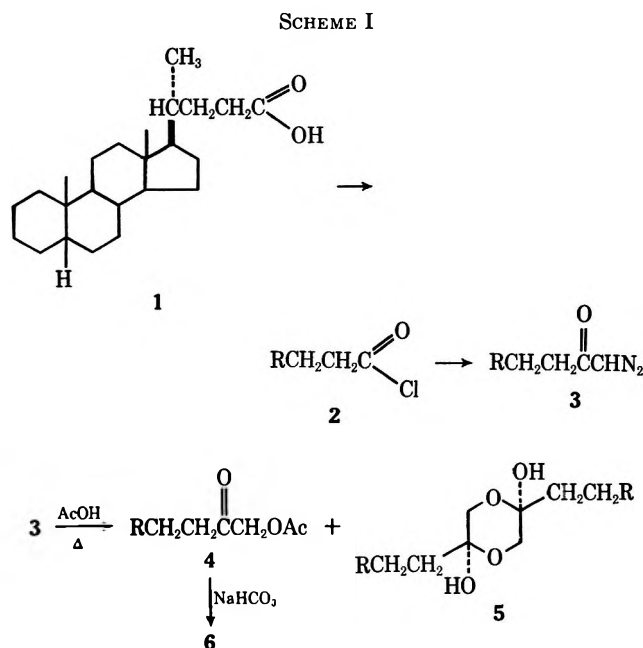
The yields of dimer **5** varied, for reasons as yet not clear, from a few per cent up to 12%, from run to run. A convenient procedure for the synthesis of dimeric compounds from ketols has been reported.[4,5]

Reaction of ketol **6** with gaseous HCl has led to the preparation and isolation of the hemimethylal **7**, which slowly decomposed into its components. The dimeric compound **5** was by no means present.

We further attempted unsuccessfully the synthesis of **5** by treating diazo ketone **3** with H_2SO_4 in various solvents. Ketol **6** and the corresponding ethyl ether **8** were obtained as the major products in aqueous THF and EtOH, respectively (Scheme II).

With dry benzene as solvent, a curious reaction took place. A colorless compound was obtained which

(1) L. L. Rodina and I. K. Korobitsyana, *Russ. Chem. Rev.*, **36**, 260 (1967).

(2) O. P. Studzinskii and I. K. Korobitsyana, *ibid.*, **39**, 834 (1970).

(3) F. Arndt, B. Eistert, and W. Partale, *Ber.*, **60**, 1364 (1927).

(4) E. Fischer, *ibid.*, **28**, 1161 (1895).

(5) L. Szotyori, L. Fey, and A. Kovendi, *Rev. Roum. Chim.*, **15**, 1615 (1970).

SCHEME II

melted at 130° and could not be stored without decomposition, yielding ketol **6** and other products (Scheme II). So far, its structure could not be solved from the physical data at hand (see Experimental Section) and its elucidation is under further study.

The monomeric ketol **6** was obtained from ketol acetate **4** by mild alkaline hydrolysis, or preferably from diazo ketone **3** by the use of acid in aqueous THF (Schemes I and II). When subjected to the action of alkali in ethanolic solution, both ketol acetate **4** and ketol **6** underwent fragmentation and rearrangement leading to cholanic acid (**1**) and α-hydroxyhomocholanic acid (**9**) (Scheme III).

SCHEME III

The intermediacy of the hydroxy aldehyde **10** could be followed by tlc, when the reaction was conducted under nitrogen atmosphere. By a known procedure[6] the hydroxy acid **9** was oxidized to the corresponding cholanic aldehyde **11**.

The sensitivity of **4** and **6** to strong base is clearly evident. Even the action of $NaBH_4$ and $LiAlH_4$ in the appropriate solvents did not give a straightforward reaction. Only when conditions were carefully observed did ketol acetate **4**, and to a lesser extent ketol **6**, afford the diol **12** (Scheme IV).

SCHEME IV
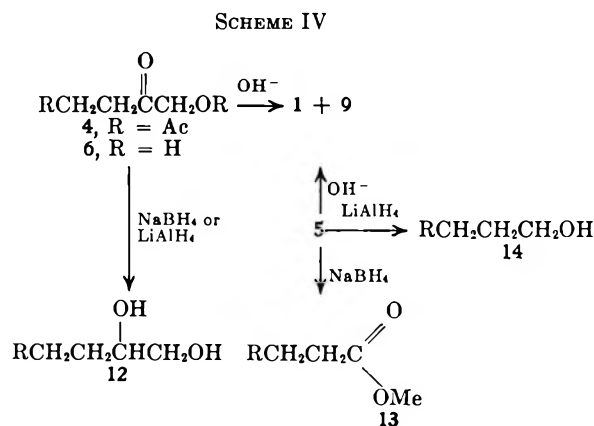
In contrast, the dimeric compound **5** failed to yield diol **12**; rather methyl cholanate (**13**) and cholanol (**14**) were the main products, on reaction with $NaBH_4$ and $LiAlH_4$, respectively.

Analysis shows that the composition of the dimeric compound **5** corresponds with the formula $(C_{25}H_{45}O_2)_n$. The parent molecular ion at m/e 748 provides evidence for its dimeric structure; it is twice as great as that of ketol **6**. The nmr data are in good accord with the structure and are unambiguous. Nevertheless, the strong absorption in the 1740 cm^{-1} region is a little puzzling.

Supporting evidence which was of great use in clarifying the nature of the dimeric structure was gained in the observation that the conversion ketol → α-hydroxy acid was stereospecific. Thus the action of OH$^-$ on ketol[7] **15** or even α-bromoaldehyde **16** provided an extremely facile synthesis of (23R)-hydroxycholanic acid (**17**) in 90–95% optical yield. Similar behavior was also observed in the lower homolog[8] **18** (Scheme V).

A comparison of our data with those reported by Griffiths and Gutsche[9] for dimers derived from mandelaldehyde is of some interest.

To account for the observed high optical yield in the above reaction, the intermediacy of dimeric structures in the oxidative isomerization ketol → α-hydroxy acid is postulated. Fortunately, such a dimeric compound **5** could be isolated and identified in the homocholanic series. We further assume that in the process of dimerization, which is involved in these reactions, the configuration of the pertinent carbon, bearing the steroidal alkyl and hydroxyl groups, is established. The bulky alkyl group is accommodated in the preferable equatorial orientation (Scheme VI).

(6) Y. Yanuka, R. Katz, and S. Sarel, *Tetrahedron Lett.*, 1725 (1968).
(7) Y. Yanuka, R. Katz, and S. Sarel, *ibid.*, **60**, 5229 (1970).
(8) Y. Yanuka, R. Katz, and S. Sarel, unpublished work.
(9) D. W. Griffiths and C. D. Gutsche, *J. Org. Chem.*, **36**, 2184 (1971).

SCHEME V

SCHEME VI
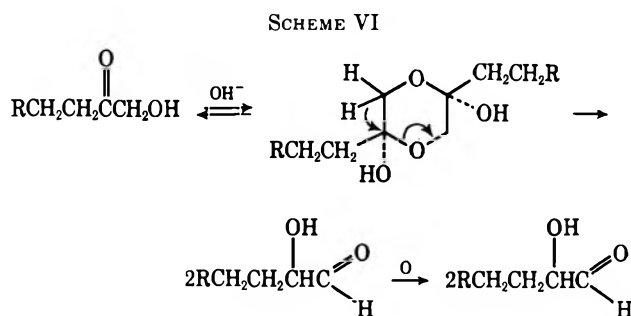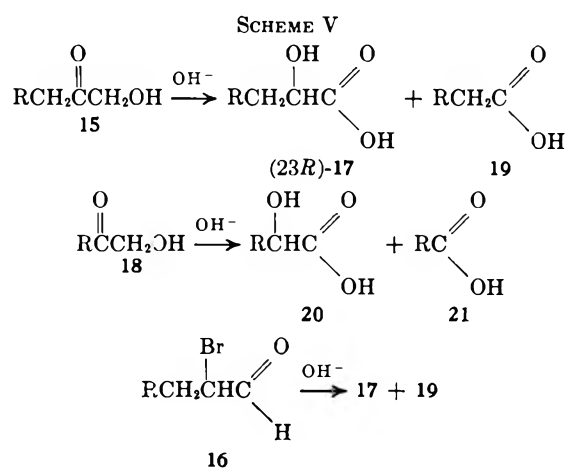
The tendency of such dimeric compounds to collapse is enhanced by virtue of the steric strain inherent in the steroidal dioxanelike derivatives. The C–O bond breaking and hydride shift are two processes in one concerted reaction.

Noteworthy is the observation that the yield of the hydroxy acid rises from 3% in the homocholanic series up to nearly 50% in the lower homologs, in line with the higher tension exercised by the molecule as the chain becomes shorter.

As no stereospecificity could be anticipated in the two following alternative mechanisms, paths a and b (Scheme VII), they are, in our opinion, unsuitable.

SCHEME VII
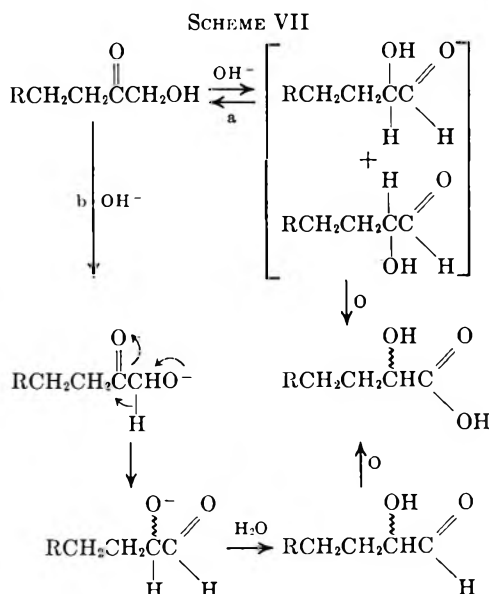
The fragmentation reaction may be visualized either as a result of a nucleophilic attack of a base on the

C=O carbon[10] or alternatively, taking place intramolecularly, again through the intermediacy of the dioxanelike structure (Scheme VIII).

SCHEME VIII
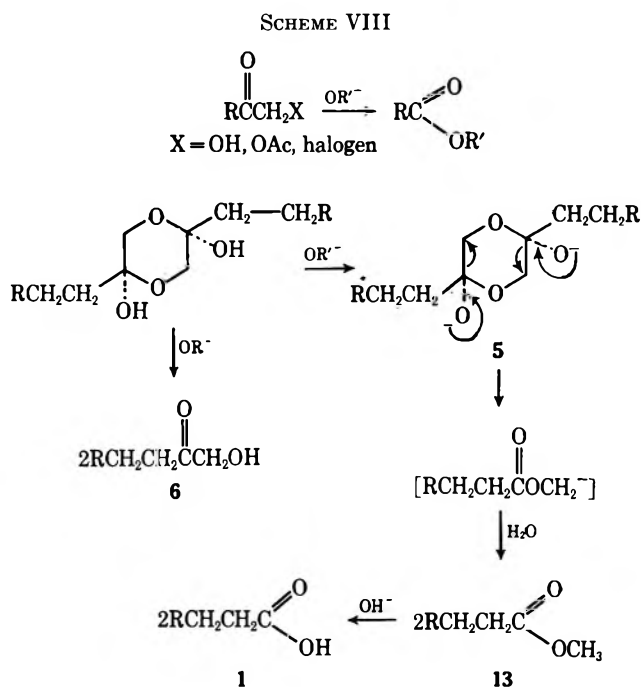
As the only product obtained in the reaction of NaBH₄ on the dimeric compound **5** was methyl cholanate (although two basic species are present in the solution, namely OR⁻ and BH₄⁻), the intramolecular mechanism is more likely in cases where the dimeric compound interferes.

Experimental Section

Cholanoyl Chloride (2).—Cholanic acid (10 g) in dry benzene (150 ml) was treated with thionyl chloride (10 ml) and the resulting solution was stirred for 3 hr at 60°. The benzene and excess thionyl chloride were removed *in vacuo* and the solid residue was dissolved in dry benzene.

24-Oxo-25-diazohomocholane (3).—To the above solution was added during 15 min a slight excess of diazomethane in benzene. After an additional 15 min, the excess diazomethane was decomposed with the aid of acetic acid. The solvent was removed *in vacuo*. The product was chromatographed on silica gel (Hopkins and Williams). Elution with 20% benzene–cyclohexane gave 24-oxo-25-chlorohomocholane: mp 111°; ir νco 1720 cm⁻¹; nmr (CCl₄) 234 cps (s, 2, CH₂); nmr (CDCl₃) 235 cps. Benzene eluted a readily crystallized diazo ketone (97%): mp 117°; $[\alpha]^{CHCl_3}D$ + 18.4°; ir ν 1215 (s), 1630 (s), 2105 cm⁻¹ (s); nmr (CDCl₃) 312 cps (s, 1, CH); nmr (CCl₄) 309 cps.

24-Oxo-25-acetoxyhomocholane (4) and Dimeric Compound 5.—Diazo ketone **3** (15.0 g) was dissolved in acetic acid (50 ml) and refluxed for 24 hr. The acetic acid was removed by distillation at reduced pressure. The residue was chromatographed on silica gel. Elution with 40% benzene–cyclohexane gave **5** (2–12%), as a viscous oil: ir 1740 cm⁻¹; nmr (CDCl₃) 255 cps (s, 2, CH₂); nmr (CCl₄) 250 cps; mass spectrum *m/e* 748; $[\alpha]^{CHCl_3}D$ +18.6°.

Anal. Calcd: C, 80.2; H, 11.2. Found: C, 80.15; H, 11.09.

Elution with 50% benzene–cyclohexane gave pure ketol acetate **4** (90%): mp 83°; $[\alpha]^{CHCl_3}D$ +22.6°; ir νco 1727 cm⁻¹; nmr (CDCl₃) 280 cps (s, 2, CH₂); nmr (CCl₄) 270 cps.

Anal. Calcd: C, 77.9; H, 10.6. Found: C, 77.55; H, 10.7.

(10) Plattens, H. ·Heusser, and Boyce, *Helv. Chim. Acta,* **31**, 603 (1948).

24-Oxo-25-hydroxyhomocholane (6). A. By Alkaline Hydrolysis of 4.—To a refluxing solution of the ketol acetate **4** (1.2 g) in *t*-BuOH (50 ml) a solution of 10% sodium bicarbonate in water (5 ml) was added, and the resulting solution was refluxed for 24 hr. The solvent was removed, and the residue was extracted with chloroform and washed with dilute HCl (1 N) and water. The chloroformic solution was dried over sodium sulfate and evaporated. The resulting ketol **6** (95%) was recrystallized from petroleum ether (bp 40–60°): mp 101°; $[\alpha]^{CHCl_3}D$ +29.5°; mass spectrum *m/e* 374; ir νco 1720 cm⁻¹; nmr (CCl₄) 245 cps (s, 2, CH₂); nmr (CDCl₃) 255 cps.

Anal. Calcd: C, 80.2; H, 11.2. Found: C, 79.9; H, 11.6.

B. By Acid Treatment of Diazo Ketone 3.—To a stirred solution of **3** (0.5 g) in THF (30 ml), 0.2 ml of 50% sulfuric acid was added. After 1 hr the reaction mixture was diluted with chloroform and washed with sodium bicarbonate and water. The chloroform layer was dried over sodium sulfate and evaporated. The residue was recrystallized from petroleum ether, mp 101°, yield 90%.

24-Oxo-25-ethoxyhomocholane (8).—A solution of diazo ketone **3** (0.5 g) in benzene (3 ml) was diluted with ethanol (30 ml) and stirred. To the resulting solution 0.1 ml of sulfuric acid was added. After 30 hr the reaction mixture was diluted with water, extracted with ether, and washed with water. The ether solution was dried over sodium sulfate and evaporated. The residue when chromatographed on silica gel gave the ethyl ether **8** (60%) (elution with 50% benzene–cyclohexane), the ketol **6** (30%) (elution with 70% benzene–cyclohexane), and cholanic acid (10%) (elution with benzene).

The ethyl ether **8** melted at 56°: ir νco 1730–1735 cm⁻¹; mass spectrum *m/e* 402; nmr (CCl₄) 229 (s, 2, CH₂), 207 (q, 2, CH₂), 78 cps (t, 3, CH₃).

Reaction of Diazo Ketone 3 with Sulfuric Acid in Benzene.—To a solution of diazo ketone **3** (300 mg) in benzene (50 ml), H₂SO₄ (0.2 ml) was added. The mixture was stirred for 1 hr and washed with water, and the solvent was removed. The product melted at 130° and could not be stored without decomposition: mass spectrum *m/e* 402; ir 1730 cm⁻¹; nmr (CDCl₃) 293 cps (s, 1, CH); nmr (CCl₄) 284 cps.

24-Methoxy-24,25-dihydroxyhomocholane (7).—A solution of ketol **6** (0.5 g) in methanol (30 ml) was treated with hydrogen chloride gas at room temperature. After standing for 24 hr the solvent was removed *in vacuo*. The residue was recrystallized from ether to give **7** (60%): mp *ca.* 200°; nmr (CDCl₃) 190 (s, 3, OCH₃), 214, 218 cps (double s, 2, –CH₂O–) (two isomers).

Reaction of Ketol Acetate 4, Ketol 6, and Dimeric Compound 5 with Potassium Hydroxide.—To a solution of **4** (5 g) in 10 ml of benzene, a 3% potassium hydroxide–ethanol solution (100 ml) was added and the reaction mixture was stirred for 10 hr, during which period solid material began to precipitate out. The mixture was acidified with dilute hydrochloric acid and extracted with chloroform. The solvent was removed and the residue was chromatographed on silica gel. Elution with benzene and chloroform gave cholanic acid (**1**, 95%) and α-hydroxyhomocholanic acid (**9**, 3%), respectively. The latter compound was oxidized (NaIO₄) by a known procedure[6] to the corresponding cholanic aldehyde **11**: mp 105°; nmr (CDCl₃) 586 cps (t, 1, –CHO, J = 1.5 cps).

Under nitrogen atmosphere the above reaction afforded beside the above two acids a mixture of nonacidic compounds. Tlc implied that one of them is α-hydroxyhomocholanic aldehyde (**10**). Oxidation with sodium periodate gave the same cholanic aldehyde (**11**), mp 105°. Ketol **6** and the dimeric compound **5** behaved similarly under the same conditions.

Reduction of Ketol Acetate 4 and Ketol 6 with NaBH₄ and LiAlH₄.—To a boiling solution of **4** (0.15 g) in 30 ml of ethanol a slight excess of NaBH₄ was added. After 0.5 hr the mixture was diluted with water and extracted with chloroform, and the solvent was removed. Pure diol **12** was obtained: mp 160°; $[\alpha]^{EtOH}D$ +28.0°; ir 860 (w), 953 (w), 1070 (w), 3400 cm⁻¹ (w); nmr (CDCl₃) 183 (s), 168 cps (d, J = 6 cps).

A similar treatment of ketol **6** afforded diol **12**. The yield was lower than for ketol **4** due to formation of unidentified less polar by-products.

Contamination of diol **12** also occurred when reduction of **4** was affected at room temperature with either NaBH₄ or LiAlH₄ in ethanol and ether solutions, respectively.

Reduction of the Dimeric Compound 5 with NaBH₄ and LiAlH₄.—To a stirred solution of **5** (0.1 g) in 30 ml of methanol a slight

excess of $NaBH_4$ was added. After 15 hr the mixture was diluted with water and extracted with chloroform. Almost pure methyl cholanate (13) was obtained: mp 87°; ir ν_{CO} 1740 cm^{-1}; nmr (CCl_4) 215 cps (s, 3, $-OCH_3$).

Reduction of 5 in ether solution with $LiAlH_4$ afforded cholanol (14) in high purity: mp 130°; [α]D +24.4 (CHCl$_3$, 1%); ir 3350–3380 (s), 1055 cm^{-1} (w); nmr (CDCl$_3$) 216 cps (t, 2, CH_2, J = 4 cps).

Acetylation of Ketol 6.—The acetylation of ketol 6 to the corresponding ketol acetate 4 could be affected by all known

procedures. The dimeric compound 5 resisted acetylation under all conditions.

Mass Spectrometry in Structural and Stereochemical Problems. CCXVIII.[1]
The Electron Impact Induced Behavior of Terpenoid Esters of the Juvenile Hormone Class[2]

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The 70- and 15-eV mass spectra of methyl 10,11-epoxy-*trans,trans*-farnesoate (III) and three deuterium-labeled analogs, *5,5-d$_2$* (VI), *8,8,8',8',8'-d$_5$* (V), and *12,12,12,12',12',12'-d$_6$* (IV), have been examined. Generation of the important peaks in the spectra of III at m/e 43, 71, 81, 114, and 135 are discussed in light of high resolution and metastable peak data as well as the shift of these peaks in the spectra of the deuterated analogs. The generation of the mass 114 ($C_6H_{10}O_2$) ion by methyl 2,6-dienoates is the subject of further study involving methyl *trans,-trans*-7-ethyl-3-methylundeca-2,6-dienoate (IX), methyl *trans,trans*-3,7-dimethyldeca-2,6-dienoate (XI), their *trans,cis* isomers, and several specifically deuterium-labeled C-8 or C-8' analogs. Methyl *trans,trans*-farnesoate (XIII) and several deuterium-labeled analogs are also subjects of investigation. In this latter case, C-12 and C-12' hydrogen transfer (*via* either a 10-, 12-, or 14-membered transition state) plays a substantial part in the mass 114 ion production.

Mass spectrometry played an essential role in the structure elucidation of the first *Cecropria* juvenile hormone I, isolated by Roeller and coworkers,[4] and again in the structure proof of the second hormone II found by Meyer and colleagues.[5] Trost has discussed

I, R' = R = C$_2$H$_5$
II, R' = C$_2$H$_5$; R = CH$_3$
III, R' = R = CH$_3$

IV

V

VI

several of the important mass spectral cleavages of the hormone I in light of the fragments observed in the spectrum of the lower homolog, methyl 10,11-epoxy-*trans,trans*-farnesoate (III),[6] and Meyer, *et al.*,[5] have presented the low-resolution spectrum of the hormone II together with high-resolution mass measurements of some of the fragment ions. The future will see the search for the juvenile hormones of other insects, and, since the acquisition of even a few micrograms of material is very difficult, a clear understanding of the mass spectral behavior of the juvenates[7] is imperative. Because of this and also because of our fundamental interest in the behavior of ionized polyfunctional molecules, we have examined the 70- and 15-eV mass spectra of the methyl 10,11-epoxy farnesoate III and three deuterium-labeled analogs (IV–VI).

Results and Discussion

Peaks in the low mass range dominate the 70-eV spectrum (Figure 1a) of the methyl epoxy farnesoate III; those at m/e 43 (66% C_3H_7), 71 (C_4H_7O), 81 (C_6H_9), 114 ($C_6H_{10}O_2$), and 135 ($C_{10}H_{15}$) are particularly intense. None of these fragments arise by simple bond cleavage; as our results show, hydrogen rearrangement is essential in each case. At low ionizing energy (15 eV), fragments in the high mass region of the spectrum (Figure 1b) assume greater importance. One of the more significant peaks is found at m/e 248 (M − H_2O) and results from the migration of two hydrogen atoms to the epoxide oxygen. Loss of CH_3OH from the molecular ion generates an ion of mass 234, which, together with the mass 206 ion [M − (CH_3OH + CO)], serves to identify the ester group. Analysis of the

(1) For preceding paper, see Y. Sheikh, R. J. Liedtke, A. M. Duffield, and C. Djerassi, *Can. J. Chem.*, in press.

(2) Financial assistance by the National Institutes of Health (Grant No. GM-06840) is gratefully acknowledged.

(3) National Institutes of Health Predoctoral Fellow, 1968–1971.

(4) H. Roeller, K. H. Dahm, C. C. Sweeley, and B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 6, 179 (1967).

(5) A. S. Meyer, H. A. Schneiderman, E. Hanzmann, and J. H. Ko, *Proc. Nat. Acad. Sci. U. S.*, 60, 853 (1968).

(6) B. M. Trost, *Accounts Chem. Res.*, 3, 120 (1970).

(7) Nomenclature suggested by E. E. van Tamelen; see ref 5.
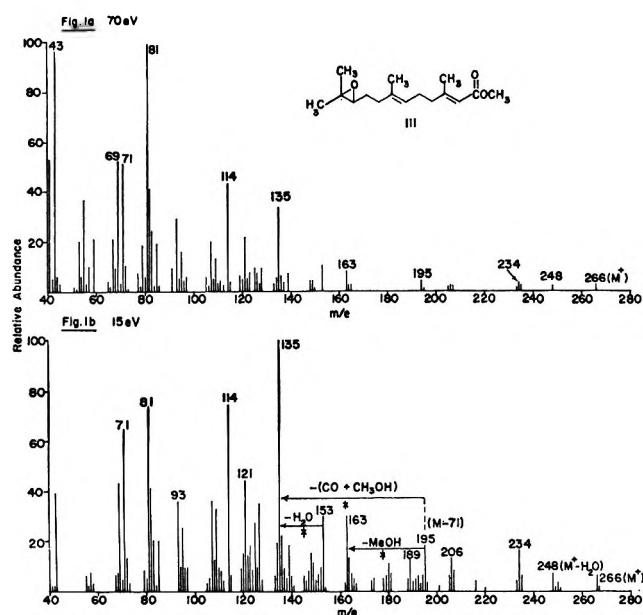
Figure 1.—Mass spectra (70 and 15 eV) of methyl 10,11-epoxy-*trans,trans*-farnesoate (III).

spectra of the deuterium-labeled analogs IV–VI and the high-resolution data presented in Table I makes

TABLE I

HIGH-RESOLUTION MASS MEASUREMENTS OF IMPORTANT METHYL 10,11-EPOXY-*trans,trans*-FARNESOATE (III) PEAKS AT 70 eV

Peak *m/e*	Composition	Peak *m/e*	Composition
41	100% C_3H_5	93	100% C_7H_9
43	34% C_2H_3O,	95	45% C_6H_7O,
	66% C_3H_7		55% C_7H_{11}
53	100% C_4H_5	105	100% C_8H_9
55	11% C_3H_3O,	107	12% C_7H_7O,
	89% C_4H_7		88% C_8H_{11}
57	31% C_3H_5O,	109	29% C_7H_9O,
	69% C_4H_9		71% C_8H_{13}
59	62% $C_2H_3O_2$,	114	100% $C_6H_{10}O_2$
	38% C_3H_7O	121	3% C_8H_9O,
67	100% C_5H_7		97% C_9H_{13}
68	100% C_5H_8	125	42% $C_7H_9O_2$,
69	22% C_4H_5O,		51% $C_8H_{13}O$,
	78% C_5H_9		7% C_9H_{17}
71	98% C_4H_7O,	127	27% $C_7H_{11}O_2$,
	2% C_5H_{11}		73% $C_8H_{15}O$
72	100% C_4H_8O	135	8% $C_9H_{11}O$,
77	100% C_6H_5		92% $C_{10}H_{15}$
79	100% C_6H_7	139	68% $C_8H_{11}O_2$,
81	2% C_5H_5O,		32% $C_9H_{15}O$
	98% C_6H_9	153	100% $C_{10}H_{17}O$
82	100% C_6H_8O	163	100% $C_{11}H_{15}O$
83	68% C_5H_7O,	195	100% $C_{12}H_{19}O_2$
	32% C_6H_{11}	206	100% $C_{14}H_{22}O$
85	100% C_5H_9O	234	100% $C_{15}H_{22}O_2$
91	100% C_7H_7	248	100% $C_{16}H_{24}O_2$
		266	100% $C_{16}H_{26}O_3$

possible the proposal of plausible mechanistic schemes for the genesis of the more important fragments.

Peaks at *m/e* 43 and 71.—In the spectrum (not reproduced) of the terminally d_6-labeled methyl epoxy-farnesoate (IV), the *m/e* 71 peak appears nearly quantitatively (>93%) at *m/e* 77, and its generation can thus be pictured as in Scheme I.

SCHEME I

III, *m/e* 266 (R = CH_3)
IV, *m/e* 272 (R = CD_3)

c, *m/e* 49 (R = CD_3)
m/e 43 (R = CH_3)

b, *m/e* 71 (R = CH_3)
m/e 77 (R = CD_3)
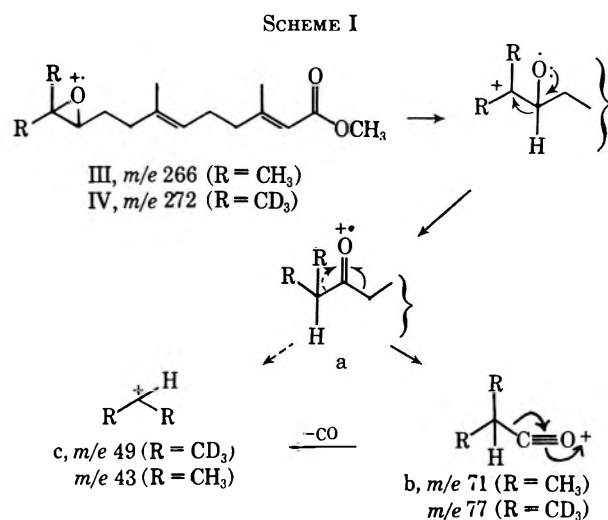
Support of this mechanism comes from the observation that >95% of the hydrocarbon *m/e* 43 fragment shifts to *m/e* 49 in the spectrum of IV (Scheme I).[8]

Peak at *m/e* 81.—The appearance of the base peak in the 70-eV spectrum (Figure 1a) of the methyl 10,11-epoxy farnesoate III at *m/e* 81 is remarkable, since the generation of this hydrocarbon ion (C_6H_9) must involve two carbon–carbon bond cleavages and the additional transfer of one hydrogen atom.[10] From the data listed in Table II, the conclusion can be drawn that the *m/e* 81 species contains carbon atoms 5, 6, 7, 8, 8′, and 9 (for numbering see Scheme II). Furthermore, the shift of the *m/e* 81 peak to *m/e* 85 in the spectrum of the deuterium-labeled epoxy ester V means that hydrogen migration from C-8 or C-8′ is involved.

The mechanisms outlined in Scheme II are in accord with these requirements. As in the generation of the mass 114 ion (see below), the hydrogen migration pictured in path B could equally well be drawn to C-2, or to C-4 with accompanying C-4 hydrogen transfer to the carbonyl oxygen. A mechanism analogous to that given for the generation of ions d and e (paths A, B) has been proposed by Meyerson[11] to explain the facility of ε cleavage in certain cis α,β-unsaturated esters.

Peak at *m/e* 135.—Metastable defocusing data demonstrate three important precursors of the mass 135 fragment, namely ions of mass 153, 163, and 195.

(8) It is of interest that in the spectrum of the simple epoxide i, the ion

i
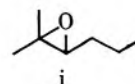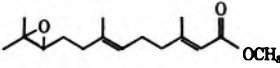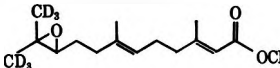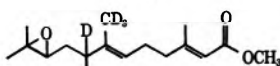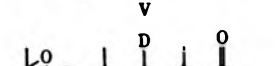
of mass 85 (β cleavage) is more abundant, ratio 5:1, than the ion of mass 71 (α cleavage), whereas in the spectrum (Figure 1) of the methyl epoxy farnesoate III the peak at *m/e* 71 (α cleavage) is the more intense.[9]

(9) The mass spectrometric behavior of simple epoxides has been extensively studied: P. Brown, J. Kossanyi, and C. Djerassi, *Tetrahedron, Suppl. 8, Part I*, 241 (1966).

(10) Eight precursors for the *m/e* 81 ions formed in the first field free region were found using the metastable defocusing procedure, but the exact masses of these precursors were not determined.

(11) S. Meyerson, *Int. J. Mass Spectrom. Ion Phys.*, 1, 309 (1968).

TABLE II

SHIFT OF THE m/e 81 PEAK IN THE SPECTRA OF THE DEUTERIUM-LABELED ANALOGS OF METHYL
10,11-EPOXY-*trans,trans*-FARNESOATE

Compd	Intensities[a] of peaks in the m/e 77-88 region at 70 eV											
	77	78	79	80	81	82	83	84	85	86	87	88
III	4	1	9	2	48	16	11	1	9	1		
IV	4	1	7	2	59	11	6	3	1	1		
V	1	1	3	3	4	14	5	7	50	9	1	
VI	1	2	3	4	8	16	53	2	12			

[a] Peak intensities are summed, then normalized to 100%; values are rounded to the nearest whole number.

SCHEME II

SCHEME III
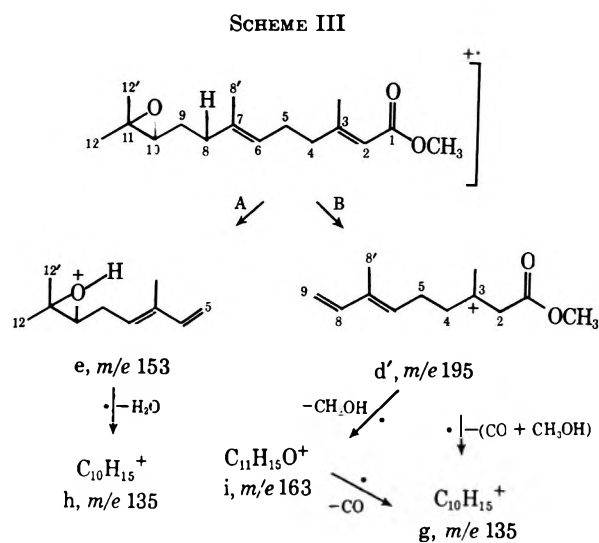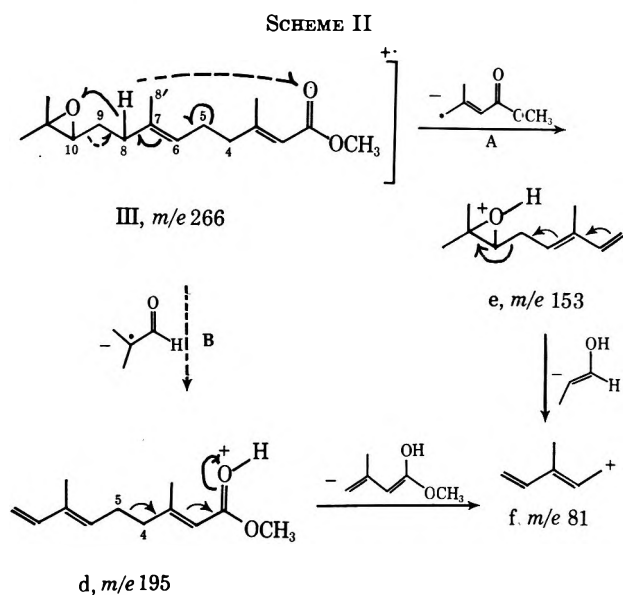
Furthermore, in the spectrum (not reproduced) of the d_6-labeled epoxy farnesoate IV, whereas 60% of the m/e 135 peak remains at m/e 135, the remaining 40% shifts to m/e 141. It is clear then that two structurally unique mass 135 ions (g and h) are generated (Scheme III). Ion h encompasses C-5 through C-12 and its formation from the C-8 protonated epoxide ion e of mass 153 is supported by evidence obtained from the spectrum of the d_5-labeled epoxy farnesoate V. Metastable peaks are observed corresponding to the ejection of HDO and D$_2$O from the mass 153 fragment but no peak for the elimination of H$_2$O is visible.[12]

Loss of 60 mass units from a mass 195 precursor to give ion g (C-2 through C-9) is more difficult to rationalize, but appears to involve the sequential and simultaneous expulsion of CH$_3$OH and CO (Scheme III). The available data does not indicate the origin of the hydrogen atom which migrates in the process of methanol elimination.

(12) In the spectrum of V, the m/e 135 peak shifts to m/e 138 (~25%), 139 (~25%), and 140 (~50%). Precise calculations and interpretation are not possible, but, if the entire m/e 140 peak is assigned to ion g, then it appears that ejection of DHO and D$_2$O occurs with about equal facility to give ion h.

Ions analogous to g and h should provide valuable structural information pertaining to hormones analogous to I. For example, in the spectrum of I, an ion produced by path A of Scheme III would be expected to appear at m/e 163, whereas an ion of mass 149 would result from operation of path B. Indeed, examination of this hormone's 70-eV mass spectrum[6] does confirm these predictions, and no doubt decreasing the ionizing voltage would enhance the abundance of these fragments.

Peak at m/e 114.—The generation of the important mass 114 ion involves transfer of one hydrogen atom to the C$_6$H$_{10}$O$_2$ charge-retaining fragment. In the spectrum of the $8,8,8',8',8'$-d_5-labeled epoxy ester V, roughly 60% of the m/e 114 peak shifts to m/e 115, thus implicating C-8 and C-8' hydrogen migration to this extent. In contrast (see below) to the case of methyl farnesoate (XIII), C-12 and C-12' hydrogen migration is only of minor importance (~10%). Hydrogen exchange or other mechanistic paths apparently are responsible for the 30% of the transferred hydrogen unaccounted for.

Occurrence of m/e 114 Peak in Methyl Dienoates.—An intense m/e 114 peak is not unique to the juvenate
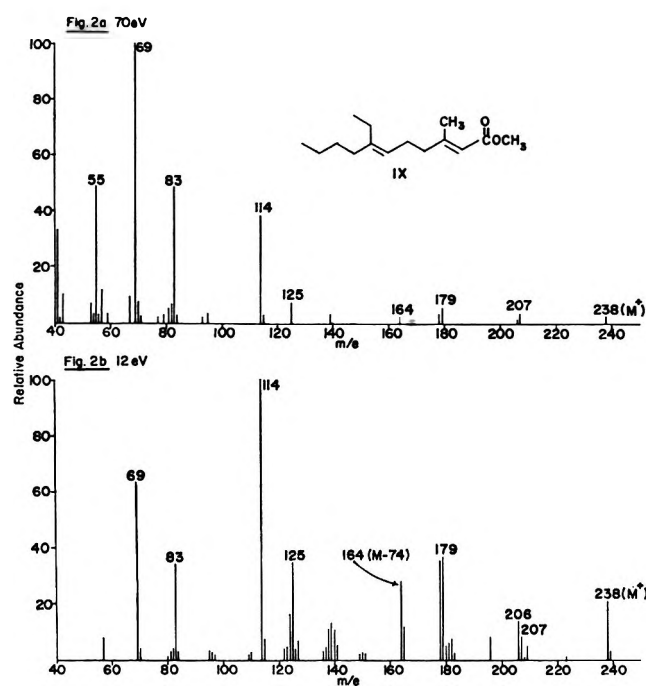
Figure 2.—Mass spectra (70 and 12 eV) of methyl *trans,trans*-7-ethyl-3-methylundeca-2,6-dienoate (IX).

mass spectra. Thomas, *et al.*,[13] have observed that the mass 114 fragment in the spectrum of methyl geranate (VII) shifts to mass 115 in the spectrum of the d_6 terminally labeled analog VIII.

Methyl *trans,trans*-7-ethyl-3-methylundeca-2,6-dienoate (IX) and its trans,cis unsaturated isomer X were
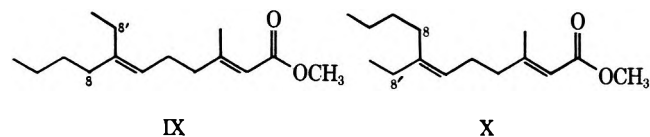
prepared to examine the behavior of compounds which possess both C-8 and C-8' hydrogens and which allow specific labeling of one of these positions with deuterium. The 70- and 12-eV spectra (see Figure 2 for the 70- and 12-eV spectra of IX) of these compounds are identical and generation of the mass 114 ion is indeed a favored fragmentation route for these esters, which accounts for the base peak at low ionizing energy. Examination of the spectra of the deuterium-labeled analogs of compounds IX and X reveals that the hydrogens attached to C-8 and C-8' have equal migratory aptitudes and that a substantial isotope effect (IE = atoms of deuterium transferred/atoms of hydrogen)[14] is operative (see Table III).

Since no preference for hydrogen migration from the C-8 or C-8' position of the unsaturated ester is apparent, examination of the shift of the m/e 114 peak in the spectra of deuterium-labeled analogs of methyl *trans,trans*-3,7-dimethyldeca-2,6-dienoate (XI) and its trans,cis double bond isomer XII will yield information

(13) A. F. Thomas, B. Willhalm, and R. Müller, *Org. Mass Spectrom.*, **2**, 223 (1969).
(14) J. K. MacLeod and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 5182 (1967).

TABLE III

SHIFT OF THE m/e 114 PEAK IN THE MASS SPECTRA OF THE DEUTERIUM-LABELED ANALOGS OF METHYL 7-ETHYL-3-METHYLUNDECA-2,6-DIENOATE AND METHYL 3,7-DIMETHYLDECA-2,6-DIENOATE

Compd		m/e 114 peak which appears at		
	70 eV 114	70 eV 115	12 eV 114	12 eV 115
IXa	64	36	64	36
IXb	64	36	62	38
Xa	65	35	65	35
Xb	61	39	61	39
XIc (trans,cis) + (trans,trans)	9	91	11	89
XIa	78	22	84	16
XIb	44	56	42	58
XIIa	76	24	82	18
XIIb	49	51	44	56

concerning the relative preference of primary allylic *vs.* secondary allylic hydrogen migration (see Table III) after correction for the greater availability of primary hydrogens, and the isotope effect (IE) as well may be estimated. At 70 eV, 76% secondary allylic hydrogen transfer occurs and this value increases to 81% at 12 eV. The calculated IE equals 0.71 at 70 eV and 0.63 at 12 eV.[15]

The spectra (70 and 12 eV) of methyl *trans,trans*-farnesoate (XIII) are shown in Figures 3a and 3b.

XIII

(15) This IE is estimated reasonably assuming no substantial IE on subsequent decompositions of the m/e 114 and 115 ions.

Analysis of the mass spectra (Table IV) of several deuterated analogs of XIII shows, remarkably, that

TABLE IV

SHIFTS OF THE m/e 114 PEAK IN THE SPECTRA OF
DEUTERIUM-LABELED ANALOGS OF METHYL FARNESOATES

| | Per cent of m/e 114 peak which appears at | | | |
| | 70 eV | | 12 eV | |
Compd	114	115	114	115
XIIIa	100	0	100	0
XIIIb	67	33	50	50
XIIIc	47	53	73	27

at 70 eV most of the hydrogen transferred in the process of mass 114 ion production originates from the terminal C-12 and C-12′ positions. On the other hand, transfer from C-8 and C-8′ is the favored route at low ionizing energy. At 70 eV, 86% of the migrating hydrogen is accounted for, but only 77% at 12 eV. The difference from 100% is probably due to a small isotope effect and some hydrogen migration from positions other than those labeled. A small amount of hydrogen randomization could also contribute to this result.

Possible Mechanistic Pathways to the m/e 114 Peak. —In analogy to the McLafferty rearrangement exhibited by carbonyl-containing compounds and olefins, the hydrogen atom could be transferred to the carbonyl oxygen through a ten-membered transition state as shown (Scheme IV, path A) for methyl geranate

SCHEME IV

VII, R = CH₃
VIII, R = CD₃

i m/e 114

j m/e 114
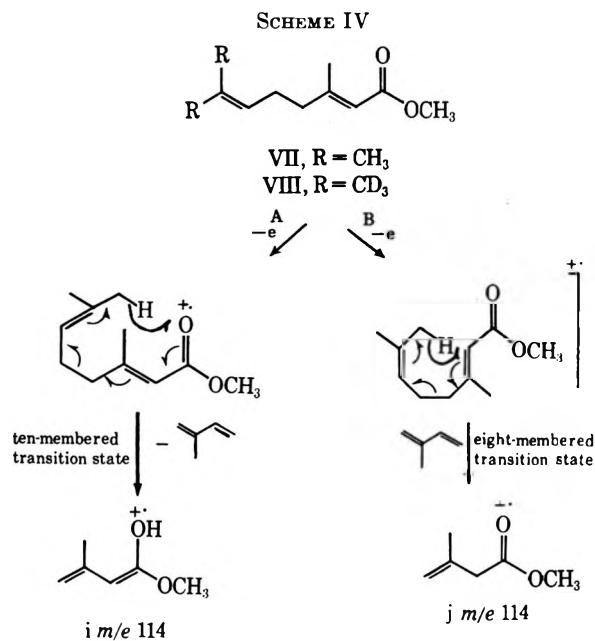
producing a dienolic ester ion of mass 114 (i). Alternatively, transfer to the C-2 carbon atom (eight-membered transition state) would generate the enone ion j (Scheme IV, path B).
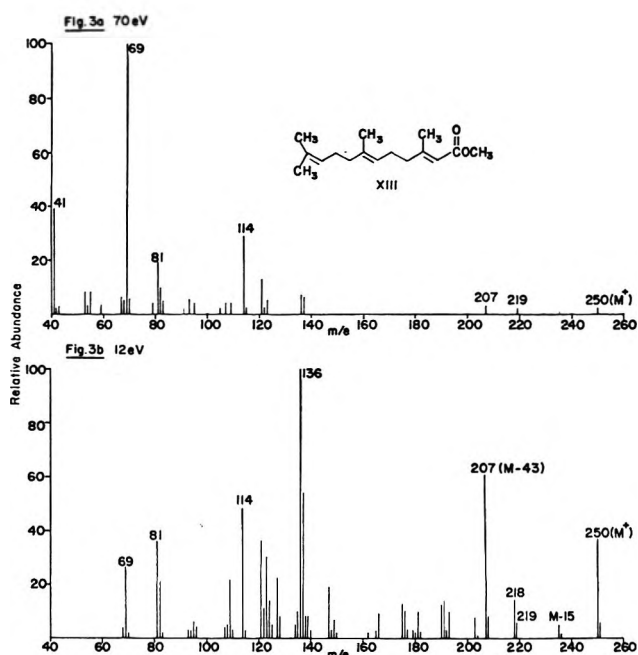
Figure 3.—Mass spectra (70 and 12 eV) of methyl *trans,trans*-farnesoate (XIII).

Thomas and coworkers[13] propose yet another possibility which involves first movement of the α,β double bond to the β,γ position *via* migration of a C-4 allylic hydrogen atom to the carbonyl oxygen, and then transfer of a hydrogen from C-8 or C-8′ to C-4, giving the dienolic ester ion i. Either our mechanism or that of Thomas would account for the terminal hydrogen migration observed in the case of methyl farnesoate (XIII).
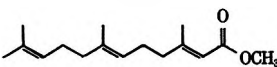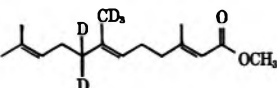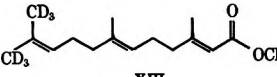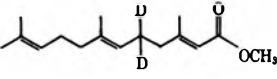
The m/e 136 Peak in Methyl Farnesoate (XIII).— The mass 136 hydrocarbon ion ($C_{10}H_{16}$) which accounts for the base peak at 12 eV in the spectrum (Figure 3b) of methyl *trans,trans*-farnesoate (XIII), results from elimination of a mass 114 neutral fragment by the molecular ion. This mass 136 ion might be expected to arise by the same processes (*cf.* Scheme IV) involved in the generation of the mass 114 species, the charge being retained in this case by the hydrocarbon fragment. However, in the spectrum of the d_5 ester XIIIb, the m/e 136 peak appears at m/e 141, whereas it moves to m/e 142 in the spectrum of the d_6 ester XIIIa (Table V). Thus, *a fundamentally different mechanistic pathway must be involved in the production of the ion of mass 136.* A plausible suggestion appears in Scheme V.

SCHEME V

XIII

k m/e 136

m m/e 136

k′ 136
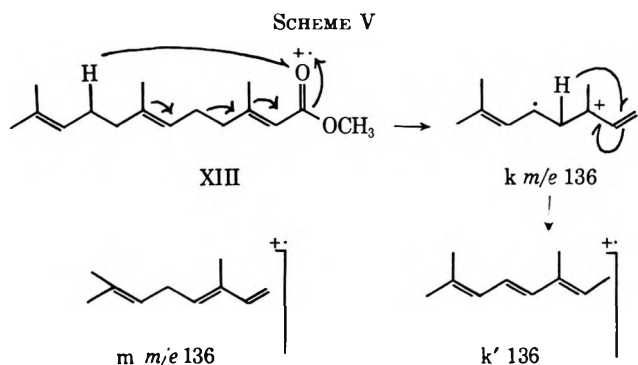
It could be the case that the ion k or the ionized triene k′ has a lower ionization potential than the expelled

TABLE V

SHIFT OF THE m/e 136 PEAK IN THE SPECTRA OF DEUTERIUM-LABELED METHYL FARNESOATES

Compd	Intensities of ions in the m/e 133 to 144 region at 12 eV[a]											
	133	134	135	136	137	138	139	140	141	142	143	144
XIII	1	2	6	56	25	2	4	2	1			
XIIIb						1[b]	4	2	55	26	1	
						2	3	6				
XIIIc			4	2	1	2	5	4	5	53	24	1
XIIIa			2	2	7	53	26	3	4	2	1	

[a] Peak intensities are summed, then normalized to 100% hydrocarbon fragment. [b] Upper number is oxygen-containing fragment, lower number is hydrocarbon fragment.

neutral mass 114 species and thus carries the positive charge. On the other hand, ion m apparently has a higher ionization potential than the mass 114 species (i or j). Similar reasoning has been used to explain the fact that the McLafferty rearrangement of hexanal involves site-specific γ-hydrogen transfer, whereas formation of the complementary olefin ion of mass 56 involves not only γ-hydrogen transfer but also δ-hydrogen migration.[16]

Synthesis of Labeled Compounds.—Several methods were employed to synthesize the deuterium-labeled methyl 2,6-dienoates. One procedure started with an appropriate cyclopropyl alkyl ketone, *e.g.*, cyclopropyl methyl ketone (Scheme VI). Preparation of

SCHEME VI
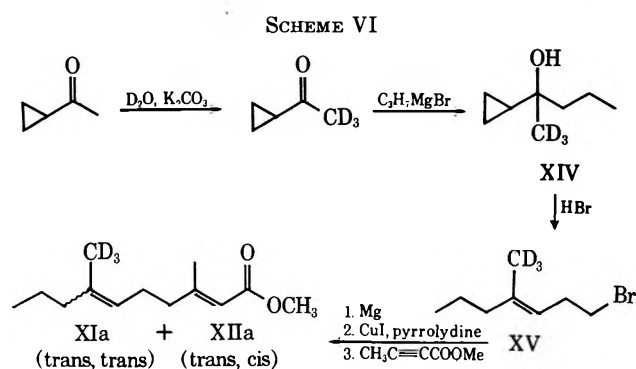
the homoallylic bromide XV (70% trans) was accomplished according to the conditions of Julia.[17] Conjugate addition[18] of the corresponding organocopper reagent to methyl 2-butynoate at −78° gave the dienoates XIa and XIIa in fair yield.

Another highly versatile method (Scheme VII) made use of the trans aldehydo unsaturated ester XVI. Alkylation of the ylide derived from the phosphonium salt XVII (butyllithium) with *1,1-d₂*-1-bromopropane gave the labeled secondary phosphonium salt XVIII

(16) S. Meyerson, C. Fenselau, J. L. Young, W. R. Landis, E. Selke, and L. C. Leitch, *Org. Mass Spectrom.*, **3**, 689 (1970).

(17) M. Julia, S. Julia, T. S. Yu, and C. Newville, *Bull. Soc. Chim. Fr.*, 1849 (1961).

(18) J. B. Siddall, M. Biskup, and J. H. Fried, *J. Amer. Chem. Soc.*, **91**, 1853 (1969).
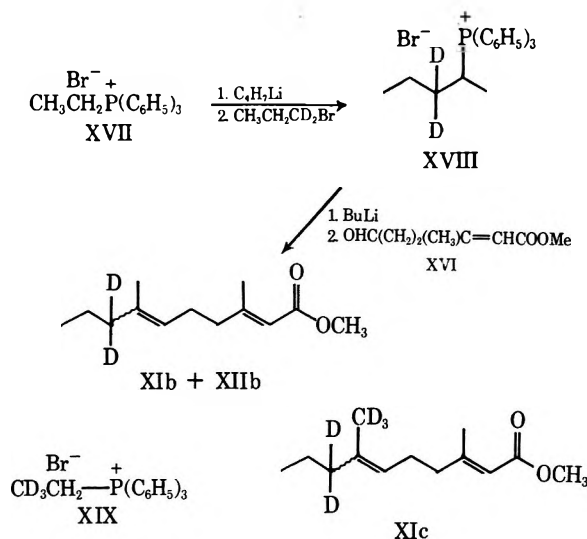
SCHEME VII

(Scheme VII). Addition of another equivalent of butyllithium followed by the reaction of the resulting phosphorane with XVI produced a mixture of trans and cis 6,7 double bond isomers XIb and XIIb. Beginning with the deuterium-labeled phosphonium salt XIX and following these procedures, the methyl dienoate XIc was produced.

The deuterium-labeled methyl epoxy farnesoates were made from the corresponding deuterated methyl farnesoates (XIIIa–c) by reaction with *N*-bromosuccinimide in water–tetrahydrofuran, purification (tlc), and treatment with a fourfold excess of dry potassium carbonate. The syntheses of the labeled farnesoates are outlined in Schemes VIII–X.

Experimental Section

Mass spectra of the α,β-unsaturated esters and epoxy farnesoates were obtained by Mr. R. G. Ross using an AEI MS-9 double-focusing mass spectrometer (heated inlet 150°, ion source temperature 180°) and by Mr. R. Conover on an Atlas CH-4 instrument using an E-4B ion source and direct insertion probe (samples adsorbed on charcoal). Spectra of compounds run on both of these instruments were essentially identical. Metasta-

SCHEME VIII

III

1. HClO$_4$–THF
2. NaIO$_4$

XX

(C$_6$H$_5$)$_3$P=C(CD$_3$)$_2$

XIIIc

SCHEME IX

D$_2$O, K$_2$CO$_3$, glyme

CH$_2$=CHMgBr

(CH$_3$O)$_2$POCH$_2$COOCH$_3$, NaH

XIIIb

SCHEME X

VII

LiAlD$_4$, AlCl$_3$

1. PBr$_3$
2. CH$_3$COČHCOOCH$_3$, Na$^+$
3. Ba(OH)$_2$, EtOH, H$_2$O

(CH$_3$O)$_2$POCH$_2$COOCH$_3$, NaH

XIIIa

ble transitions in the first field-free region were observed with the aid of the defocusing procedure.[19] The 2,6-dienoates were submitted for mass spectral measurement only after purification by vapor phase chromatography (unless otherwise noted a 6 ft × 0.25 in., 3% OV 25 on Gas-Chrom Q column, or a 6 ft × 0.25 in., 5% Carbowax 20M on Chromosorb W column were used, both columns glass). The methyl epoxy farnesoates were purified by tlc.

Infrared characterization was carried out using a Perkin-Elmer Model 700 spectrophotometer. Nmr spectra were obtained with either a Varian Model T-60 spectrometer or a Varian HA-100 spectrometer (measured by Mr. M. Bramwell) and are recorded in δ values with carbon tetrachloride as solvent and tetramethylsilane as an internal reference standard. The spectral characteristics not explicitly stated of all compounds used in this study were found to be in agreement with the material's assigned structure. The elementary composition of all new compounds was determined by mass spectral molecular weight determination.

Methyl *trans*-3-Methyl-6-oxohex-2-enoate (XVI).—In a dry 1-l. flask (nitrogen) were placed dimethylformamide (250 ml) and sodium methoxide (17.1 g, 0.95 equiv). Trimethyl phosphonoacetate[20] (60 g) in dimethylformamide (50 ml) was added over 15 min, the mixture was stirred for 15 min, and then 6-methylhept-5-en-2-one[20] (40 g) in 50 ml of dimethylformamide was added. After stirring overnight, the mixture was poured into 90% brine–water and extracted with ether. The organic

material was washed with brine and dried over sodium sulfate. Methyl geranate (14 g, 99% trans) was isolated by spinning band distillation.

To methyl *trans*-geranate (VII) (10 g) in 30 ml of dichloromethane at 0° was added *m*-chloroperbenzoic acid (12.3 g, 10% excess) and the reaction was worked up after 30 min by pouring into 10% sodium sulfite. The organic material was separated, washed with 5% potassium bicarbonate and brine, and dried over magnesium sulfate, and the solvent was evaporated. The crude epoxy geranate (10 g) was dissolved in tetrahydrofuran (50 ml) and water (50 ml). Perchloric acid (3%, 4 ml) was added; and after 30 min sodium chloride (20 g) was added, the organic material separated, and the aqueous phase was extracted three times with ether. The combined organic extracts were washed with saturated sodium carbonate and brine and dried over magnesium sulfate. Evaporation of the solvent gave the corresponding crude diol (10 g). The diol was dissolved in 50 ml of tetrahydrofuran (nitrogen), and sodium periodate (11 g in 75 ml of water) was added at 0°. The mixture was stirred at 0° for 1 hr and at 25° for 0.5 hr. Brine and ether were added and the organic material was separated, washed with sodium bicarbonate and brine, and dried over calcium chloride. Distillation gave 5.5 g of methyl *trans*-3-methyl-6-oxohex-2-enoate (XVI), bp 150–152 (aspirator pressure), one peak by vpc.[21]

Methyl *trans,trans*-3,7-Dimethyldeca-2,6-dienoate (XI) and Methyl *trans,cis*-3,7-Dimethyldeca-2,6-dienoate (XII).—Cyclopropyl methyl ketone (12 g) was added to propylmagnesium bromide (10% excess) and the mixture was stirred for 3 hr and worked up in the usual fashion to yield 13 g of 2-cyclopropylpentan-2-ol (XXI),[22] bp 78–80° at aspirator pressure. The alcohol XXI was treated with 49% hydrobromic acid[17] to give 1-bromo-4-methylhept-3-ene (XXII),[22] yield 13.7 g after distillation. A better purification procedure involves eluting the bromide from a column of acid-washed alumina with hexane.

In a dry flask (argon) was placed magnesium (1.77 g, 73 mmol) and ether (3 ml); a little of the bromide XXII was added and the reaction began quickly. Ether (110 ml) was added and the remaining bromide (12 g, 62.8 mmol) in ether (100 ml) was added dropwise over 2 hr; the mixture was stirred overnight. Titration of an aliquot according to the procedure of Watson and Eastham[23] indicated a 65% yield (0.22 M solution). To 100 ml of the 0.22 M homoallylic Grignard reagent at −10° were added copper iodide (5 g, 1.2 equiv) and pyrrolidine (1.88 g, 1.2 equiv);

(19) (a) K. R. Jennings, "Some Newer Physical Methods in Structural Chemistry," R. Bonnett and J. G. Davies, Ed., United Trade Press, London, 1967, p 105; (b) T. W. Shannon, T. E. Mead, C. G. Warner, and F. W. McLafferty, *Anal. Chem.*, **39**, 1748 (1967).

(20) Available from the Aldrich Chemical Co.

(21) The procedures used were suggested by Dr. Clive Henrick of the Zoecon Corp., who also supplied an authentic sample of the material.

(22) J. Kulesza, J. Gora, and K. Katarzyna, *Riechst., Aromen, Koerperpflegem.*, **19**, 192, 194, 199–200 (1969); *Chem. Abstr.*, **71**, 102020q (1969).

(23) S. Watson and J. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

this mixture was stirred at 20° for 1 hr (Gilman test can be used) and cooled to −78°. Methyl 2-butynoate (1 equiv) was then added, and the mixture was stirred at 78° for 1 hr and worked up by first the slow addition of methanol (−78°) and then pouring into saturated ammonium chloride. The mixture was filtered, and the organic material in the filtrate was separated and washed with water and brine. Evaporation of the solvent gave 4.5 g of crude product which was best purified by column chromatography (silica gel, 3% ether–hexane) giving a mixture of the four possible double-bond isomers of methyl 3,7-dimethyldeca-2,6-dienote (2.4 g); the trans α,β-unsaturated isomers (XI and XII) predominated (85%). The main two peaks (XI and XII) overlapped on vpc; these were collected together. Nmr indicated the presence of the trans 6,7 double bond compound XI (73%) and the cis 6,7 isomer XII (27%). Repetitive vpc runs made separation of XI and XII possible. XI had ir λ_{max}^{neat} 1720, 1646 cm^{-1}; nmr δ 0.85 (t, 3 H, CH$_3$CH$_2$), 1.37 (m, 2 H, CH$_3$CH$_2$), 1.59 [s, 3 H, C$_3$H$_7$(CH$_3$)=C], 1.95 (t, 2 H, CH$_3$CH$_2$CH$_2$C=C), 2.16 [m, 7 H, CHCH$_2$CH$_2$(CH$_3$)=C], 3.67 (s, 3 H, COOCH$_3$), 5.08 [m, 1 H, C$_3$H$_7$ (CH$_3$)C=CH], 5.66 (broad s, 1 H, CH-COOCH$_3$); M$^+$ 210. The chemical shift of the C-7 methyl group allows the assignment of the 6,7 double bond stereochemistry.[24]

The deuterium-labeled methyl dienoates XIa and XIIa were prepared in an analogous manner starting with cyclopropyl d_3-methyl ketone.

Methyl *trans,trans* 8,8-d_2-3,7-Dimethyldeca-2,6-dienoate (XIb) and Methyl *trans,cis*-8,8-d_2-3,7-Dimethyldeca-2,6-dienoate (XIIb).—To ethyltriphenylphosphonium bromide (1.1 g, 3.22 mmol) in 50 ml of ether (distilled from lithium aluminum hydride) under argon was added butyllithium (1 equiv, 1.6 M in hexane). After 2 hr at 25°, 1,1-d_2-1-bromopropane[25] (1.3 equiv) was added. The red phosphorane reacted slowly, but after 2 days at reflux the solution was essentially clear with a white precipitate of the labeled secondary phosphonium salt present. Addition of butyllithium (1 equiv) generated the corresponding dark red ylide, to which was added the aldehydo ester XVI (1 equiv); an immediate white precipitate formed. The mixture was stirred overnight (25°), hexane was added, and this mixture was filtered and finally extracted with water and brine and dried over magnesium sulfate. Evaporation of the solvent and bulb-to-bulb distillation gave a mixture (~1:1) of the deuterium-labeled methyl dienoates XIb and XIIb (350 mg). These were separated by preparative vpc: XIb M$^+$ 212 (99% d_2), 211 (1% d_1); XIIb M$^+$ 212 (99% d_2), 211 (1% d_1).

In a similar manner, starting with (2,2,2-d_3-ethyl)triphenylphosphonium bromide,[26] methyl 8,8,8',8',8'-d_5-3,7-dimethyldeca-2,6-dienoate (XIc) was prepared. This material, after preparative vpc, was submitted for mass spectral analysis as a mixture of the trans,cis and trans,trans isomers, M$^+$ 215 (98% d_5), 214 (2% d_4).

Methyl *trans,trans*-7-Ethyl-3-methylundeca-2,6-dienoate (IX) and Methyl *trans,cis*-7-Ethyl-3-methylundeca-2,6-dienoate (X).— These compounds were prepared by procedures analogous to those employed to make the methyl dienoates XI and XII. The starting material, cyclopropyl butyl ketone, was prepared by the addition of butyllithium to the lithium salt of cyclopropanecarboxycyclic acid in glyme.[28] Treatment of cyclopropyl butyl ketone in glyme with deuterium oxide and potassium carbonate at reflux (three successive times) gave cyclopropyl α,α-d_2-butyl ketone. This labeled ketone was the precursor of methyl *trans,trans*-8,8-d_2-7-ethyl-3-methylundeca-2,6-dienoate (IXb) and methyl *trans,cis*-8,8-d_2-7-ethyl-3-methylundeca-2,6-dienoate (Xb): XVIb M$^+$ 240 (99% d_2), 239 (1% d_1); Xb M$^+$ 240 (99% d_2), 239 (1% d_1).

In order to unequivocally assign the 6,7 double bond stereochemistry of the dienoates IX and X, the trans,trans isomer IX was synthesized stereoselectively.[29] Propyl bromide (0.4 ml, 10% excess) was added to lithium wire (58 mg) in 5 ml of dry

ether (argon) at −10° until the lithium disappeared (about 2 hr). After further cooling to −25°, cuprous iodide (2 mmol) was added, giving a black solution of dipropylcopper lithium. The acetate ester of methyl *trans*-6-hydroxy-7-ethyl-3-methylocta-2,7-dienoate[30] (0.5 mmol) was next added, giving (after work-up in the usual fashion with saturated ammonium chloride) in 90% yield the trans,trans dienoate (less than 10% of the trans,cis isomer was present).

Methyl *trans,trans*-8',8'-d_2-7-Ethyl-3-methylundeca-2,6-dienoate (IXa) and Methyl *trans,cis*-8'-d_2-7-Ethyl-3-methylundeca-2,6-dienoate (Xa).—The deuterium-labeled methyl dienoates IXa and Xa were prepared following an analogous method to that used for the methyl dienoates XI and XIIb. The phosphorane derived from *n*-pentyltriphenylphosphonium bromide (butyllithium) was alkylated with 1,1-d_2-1-iodoethane (12 hr, 25°); another equivalent of butyllithium was added and finally the aldehydo ester XVI. Work-up followed as usual and the isomers IXa and Xa were separated by repetitive vpc: IXa M$^+$ 240 (98% d_2), 239 (2% d_1); Xa M$^+$ 240 (98% d_2), 239 (2% d_1).

Methyl *trans,trans*-Farnesoate (XIII).—6-Methylhept-5-en-2-one was added to a solution of vinylmagnesium bromide[31] (10% excess) in tetrahydrofuran to give 3-hydroxy-3,7-dimethylocta-1,6-diene (XXIII). The alcohol XXIII was heated (200°) overnight with a 1.5-fold excess of methyl acetoacetate according to the conditions of Carroll.[32] Distillation gave in 60% yield 6,10-dimethylundeca-5,9-dien-2-one (XXIV).

Sodium hydride (497 mg of 55% dispersion, 11.1 mmol) was washed with pentane under argon; dimethylformamide (4 ml) was added and then trimethyl phosphonoacetate (1.88 g, 10.3 mmol). This mixture was stirred for 1 hr and the ketone XXIV (2.0 g, 10.3 mmol) was added in 3 ml of dimethylformamide. After stirring for 6 hr, the mixture was poured into 90% brine, the aqueous layer was extracted with ether, and the organic material was combined, washed with water and brine, and dried. Distillation (bulb-to-bulb, 1 Torr) gave methyl farnesoate as a mixture of four isomers. Methyl *trans,trans*-farnesoate (XIII) was purified by preparative vpc: nmr δ 1.57 (s, 6 H, CH$_3$C=C), 1.65 (s, 3 H, CH$_3$C=C), 1.96 [s, 4 H, CHCH$_2$CH$_2$(CH$_3$)C=C], 2.12 [m, 7 H, CH$_2$CH$_2$(CH$_3$)C=CHCO], 3.59 (s, 3 H, COOCH$_3$), 5.02 (broad s, 2 H, C=CH), 5.55 (s, 1 H, C=CHCOOCH$_3$); M$^+$ 250.

In a similar manner, using 1,1,1,3,3-d_5-6-methylhept-5-en-2-one as a starting material, methyl 8,8,8',8',8'-d_5-*trans,trans*-farnesoate (XIIIb) was prepared, M$^+$ 255 (95% d_5), 254 (5% d_4).

Methyl 8,8,8',8',8'-d_5-10,11-Epoxy-*trans,trans*-farnesoate (V). —Methyl *trans,trans*-farnesoate (66.3 mg, 0.26 mmol, purified by vpc) was dissolved in tetrahydrofuran (5 ml), and water (~3 ml) was added until the solution was cloudy; tetrahydrofuran was again added dropwise until the solution was clear. *N*-Bromosuccinimide (49.2 mg, 5% excess) was added and the mixture was stirred (argon) for 2.5 hr. Solid sodium chloride and ether were added, and the organic material was separated, washed with water and brine, and dried. Purification by tlc (40% ether–hexane) gave 54 mg (58%) of the corresponding terminal bromohydrin. The bromohydrin (54 mg) was dissolved in anhydrous methanol (5 ml) and anhydrous potassium carbonate (83 mg, fourfold excess) was added. After stirring (argon) for 1 hr, ether, water, and hexane were added, and the organic material was separated, washed with water and brine, and dried. Purification by tlc gave the deuterium-labeled methyl epoxy farnesoate V (37 mg) as a clear oil: one peak by vpc (4 ft, 3% w/w PDEAG 100/120 CHSBW-AW-DMCS, glass, 160°); nmr δ 1.18 (s, 3 H, epoxy CH$_3$), 1.21 (s, 3 H, epoxy CH$_3$), 1.51 (d, 2 H, epoxy CH$_2$), 2.14 [m, 7 H, CHCH$_2$CH$_2$(CH$_3$)C=CH], 2.47 (t, 1 H, epoxy H), 3.59 (s, 3 H, COOCH$_3$), 5.12 (m, 1 H, C=CH), 5.58 (broad s, 1 H, CHCOOCH$_3$); M$^+$ 227 (>95% d_5).

Methyl 5,5-d_2-10,11-Epoxy-*trans,trans*-farnesoate (VI).—*trans*-1,1-d_2-3,7-Dimethylocta-2,6-dien-1-ol (XXV) was prepared by aluminum deuteride reduction of methyl *trans*-geranate. The d_2 alcohol XXV was converted to its bromide (phosphorus tribromide) and used to alkylate the sodium enolate of methyl acetoacetate in tetrahydrofuran. Decarbomethoxylation was effected by treatment with barium hydroxide to give *trans*-4,4-d_2-

(24) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, **90**, 2882 (1968).

(25) Prepared from propionic acid by lithium aluminum deuteride reduction and conversion of the resulting alcohol to its bromide using 48% hydrobromic acid and sulfuric acid.

(26) Prepared by treating 2,2,2-d_3-ethyl bromide[27] with triphenylphosphine.

(27) R. Liedtke and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 6814 (1969).

(28) T. M. Bare and II. O. House, *Org. Syn.*, **49**, 81 (1969).

(29) R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 735 (1970).

(30) Prepared by the addition of the vinyl Grignard reagent derived from 2-bromobut-1-ene to the aldehydo ester XVI at −78° and treatment of the resulting allylic alcohol with acetic anhydride in pyridine.

(31) H. L. Normant, *Bull. Soc. Chim. Fr.*, 728 (1957).

(32) (a) M. F. Carroll, *J. Chem. Soc.*, 507 (1941); (b) W. Hoffman, H. Pasedach, and H. Pommer, *Justus Liebigs Ann. Chem.*, **729**, 52 (1969).

6,10-dimethyldeca-5,9-dien-2-one. This ketone was converted to the labeled methyl farnesoate XIIIa as described above for XIIIb and then to the terminal epoxy farnesoate VI also as described above for V. VI had nmr δ 1.18 (s, 3 H, epoxy CH₃), 1.21 (s, 3 H, epoxy CH₃), 1.51 (m, 2 H, epoxy CH₂), 1.61 (d, 3 H, CH₃C=C), 2.14 [m, 7 H, CH₂C=CHCD₂CH₂(CH₃)C=C], 2.47 (t, 1 H, epoxy H), 3.59 (s, 3 H, COOCH₃), 5.12 (broad s, 1 H, C=CH), 5.58 (m, 1 H, CHCOOCH₃); M⁺ 268. (>98% d_2).

Methyl *12,12,12,12′,12′,12′-d_6-10,11-Epoxy-trans,trans-farnesoate* **(IV).**—d_6-Acetone was reduced with lithium aluminum hydride and the resulting alcohol was converted to *1,1,1,3,3,3-d_6-2-bromopropane* according to the conditions of Wiley.[33] The bromide was mixed with an equimolar amount of triphenylphosphine and heated at 130° for 2 days to give *(1,1,1,3,3,3-d_6-isopropyl)triphenylphosphonium bromide* (XXVI) in 30% yield. Methyl 10,11-epoxy-*trans,trans*-farnesoate[34] was converted to methyl *trans,trans*-3,7-dimethyl-9-oxonona-3,6-dienoate (XX) as described above for XVI. The aldehydo ester XX (0.5 g) was added to the dark red ylide (1 equiv), derived from the phos

phonium salt XXVI in ether, and the mixture was stirred at reflux overnight. Work-up in the usual manner and bulb-to-bulb distillation (0.5 Torr) gave the d_6-labeled methyl farnesoate. After purification by preparative vpc, this *trans,trans*-farnesoate was converted to the 10,11-epoxy compound IV (as described above for V): nmr same as for VI except for absence of the methyl singlets at δ 1.18 and 1.21, and the presence of nine allylic protons at δ 2.14; M⁺ 272 (91% d_6), 271 (9% d_5).

(33) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chang, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

(34) A generous sample was provided by Dr. Clive Henrick, Zoecon Corp.

Stereospecific Synthesis of (20S,22R)-17α,20,22-Trihydroxycholesterol and (20S,22S)-17α,20,22-Trihydroxycholesterol[1]

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Addition of vinyl Grignard to the known 16α,17α-oxidopregnenolone acetate followed by reduction of the epoxide, conversion of the product to a 3,5-cyclo steroid, and epoxidation of the remaining double bond yields a C-22 epimeric mixture of epoxides which, when condensed with *sec*-butyllithium and reconverted to the 3β-hydroxy-Δ⁵-sterols, yield the title compounds.

Interest in the preparation of compounds which are postulated intermediates in the catabolism of cholesterol to C₂₁ and C₁₉ hormones has led numerous investigators to synthesize cholesterol derivatives possessing hydroxyl groups at C-17, C-20, and C-22. Specifically, the syntheses of (22R)-22-hydroxycholesterol and its C-22 epimer,[3-5] 20α-hydroxycholesterol,[6] 20β-hydroxycholesterol,[7] and (20R,22R)- and (20R,22S)-20,22-dihydroxycholesterol[8,9] have been described previously.

In recent years, the suggestion that cholesterol can be enzymatically cleaved between C-17 and C-20 to yield dehydroepiandrosterone[10-12] has prompted the synthesis of side-chain hydroxylated cholesterols which

could serve as substrates for this transformation. Compounds of importance in this series include 17α,-20α-dihydroxycholesterol, its C-20 epimer,[13] and 17α-hydroxycholesterol.[14] We now describe the synthesis of (20S,22R)-17α,20,22-trihydroxycholesterol (21) and (20S,22S)-17α,20,22-trihydroxycholesterol (23), sterols which could conceivably undergo desmolytic cleavage between C-20 and C-22 to yield 17α-hydroxypregnenolone. Alternatively, oxidative cleavage between C-17 and C-20 could occur to yield dehydroepiandrosterone, as suggested for a direct biosynthetic pathway from cholesterol to the C₁₉ hormones.[10]

The stereospecific introduction of hydroxyl groups at C-17, C-20, and C-22 of the cholesterol side chain presents a problem of some complexity. Of immediate interest was the preparation of a 17,20-glycol possessing a two-carbon, unsaturated side chain which, after epoxidation, can be treated with a suitable alkyllithium to produce the desired 17,20,22-hydroxylation pattern (see Scheme I). The preparation of 17α,20-dihydroxysterols can be easily accomplished by the addition of Grignard reagents to 17α-hydroxypregnenolone acetate 29. However, this method of preparation is unsuitable for our purposes, as the only alcohol obtained has been

(2) Taken in part from a dissertation by R. C. Nickolson in partial fulfillment of the requirements for the Ph.D. degree in organic chemistry, Clark University, Worcester, Mass. 01610.

(3) K. Tsuda and R. Hayatsu, *Chem. Pharm. Bull.*, **6**, 680 (1958).

(4) K. Tsuda and R. Hayatsu, *J. Amer. Chem. Soc.*, **81**, 5987 (1959).

(5) H. Mori, K. Shibata, K. Tsuneda, M. Sawai, and K. Tsuda, *Chem. Pharm. Bull.*, **16**, 1407 (1968); E. P. Burrows, G. M. Hornby, and E. Caspi, *J. Org. Chem.*, **34**, 103 (1969).

(6) V. Petrow and I. A. Stewart-Webb, *J. Chem. Soc.*, **46**, 75 (1956).

(7) A. Mijares, P. I. Cargill, J. A. Glasel, and S. Lieberman, *J. Org. Chem.*, **32**, 810 (1967).

(8) K. Shimizu, M. Gut, and R. I. Dorfman, *J. Biol. Chem.*, **237**, 699 (1962).

(9) N. K. Chaudhuri, R. Nickolson, H. Kimball, and M. Gut, *Steroids*, **15**, 525 (1970).

(10) R. A. Jungmann, *Biochim. Biophys. Acta*, **164**, 110 (1968).

(11) S. Burstein, H. Zamoscianyk, N. Co, M. Adelson, D. S. M. Prasad, A. Greenberg, and M. Gut, *ibid.*, **231**, 223 (1971).

(12) R. B. Hochberg, H. Mickan, and S. Lieberman, *ibid.*, **231**, 208 (1971).

(13) N. K. Chaudhuri, J. G. Williams, R. C. Nickolson, and M. Gut, *J. Org. Chem.*, **34**, 3759 (1969); for information concerning the metabolism of these 17,20-dihydroxycholesterols see S. Burstein, H. L. Kimball, N. K. Chaudhuri, and M. Gut, *J. Biol. Chem.*, **243**, 4417 (1968).

(14) N. K. Chaudhuri, R. C. Nickolson, and M. Gut, *Steroids*, **16**, 495 (1970).

SCHEME I

PLAN FOR THE CONSTRUCTION OF THE
17,20,22-GLYCEROL SIDE CHAIN

20α-triol 6, involving initially the condensation of vinylmagnesium bromide with 16α,17α-oxidopregnenolone acetate (1), was attempted (Scheme II). Previous work has shown[13] that a mixture of C-20 epimeric alcohols is formed when the epoxy ketone is reacted with Grignard reagents. The ratio of 20α- to 20β-alcohol which results depends markedly on the size and reactivity of the particular alkylmagnesium halide used. For instance, addition of isohexyl Grignard results in predominant formation of the 20β-alcohol

SCHEME II

SYNTHESIS OF C-22 EPIMERIC 17α,20α,22-TRIHYDROXYCHOLESTEROLS
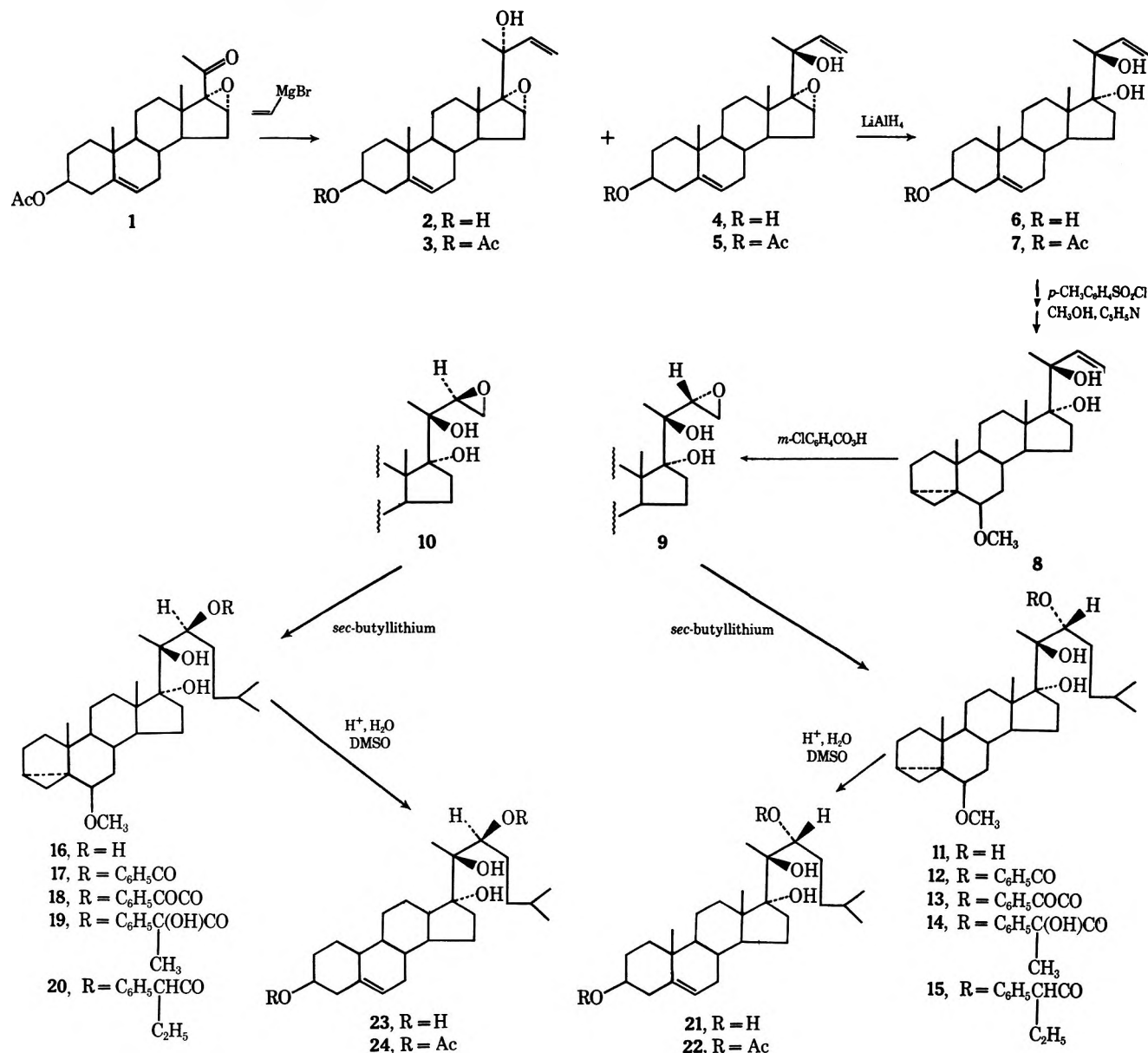
previously shown[13] to possess the unnatural 20β stereochemistry.[15]

In view of this unfortunate stereochemical consequence, an alternate synthesis of the "natural" 3β,17α,-

($\alpha/\beta = {}^1/_3$), whereas use of ethyl Grignard produces a preponderance of the 20α-alcohol ($\alpha/\beta = {}^3/_2$). It was expected that addition of vinyl Grignard would produce a substantial yield of the 20α-alcohol 4 which, after separation from its 20β epimer 2, could be treated with lithium aluminum hydride to produce the desired 17α,20α-glycol 6 (see Scheme III). Fortunately, the addition of vinylmagnesium bromide to the epoxy ketone 1 was found to proceed with greater than 90% stereoselectivity to give the epoxy diol 4, possessing the

(15) Sterols possessing a 20α-hydroxy group belong to the natural series and correspond in configuration to that of cholesterol in which the 20 H is α oriented. Both the α,β nomenclature (L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 344) and the R,S sequence rule (E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 92) will be used to designate the configuration of the side chain carbons.

SCHEME III
CORRELATION OF CONFIGURATION AT C-20
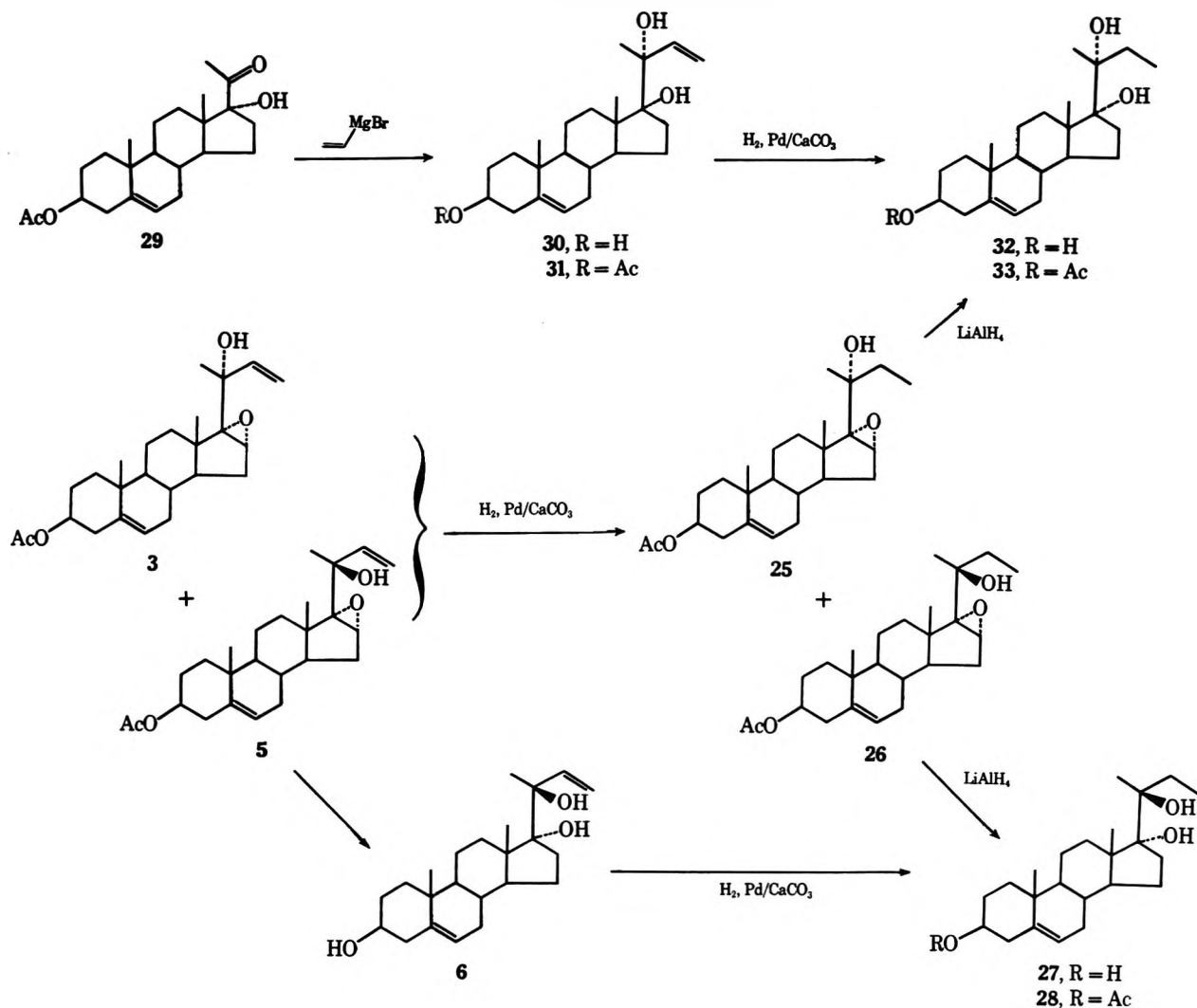
20α-hydroxyl group, which could be isolated in pure form by crystallization in 70% overall yield. Reduction of the epoxy diol 4 or the epoxy diol acetate 5 with lithium aluminum hydride gave the 3β,17α,20α-triol 6, which was compared with an authentic sample of the 3β,17α,20β-triol[16] 30, the C-20 epimer of 6. The two triols 6 and 30 exhibited similar nmr spectra and could not be separated on thin layer chromatography. The melting points, infrared spectra, and crystalline properties are, however, different and a clean separation of these epimeric triols could be effected by partition chromatography (see Experimental Section). The triol 6 possessing the 20α-hydroxyl group was found to be homogeneous and free from contamination with the 20β epimer.

Selective hydrogenation of the terminal olefinic bond converted the triols 6 and 30 into their respective 22,23-dihydro derivatives, 27 and 32 (see Scheme III), whose nmr spectra are readily distinguishable. In particular, there is noted a 2 and a 4 cps difference in the chemical shifts of the 18- and 21-methyl resonances, respectively. A simple diagnostic procedure based on these nmr characteristics was used to routinely monitor the approximate purity of the triol 6.

(16) A sample of this triol was prepared by addition of vinyl Grignard to 17α-hydroxypregnenolone acetate (29).

The addition of vinyl Grignard to epoxypregnenolone acetate (1) was not totally stereospecific as there was obtained from the mother liquors some material which is an evident mixture of C-20 epimeric epoxy diols 2 and 4. The mother liquors from the crystallization of the epoxy diol 4 were acetylated and the acetate, after chromatography, gave a solid. The nmr spectrum of this material exhibited two 18-methyl resonances appearing at 58 and 54 cps attributable to the 20α- and 20β-hydroxy epimers, respectively. The mixture of epoxy diol acetates 3 and 5 was converted to known compounds by selective hydrogenation of the 22,23 double bond to produce the dihydro derivatives 25 and 26, followed by reduction of the epoxides with lithium aluminum hydride and reacetylation, yielding the triol acetates 33 and 28. All nmr data were found to be consistent with that reported by Chaudhuri, et al.,[13] for a similar mixture of dihydroepoxy diol acetates and triol acetates prepared by a different route.

On the basis of the above evidence, there can be no question that the epoxy diol 4 isolated in predominant yield from the vinyl Grignard condensation is a single pure isomer possessing the desired stereochemistry at C-20 (20S). Reduction of this epoxy diol with lithium aluminum hydride gave, in nearly quantitative yield, the unsaturated triol 6 which is converted to the 3,5-

cyclo steroid **8**, in order to protect the 5,6 double bond from the subsequent epoxidation.

The nmr spectra of all compounds containing the 22,23 double bond exhibited a characteristic ABX pattern in the olefinic region very similar in appearance to the vinyl proton resonances of 17α-vinylestradiol.[17]

Completion of the synthesis follows the scheme outlined in Scheme II. Epoxidation of the 22,23 olefin produces a new center of asymmetry at C-22. Treatment of a methylene chloride solution of the unsaturated cyclo steroid **8** with 3 molar equiv of *m*-chloroperbenzoic acid converted the olefin quantitatively to the epoxides **9** and **10**, which were purified by chromatography over alumina. Elution with 15% ethyl acetate in benzene gave an oil which appeared as a homogeneous single spot on thin layer chromatography. The nmr spectrum, however, exhibited two widely separated 21-methyl resonances (at 79.5 and 86 cps) and a similar, but less pronounced splitting of the 18-methyl resonances (appearing at 59 and 57 cps) indicative of a C-22 epimeric mixture. The mixture was chromatographed on a Bush A partition system yielding the 22*R*- and 22*S*-epoxides **9** and **10** in a 2:3 ratio, respectively.

Condensation of the epoxides with *sec*-butyllithium gave the C-22 epimeric alcohols **11** and **16**, the configurations of which were determined by comparing the CD spectra of the respective C-22 benzoates **12** and **17** with C-22 benzoyloxy steroids of known configuration (see Discussion under "Determination of Configuration at C-22"). Each epoxide isolated in pure form by partition chromatography was condensed separately with *sec*-butyllithium. From the less abundant epoxide **9** there was isolated the 22*R*-alcohol **11** (mp 160°), whereas from the more abundant epoxide **10** there was isolated a higher melting alcohol **16** (mp 169°) possessing the 22*S* configuration.

The separation of the C-22 epimers can be deferred to this stage of the synthesis. The mixture of C-22 epimeric epoxides can be treated directly with *sec*-butyllithium and the epimeric alcohols which result can be easily purified by chromatography over alumina.

Completion of the synthesis involves solvolysis of the 6-methoxy-3,5-cyclo steroid moiety to regenerate the 3β-hydroxy-Δ⁵-sterols **21** and **23**. Treatment with acid[18] is known to . effect this conversion; however, mild conditions had to be developed which would leave the 17,20,22-glycerol side chain intact. After some experimentation, it was found that aqueous dimethyl sulfoxide containing 0.3% perchloric acid was an ideal reagent to effect the retro cyclo steroid reaction. In separate experiments both methoxy triols **11** and **16** were converted to their corresponding cholesterol derivatives **21** and **23** possessing the indicated stereochemistry at C-22.

Support for the assigned structures was obtained from degradation experiments and spectral data (mass and nmr). Each of the tetrols, when oxidized with lead tetraacetate in acetic acid, gave a high yield of 17α-hydroxypregnenolone (isolated as the 3-acetate) and isocaproaldehyde,[19] thereby confirming the pres-

(17) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 85.

(18) S. Winstein and R. Adams, *J. Amer. Chem. Soc.*, **70**, 838 (1948).

(19) We are indebted to Dr. Shlomo Burstein of the Institute for Muscle Disease, New York, for performing the gas chromatographic analysis of the isocaproaldehyde.

ence of a normal steroid skeleton and hydroxy groups at C-17, C-20, and C-22. No trace of dehydroepiandrosterone acetate, the product which would result if glycol cleavage had occurred between C-17 and C-20, was found.
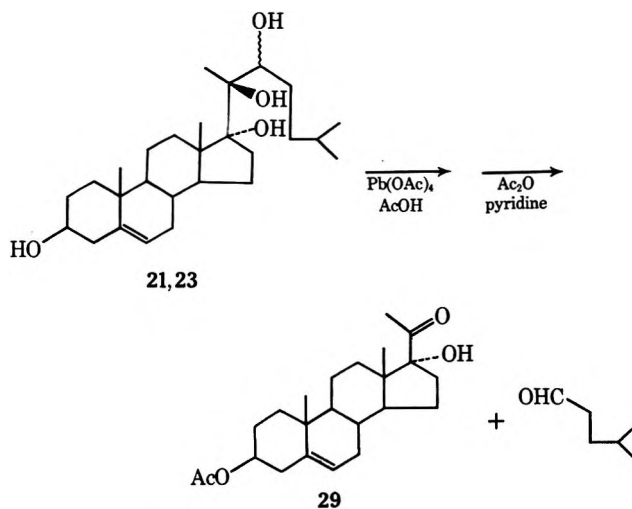
The mass spectra of the C-22 epimeric alcohols are qualitatively identical. Both exhibited peaks of high relative abundance resulting from cleavage of carbon–
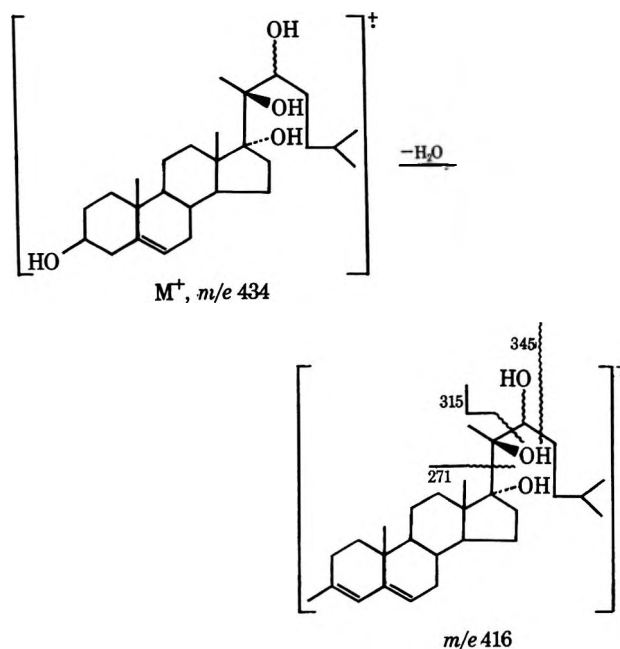
carbon bonds adjacent to hydroxyl groups. The base peak, appearing at *m/e* 271, is characteristic not only of the tetrols but of all compounds prepared in this series containing hydroxyl groups at C-17 and C-20.

The chemical shift data for the 18,19 and 21-methyl protons are shown below (Table I). The 18- and 21-methyl resonances are deshielded (relative to cholesterol) and their low field positions are indicative of a hydroxylated side chain.

The tetrols **21** and **23** are highly crystalline solids which give variable elemental analyses depending on the degree of solvation. The corresponding 3,22-diacetates **22** and **24** are crystallized from ether–hexane or acetone–hexane mixtures and show no tendency to cocrystallize with these solvents. Accordingly, their

Table I
Nmr Data for Quaternary Methyl Resonances (in Cycles per Second Downfield from TMS) of the Tetrols and Methoxytriols

Compd	Solvent	18-CH₃	19-CH₃	21-CH₃
16	CDCl₃	62	62	80
	C₆D₆N	83	72	108
23	C₆D₆N	82	66	110
11	CDCl₃	51	62	74
	C₆D₆N	65	72	93
21	C₆D₆N	62	65	91.5

elemental analyses are in excellent agreement with the calculated composition.

The metabolism of these tetrols is now under study and will be the subject of subsequent communications.

Determination of Configuration at C-22.—Experiments to determine the configuration at C-22 were performed using the cyclo steroid alcohols 11 and 16 rather than the free tetrols 21 and 23 in order to avoid complications arising from the presence of an additional asymmetric secondary hydroxyl group at C-3. Of the methods available for the determination of configuration of secondary alcohols, two approaches were tried, namely, the Prelog atrolactate synthesis[20,21] and the Horeau α-phenylbutyric acid method[22,23] but both failed to give significant optical data which would permit an unequivocal assignment.

Application of the Prelog method to the C-22 epimeric alcohols was performed following well-standardized procedures. The benzoyl formate esters 13 and 18 were formed in quantitative yield and treated with 4.5 equiv of methylmagnesium iodide to give the atrolactates 14 and 19. Hydrolysis of the esters resulted in recovery of 95% of the theoretical amount of atrolactic acid (based on starting alcohol). The atrolactic acid formed from the lower melting alcohol 11 was devoid of optical activity (c 2.2, ethanol, l = 2) whereas the acid isolated from the C-22 epimeric alcohol 16 exhibited a slightly positive rotation, [α]D +1.4° (c 5.4, ethanol, l = 2) which corresponds to a 4% asymmetric synthesis.[24]

A priori, it was expected that difficulties would be encountered using the Prelog method to determine the configuration of these particular secondary alcohols. Even if the atrolactic acid isolated from these determinations had possessed significant activity, the capability of the method to yield reliable information concerning the configuration of a secondary alcohol which is in the proximity of two tertiary alcohols (at C-17 and C-20) is in serious doubt. The C-22 benzoylformyloxy group is expected to be severely constrained and the transition state leading to attack of methyl Grignard to a preferred orientation of the α-keto ester moiety is probably influenced by factors other than the relative steric arrangement of groups around the chiral carbon.

Formally, the Prelog generalization applies only to those secondary alcohols in which the chiral carbon is is attached to hydrocarbon residues. Extension of the

Prelog method to more complex systems, e.g., dihydrocodeine,[25] has been made with reservations.

Application of the method developed by Horeau to determine the configuration of these alcohols was also unsuccessful. Briefly, the method involves reaction of an optically active secondary alcohol with racemic α-phenylbutyric anhydride to form the α-phenyl butyrate esters 15 and 20. Alcohols with the R configuration react preferentially with the R-(−) antipode of α-phenylbutyric acid, resulting in the accumulation of the (S)-(+)-α-phenylbutyric acid. If the acid isolated after esterification exhibits a positive rotation, the original alcohol possesses the R configuration. Conversely, if the acid isolated is laevorotatory, the original alcohol possesses the S configuration.

The alcohols 11 and 16 were dissolved in pyridine containing a 3-mol excess of α-phenylbutyric anhydride and allowed to stand for 10 hr. The excess anhydride is hydrolyzed and the extent of ester formation was determined by titration of the liberated acid. In neither instance did the yield of α-phenyl butyrate esters 15 and 20 exceed 10%. The recovered α-phenylbutyric acid from both determinations exhibited no significant rotation. The poor chemical yield coupled with a small optical yield was the obvious cause of failure.

Determination of the C-22 configuration was secured by examination of the ORD/CD spectra[26] of the 22-benzoate esters 12 and 17. From previous investigations, there were available a number of C-22 epimeric alcohols of known configuration; specifically, (22R)- and (22S)-22-hydroxycholesterol and the pair of 20α,22-dihydroxycholesterols. The 22-monobenzoate esters of each of these compounds were prepared, and the CD and ORD spectra were obtained and compared to the CD spectra of the benzoates 12 and 17 of unknown configuration.
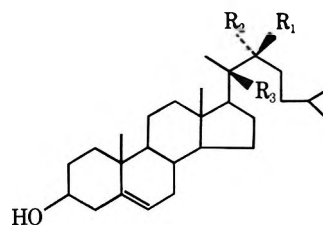
	R₁	R₂	R₃
(22R)-22-Hydroxycholesterol	H	OH	H
(22S)-22-Hydroxycholesterol	OH	H	H
(20R,22R)-20,22-Dihydroxycholesterol	H	OH	OH
(20R,22S)-20,22-Dihydroxycholesterol	OH	H	OH

Analysis of the CD spectra obtained from the compounds of known stereochemistry showed a positive Cotton effect in the 226–233-mμ region followed by a negative Cotton effect at 218 mμ to be indicative of the 22S configuration, whereas mirror image Cotton curves were exhibited by the benzoates of opposite (22R) chirality.

The 22-benzoate prepared from the lower melting (mp 160°) methoxy triol 11 exhibited a trough at 238 mμ followed by a pronounced peak at 218 mμ, thus establishing its configuration as belonging to the 22R series, whereas the benzoate of the higher melting (169°) cyclo steroid 16 exhibited a peak at 239 mμ fol-

(20) V. Prelog, *Bull. Soc. Chim. Fr.*, 987 (1956).

(21) V. Prelog, E. Philbrin, E. Watanabe, and M. Wilhelm, *Helv. Chim. Acta*, **39**, 1086 (1956).

(22) A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964).

(23) A. Horeau and J. K. Sutherland, *J. Chem. Soc. C*, 247 (1966).

(24) Based on (R)-(−)-atrolactic acid, [α]¹¹·⁸D −37.7° (cf. J. D. Morrison and H. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, p 58).

(25) K. W. Bentley and H. M. E. Cardwell, *J. Chem. Soc.*, 3252 (1955).

(26) The full details of this method and its extension to other alcohols will be presented in a subsequent paper.

lowed by a trough at 220 mμ indicating the 22S configuration.

Experimental Section

Melting points are uncorrected. Nmr spectra were obtained in deuteriochloroform solution (unless otherwise stated) on a 60-Mc Varian Associates DA-60 spectrometer using tetramethylsilane as an internal reference. Mass spectra were determined on a Varian Associates M-66 mass spectrometer.

(20S)-16α,17α,Oxido-24-norchola-5,22-diene-3β,20-diol (4).—A solution of vinyl Grignard was prepared by the dropwise addition of a solution of 77.0 g of vinyl bromide in 500 ml of tetrahydrofuran to 17.3 g of magnesium shavings. The Grignard solution was refluxed for 0.5 hr and then cooled to −10°. A solution of 50.0 g of 16α,17α-oxidopregnenolone acetate (1) in 900 ml of tetrahydrofuran (precooled to −10°) was added to the Grignard reagent, care being taken to maintain the temperature of the solution below 5°. After addition was complete, the mixture was stirred vigorously for 10 min while cooling, after which time the Grignard complex was decomposed by the cautious addition of iced, saturated ammonium chloride solution. The contents of the reaction flask were transferred to a separatory funnel and the tetrahydrofuran layer was removed. The aqueous layer was extracted with two 500-ml portions of ethyl acetate, and the organic extracts were combined, washed with water and saturated brine, and dried over anhydrous sodium sulfate. Excess solvent was removed by vacuum distillation until the residue amounted to *ca.* 600 ml. The solid material which precipitated during evaporation of the solvent was redissolved by addition of hot benzene and the epoxy diol 4 is allowed to crystallize from this solvent mixture. Concentration of the mother liquors and subsequent crystallizations afforded two additional fractions of suitable purity for further transformation (total yield 35.2 g). An analytical sample was prepared by crystallization from benzene: s 190°, mp 199–202°; nmr 58 (18 CH$_3$), 61 (19 CH$_3$), 84 (21 CH$_3$), 206 (16β H), 208 (3α H), 320 (6 H), 315 (23 H) and 367 cps (22 H); mass spectrum *m/e* (rel intensity) 358 (M+, 60), 343 (M − CH$_3$, 40), 340 (M − H$_2$O, 15), 325 (340 − CH$_3$, 45), 297 (325 − C$_2$H$_4$, 30), 287 (M − C$_4$H$_7$O, base peak).

Anal. Calcd for C$_{23}$H$_{34}$O$_3$: C, 77.05; H, 9.56. Found: C, 76.76; H, 9.41.

The 3-acetate 5 was prepared by dissolving the epoxy diol 4 in pyridine and adding an excess of acetic anhydride. The solution was allowed to stand overnight, after which time water was added and the mixture was extracted with ethyl acetate. After the pyridine was removed by extraction with iced dilute acetic acid, the ethyl acetate layer was washed two times with water, once with saturated bicarbonate solution, and once with saturated brine. The organic solution was dried over anhydrous sodium sulfate and evaporated *in vacuo*, yielding a solid residue which was dissolved in benzene and chromatographed over alumina. Elution with 10–15% ethyl acetate in benzene yielded the desired acetate 5. An analytical sample was prepared by crystallization from methanol: mp 180–181°; nmr 58 (18 CH$_3$), 62 (19 CH$_3$), 85 (21 CH$_3$), 122 (acetate methyl), 207 (16β H), 276 (3α H), 314 (23 H), 324 (6 H), and 366 cps (22 H); mass spectrum *m/e* (rel intensity) 340 (M − CH$_3$CO$_2$H, base peak), 325 (340 − CH$_3$, 22), 307 (325 − H$_2$O, 11), 269 (340 − C$_4$H$_7$O, 28).

Anal. Calcd for C$_{25}$H$_{36}$O$_4$: C, 74.96; H, 9.06. Found: C, 74.85; H, 9.13.

The epoxy diol 4 obtained in the manner described above was a single C-20 epimer as shown by its nmr spectrum and thin layer and paper chromatogram (see Experimental Section under "Correlation of Configuration at C-20;" physical constants and other pertinent data are reproduced therein).

Evidence for a mixture of C-20 epimeric alcohols 2 and 4 was found by analyzing the residue remaining after isolation of the major crystalline product. Acetylation of the mother liquors followed by chromatography over alumina yielded 3.3 g of epoxy acetates 3 and 5, the nmr of which exhibited two distinct 18-methyl resonances (58 cps, 18 CH$_3$ of 20S epimer; 54 cps, 18 CH$_3$ of 20R epimer), a broadened 21-methyl resonance, and two resonances appearing at 207 and 211 cps attributable to the 16β proton of the 20S and 20R hydroxy epimers, respectively. Selective hydrogenation of the 22,23 double bond converted the initial mixture of epoxy acetates 3 and 5 into the corresponding side chain saturated derivatives 25 and 26, whose nmr spectrum was identical with that obtained for a similar mixture prepared previously[13] by the reaction of an ethyl Grignard with 16α,17α-

oxidopregnenolone acetate (1) followed by acetylation: nmr 57 (18 CH$_3$ of 20S epimer), 58 (18 CH$_3$ of 20R epimer), 62 (19 CH$_3$), 78 (21 CH$_3$), 121 (acetate methyl), 203 (16β H of 20S epimer), 208 (16β H of 20R epimer), 275 (3α H), and 324 cps (6 H).

Further correlation of the dihydro epoxides 25 and 26 with compounds of known stereochemistry was achieved by treatment of the mixture with lithium aluminum hydride, followed by acetylation, to produce a mixture of the respective 17α,20-diol acetates 28 and 33: nmr 52 (18 CH$_3$ of 20S epimer), 54 (18 CH$_3$ of 20R epimer), 62 (19 CH$_3$), 73 (21 CH$_2$ of 20R epimer), 77 (21 CH$_3$ of 20S epimer), 122 (acetate methyl), 275 (3α H), and 324 cps (6 H).

(20S)-24-Norchola-5,22-diene-3β,17α,20-triol (6).—To the solution of 26 g of epoxy diol 4 in 1.6 l. of tetrahydrofuran was added 7.5 g of lithium aluminum hydride and the suspension was allowed to reflux for 8 hr. Excess lithium aluminum hydride was then decomposed by the dropwise addition of 2 N sodium hydroxide. The white, granular lithium salts were filtered and washed with hot ethyl acetate. Evaporation of the filtrate yielded 26 g of crude triol 6, which was recrystallized from ethyl acetate, yielding 23 g of material. An analytical sample was prepared by two more recrystallizations from the same solvents: mp 193–195°; nmr 52 (18 CH$_3$), 61 (19 CH$_3$), 83 (21 CH$_3$), 210 (3α H), 313 (23 H), 324 (6 H) and 371 cps (22 H); mass spectrum *m/e* (rel intensity) 342 (M − H$_2$O, 8), 327 (342 − CH$_3$, 2), 324 (342 − H$_2$O, 2), 309 (324 − CH$_3$, 4), 289 (M − C$_4$H$_7$O, 45), 271 (289 − H$_2$O, base peak), 253 (271 − H$_2$O, 70).

Anal. Calcd for C$_{23}$H$_{36}$O$_3$: C, 76.62; H, 10.07. Found: C, 76.83; H, 10.23.

The 3-acetate 7 was made in the usual manner. Crystallization from hexane gave an analytical sample: mp 167–168°; nmr 52.5 (18 CH$_3$), 62 (19 CH$_3$), 83.5 (21 CH$_3$), 270 (3α H), 313 (23 H), 324 (6 H), and 370 cps (22 H); mass spectrum *m/e* (rel intensity) 384 (M − H$_2$O, 1), 342 (M − CH$_3$CO$_2$H, 1), 324 (342 − H$_2$O, 4), 271 (342 − C$_4$H$_7$O, base peak), 253 (271 − H$_2$O, 75).

Correlation of Configuration of C-20. (20S)-24-Norchol-5-ene-3β,17α,20-triol (27) by Selective Catalytic Reduction of (20S)-24-Norchola-5,22-diene-3β,17α-20-triol (6).—To the solution of 361 mg of triol 6 in 20 ml of 95% ethanol was added 40 mg of 5% palladium on calcium carbonate and the suspension was stirred under an atmosphere of hydrogen. Uptake of hydrogen was rapid but ceased abruptly after 1 mol was absorbed (*ca.* 15 min). The ethanol suspension was filtered through Celite, the filtrate was evaporated, and the crude dihydrotriol 27 was crystallized from acetone: mp 229–236°; nmr 52 (18 CH$_3$), 61 (19 CH$_3$), 77 (21 CH$_3$), 210 (3α H), and 324 cps (6 H); mass spectrum *m/e* (rel intensity) 344 (M − H$_2$O, 6), 326 (M − 2H$_2$O, 3), 315 (344 − C$_2$H$_5$, 5), 311 (326 − CH$_3$, 4), 297 (326 − C$_2$H$_5$, 4), 289 (M − C$_4$H$_9$O, 50), 271 (344 − C$_4$H$_9$O, base peak), 253 (271 − H$_2$O, 65%).

Anal. Calcd for C$_{23}$H$_{38}$O$_3$: C, 76.19; H, 10.57. Found: C, 76.10; H, 10.58.

The 3-acetate 28 was prepared in the usual manner. Crystallization from acetone–hexane gave an analytical sample: mp 183–186°; nmr 52 (18 CH$_3$), 62 (19 CH$_3$), 77 (21 CH$_3$), 275 (3α H), and 324 cps (6 H); mass spectrum *m/e* (rel intensity) 386 (M − H$_2$O, 1), 344 (M − CH$_3$CO$_2$H, 1), 331 (M − C$_4$H$_9$O, 6), 326 (386 − CH$_3$CO$_2$H, 10), 297 (326 − C$_2$H$_5$, 14), 271 (344 − C$_4$H$_9$O, base peak), 253 (326 − C$_4$H$_9$O, 66).

Anal. Calcd for C$_{25}$H$_{40}$O$_4$: C, 74.21; H, 9.97. Found: C, 74.28; H, 9.97.

For comparison purposes it was desirable to synthesize the triols 30 and 32, which are C-20 epimers of the triols 6 and 27 described above. Synthesis of the C-20 epimeric triols can be readily accomplished by reaction of 17α-hydroxypregnenolone acetate (29) with vinyl Grignard followed by selective reduction of the 22,23 double bond, as described below.

(20R)-24-Norchola-5,22-diene-3β,17α,20-triol (30) and Its Conversion to (20R)-24-Norchol-5-ene-3β,17α,20-triol (32).—To a solution of vinyl Grignard (prepared from 10.7 g of vinyl bromide in 60 ml of tetrahydrofuran and 2.40 g of magnesium shavings) was added 7.48 g of 17α-hydroxypregnenolone acetate in 200 ml of tetrahydrofuran over the course of 20 min. The solution was allowed to stir at ice temperature for 30 min and then brought to reflux for 4 hr. The solution was cooled and the Grignard complex was decomposed by addition of iced, saturated ammonium chloride solution. The contents of the flask were transferred to

a separatory funnel, the tetrahydrofuran layer was removed, and the aqueous solution was extracted two times with ethyl acetate. The organic extracts were combined, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated to yield 10 g of semisolid residue. This material was triturated with boiling hexane and the resulting suspension was filtered and washed with another portion of hexane. The hexane filtrate was discarded and the solid which remains was crystallized from aqueous methanol: mp 167–169°; nmr 51 (18 CH_3), 60 (19 CH_3), 81 (21 CH_3), 210 (3α H), 315 (23 H), 324 (6 H), and 374 cps (22 H); mass spectrum m/e (rel intensity) 342 (M − H_2O, 32), 324 (342 − H_2O, 1), 309 (324 − CH_3, 3), 289 (M − C_4H_7O, 25), 271 (289 − H_2O, base peak), 253 (271 − H_2O, 65).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.53; H, 10.23.

The 3-acetate 31 was prepared in the usual way. An analytical sample was prepared by crystallization from acetone–hexane: mp 199–204°; nmr 51 (18 CH_3), 62 (19 CH_3), 81 (21 CH_3), 122 (acetate methyl), 275 (3α H), 314 (23 H), 324 (6 H), and 374 cps (22 H); mass spectrum m/e (rel intensity) 342 (M − CH_3CO_2H, 1), 324 (342 − H_2O, 7), 314 (342 − C_2H_4, 18), 297 (324 − C_2H_3, 8), 279 (297 − H_2O, 21), 271 (342 − C_4H_7O, base peak), 253 (271 − H_2O, 66).

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.67; H, 9.67.

The nmr spectra of the C-20 epimeric triols 6 and 30 were almost identical. There is noted a 3-cps difference in the chemical shift of the vinyl protons associated with the 22,23 unsaturation; however this shift is only of qualitative significance and cannot be used to estimate the relative amounts of each isomer which may be present in a mixture. These triols behave similarly on thin layer chromatography (R_f 0.32) in a benzene (65)–ethyl acetate (33)–methanol (2) solution. However, a clean separation was achieved using paper partition chromatography (20S epimer, R_f 0.91; 20R epimer, R_f 0.96) in a hexane (60)–benzene (40)–methanol (80)–water (20) system.

Conversion of the triol 30 to the 22,23-dihydro derivative 32 was accomplished by catalytic hydrogenation using the same procedure as was used to reduce its C-20 epimer 6. An analytical sample was prepared by crystallization from acetone: mp 197–201°; nmr 54 (18 CH_3), 61 (19 CH_3), 72 (21 CH_3), 210 (3α H), and 324 cps (6 H); mass spectrum m/e (rel intensity) 344 (M − H_2O, 9), 326 (M − 2 H_2O, 90), 311 (326 − CH_3, base peak), 293 (311 − H_2O, 25), 271 (344 − C_4H_9O, 31), 253 (326 − C_4H_9O, 12).

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.40; H, 10.67.

The 3-acetate 33 was prepared in the usual manner. An analytical sample was prepared by crystallization from acetone–hexane: mp 183–186°; nmr 54 (18 CH_3), 62 (19 CH_3), 72 (21 CH_3), 122 (acetate methyl), 275 (3α H), and 324 cps (6 H); mass spectrum m/e (rel intensity) 386 (M − H_2O, 1), 344 (M − CH_3CO_2H, 1), 331 (M − C_4H_9O, 4), 326 (344 − H_2O, 10), 311 (326 − CH_3, 1), 308 (326 − H_2O, 2), 297 (326 − C_2H_5, 14), 271 (344 − C_4H_7O, base peak), 253 (271 − H_2O, 65).

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.28; H, 9.97.

As stated in the text, the nmr spectra of the two C-20 isomeric dihydrotriols 27 and 32 are quite distinctive (in regard to the chemical shifts of their respective 18- and 21-methyl resonances) and can be used to routinely analyze each C-20 isomer for contamination with the other (see ref 13).

The unsaturated triol 6 possessing the natural stereochemistry at C-20 (20S) was subjected to partition analysis in the system described previously before being converted to the cyclo steroid 8. Only that material which was demonstrably free of the 20R isomer was used in succeeding steps of the synthesis.

(20S)-3α,5-Cyclo-24-nor-5α-chol-22-ene-6β,17α,20-triol 6-Methyl Ether (8).—To a solution of 22.1 g of triol 6 in 400 ml of pyridine was added 20 g of p-toluenesulfonyl chloride. The solution was allowed to stand for 24 hr, after which time it was cooled to ice temperature and excess tosyl chloride was decomposed by slowly adding ice water. The crude tosylate crystallized from the aqueous pyridine solution and was filtered. After the residue was washed with water, the material was dried at 50° for 12 hr. The weight of crude tosylate amounted to 28 g and was dissolved in 145 ml of pyridine and 1960 ml of methanol. The solution was refluxed for 3 hr, after which time the excess methanol was removed by distillation *in vacuo*. Water was then

added and the solution was extracted two times with ethyl acetate. The organic extracts were combined and washed with sufficient dilute, iced acetic acid to remove all pyridine. The ethyl acetate layer was washed two times with water and once with saturated bicarbonate and saturated brine. After drying over anhydrous sodium sulfate and evaporation of solvent, there was obtained 24 g of oil which was dissolved in benzene and chromatographed on 400 g of alumina. The desired cyclo steroid was eluted with 8–10% ethyl acetate in benzene and was crystallized from hexane, giving 17.5 g of needles: mp 90–91°; nmr 54 (18 CH_3), 61 (19 CH_3), 83 (21 CH_3), broad multiplet at 20–40 (cyclopropyl hydrogens), 167 (6α H), 200 (6β OCH_3), 312 (23 H) and 372 cps (22 H); mass spectrum m/e (rel intensity) 342 (M − CH_3OH, 3), 324 (342 − H_2O, 2), 309 (324 − CH_3, 6), 271 (342 − C_4H_7O, base peak), 253 (271 − H_2O, 65).

Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.81; H, 10.08.

(20S,22R)-3α,5-Cyclo-22,23-oxido-24-nor-5α-cholane-6β,17α,-20-triol 6-Methyl Ether (9) and (20S,22S)-3α,5-Cyclo-22,23-oxido-24-nor-5α-cholane-6β,17α,20-triol 6-Methyl Ether (10).— To a solution of 9.1 g of unsaturated cyclo steroid 8 in 180 ml of methylene chloride cooled to ice temperature was added 10.0 g of m-chloroperbenzoic acid and the solution was allowed to stand overnight at 5°. The methylene chloride solution was extracted with 150 ml of iced 2 N sodium hydroxide solution. The aqueous layer was back-extracted with two 50-ml portions of methylene chloride, and the organic extracts were combined and washed with water (to neutrality) and saturated brine. After drying over anhydrous sodium sulfate and evaporation of solvent there was obtained 14 g of oily residue which was dissolved in benzene and chromatographed on alumina. The desired diol epoxides 9 and 10 are eluted with 12–15% ethyl acetate in benzene. Combination of appropriate fractions and evaporation of solvent yielded 6.7 g of oil, whose thin layer chromatogram showed only one spot (R_f 0.40, 20% ethyl acetate in benzene). The nmr spectrum, however, exhibited two 18-methyl resonances (at 57 and 59 cps) and two 21-methyl resonances (at 79.5 and 86 cps) indicative of a 3:2 mixture of C-22 epimeric epoxides. The epoxide mixture (120 mg) was partition chromatographed using a 4 × 110 cm Celite column on a Bush A (heptane-methanol-water, 10:8:2) system. Separation in this manner gave 40 mg of the (22R)-epoxy diol 9 (fractions 70–79) and 61 mg of the (22S)-epoxy diol 10 (fractions 83–94).

The oxides, either as the mixture or in pure form, are noncrystalline oils. Data for (22R)-epoxide 9 follow: nmr 59 (18 CH_3), 62 (19 CH_3), 80 (21 CH_3), broad multiplet at 20–40 (cyclopropyl hydrogens), 167 (6α H), 170 (23 H), 195 (22 H) and 200 cps (6β OCH_3); mass spectrum m/e (rel intensity) 358 (M − CH_3OH, 11), 343 (358 − CH_3, 5), 335 (M − C_4H_7, 8), 271 (358 − $C_4H_7O_2$, base peak), 253 (271 − H_2O, 66). Data for (22S)-epoxide 10 follow: nmr 57 (18 CH_3), 62 (19 CH_3), 86 (21 CH_3), broad multiplet at 20–40 (cyclopropyl hydrogens), 167 (6α H), 170 (23 H), 195 (22 H) and 200 cps (6β OCH_3); mass spectrum m/e (rel intensity) 390 (M^+, 4), 375 (M − CH_3, 9), 372 (M − H_2O, 2) 358 (M − CH_3OH, 40), 343 (358 − CH_3, 16), 335 (M − C_4H_7, 20), 297 (372 − C_2H_3O − CH_3OH, 7), 271 (358 − $C_4H_7O_2$, base peak), 253 (271 − H_2O, 60).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 74.02; H, 9.76.

(20S,22R)-3α,5-Cyclo-5α-cholestane-6β,17α,20,22-tetrol 6-Methyl Ether (11) and (20S,22S)-3α,5-Cyclo-5α-cholestane-6β,17α,20,22-tetrol 6-Methyl Ether (16).—sec-Butyllithium[27] was prepared by direct metalation of the corresponding bromide (Eastman reagent grade). The sec-butyl bromide was washed three times with concentrated sulfuric acid, two times with water, and once with saturated bicarbonate. The bicarbonate-washed bromide was shaken with water and saturated brine and dried for 24 hr over anhydrous calcium chloride. The bromide was decanted, distilled two times (bp 91–93°), and stored over anhydrous calcium chloride. sec-Butyl bromide, purified in

(27) Commercial sec-butyllithium purchased from two sources (Alfa Inorganics and Foote Mineral Corp.) was found to be unsatisfactory for completion of the synthesis of the cholesterol side chain. The nmr spectrum of the product resulting from condensation of the commercial lithium reagent with the epoxides did not exhibit the characteristic signals for the 26,27-methyl groups (doublet at 52 cps, J = 6 Hz). The lack of secondary methyl resonances would seem to indicate the attachment of a straight chain alkyl residue to C-23 of the epoxide. The structure of the commercial reagent was not investigated further, as it was more convenient to prepare sec-butyllithium in the manner described above.

this manner, can be used without any further treatment for preparation of the *sec*-butyllithium.

In a flask flushed with argon and protected from atmospheric moisture was placed 15 ml of ether and 70 mg of lithium ribbon. The ether suspension of lithium was cooled to $-15°$ in a Dry Ice–acetone bath and 725 mg of *sec*-butyl bromide was added over 1.5 hr. After addition of all bromide, the solution was stirred at $-10°$ for 30 min, after which the temperature of the solution was increased to $10°$ and the mixture was stirred for an additional 30 min. A solution of 390 mg of 22R epoxide 9 in 30 ml of anhydrous ether was added at once to the solution of *sec*-butyllithium (precooled to $-20°$). The temperature of the solution was maintained between -10 and $-15°$ for 30 min and gradually raised to room temperature over 15 min. The lithium complex was decomposed by cautious addition of iced saturated ammonium chloride solution. The contents of the flask were transferred to a separatory funnel and the aqueous layer was extracted two times with ethyl acetate. The organic extracts were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was dissolved in benzene and chromatographed over alumina and the desired methoxy triol 11 was eluted with 30–40% ethyl acetate in benzene. An analytical sample was prepared by crystallization from methylene chloride–hexane, giving 140 mg of pure compound: mp 160–162°; nmr 51 (18 CH$_3$), 62 (19 CH$_3$), 74 (21 CH$_3$), broad multiplet at 20–40 (cyclopropyl hydrogens), doublet centered at 54 ($J = 6$ Hz, 26, 27 CH$_3$), 167 (6α H), 200 (6β OCH$_3$), and 225 cps (22 H); nmr (pyridine-d_5) 65 (18 CH$_3$), 72 (19 CH$_3$), 93 (21 CH$_3$), broad multiplet at 20–40 (cyclopropyl hydrogens), doublet centered at 54 ($J = 6$ Hz, 26, 27 CH$_3$), 165 (6α H), 200 (6β OCH$_3$), and cps 242 (22 H); mass spectrum m/e 416 (M $-$ CH$_3$OH, 7), 315 (416 $-$ C$_6$H$_{13}$O, 39), 297 (315 $-$ H$_2$O, 68), 271 (416 $-$ C$_8$H$_{17}$O$_2$, base peak), 253 (271 $-$ H$_2$O, 50).

Anal. Calcd for C$_{28}$H$_{48}$O$_4$: C, 74.95; H, 10.78. Found: C, 75.04; H, 10.70.

The synthesis of the methoxy triol 16, possessing the 22S configuration, is performed in the same manner as described above using the epimeric epoxy triol 10 as starting material. The crude product was dissolved in benzene and chromatographed on alumina. The desired methoxy triol was eluted with 12% ethyl acetate in benzene. After combination of the appropriate chromatographic fractions, the solvent was evaporated and the residue was recrystallized from methylene chloride–hexane, giving plates: mp 169–173°; nmr 62 (18 CH$_3$, 19 CH$_3$), 80 (21 CH$_3$), broad multiplet at 20–40 (cyclopropyl hydrogens), doublet centered at 53 ($J = 6$ Hz, 26, 27 CH$_3$), 165 (6α H), 200 (6β OCH$_3$), and 225 (22 H) cps; nmr (pyridine-d_5) 83 (18 CH$_3$), 72 (19 CH$_3$), 108 (21 CH$_3$), multiplet at 20–40 (cyclopropyl hydrogens), doublet centered at 53 ($J = 6$ Hz, 26, 27 CH$_3$), 165 (6α H), 198 (6β OCH$_3$), and 225 cps (22 H); mass spectrum m/e (rel intensity) 416 (M $-$ CH$_3$OH, 12), 401 (416 $-$ CH$_3$, 6), 330 (401 $-$ C$_5$H$_{11}$, 20), 315 (416 $-$ C$_6$H$_{13}$O, 70), 297 (315 $-$ H$_2$O, 95), 271 (416 $-$ C$_8$H$_{17}$O$_2$, base peak), 253 (271 $-$ H$_2$O, 55).

Anal. Calcd for C$_{28}$H$_{48}$O$_4$: C, 74.95; H, 10.78. Found: C, 74.80; H, 10.94.

Because of the remarkable difference in polarity between the methoxy triol 11 and 16, the separation of the C-22 epimers does not have to be performed by partition chromatography of the epoxides 9 and 10. Alternatively, the C-22 epoxide mixture can be condensed with *sec*-butyllithium to yield the mixture of methoxy triol which can be easily separated by chromatography over alumina.

(20S,22R)-17α,20,22-Trihydroxycholesterol (21) and (20S,-22S)-17α,20,22-Trihydroxycholesterol (23).—To 70 ml of dimethyl sulfoxide were added 10.0 ml of water and 4.0 ml of 7% perchloric acid. The resulting solution was cooled to 0° and 500 mg of (22R)-methoxy triol 11 was added with stirring to the dimethyl sulfoxide solution. If, after 1 hr, the steroid had not completely dissolved, 3–4 ml of tetrahydrofuran was added to the solution. The mixture was allowed to stand at room temperature for 3 days, after which time it was poured onto ice and extracted three times with ethyl acetate. These extracts were washed thoroughly with water and once with saturated bicarbonate and saturated brine. After drying the organic extracts over anhydrous sodium sulfate, decanting the solvent, and evaporation, there was obtained a crystalline residue which was washed quickly with 5 ml of cold acetone. Filtration of the acetone suspension followed by recrystallization of the solid from aqueous acetone gave fine needles: mp 168–170°; nmr

(pyridine-d_5) 62 (18 CH$_3$), 65 (19 CH$_3$), 91.5 (21 CH$_3$), doublet centered at 53 ($J = 6$ Hz, 26, 27 CH$_3$), 220 (3α H), 240 (22 H), and 320 cps (6 H); mass spectrum m/e (rel intensity) 416 (M $-$ H$_2$O, 1), 398 (M $-$ 2 H$_2$O, 1), 383 (398 $-$ CH$_3$, 1), 365 (383 $-$ H$_2$O, 1), 345 (416 $-$ C$_5$H$_{11}$, 10), 333 (M $-$ C$_6$H$_{13}$O, 7), 316 (416 $-$ C$_6$H$_{12}$O, 37), 315 (416 $-$ C$_6$H$_{13}$O, 74), 301 (316 $-$ CH$_3$, 43), 297 (398 $-$ C$_5$H$_{13}$O, 71), 271 (416 $-$ C$_8$H$_{17}$O$_2$, base peak), 253 (271 $-$ H$_2$O, 44).

The (22R)-tetrol analyzed for an acetone of crystallization and is reported as such.

Anal. Calcd for C$_{27}$H$_{46}$O$_4$·C$_3$H$_6$O: C, 73.12; H, 10.64. Found: C, 73.58; H, 10.40.

The 3,22-diacetate 22 was prepared by allowing a pyridine solution of the free tetrol to stand at room temperature for 48 hr in the presence of excess acetic anhydride. Isolation in the usual manner gave a solid residue which was dissolved in benzene and chromatographed on alumina. The diacetate is eluted with 10% ethyl acetate in benzene and recrystallized from methylene chloride–hexane: mp 223–226°; nmr 56 (18 CH$_3$), 61 (19 CH$_3$), 78 (21 CH$_3$), doublet centered at 52 ($J = 6$ Hz, 26, 27 CH$_3$), 122 (3β-acetate methyl), 127 (22-acetate methyl), 275 (3α H), 308 (22 H), and 323 cps (6 H); mass spectrum m/e (rel intensity) 500 (M $-$ H$_2$O, 2), 458 (M $-$ CH$_3$CO$_2$H, 1), 440 (500 $-$ CH$_3$-CO$_2$H, 23), 429 (500 $-$ C$_5$H$_{11}$, 6), 380 (440 $-$ CH$_3$CO$_2$H, 22), 357 (500 $-$ C$_5$H$_{13}$O$_2$, 25), 313 (500 $-$ C$_{10}$H$_{19}$O, 16), 298 (357 $-$ CH$_3$CO$_2$, 36), 297 (357 $-$ CH$_3$CO$_2$H, 25), 271 (458 $-$ C$_{10}$H$_{19}$O$_3$, 74), 270 (458 $-$ C$_{10}$H$_{20}$O$_3$, 78), 253 (271 $-$ H$_2$O, 43), 226 (298 $-$ H$_2$O $-$ C$_4$H$_6$, base peak).

Anal. Calcd for C$_{31}$H$_{50}$O$_6$: C, 71.78; H, 9.72. Found: C, 71.93; H, 9.71.

The (22S)-methoxy triol 16 was converted to the corresponding 3β-hydroxy-Δ^5-sterol following the same procedure as was used to solvolyze its 22R epimer. The residue remaining after evaporation of the ethyl acetate extracts was washed with 2–3 ml of methylene chloride before being crystallized from aqueous methanol. An analytical sample was prepared by two more crystallizations from the same solvent, giving needles: mp 192–196°; nmr (pyridine-d_5) 82 (18 CH$_3$), 66 (19 CH$_3$), 110 (21 CH$_3$), doublet at 53 ($J = 6$ Hz, 26, 27 CH$_3$), 225 (3α H), 255 (22 H), and 320 cps (6 H); mass spectrum m/e (rel intensity) 434 (M$^+$, 0.3), 416 (M $-$ H$_2$O, 0.4), 398 (416 $-$ H$_2$O, 0.7), 383 (398 $-$ CH$_3$, 0.7), 380 (398 $-$ H$_2$O, 0.4), 365 (380 $-$ CH$_3$, 0.9), 345 (416 $-$ C$_5$H$_{11}$, 3), 333 (M $-$ C$_6$H$_{13}$O, 1), 316 (333 $-$ OH, 41), 315 (333 $-$ H$_2$O, 33), 301 (316 $-$ CH$_3$, 85), 297 (398 $-$ C$_6$H$_{13}$O, 50), 271 (416 $-$ C$_8$H$_{17}$O$_2$, base peak), 253 (271 $-$ H$_2$O, 42).

Anal. Calcd for C$_{27}$H$_{46}$O$_4$·H$_2$O: C, 71.64; H, 10.69. Found: C, 71.45; H, 10.95.

The 3,22-diacetate 24 was prepared and purified following exactly the same procedure as was used to prepare the diacetate of the C-22 epimeric tetrol. Recrystallization from hexane–ether gave stout needles: mp 185–188°; nmr 55 (18 CH$_3$), 61 (19 CH$_3$), 74 (21 CH$_3$) doublet centered at 52 ($J = 6$ Hz, 26, 27 CH$_3$), 121 (3β-acetate methyl), 124 (22-acetate methyl), 275 (3α H), 306 (22 H), and 323 cps (6 H); mass spectrum m/e 458 (M $-$ CH$_3$CO$_2$H, 1), 440 (458 $-$ H$_2$O, 10), 380 (M $-$ 2 CH$_3$CO$_2$H, 10), 357 (M $-$ H$_2$O $-$ C$_8$H$_{15}$O$_2$, 46), 313 (M $-$ H$_2$O $-$ C$_{10}$H$_{19}$O$_3$, 20), 297 (357 $-$ CH$_3$CO$_2$H, 23), 271 (458 $-$ C$_{10}$H$_{19}$O$_3$, 90), 270 (458 $-$ C$_{10}$H$_{20}$O$_3$, base peak), 253 (271 $-$ H$_2$O, 77%).

Lead Tetraacetate Oxidation of (20S,22S)-17α,20,22- and (20S,22R)-17α,20,22-Trihydroxycholesterols. Isolation and Identification of the Glycol Cleavage Products.—To a solution of 40 mg of tetrol 21 or 23 in 10 ml of glacial acetic acid was added a solution of 80 mg of lead tetraacetate in an additional 15 ml of glacial acetic acid. The solution was allowed to stand for 48 hr, after which time water was added and the resulting suspension was extracted with four aliquots of ethyl acetate. The ethyl acetate extracts were washed with bicarbonate until all acetic acid was removed, followed by two washes with water and saturated brine. After the organic extracts were dried over anhydrous sodium sulfate and the solvent was evaporated, there was obtained 26 mg of solid which was directly esterified by treatment with pyridine and acetic anhydride. Work-up in the usual fashion gave a solid residue which was crystallized from a small amount of ether–hexane and was found to be identical in all respects (melting point, ir, nmr) with 17α-hydroxypregnenolone acetate (29). Thin layer chromatographic analysis of the crude acetylated material showed no trace of dehydroepiandrosterone acetate.

To isolate the isocaproaldehyde which results from treatment of the tetrols with tetraacetate, the oxidation was performed as stated above. After the acetic acid solution was allowed to stand for 48 hr, water was added and the suspension was extracted two times with methylene chloride. The organic extracts were washed with bicarbonate to remove all acetic acid and then shaken with water. The methylene chloride solution was cooled to 0° and dried over anhydrous sodium sulfate. After drying, the organic extract was decanted off, cooled to 0°, and evaporated to 0.1 ml in a stream of nitrogen. Identification of the isocaproaldehyde as the only volatile product resulting from tetraacetate oxidation of the tetrol side chain was performed gas chromatographically utilizing the conditions previously described by Burstein, *et al.*[11]

Synthesis of 14β-Fluoro Steroids

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Received December 6, 1971

14β-Fluoro-17α-hydroxy analogs of testosterone, estrone, and estradiol have been prepared from ring D unsaturated 17 ketones *via* perchloryl fluoride fluorination of the corresponding enol acetates. Small amounts of 14β-hydroxylated compounds were also isolated from the fluorination mixture.

For the use of steroid sex hormones in the chemotherapy of certain types of cancer, their primary hormonal activity is usually undesirable and may limit the applicable dose level or the duration of treatment. Consequently, efforts were directed toward the synthesis of such analogs of sex hormones that, ideally, would be hormonally inactive or at least have a favorable ratio of tumor inhibitory *vs.* hormonal activity. In the hope that substituting the strongly electronegative and somewhat larger fluorine atom for a hydrogen atom might suitably alter receptor site affinity of the resulting sex hormone analogs, we have synthesized compounds which are related to testosterone, estrone, and estradiol but are fluorinated in position 14β of the steroid nucleus differing from the normal steroid hormones in the cis juncture of rings C and D. This work reports the preparation and characterization of these compounds and of their synthetic intermediates.

The synthesis of the testosterone analog 10 is shown in Scheme I. Starting with dehydroepiandrosterone 1, the bromo ketone 2 was prepared without attack upon the homoallylic group by direct bromination of 1 with cupric bromide in methanol.[1-3] Following dehydrobromination of the bromo ketone 2 with lithium bromide and lithium carbonate in dimethylacetamide,[3] compounds 3 and 4 were separated by fractional crystallization of the resulting equilibrium mixture. The nmr spectrum of the conjugated ketone 3 showed the vinylic protons at C_{15} and C_{16} as two doublets of doublets centered at 7.81 and 6.26 ppm (J = 6 and 2.5 Hz), and the vinyl proton at C_6 (unresolved) at 5.43 ppm. In the region corresponding to the n → π* transition, the ORD spectrum of 3 exhibited a positive Cotton effect. Sondheimer[4] reported the Cotton effect negative for 3β-hydroxyandrost-15-en-17-one but found it positive for the corresponding 14β-isomeric steroid.

Recently, using circular dichroism measurements, Crabbé, Cruz, and Iriarte[5,6] found analogously oriented Cotton effects for a pair of epimeric 3-methoxyestra-1,3,5(10),15-tetraen-17-ones, *i.e.*, negative for the 14α and positive for the 14β isomer. The nmr spectrum of ketone 4 showed a broad peak at 5.53 ppm due to the two vinylic protons at C_6 and C_{15}. When 4 was acetylated, the product had the same melting point and opposite specific rotation of the same absolute value as the acetate described by St. André and coworkers.[7]

The enol diacetate 5 was prepared directly from the crude equilibrium mixture of 3 and 4. Its nmr spectrum showed the vinyl proton resonances as an unresolved peak at 5.53 ppm (proton at C_6) and as a pair of doublets centered at 6 (J = 2.1 Hz) and 5.8 ppm (J = 2.1 Hz). Since the proton at C_{16} interacts with, and is also somewhat shielded by, the protons of the C_{17} acetoxy group, its signal is probably the less well defined doublet at higher field, while the sharper doublet at 6 ppm arises from the proton at C_{15} which only interacts with the proton at C_{16}. The ultraviolet absorption spectrum shows a maximum at 268 nm (ϵ 6700) due to the ring D chromophore of 5.

Perchloryl fluoride treatment of the enol acetate 5 in aqueous tetrahydrofuran gave a mixture of fluorinated and hydroxylated products which were separated by column chromatography. The hydroxy ketone 7, isolated in small amounts from the more polar fractions, was identified as androsta-5,15-diene-3β,14β-diol-17-one 3-acetate by its elementary analysis ($C_{21}H_{28}O_4$), presence of OH-stretching absorption at 2.88 μ, and by its nmr spectrum showing two doublets centered at 7.63 and 6.08 ppm (J = 6 Hz for both) indicating the C_{15} and C_{16} vinyl protons as well as the absence of a proton at C_{14} since further splitting was lacking. Nonreactivity of the product under acetylating conditions and observation of a positive Cotton

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SCHEME I

1, R = H
2, R = Br

3, R = H
3a, R = Ac

4

6

7

5

8, R = Ac
8a, R = H

9

10, R = H
10a, R = Ac
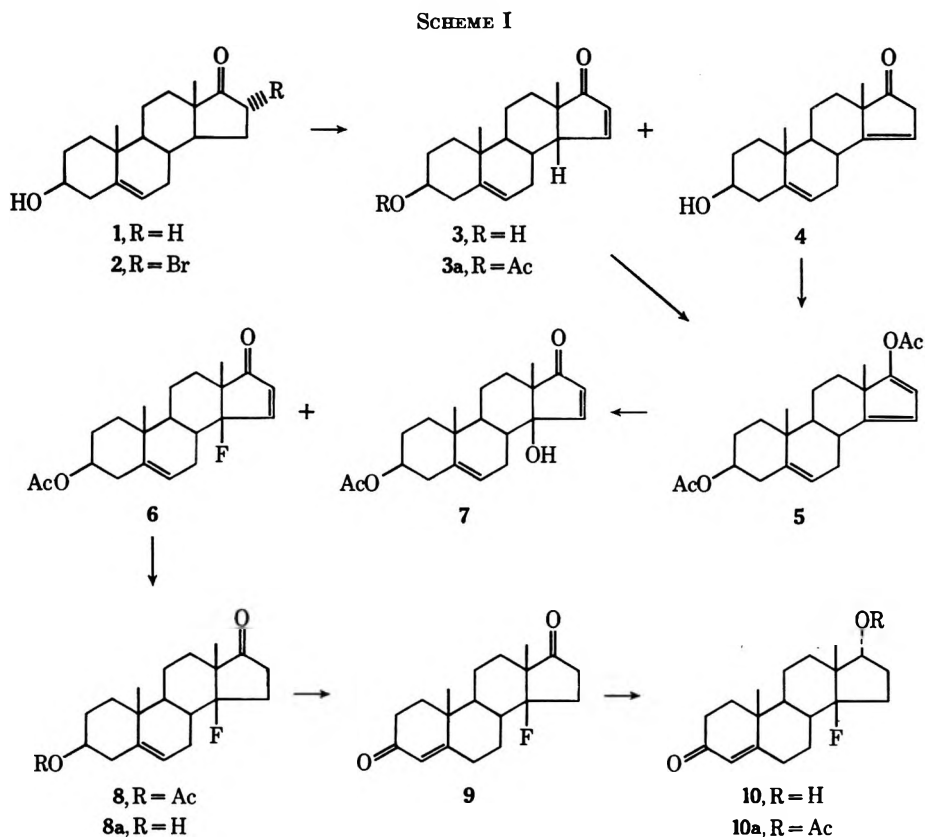
effect in the ORD spectrum confirmed the presence of a 14β-oriented tertiary hydroxyl group.

The less polar main product was a fluoro ketone, $C_{21}H_{27}FO_3$, characterized as 14β-fluoroandrosta-5,15-dien-3β-ol-17-one acetate (6) based on the following evidence. Its ORD spectrum showed a positive Cotton effect in accord with the 14β configuration expected for products of addition across the 14,15 double bond.[4,8] In the nmr spectrum the vinyl protons on C_{15} and C_{16} resonated as a pair of doublets of doublets centered at 7.63 and 6.36 ppm, respectively, with a proton–proton coupling constant of $J_{HH} = 6$ Hz. The proton–fluorine coupling constants were the same both for the vicinal $C_{15}H$, and for the coplanar, allylic C_{16} H, with the value of $J_{HF} = 2.5$ Hz. This coupling constant would seem rather high for the dihedral angle of about 80–85° which appears between the 14β C–F bond and the 15 C–H bond when a Dreiding model of compound 6 is constructed with ring C in its usual chair form. However, a model with its ring C in the boat form shows a more acute angle approaching 60°. Taking into account the Karplus curve[9] the observed coupling constant might thus indicate a preferred boat conformation for ring C of 6. Shoppee[10] reported similar conformational preferences for a number of 14β steroids. Due to interaction with the 14β fluorine, the protons of the C_{18} methyl group were split into a doublet centered at 1.13 ppm ($J_{HF} = 4.5$ Hz). Long-range proton–fluorine coupling through four σ bonds (or, conceivably, across space) involving the C_{18} methyl protons has

been found in 12α- and 17α-fluoro 14α-steroids[11,12] but was not observed for the C_{19} methyl protons in 5α- or 9α-fluoro steroids.[11b]

The double bond in ring D of the fluoro ketone 6 was selectively reduced with palladium–calcium carbonate catalyst in dimethoxyethane. In the nmr spectrum of the saturated ketone 8 the vinylic proton signals at C_{15} and C_{16} disappeared, while the signal of the C_6 vinylic proton persisted at 5.4 ppm. The angular methyl protons at C_{18} again appear as a doublet centered at 1.1 ppm, due to 14β-fluorine coupling, but the constant ($J_{HF} = 1.5$ Hz) now reflects the change of geometry resulting from reduction of the Δ^{15} double bond.

The free alcohol 8a was obtained by methanolysis and used to prepare the diketone 9 by Jones oxidation. After chromatographic purification, the ultraviolet spectrum of 14β-fluoroandrost-4-ene-3,17-dione (9) exhibited a maximum at 239 nm (ε 15,800) in agreement with the Δ^4-3-one chromophore. In the nmr spectrum, there was a signal centered at 5.8 ppm attributed to the vinylic proton at C_4. The C_{19} methyl signal had shifted to lower field (1.23 ppm) due to deshielding by the unsaturated ketone grouping, and the doublet corresponding to the angular C_{18} methyl appeared centered at 1.13 ppm ($J = 1.5$ Hz). Diketone 9 was reduced with sodium borohydride, and the crude allylic alcohol was reoxidized by the modified Oppenauer oxidation method described by Heusler and coworkers.[13] The product was purified by chromatography. Compound 10 showed in the infrared spectrum a hydroxyl band at 2.85 μ and carbonyl absorption at 6.01 μ (α,β-unsat-

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SCHEME II
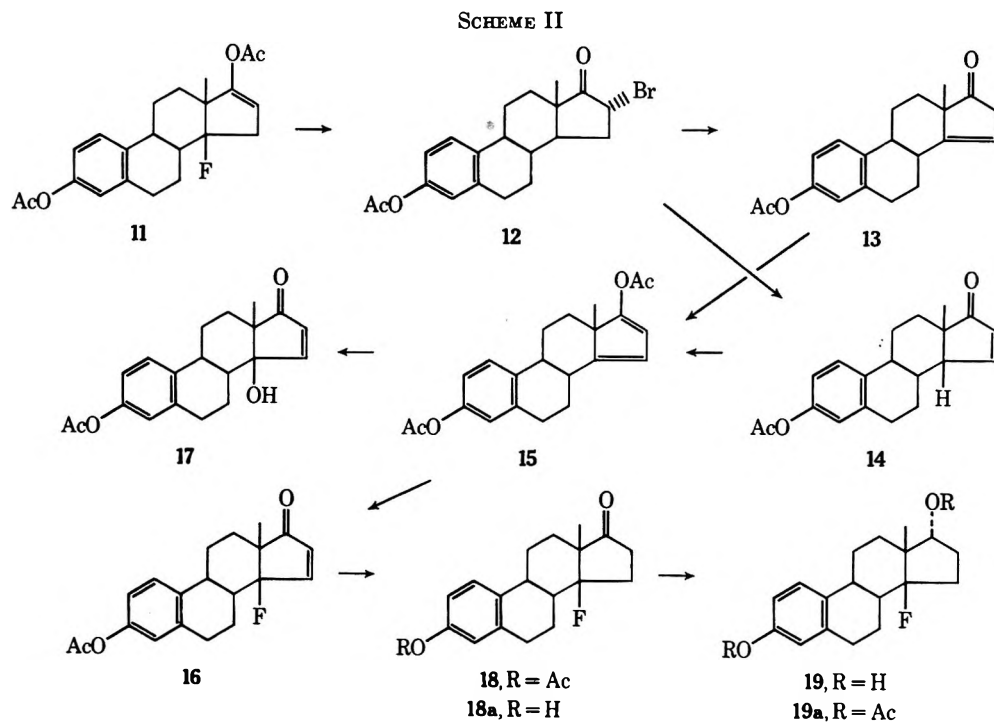
urated ketone). The nmr spectrum is in agreement with the assigned structure: a broad singlet at 5.76 ppm corresponding to the C_4 proton, a singlet at 1.21 ppm belonging to the angular methyl at C_{19}, and a doublet at 1.1 ppm (J = 1.5 Hz) for the C_{18} methyl group were seen. The signal for the proton at C_{17} appeared as a not very well-defined triplet at 3.7 ppm. Configuration at C_{17} follows from the mode of preparation since hydride reduction of 17-keto steroids yields mainly 17α-hydroxy steroids if their C/D ring junction is cis.[7,14] Thus, the principal product of the above sequence is 17α-hydroxy-14β-fluoroandrost-4-en-3-one (10).

For the synthesis of the estrogen analogs the diacetate 11[15] served as a starting material (Scheme II). It was brominated to give the bromo ketone 12[16,17] which was dehydrobrominated[3] to the mixture of ketones 13 and 14. The mixture could be separated by column chromatography. The nmr spectrum of 13 exhibited a broad signal at 5.65 ppm corresponding to the vinylic proton at C_{15}. The aromatic multiplet appeared centered at about 7.0 ppm. A singlet at 1.16 ppm with area equal to three protons was attributed to the methyl protons at C_{18}. Compound 14 showed in its nmr spectrum a doublet of doublets centered at 7.6 and 6.21 ppm with coupling constants of 6.0 and 2.5 Hz, respectively, representing the proton signals at C_{15} and C_{16}. The multiplet of the aromatic protons appeared at about 7 ppm, and the singlet for the C_{18} methyl was at 1.15 ppm. The ORD curve showed a positive Cotton effect, again indicating 14β configuration.

The preparation of estra-1,3,5(10),14,16-pentaene-3,17-diol diacetate (15) was similar to that of the enol acetate 5 of the androstane series. In the ultraviolet 15 showed a maximum at 268 nm, with the high extinc-

tion of ε 14,800, due to its ring D chromophore augmented by the presence of an aromatic ring in the molecule.[4] In the nmr spectrum, a doublet appeared centered at 6.13 ppm (J = 2.5 Hz); it was assigned to the C_{15} proton; the less well-defined doublet centered at 5.83 ppm corresponded to the C_{16} proton.

The fluorination of 15 was carried out under the same conditions as that of the enol acetate 5. Pure 14β-fluoroestra-1,3,5(10),15-tetraen-17-one acetate (16) was obtained after chromatography on Florisil. In its nmr spectrum the C_{15} proton appeared as a doublet of doublets centered at 7.5 ppm (J = 6 and 3.5 Hz). The C_{16} proton signal was a doublet of doublets centered at 6.4 ppm (J = 6 and 2.4 Hz). The C_{18} protons appeared as a doublet centered at 1.17 ppm with J_{HF} = 3.5 Hz, due to fluorine–proton interaction. The compound showed a positive Cotton effect in its ORD curve.

From the more polar fractions estra-1,3,5(10),15-tetraene-3,14β-diol-17-one acetate (18) was isolated and identified by its analysis and spectroscopic properties. The ir spectrum showed hydroxyl absorption at 3.05 μ, the acetate carbonyl at 5.68 μ, and a carbonyl band for the α,β-unsaturated five-membered ring ketone at 5.87 μ. The nmr spectrum showed two doublets centered at 7.4 and 6.3 ppm (J = 6 Hz) due to the vinylic protons at C_{15} and C_{16}, respectively, a singlet at 2.03 ppm which disappeared upon treatment with D_2O (1H, 14β OH), and a singlet at 1.11 ppm pertaining to the C_{18} methyl group. The ORD spectrum showed positive Cotton effect indicating cis junction of rings C and D.

The reduction of 16 to 18 was effected with palladium on carbon catalyst. Treatment of 18 with sodium borohydride led directly to 14β-fluoroestra-1,3,5(10)-triene-3,17α-diol (19). Its nmr spectrum showed broad singlets at 5.4 ppm for the 3-hydroxyl and at 1.65 ppm for the 17α-hydroxyl. Both signals disappeared on treatment with D_2O. A triplet centered at 4.33 ppm and corresponding to one proton (J = 8 and 7 Hz) was

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assigned to the 17β hydrogen. The C_{18} methyl signal at 1.11 ppm was a doublet with a coupling constant of 1.6 Hz.

Experimental Section

Melting points were determined in open capillary tubes and are not corrected. Specific rotations were taken in chloroform solutions. Ultraviolet spectra were obtained in EtOH on a Cary 11 recording spectrophotometer. The nmr spectra were taken in CDCl$_3$ solution on a Varian 60 instrument; chemical shifts (δ) are expressed in parts per million downfield from internal tetramethylsilane. Optical rotatory dispersions were recorded on a Cary instrument. Microanalyses were performed by Mr. J. Alicino, Metuchen, N. J.

16α-Bromoandrost-5-en-3β-ol-17-one (2).—To a solution of 100 g of dehydroepiandrosterone in 1 l. of benzene and 2 l. of MeOH, 150 g of cupric bromide was added. The mixture was heated under reflux for 3.5 hr. The warm solution was filtered and concentrated to about $^2/_3$ volume under reduced pressure. The remainder was diluted with 2 l. of benzene and washed with H$_2$O. The dried solution was evaporated and the residue was crystallized from MeOH: first crop, 47.0 g, mp 172–175°; second crop, 30.6 g, mp 173–174°; third crop, 10.4 g, mp 172–175°; yield 69%.

14β-Androsta-5,15-dien-3β-ol-17-one (3) and Androsta-5,14-dien-3β-17-one (4).—The bromo ketone 2 (90.7 g) was dissolved in 1.8 l. of dimethylacetamide, and 133 g of lithium bromide and 115 g of lithium carbonate were added. The mixture was refluxed for 3.5 hr under nitrogen. The cooled mixture was poured into 2.7 l. of 20% acetic acid and extracted with a 1:1 mixture of benzene–ether. The organic layer was washed with a 5% NaHCO$_3$ solution and with H$_2$O. The dried solution left after evaporation of the solvents 77.9 g of a mixture of 3 and 4. A portion of this mixture was fractionated by crystallization from acetone–hexane. The Δ^{15} ketone was the less soluble component. 14β-Androsta-5,15-dien-3β-ol-17-one (3) had mp 216–217°; [α]D +329°; ir 2.88 and 5.9 μ; nmr δ 7.81 (d, d, 1, J = 6 and 2.5 Hz, H-15), 6.26 (d, d, 1, J = 6 and 2.5 Hz, H-16), 5.43 (s, 1, H-6), 1.1 (s, 3, CH$_3$-18), 1.0 (s, 3, CH$_3$-19); λmax 228 nm (ε 8110).

Anal. Calcd for C$_{19}$H$_{26}$O$_2$: C, 79.50; H, 9.10. Found: C, 79.69; H, 9.15.

Androsta-5,14-dien-3β-ol-17-one (4) had mp 167–168°; ir 5.76 μ; nmr δ 5.53 (s, 2, H-6 and H$_{15}$), 1.15 (s, 3, CH$_3$-18), 1.1 (s, 3, CH$_3$-19). The compound was characterized as its acetate, mp 130–131°, [α]D −55.40 (lit.[7] mp 130–132°, [α]D +54°).

Androsta-5,14-triene-3β,17-diol Diacetate (5).—The solution of the crude dehydrobromination mixture (77.9 g) in 1060 ml of isopropenyl acetate and 1060 ml of acetic anhydride was refluxed with 31.5 g of *p*-toluenesulfonic acid. After 4 hr, the solution was poured on ice and the mixture was stirred for 1 hr. The oily product was taken up in ether, and the solution was washed with a 5% NaHCO$_3$ solution and with H$_2$O. After drying, the ether was removed *in vacuo*. The residue gave from MeOH 45.3 g of 5, mp 151–154°. From the mother liquors an additional 14.2 g, mp 151–153°, was secured, yield 65% based on 2. The analytical sample melted at 154.5–156.5°; [α]D +19.1°; λmax 268 nm (ε 6774); ir 5.71, 5.78, 8.02, 8.20 μ.

Anal. Calcd for C$_{23}$H$_{30}$O$_4$: C, 74.56; H, 8.16. Found: C, 74.47; H, 8.11.

14β-Fluoroandrosta-5,15-dien-3β-ol-17-one Acetate (6) and Androsta-5,15-diene-3β,14β-diol-17-one 3-Acetate (7).—Perchloryl fluoride was bubbled into a stirred solution of 15.0 g of 5 in 760 ml of tetrahydrofuran and 380 ml of H$_2$O for 50 min at room temperature. Most of the tetrahydrofuran and excess reagent were removed on the water pump and the residue was extracted with ether. The extract was washed with a 5% NaHCO$_3$ solution and with H$_2$O. The solvent was evaporated from the dried solution and the residue (15.5 g) was chromatographed on 450 g of Florisil. Petroleum ether containing 4–6% of acetone eluted 7.34 g of a partly crystalline material which gave, from hexane, 5.28 g of 14β-fluoroandrosta-5,15-dien-3β-ol-17-one acetate (6), mp 109–111°, yield 38%. The analytical sample melted at 113.5–114.5°: [α]D +111.2°; ir 5.79, 5.83 μ; nmr δ 7.63 (d, d, 1, J = 6 and 2.5 Hz, H-15), 6.36 (d, d, 1, J = 6 and 2.5 Hz, H-16), 5.5 (s, 1, H-6), 4.6 (s, 1, H-3), 2.01 (5.3, CH$_3$CO), 1.13 (d, 3, J = 4.5 Hz, CH$_3$-18), 1.06 (s, 3, CH$_3$-19).

Anal. Calcd for C$_{21}$H$_{27}$FO$_3$: C, 72.80; H, 7.85; F, 5.48. Found: C, 72.96; H, 7.97; F, 5.55.

The petroleum ether–acetone (8:2) eluates (1.12 g) gave from MeOH–H$_2$O 0.37 g of androsta-5,15-diene-3β,14β-diol-17-one 3-acetate (7), mp 162–163.5°. One additional crystallization furnished the analytical sample: mp 165–166°; [α]D +115.9°; ir 2.88, 5.77, 6.25 μ.

Anal. Calcd for C$_{21}$H$_{28}$O$_4$: C, 73.22; H, 8.19, Found: C, 73.35; H, 8.26.

14β-Fluoroandrost-5-en-3β-ol-17-one Acetate (8).—VI (10.2 g) was hydrogenated in 250 ml of dimethoxyethane (freshly distilled from calcium hydride) in the presence of 2.0 g of 10% Pd/CaCO$_3$ catalyst. The hydrogen uptake ceased after 1.04 mol equiv was absorbed. The solution was filtered from the catalyst and the solvent was removed *in vacuo*. The crystalline residue was purified from hexane to afford 6.2 g of 8, mp 134–135°; from the mother liquors 2.0 g of the compound, mp 121–126°, was recovered, yield 81%. The analytical sample had mp 139.5–141°; [α]D +6°; ir 5.71, 5.76, 8.03 μ; nmr δ 5.4 (s, 1, H-6), 4.58 (3, 1, H-3), 2.01 (s, 3, CH$_3$CO), 1.1 (d, 3, J = 1.5 Hz, CH$_3$-18), 1.05 (s, 3, CH$_3$-19).

Anal. Calcd for C$_{21}$H$_{29}$FO$_3$: C, 72.38; H, 8.39; F, 5.45. Found: C, 72.14; H, 8.55; F, 5.61.

14β-Fluoroandrost-5-en-3β-ol-17-one (8a).—To a solution of 20.0 g of 8 in 750 ml of MeOH, 11.6 ml of concentrated HCl was added and the solution was kept for 23 hr at room temperature. Sodium acetate (12.0 g) in 180 ml of H$_2$O was added and about 500 ml of MeOH was distilled off under reduced pressure. After cooling, the crystalline product was filtered off, washed well with H$_2$O, and dried. The crude 8a was recrystallized from MeOH, yield 11.03 g, mp 195–196.5°. From the mother liquors 5.43 g of product melting at 182–190° was obtained. The analytical sample had a melting point of 197.5–200°; [α]D +9.60; ir 2.84, 5.73 μ.

Anal. Calcd for C$_{19}$H$_{27}$FO$_2$: C, 74.47; H, 8.88; F, 6.20. Found: C, 74.62; H, 9.18; F, 6.31.

14β-Fluoroandrost-4-ene-3,17-dione (9).—To a solution of 11.00 g of 8a in 1640 ml of acetone (distilled from potassium permanganate), cooled in an ice bath, 7.4 ml of an 8 N chromium trioxide solution (Jones reagent) was added with stirring. After 2 min, 6 ml of EtOH was added and the reaction mixture was poured into 6 l. of ice water. The mixture was extracted with methylene chloride, and organic layer was washed with H$_2$O and saturated NaCl solution. After drying with Na$_2$SO$_4$, the solvent was evaporated. The crystalline residue (10.5 g) was suspended in 800 ml of MeOH and 9.5 ml of concentrated HCl was added. After the crystals had dissolved (about 3 min), the solution was stirred in a nitrogen atmosphere for 15 min at room temperature. Sodium acetate (12.75 g) was added and the MeOH was removed *in vacuo*. The residue was extracted with ether and washed with H$_2$O and with a 5% NaHCO$_3$ solution. The solution was dried and the ether was evaporated. The remaining product (9.47 g) was chromatographed on 275 g of florisil. The dione 9 (7.2 g) was eluted with petroleum ether containing 7% acetone. Crystallization from acetone–hexane gave 5.54 g, mp 153–156°. From the mother liquors 0.648 g, mp 149–151°, was obtained, yield 56.7%. The analytical sample melted at 158.5–160°; [α]D +140.6°; ir 5.72, 5.98 μ; λmax 239 nm (ε 15,801).

Anal. Calcd for C$_{19}$H$_{25}$FO$_2$: C, 74.96; H, 8.28; F, 6.24. Found: C, 75.17; H, 8.09; F, 6.20.

14β-Fluoroandrost-4-en-17α-ol-3-one (10).—To a solution of 5.47 g of diketone 9 in 650 ml of MeOH, 2.16 g of sodium borohydride was added. The solution was cooled in an ice bath during the addition, then kept at room temperature for 21 hr. Acetic acid (5 ml) was added and most of the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride and the solution was evaporated. The residue (5.40 g) was dissolved in 270 ml of anhydrous benzene, and the solution of 5.5 g of aluminum isopropoxide in 20 ml of acetone was added. After standing for 24 hr at room temperature, the solution was washed with 2 N HCl solution and with H$_2$O and dried. Evaporation of the solvent left a semicrystalline residue (5.1 g) which was chromatographed on 150 g of Florisil. The fractions obtained with mixtures of petroleum ether containing 8–10% of acetone weighed 2.80 g and gave, after crystallization from acetone–hexane, 2.60 g of 10, mp 150° dec, yield 47.2%. The analytical sample melted at 160–162° dec; [α]D +98.7°; ir 2.85, 6.01 μ; λmax 240 nm (ε 15,870); nmr δ 5.76 (s, 1, H-4), 1.21 (s, 3, CH$_3$-19), 1.1 (d, 3, J = 1.5 Hz, CH$_3$-18).

Anal. Calcd for $C_{19}H_{27}FO_2$: C, 74.47; H, 8.88; F, 6.20. Found: C, 74.41; H, 9.02; F, 6.12.

14β-Fluoroandrost-4-en-17α-ol-3-one Acetate (10a).—10 (200 mg) was acetylated with acetic anhydride–pyridine. The solution was evaporated to dryness and the residue was recrystallized several times from ether–petroleum ether. The melting point of the analytical sample was 111.5–112.5°, ir 5.74, 5.98 μ.

Anal. Calcd for $C_{21}H_{29}FO_3$: C, 72.80; H, 7.38; F, 5.48. Found: C, 72.67; H, 7.79; F, 5.67.

16α-Bromoestra-1,3,5(10)-trien-3-ol-17-one Acetate (12).—A solution of 50 g of estra-1,3,5(10),16-tetraene-3,17-diol diacetate (11) (15) in 31 ml of carbon tetrachloride was stirred with 40 g of anhydrous K_2CO_3 at −8°. To the mixture, 27.37 g of bromine was added over a period of 30 min. The mixture was poured into ice water containing a small amount of $NaHSO_3$. The organic layer was washed with a 5% $NaHCO_3$ solution and with H_2O and dried with Na_2SO_4. After the solvent was evaporated, the residue crystallized from MeOH to yield 46.08 g of 12, mp 164–163°. The mother liquors gave after acetylation and the usual work-up an additional 5.9 g of 12, mp 161–169°, yield 78.5%

Estra-1,3,5(10),14-tetraen-3-ol-17-one Acetate (13) and 14β-Estra-1,3,5(10),15-tetraen-3-ol-17-one Acetate (14).—12 (1 g) in 25 ml of dimethylacetamide was refluxed with 1.5 g of lithium bromide and 1.35 g of lithium carbonate under nitrogen for 3.5 hr. The mixture was poured into 25 ml of 20% acetic acid and extracted with ether. The ether solution was washed with 5% $NaHCO_3$ solution and with H_2O. The residue (0.879 g) left after evaporation of the solvent was chromatographed on 30 g of silica gel. Petroleum ether containing 3–4% acetone eluted 0.32 g of 13, which was recrystallized from acetone–hexane to give 0.266 g of pure estra-1,3,5(10),14-tetraen-3-ol-17-one acetate (13): mp 141.5–142.5°; [α]D +255°; ir 5.68, 5.76 μ.

Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.41; H, 7.09. Found: C, 77.50; H, 7.09.

The fractions obtained with petroleum ether containing 5–6% acetone (0.310 g) gave from acetone–hexane 0.135 g of estra-1,3,5(10),15-tetraen-3-ol-17-one acetate (14), mp 123–125°. The purest sample had mp 125.5–126°: [α]D +420°; ir 5.68, 5.75 μ; λmax 280 nm (ε 13,400).

On a preparative scale, 51 g of the bromo ketone 12 afforded 20.10 g of 13 (49.7%) and 9.8 g of 14 (24.2%).

Estra-1,3,5(10),14,16-pentaene-3,17-diol diacetate (15).—The solution of 20 g of crude 13 in 240 ml of isopropenyl acetate and 240 ml of acetic anhydride was refluxed with 8.0 g of p-toluenesulfonic acid for 4 hr. The reaction mixture was worked up a described in the preparation of 5. The enol diacetate crystallized from MeOH, yield 18.6 g of 15, mp 149–150.5°. A second crop of 2.14 g obtained from the mother liquors melted at 143–146°, yield 91.1%. The melting point of the analytical sample was 151–152.5°: [α]D +263°; λmax 268 nm (ε 14,800); ir 5.68, 8.3 μ; nmr δ 2.26 (s, 3, CH₃CO-3), 2.20 (s, 3, CH₃CO-17), 1.1 (s, 3, CH₃-18).

Anal. Calcd for $C_{22}H_{24}O_4$: C, 75.00; H, 6.81. Found: C, 75.02; H, 6.88.

Starting with 9.8 g of 14, the same reaction gave 9.4 g of 15, mp 147–150°.

14β-Fluorestra-1,3,5(10),15-tetraen-3-ol-17-one Acetate (16) and Estra-1,3,5(10),15-tetraene-3,14β-diol-17-one 3-Acetate (17). —Perchloryl fluoride was bubbled into a stirred solution of 23.3 g of 15 in 1165 ml of tetrahydrofuran and 580 ml of H_2O for 50 min at room temperature. The work-up of the reaction mixture was essentially the same as in the androstane series. The crude reaction product was chromatographed on 650 g of Florisil.

Petroleum ether–acetone (3–5%) eluted 10.19 g of 16 which crystallized from acetone–hexane, yield 7.95 g (36.6%), mp 103–109°. The analytical sample of 14β-fluoroestra-1,3,5(10),-15-tetraen-3-ol-17-one acetate showed a melting point of 112.5–113.5°: [α]D +265°; ir 5.68, 5.81 μ; nmr δ 7.5 (d, d, 1, J = 6 and 3.5 Hz), ca. 7 (m, 3, aromatic H), 5.4 (d, d, 1, J = 6 and 2.4 Hz, H-16), 2.26 (s, 3, CH₃CO), 1.17 (d, 3, J = 3.5 Hz, CH₃-18).

Anal. Calcd for $C_{20}H_{21}FO_3$: C, 73.19; H, 6.39; H, 5.78. Found: C, 72.88; H, 6.34; F, 6.02.

The material eluted with petroleum ether–15% acetone gave from acetone–hexane 0.486 g of 17, mp 170–170.5°. The analytical sample of estra-1,3,5(10),15-tetraene-3,14β-diol-17-one 3-acetate melted at 177.5–178°:[α]D +240°; ir 3.05, 5.65, 5.87 μ.

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.64; H, 6.74. Found: C, 73.61; H, 6.82.

14β-Fluoroestra-1,3,5(10)-trien-3-ol-17-one Acetate (18).—16 (5.3 g) was hydrogenated in 135 ml of freshly distilled dimethoxyethane in the presence of 1.05 g of 10% Pd/C catalyst. After the hydrogen uptake ceased, the mixture was filtered and the filtrate was evaporated to dryness. The residue was crystallized from acetone–hexane and yielded 3.66 g of 18, mp 141–144°. From the mother liquors 0.66 g of the same compound was obtained, yield 81.5%. The analytical sample had mp 147–148°: [α]D +116°; ir 5.68, 5.75 μ; nmr δ ca. 7 (m, 3, aromatic H), 2.26 (s, 3, CH₃CO), 1.13 (d, 3, J = 1.5 Hz, CH₃-18).

Anal. Calcd for $C_{20}H_{23}FO_3$: F, 72.75; H, 6.96; H, 5.75. Found: C, 72.67; H, 7.00; F, 5.85.

14β-Fluoroestra-1,3,5(10)-trien-3-ol-17-one (18a).—A solution of 1.3 g of 18 in 40 ml of EtOH and 2.2 ml of concentrated HCl was refluxed for 1 hr. The solution was poured into H_2O and the mixture was extracted with ether. The ether solution was washed with a 5% $NaHCO_3$ solution and with H_2O and dried. The evaporation residue crystallized from benzene, first crop 0.88 g, mp 183° dec, second crop 0.155 g, mp 178° dec, yield 91%. The analytical sample melted at 183° with decomposition, [α]D +139°, ir 3.05, 5.75 μ.

Anal. Calcd for $C_{18}H_{21}FO_2$: C, 75.02; H, 7.28; F, 6.59. Found: C, 75.13; H, 7.47; F, 6.80.

14β-Fluoroestra-1,3,5(10)-triene-3,17α-diol (19).—To a cold solution of 2.18 g of 14β-fluoroestra-1,3,5(10)-trien-3-ol-17-one acetate in 300 ml of EtOH, 1.1 g of sodium borohydride was added. The solution was allowed to stand for 23 hr at room temperature. Acetic acid (2 ml) was added and most of the solvent was removed under diminished pressure. The residue was poured into H_2O and extracted with ether. After the usual work-up, 1.028 g of 19, mp 151° dec, was obtained from MeOH, yield 53.8%. The analytical sample had mp 159° dec: [α]D +70.7°; ir 3.05 μ; nmr δ ca. 7 (m, 3, aromatic H), 5.4 (m, 1, HO-3), 4.33 (t, 1, J = 8 and 7 Hz, H-17), 1.15 (s, 1, HO-17), 1.11 (d, 3, J = 1.6 Hz, CH₃-18).

Anal. Calcd for $C_{18}H_{23}FO_2$: C, 74.50; H, 7.92; F, 6.54. Found: C, 74.35; H, 7.80; F, 6.80.

14β-Fluoroestra-1,3,5(10)-triene-3,17α-diol Diacetate (19a).—The mother liquors of 19 were evaporated to dryness and the residue (1.2 g) was acetylated with acetic anhydride–pyridine overnight. After the solvents were removed *in vacuo*, the residue was crystallized from acetone–hexane to give 0.564 g of 19a, mp 127–130°. The analytical sample melted at 136–137°, [α]D +48°, ir 5.7, 5.81 μ.

Anal. Calcd for $C_{22}H_{27}FO_4$: C, 70.61; H, 7.21; F, 5.07. Found: C, 70.60; H, 7.40; F, 5.17.

Pure 19 (20 mg) was acetylated as above. The acetylated product displayed the same nmr as 19a from the mother liquors of 19, mmp 136–137°.

Prostaglandins. IV. Total Syntheses of *dl*-11-Deoxy PGE₁ and 13,14-Dihydro Derivatives of 11-Deoxy PGE₁, PGF₁α, and PGF₁β

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Received January 10, 1972

A photoannelation reaction between two α,β-unsaturated ketones 1 and 2 is described. The photoadduct **5** was isolated and characterized by spectral analysis and was transformed into methoxy and acetoxy derivatives **6** and **7**. A minor product **9** was also isolated from the reaction and its structure elucidated. Some data on the effect of the concentration of the substrates and the temperature and on the photoannelation reaction are reported. Treatment of photoadduct **5** with zinc–acetic acid led to the cyclobutane dione **13** and the cleaved diketone **14**. These products were also obtained from a similar treatment of **7**. Under the same conditions, methoxy compound **6** yielded a rearrangement product. Some mechanistic implications of (a) photoannelation and (b) the rearrangement product **16** are discussed. Finally, the transformation of diketone **14** to other prostanoic acid derivatives is described.

In recent years prostaglandins, a class of naturally occurring 20-carbon fatty acids, have occupied the attention of several research groups.[1-6]

In an earlier communication[7] we reported a novel method of constructing the prostanoic acid skeleton. This article describes further studies of the photoannelation reaction involved, and the chemical transformation of several of the intermediates.

It was conceived that photoannelation of a suitably substituted acyclic ketone such as **2** with 2-(6-carbomethoxyhexyl)-cyclopent-2-en-1-one (**1**) can give rise to two possible head-to-head (HH) and head-to-tail (HT) products, **3** and **4**. The cleavage of the C–C bond (a) of **3** can then generate the prostanoic acid derivatives.

1, R = (CH₂)₆COOCH₃

2, R¹ = C₅H₁₁

3

4
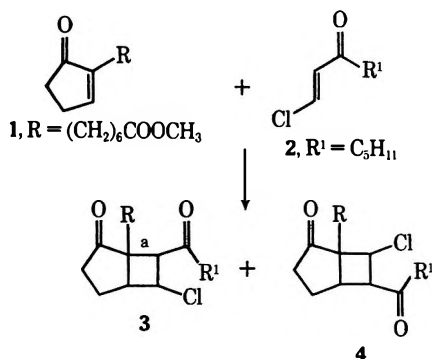
Photoannelation.—Photoannelation of the α,β-unsaturated ketones between two molecules of the same ketone[8] or between a ketone and an olefin[9] has proven

of great synthetic utility.[10] The first example of photoannelation of a substituted vinyl ketone and an α,β-unsaturated ketone was recently reported[11] when our work was in progress.

In our initial studies we irradiated cyclopentenone **1** and 1-chlorooct-1-en-3-one (**2**) (1:5 molar ratio) with a 550-W Hanovia burner at 35–40° for about 40 hr and obtained after purification a homogeneous product having empirical formula $C_{21}H_{33}ClO_4$ in ~35% yield, based on recovered starting materials. The adduct was assigned HH structure **5**, based on its spectroscopic data and its chemical transformations.

a   b   8

5, R = Cl

6, R = OCH₃

7, R = OCOCH₃

R¹ = (CH₂)₆COOCH₃
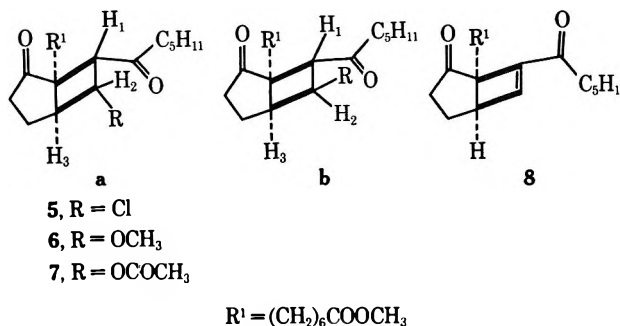
The cis stereochemistry at the ring junction is assumed from the earlier analogies.[9] That it is an HH adduct follows from its nmr spectrum. The spectrum exhibited a quartet at δ 4.5 and a triplet at δ 4.9. The two together integrated for one proton. These signals were assigned to protons H₂ in **5a** and **5b**, respectively. These assignments are based on the long-range deshielding caused by the ketone function located between the cyclobutane ring and the –C₅H₁₁ chain.[12a] The

(1) (a) For a review of recent chemical literature, see J. F. Bagli, *Annu Rep. Med. Chem.*, 170 (1970); (b) G. Bundy, *ibid.*, 137 (1971).

(2) D. Taub, R. D. Hoffsommer, C. H. Duo, H. L. Slates, Z. S. Zelawski, and N. L. Wendler, *Chem. Commun.*, 1258 (1970).

(3) D. P. Strike and H. Smith, *Tetrahedron Lett.*, 4393 (1970).

(4) M. Miyano, *J. Org. Chem.*, **35**, 2314 (1970).

(5) R. Klok, H. J. J. Pabon, and D. A. Van Dorp, *Recl. Trav. Chim. Pays-Bas*, **89**, 1043 (1970).

(6) (a) E. J. Corey, U. Koelliker, and J. Neuffer, *J. Amer. Chem. Soc.*, **93**, 1489 (1971); (b) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971); (c) E. J. Corey, S. M. Albonico, U. Koeliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971); (d) E. J. Corey and R. K. Varma, *ibid.*, **93**, 7318 (1971); (e) J. Fried, M. M. Mehra, and W. L. Kao, *J. Amer. Chem. Soc.*, **93**, 5594 (1971), and references cited therein.

(7) J. F. Bagli and T. Bogri, *Tetrahedron Lett.*, 1639 (1969).

(8) P. E. Eaton, *Accounts Chem. Res.*, **1**, 50 (1968).

(9) (a) P. de Mayo, *ibid.*, **4**, 41 (1971); (b) P. G. Banslaugh, *Synthesis*, 290 (1970).

(10) (a) E. J. Corey, R. B. Mitra, and H. Uda, *J. Amer. Chem. Soc.*, **86**, 485 (1964); (b) J. D. White and D. N. Gupta, *ibid.*, **88**, 5364 (1966); (c) *ibid.*, **90**, 6171 (1968); (d) Z. Koblicova and K. Wiesner, *Tetrahedron Lett.*, 2563 (1967); (e) E. J. Corey and S. Nazoe, *J. Amer. Chem. Soc.*, **86**, 1652 (1964); (f) B. D. Challand, H. Hikino, G. Kornis, G. Lange, and P. Mayo, *J. Org. Chem.*, **34**, 794 (1969).

(11) P. Sunder-Plassmann, P. H. Nelson, L. Durham, J. A. Edwards, and J. H. Fried, *Tetrahedron Lett.*, 653 (1967).

(12) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 100. For a case in cyclobutanes, see V. Georgian, L. Georgian, A. V. Robertson, and L. F. Johnson, *Tetrahedron*, **19**, 1219 (1963). (b) When the reaction was carried out without solvent the mixture of cis and trans isomers varied from batch to batch. Conversely, in the presence of solvent the major component was consistently trans isomer **5b** (80%). (c) Each of the signals of the doublet had a shoulder, indicating the slight differences in the chemical shift due to the difference in structure of **5a** and **5b**. (d) In both cases the singlet was not sharp. This may be attributed (i) to the presence of two isomers, and (ii) to 1,3 splitting in cyclobutane series [K. B. Wiberg, *et al.*, *J. Amer. Chem. Soc.*, **84**, 1594 (1962)].

proportion of the *cis*-5a and *trans*-5b isomers varied with the reaction conditions.[12b] The nmr spectrum also showed a doublet[12c] at δ 3.17, attributable to H_1. The signals at δ 4.9 and 4.5 collapsed to doublets ($J = 7.5$ and 6.5 Hz, respectively) during the irradiation at resonance frequency of H_1. Conversely, the doublet of H_1 collapsed to a singlet[12d] when observed during irradiation at resonance frequency of H_2.

Refluxing the adduct **5** in collidine yielded the olefin **8**. This was characterized by a new olefinic proton in the nmr at δ 6.92 ($J = 2$ Hz). The photoadduct **5** was readily transformed with methanolic sodium methoxide at room temperature to the methoxy derivative **6**. The corresponding acetate **7** was also obtained from silver acetate–acetic acid treatment of **5**. The nmr spectral data (Table I) of these compounds were in accordance with the assigned structures.

TABLE I

Compd	H_1, δ	H_2, δ
5a	3.19 (d, $J = 7$ Hz)	4.5 (t, $J_{1,2} = J_{2,3} = 7.5$ Hz)
5b		4.9 (q, $J_{1,2} = 7$, $J_{2,3} = 6.5$ Hz)
6	2.95 (d, $J = 7$ Hz)	4.04[a] (q, $J_{1,2} = 7$, $J_{2,3} = 5$ Hz)
7	3.17 (d, $J = 6$ Hz)	5.07 (q, $J_{1,2} = 7$, $J_{2,3} = 5$ Hz)
10	4.03 (d, $J = 6$ Hz)	2.93 (m)
11	5.00 (d, $J = 7$ Hz)	3.00 (t, $J_{1,2} = J_{2,3} = 7$ Hz)

[a] It is assumed that methoxy compound is formed by an elimination addition pathway, and therefore should lead predominantly to isomer **6b**. However, in the nmr of the pure product there were very small signals present (q) centered at δ 3.5 (partially buried under methoxyl) which might be due to the presence of the methoxy isomer **6a**.

A second product isolated (8% yield) from the chromatogram of the crude photoannelation product showed in its infrared spectrum bands at 1670 and 1590 cm⁻¹, attributable to an α,β-unsaturated ketone. The nmr spectrum exhibited a signal at δ 6.54 (1 H) as a sharp singlet and the ultraviolet had maxima at 229 and 249[13] mμ (ε 4000 and 3800, respectively). Based on the above evidence the enone was assigned structure **9**. The generation of the enone **9** must involve dehydrochlorination of the HT adduct **4**, formed as a minor product in the photoannelation. The confirmation of the above structural assignment was afforded by the following chemical transformation. Treatment of **9** with methanolic sodium methoxide readily gave a methoxy derivative **10**. The corresponding acetate

10, $R^1 = OCH_3$
11, $R^1 = OCOCH_3$

$R = (CH_2)_6COOCH_3$
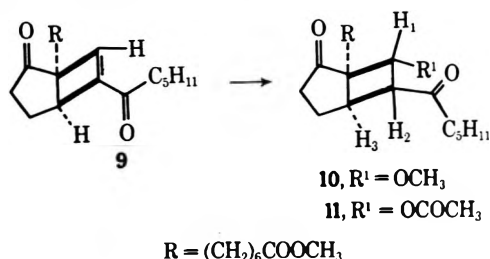
11 was obtained with sodium acetate–acetic acid treatment. When the doublet of H_1 in acetate **11** was ob-

(13) This band may be attributed to a charge transfer transition observed in unsaturated carbonyl compounds [see J. F. Bagli, *et al.*, *J. Org. Chem.*, **28**, 1207 (1963)].

served while irradiating with the resonance frequency of H_2, the doublet collapsed to a singlet. Conversely, the quartet of H_2 collapsed to a doublet when irradiated with the resonance frequency of H_1.

The influence of solvents and concentration of the substrate in photodimerization[14] and photoannelation[15] has been a subject of study by various groups. Recently, a report on the role of temperature[16] in photoannelation has also been published.

Hexane was chosen as a solvent for the study of the influence of the temperature and concentration of the substrates on the course of the reaction. The results of this study are recorded in Table II. It was noted that

TABLE II

Expt[b]	Concn of 1,[f] mol	Mol ratio, 1:2	Temp, °C	Yield[a] of 3, %
1	0.15	1:5	35–40	19
2	0.15	1:5	−10 to −20	16.5
3	0.15	1:1	35–40	41.2
4	0.15	1:1	−10 to −20	47
5	0.015	1:1	35–40	4.5
6	0.03	1:1	35–40	e
7	0.045	1:1	35–40	e
8[c]	0.15	1:1	35–40	82
9[d]	0.3	1:1	35–40	88

[a] Yields are calculated based on recovered starting materials from chromatography. [b] Unless otherwise mentioned, the irradiations were carried out for 7 hr in a nitrogen atmosphere. [c] Irradiation time 15 hr. [d] Irradiation time 40 hr. [e] No pure product could be isolated by chromatography. [f] The solutions were made up to 1 l. with reagent grade hexane.

temperature had little influence on the yield of the desired product **5** (expt 1, 2 and 3, 4). Reducing the concentration of chlorovinyl ketone from 5 mol to 1 mol resulted in approximately threefold improvement of the yield of the HH adduct (expt 1, 3 and 2, 4). At lower concentrations of the substrates (expt 6, 0.03 mol, and expt 7, 0.045 mol) a significant amount of polymeric materials was formed. The desired product was indeed present in the reaction mixture, as noted by tlc, but could not be isolated in pure form. In photodimerization a marked increase in the formation of the HT adduct has been observed at the lower concentration.[14] It was apparent that at lower concentrations the photodimerization reaction predominated. When the experiment was performed as in expt 3 and the irradiation time was doubled (expt 8) the yield of the HH adduct **5** was essentially doubled. Further doubling the concentration of the substrates and the time of irradiation (expt 9) had no detrimental effect on the yield of the product.

The predominant formation of HH adduct may be partly accounted for by invoking the interaction between the excited species of cyclopentenone (a) with the ground state species (b) of acyclic ketone shown below.

The formation of **5a** and **5b** could result from equilibration of stabilized anion radical **12**, or by direct formation of the C–C bond with the cis isomer of ketone **2**. The presence of the cis isomer of **2** in the reaction

(14) (a) P. C. Eaton and W. S. Hurt, *J. Amer. Chem. Soc.*, **88**, 5038 (1966); (b) J. L. Ruhlen and P. A. Leermakers, *ibid.*, **89**, 4944 (1967).

(15) P. de Mayo, J. P. Pete, and M. Tachir, *Can. J. Chem.*, **46**, 2535 (1968).

(16) R. O. Loutfy, P. de Mayo, and M. F. Tachir, *J. Amer. Chem. Soc.*, **91**, 3984 (1969).

a   b

12 → **5a, 5b**
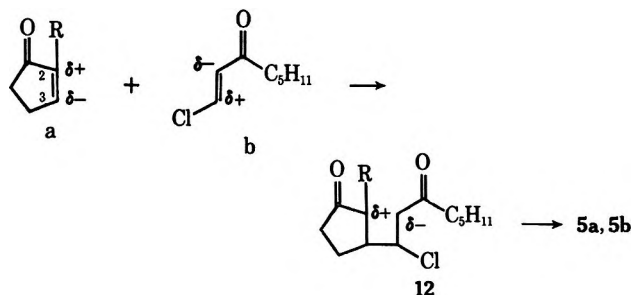
mixture was confirmed by its isolation and characterization by nmr from recovered chloro vinyl ketone. The formation of the cis ketone **2** is readily explained by the extremely rapid decay of its excited triplet by rotation around the C–C bond.[8]

Reductive Cleavage of Cyclobutane.—Opening of a small ring conjugated to a carbonyl function has been the subject of a recent study.[17] A special case of reductive opening of cyclobutane in a cage system has also been reported.[18]

We considered the opening of adduct **5** with the idea that such a reaction would be an extension of a 1,4-enedione → 1,4-diketone transformation (reduction). provided proper σ–π[19] orbital overlap is possible as suggested by Dauben.[17] Zinc–acetic acid treatment at reflux temperature of the photoadduct **5** gave rise to two compounds, to which structures **13** and **14** were assigned based on their spectral properties.

R = (CH₂)₆COOCH₃
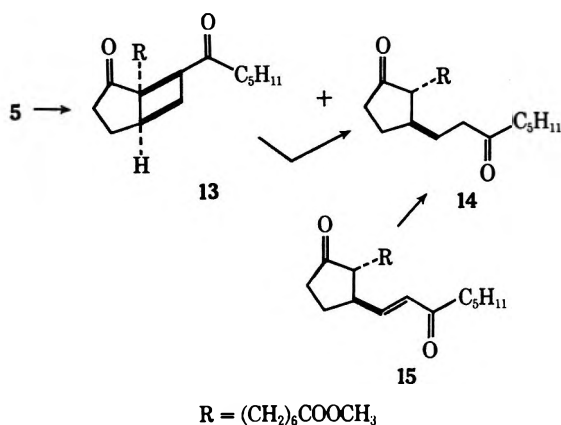
The structure of cyclobutane dione **13** was confirmed by its generation both by chemical (zinc–acetic acid) as well as by catalytic reduction of enone **8**. The structure of compound **14** was confirmed by its obtention from the hydrogenation of enone **15**.[20]

The formation of dechloro ketone **13** in the reductive cleavage is worthy of comment. Loss of a halogen atom β to a ketone function under reductive condition

(17) W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).

(18) E. Wenkert and J. E. Joder, *ibid.*, **35**, 2986 (1970).

(19) The probability of such σ–π overlap in adduct **3** appeared quite high, in view of a free rotating carbonyl group which can align itself in a desired conformation.

(20) This compound was readily obtained by oxidation of **i** described earlier [J. F. Bagli and T. Bogri, *Tetrahedron Lett.*, 5 (1967)].

i
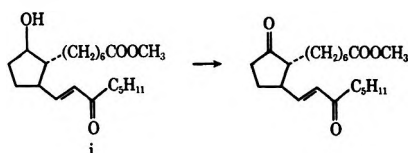
is not very facile except under certain circumstances.[21] The formation of diketone **13** via an elimination–reduction mechanism might be preferred, based on the following facts. (1) Whereas 16–20 hr at 115° (bath temperature) was required for all the photoproduct to disappear, the unsaturated ketone **8** was quantitatively consumed in zinc–acetic acid reduction in 10 min at room temperature to yield dione **13**. (2) The treatment of acetate **7** under similar reaction conditions also led to the formation of cyclobutane dione **13** and diketone **14** as identified by tlc and glc. The high propensity of the reduction of the double bond of **8** with zinc–acetic acid must be attributed to the relief of strain in going from the sp² to sp³ state. The above evidence does not, however, preclude a possible direct reductive loss of chlorine under these conditions. The cyclobutane dione **13** can be transformed essentially quantitatively to the diketone **14** by a further treatment with zinc–acetic acid.

Treatment of methoxy diketone **6** with zinc–acetic acid gave in good yield the α,β-unsaturated ketone **16**. This reaction proceeded in the absence of zinc to give the same compound at essentially the same rate. The above structural assignment followed from the spectral analysis of **16** and its derivatives **17** and **18**. Striking evidence of the rearrangement was afforded by the mass spectrum of **16**, which showed no fragments for –COC₅H₁₁ (m/e 99) and –C₅H₁₁ (m/e 71) commonly

6 →

16, R' = R = ⟩=O

17, R' = R = X⟨H OH

18, R' = R = X⟨H OAc

19
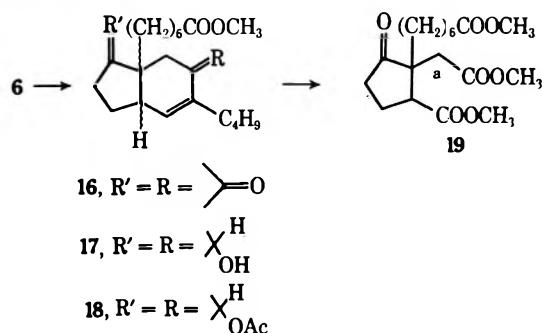
present in 15-oxygenated prostanoic acid derivatives. Ozonolysis of enone **16** followed by oxidative cleavage and esterification yielded the triester **19**. This compound was characterized in its nmr by the absence of the terminal methyl, and a poorly resolved doublet due to methylene protons at carbon a.

This rearrangement product was also formed when the photoadduct **5** was allowed to remain at room temperature without solvent over a certain length of time. Treatment of the adduct **5** with ethylamine at ice-bath temperature also led to the formation of the ring expansion product **16**. The formation of enone **16** under acidic as well as basic conditions implicates nucleophillic attack by carbon a on the cyclobutane carbon bearing the substituent (–Cl or –OCH₃) leading to the ring expansion. A β elimination of the substituent can then generate enone **16**.

Reduction of ketone **14** with sodium borohydride in methanol led to a mixture of isomeric diols **20** and **21** which were separable by chromatography. When the reduction was conducted in dimethoxyethane at −50° using sodium borohydride, under controlled conditions,

(21) (a) A. Nickon and N. Werstuik, *J. Amer. Chem. Soc.*, **89**, 3914 (1967); (b) D. P. G. Hamon and R. W. Sinclair, *Chem. Commun.*, 890 (1968).

5

6

$R = (CH_2)_6COOCH_3$

16

room temperature
or
$C_2H_5NH_2/0°$

Zn/AcOH
or
AcOH

32, R = OH; R¹ = H
33, R = H; R¹ = OH

25, R = OH; R¹, R² = =O
26, R = OTHP; R¹, R² = =O
27, R = OTHP; R¹, R² = $<^{OH}_H$
28, R = OTHP; R¹, R² = $<^{OAc}_H$
29, R = —OH; R¹, R² = $<^{OAc}_H$
30, R = =O; R¹ = OH; R² = H
31, R = =O; R¹ = H; R² =OH
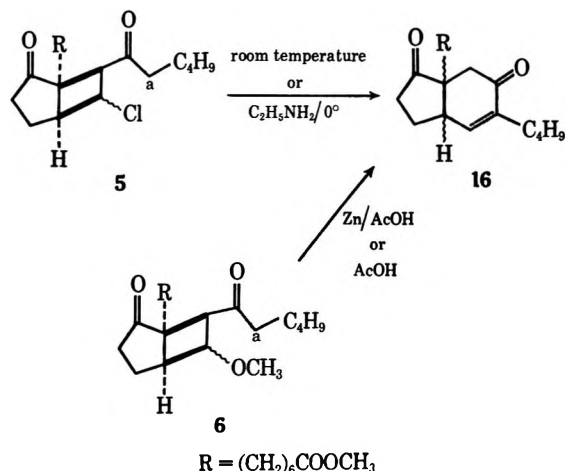
a mixture of monoalcohols was obtained together with some unchanged starting material.

The chromatographic separation yielded a faster moving product homogeneous by tlc and glc, and structure 24 (11.2%) was assigned to it based on analytical data. Further elution led to the isolation of a major

20, R¹ = $<^{OH}_H$; R = $<^{OH}_H$

21, R¹ = $<^{H}_{OH}$; R = $<^{OH}_H$

22, R¹ = $>$=O; R = $<^{OH}_H$

23, R¹ = $<^{OH}_H$; R = $>$=O

24, R¹ = $<^{H}_{OH}$; R = $>$=O
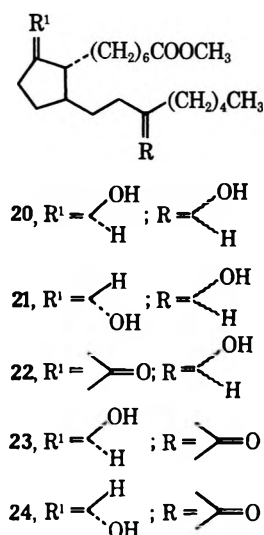
component homogeneous by tlc. Gas chromatography, however, showed it to be a mixture of a major and a minor component (3:1). This mixture was converted to the corresponding tetrahydropyranyl ether, followed by chromatographic separation, and the acid hydrolysis yielded the two compounds in pure form. The minor component was characterized by a carbonyl absorption at 1710 and 1730 cm⁻¹ indicating an acyclic ketone and an ester carbonyl. In contrast, the major product showed carbonyl absorption at 1730 cm⁻¹. The former was assigned structure 23 (7.5%) and the latter 22 (56.5%). It must be noted that the above method of preparation of 13,14-dihydro derivatives gives the mixture of two C-15 hydroxy epimers. These epimers are not separable either by tlc or glc. In order to obtain the pure epimeric alcohol the following synthetic route was followed. Enone 25[22] could be transformed via (1) THP ether, (2) borohydride reduction, (3) acetylation, (4) hydrolysis of ether, (5) Jones oxidation, (6) selective hydrolysis of the acetoxy group in an overall yield of 52–54%, into a mixture of epimeric
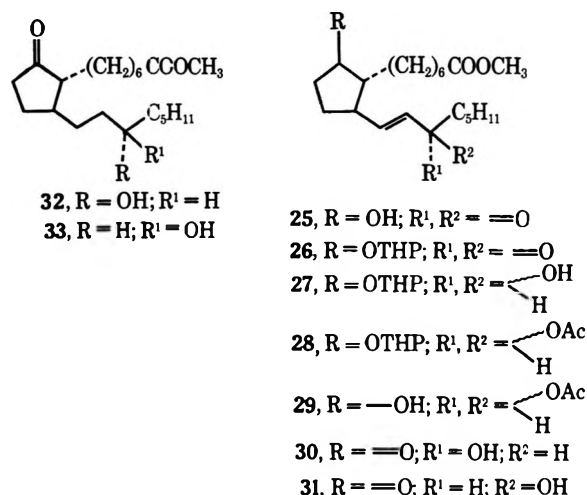
alcohols[23] **30** and **31**. It was possible to separate the alcohol **30** and **31** by silicic acid chromatography. Subsequent reduction of the double bond catalytically led to the isolation of 13,14-dihydro epimers **32** and **33** in pure form.

Although detailed accounts of pharmacology of these compounds will appear elsewhere, suffice it to say that some derivatives of prostanoic acid described above possess a profile closely similar to that of natural prostaglandins.

Experimental Section[24]

5-Oxo-1-cyclopentene-1-heptanoic Acid Methyl Ester (1).— To a suspension of the potassium salt[25] of cyclopentanone ethyl carboxylate[26] (31.04 g) in dry toluene (160 ml) was added methyl ω-bromoheptanoate[27] (37.92 g). The mixture was refluxed overnight, cooled, and acidified with 10% H_2SO_4 (120 ml). The aqueous layer was separated, saturated with sodium chloride, and extracted several times with ether. The organic extract was washed with sodium bicarbonate and water and dried, and the solvent was removed. The residue (46.3 g) was distilled to yield 1-carbomethoxy-2-oxocyclopentaneheptanoic acid methyl ester (24.9 g, 50%): bp 146–148° (0.07–0.05 mm); $n^{22}D$ 1.4557; ν_{max} 1718, 1740 cm⁻¹ (carbonyl absorptions).

The diester (10 g) obtained above was decarboxylated by refluxing with 10% sulfuric acid (45 ml) overnight. The usual work-up gave 2-oxocyclopentaneheptanoic acid (4.5 g, 69%), ν_{max} 1710, 1725 cm⁻¹. Its 2,4-dinitrophenylhydrazone was crystallized from ethanol, mp 74–76°.

Anal. Calcd for $C_{18}H_{24}O_6N_4$ (420): C, 57.13; H, 6.71; N, 13.33. Found: C, 57.06; H, 6.57; N, 13.1.

The keto diester (105.6 g) obtained above was taken in chloroform (300 ml) and was brominated with bromine (53.9 g) in chloroform (200 ml) at 0° over a period of 1 hr. The crude product (135 g) was isolated in the usual way, suspended in 20% sulfuric acid (1000 ml), and refluxed for 48 hr. The reaction mixture was cooled, saturated with sodium chloride, and extracted with ether. The acidic compound was isolated via alkaline extract followed by acidification to yield a crude product

(22) J. F. Bagli and T. Bogri, *Tetrahedron Lett.*, 5 (1967)

(23) The assignments of the stereochemistry of the hydroxyl at C-15 are based solely on certain physical behavior and pharmacological data, and is therefore tentative. Absolute proof will be forthcoming in a later publication.

(24) The Varian spectrometer was used for 60-Mc nmr, whereas the Jeolco machine was used for 100-Mc nmr, and for all spin decoupling studies. Unless otherwise mentioned all infrareds were done on film, nmr in chloroform, and uv in ethanol. Merck silica gel (mesh 0.05–0.2 mm) was used for column chromatography. Organic extracts were dried over anhydrous magnesium sulfate, and the solvents were always removed under vacuum. Mass spectra were recorded on a Hitachi RMU-6D spectrometer. Double resonance studies were all carried out on the 100-Mc machine.

(25) R. Mayer, "Newer Methods of Preparative Organic Chemistry," Vol. 2, Academic Press, New York, N. Y., 1963, p 122.

(26) Commercial Aldrich sample is a mixture of methyl and ethyl esters (1:1).

(27) D. E. Ames, R. E. Bowman, and R. G. Mason, *J. Chem. Soc.*, 174 (1950).

(53.2 g). This was passed through a silica gel (1 kg) column and the product was eluted with 1% methanol in chloroform to give crystalline 5-oxo-1-cyclopentene-1-heptanoic acid (26.3 g, 37%): mp 40–42°; ν_{max} 3000, 1700, 1630 cm^{-1}; λ_{max} 228 nm; nmr (CCl$_4$) δ 7.27 (1 H, vinylic).

Anal. Calcd for C$_{12}$H$_{18}$O$_3$ (210.2): C, 68.57; H, 8.57. Found: C, 68.42; H, 8.65.

Methyl ester of 5-oxo-1-cyclopentene-1-heptanoic acid (1) was prepared in the usual manner with methanol and *p*-toluenesulfonic acid: ν_{max} 1730, 1694, 1630, 1220 cm^{-1}; λ_{max} 228 (10,250) nm.

6-Chloro-7-hexanoyl-2-oxobicyclo[3.2.0]heptane-1-hexanoic Acid Methyl Ester (5).—A solution of 1-chloroöct-1-en-3-one (2) (48 g, 0.3 mol) and cyclopentenoneheptanoic acid methyl ester (1) (67.2 g, 0.3 mol), made up to 1 l. with reagent grade hexane, was irradiated with a 550-W mercury arc Hanovia lamp in a Pyrex vessel. The apparatus used is shown schematically below.
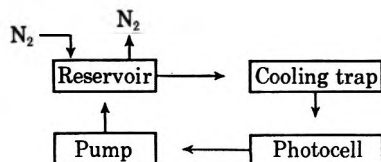
The solution was continuously circulated under a nitrogen atmosphere through a photocell equipped with a water-cooled condenser. The irradiation was continued for 30–32 hr. After this time the solution was removed from the apparatus and the solvent was evaporated. The resulting residue (120 g) was filtered through a column of silica gel (2 kg) in benzene. The elution with benzene yielded first the unchanged chlorovinyl ketone 2[28] (31.3 g). Changing the solvent to 5% ethyl acetate–benzene yielded the photoadduct 5 (23.3 g, *ca.* 88%), and finally the column was washed with 50% ethyl acetate–benzene to elute the unchanged cyclopentenone 1 (49.37 g). The photoadduct thus obtained was essentially homogeneous by tlc and was used for subsequent reactions. A sample was rechromatographed to yield an analytically pure sample: ν_{max} 1730, 1712 cm^{-1}; nmr δ 3.65 (3 H, s, methoxy), 0.88 (4 H, t, methyl) (also see Table I); *m/e* 348 (M$^+$ − 36).

Anal. Calcd for C$_{21}$H$_{33}$O$_4$Cl (384): C, 65.60; H, 8.58; Cl, 9.24. Found: C, 65.25; H, 8.44; Cl, 9.26.

Methyl 6-Hexanoyl-2-oxobicyclo[3.2.0]hept-6-ene-1-heptanoate (9).—When the irradiation was conducted without a solvent, it was possible to isolate a compound having an R_f slightly above that of the HH photoadduct. This product was obtained in *ca.* 8% yield. An analytical sample purified chromatographically gave a pure sample of enone 9: ν_{max} 1727, 1670, 1590 cm^{-1}; λ_{max} 227 nm (ε 4000), 249 (3800);[13] nmr δ 6.54 (1 H, s, vinylic), 3.59 (3 H, s, carbomethoxy), 0.92 (3 H, t, terminal methyl); mass spectrum M$^+$ (*m/e* 348), M$^+$ − 31 (*m/e* 317), M$^+$ − 71 (*m/e* 277), M$^+$ − 99 (*m/e* 249).

Anal. Calcd for C$_{21}$H$_{32}$O$_4$ (348): C, 72.38; H, 9.26. Found: C, 72.45; H, 9.39.

Methyl 7-Hexanoyl-2-oxobicyclo[3.2.0]hept-6-ene-1-heptanoate (8).—A solution of the photoadduct 5 (0.603 g) in redistilled collidine (25 ml) was refluxed for 4.5 hr. The solvent was then removed, the residue was taken up in ether, washed with water, and dried, and the solvent was evaporated. The residue was purified by chromatography to yield pure enone 8 (0.442 g, 81%): ν_{max} 1730, 1672, 1590 cm^{-1}; λ_{max} 225 nm (ε 5000); nmr δ 6.92 (1 H, d, J = 2 Hz, vinylic), 3.65 (3 H, s, carbomethoxy), 0.88 (3 H, t, terminal methyl).

Anal. Calcd for C$_{21}$H$_{32}$O$_4$ (348): C, 72.38; H, 9.26. Found: C, 72.45; H, 9.39.

Methyl 7-Hexanoyl-6-methoxy-2-oxobicyclo[3.2.0]heptane-1-heptanoate (6).—To a solution of photoadduct 5 (1.4 g) in methanol (21 ml) was added sodium (0.174 g) and the mixture was stirred at room temperature for 30 min. The mixture was then diluted with ether, washed with dilute hydrochloric acid followed by water, and dried and the solvent was removed. The residue was purified through a column of silica gel (35 g). The compound 6 (0.806 g, 81.5%) was eluted with 10% ethyl acetate–benzene: ν_{max} 1725, 1700 cm^{-1}; nmr δ 4.04 (1 H, q, car-

(28) The recovered chlorovinyl ketone showed on a tlc plate as two spots which were separated and shown to be cis and trans isomers (*vide infra*).

binolic), 3.64 (3 H, s, carbomethoxy), 3.11 (3 H, s, methoxyl), 2.95 (1 H, d, α-keto methine), 0.88 (3 H, t, terminal methyl).

Anal. Calcd for C$_{22}$H$_{36}$O$_5$ (380.5): C, 69.44; H, 9.54. Found: C, 69.47; H, 9.57.

Methyl 6-Acetoxy-7-hexanoyl-2-oxobicyclo[3.2.0]heptane-1-heptanoate (7).—To a solution of photoadduct 5 (1 g) in acetic acid (45 ml) was added silver acetate (1.4 g) and the mixture was refluxed overnight. The mixture was cooled, diluted with ether, and filtered. The solvent was evaporated, the residue was taken up in ether, washed with water, and dried, and the solvent was removed. Residue was purified by chromatography to yield pure acetoxy derivatives 7 (0.9 g, 68.2%): M$^+$ − 60 (*m/e* 348), M$^+$ − (60 + 31) (*m/e* 317); ν_{max} 1725, 1228, 1220 cm^{-1}; nmr δ 5.07 (1 H, q, carbinolic), 3.67 (3 H, s, carbomethoxy), 3.17 (1 H, d, α-keto methine), 2.05 (3 H, s, acetoxy methyl), 0.88 (3 H, t, terminal methyl).

Anal. Calcd for C$_{23}$H$_{36}$O$_6$ (408.5): C, 67.62; H, 8.88. Found: C, 68.02; H, 8.97.

Methyl 6-Hexanoyl-7-methoxy-2-oxobicyclo[3.2.0]heptane-1-heptanoate (10).—To a solution of the enone 9 (0.397 g) in methanol (3 ml) was added a solution of sodium (0.112 g) in methanol (6 ml). The mixture was stirred for 1 hr, diluted with ether, and washed with water. The ether extract was worked up in the usual manner to yield the crude product (0.518 g). The chromatographic purification gave the methoxy compound 10 (0.360 g, 83.1%): ν_{max} 1737, 1712 cm^{-1}; nmr δ 4.04 (1 H, d, J = 6 Hz, carbinolic), 3.68 (3 H, s, carbomethoxy), 3.28 (3 H, s, methoxy), 2.93 (1 H, m, α-keto methine).

Anal. Calcd for C$_{22}$H$_{36}$O$_5$ (380.0): C, 69.44; H, 9.54. Found: C, 69.16; H, 9.27.

Methyl 7-Acetoxy-6-hexanoyl-2-oxobicyclo[3.2.0]heptane-1-heptanoate (11).—A mixture of enone 9 (0.3 g), sodium acetate (0.08 g), and acetic acid (16 ml) was stirred overnight at 120° (bath temperature). After the solvent was removed, the residue was taken in ether, washed with water, and dried and the solvent was evaporated. The residue was purified through a silica gel column to yield acetoxy ketone 11 (0.097 g, 36.6%): ν_{max} 1730, 1708 cm^{-1}; nmr δ 5.0 (1 H, d, J = 7 Hz, carbinolic), 3.64 (3 H, s, carbomethoxyl), 3.00 (1 H, t, α-keto methine), 2.03 (3 H, s, acetoxy methyl).

Anal. Calcd for C$_{23}$H$_{36}$O$_6$ (408.5): C, 67.62; H, 8.88. Found: C, 67.64; H, 8.95.

Methyl 7-Hexanoyl-2-oxobicyclo[3.2.0]heptane-1-heptanoate (13). A.—A solution of photoadduct 5 (0.454 g) in glacial acetic acid (30 ml) was stirred overnight at reflux temperature in the presence of zinc (2.76 g). The reaction mixture was filtered and the acetic acid was removed. The residue was taken in ether, washed with water, and dried and the solvent was removed to yield crude product (0.45 g). Chromatographic separation gave pure diketone 13 (0.233 g, 54.4%): ν_{max} 1700, 1725 cm^{-1}; nmr δ 3.65 (3 H, s, methoxyl), 3.05 (1 H, α-keto methine), 0.88 (3 H, terminal methyl): mass spectrum M$^+$ (*m/e* 350), M$^+$ − 31 (*m/e* 319), M$^+$ − 99 (*m/e* 251), and M$^+$ − 71 (*m/e* 279).

Anal. Calcd for C$_{21}$H$_{34}$O$_4$ (350): C, 71.96; H, 9.78. Found: C, 72.07; H, 9.76.

B.—Hydrogenation of the cyclobutenone 8 (0.1 g) in methanol (5 ml) and 5% palladium/charcoal gave, after chromatography, a product (0.06 g) identical in all respects with diketone 13.

C.—To a solution of cyclobutenone 8 (0.2 g) in acetic acid (6 ml) was added zinc dust (2.2 g). The reaction was followed by uv and tlc. An aliquot after stirring for *10 min at room temperature* showed complete absence of uv. The reaction mixture was filtered, the acetic acid was removed, and the product (0.1 g) was isolated by extraction with ether, followed by chromatography. The product was shown to be identical in all respects (gc, tlc, mass spectrum) with the dione 13.

Methyl 2-Oxo-5-(3-oxo-1-octyl)cyclopentaneheptanoate (14). A.—A solution of diketone 13 (20 g) in acetic acid (600 ml) was heated to 120° (bath temperature). To the hot solution was added zinc (70 g), and the heating was continued. A further 70, 60, and 60 g of zinc were added after 7, 24, and 31 hr, respectively. The heating was stopped after 37 hr. The mixture was cooled and filtered. The acetic acid was evaporated, the residue was worked up with ether, washed with water, and dried, and the solvent was removed to yield crude product (21 g). Chromatography on a silica gel column and elution with 10% ethyl acetate–benzene gave pure ketone 14 (14.32 g, 75%): ν_{max} 1726, 1708 cm^{-1}; nmr δ 3.67 (3 H, s, carbomethoxyl); mass spectrum M$^+$ (*m/e* 352), M$^+$ − 31 (*m/e* 321).

Anal. Calcd for $C_{21}H_{36}O_4$ (352.5): C, 71.55; H, 10.30. Found: C, 71.27; H, 10.00.

B.—A solution of enedione 15 (0.101 g) was hydrogenated in methanol with 5% palladium on charcoal (0.1 g) overnight. The reaction mixture was filtered and the product was isolated in the usual manner to yield pure compound (0.07 g) identical in all respects with the diketone 14.

C.—A solution of photoadduct 5 (50 g) in acetic acid (1520 ml) was brought to gentle reflux. Zinc (228 g) was added to the solution. After 6, 22, 28, and 42 hr, 104, 104, 100, and 100 g of zinc were added, respectively, with vigorous stirring. The reaction was monitored by tlc and was stopped after 48 hr. Most of the acetic acid was carefully removed under vacuum, the mixture was filtered, and the residue was washed well with ether. After removal of all the solvent the residue was taken up in ether, washed with water, and dried and the solvent was removed. The residue (37.1 g) was chromatographed to yield the diketone 13 (4.1 g, *ca.* 10%) and diketone 14 (18.2 g, *ca.* 40%).

Methyl 6-Butyl-2,3,3a,4,5,7a-hexahydro-3,5-dioxo-3a-indanheptanoate (16).—A solution of methoxy ketone 6 (0.47 g) in acetic acid (35 ml) was refluxed for 4 hr. The acetic acid was removed, the residue was diluted with ether, washed with water, and dried, and the solvent was removed to yield the crude product (0.366 g). Purification by chromatography gave pure enone 16 (0.202 g, 47%): ν_{max} 1674, 1737 cm^{-1}; λ_{max} 235 nm (ϵ 8000); nmr δ 6.52 (1 H, d, vinylic), 3.65 (3 H, s, carbomethoxy); mass spectrum M$^+$ (m/e 348), M$^+$ − 31 (m/e 317), M$^+$ − 56 (m/e 292).

Anal. Calcd for $C_{21}H_{32}O_4$ (348): C, 72.38; H, 9.26. Found: C, 72.62; H, 9.38.

Sodium borohydride reduction of the above diketone in methanol led to the isolation of diol 17. The diol showed in its infrared absorptions at 3400, 1730, 1715 cm^{-1}; nmr 5.44 (1 H, m, vinylic), 3.8–4.4 (2 H, m, carbinolic), and 3.69 (1 H, s, carbomethoxy). Acetylation of the diol led to the diacetate 18: ν_{max} 1730, 1240 cm^{-1}; nmr δ 5.6 (1 H, vinylic), 4.95 (1 H, m, carbinolic), 3.69 (1 H, s, carbomethoxy), 2.08 (6 H, two acetoxy methyls).

Anal. Calcd for $C_{25}H_{38}O_6$ (436): C, 68.78; H, 9.23. Found: C, 68.71; H, 9.42.

2-Carboxy-1-(carboxymethyl)-5-oxocyclopentaneheptanoic Acid Trimethyl Ester (19).—A solution of enone 16 (0.45 g) in chloroform (45 ml) was cooled to −20 to −30° and the ozone was passed through the solution for 1 hr; when dark blue color persisted, ozone was stopped and the mixture was warmed to room temperature. The solvent was removed to yield crude ozonide (0.554 g). The above ozonide was dissolved in acetic acid (24 ml) and oxidized with 30% hydrogen peroxide (6 ml). The reaction mixture was stirred at 50° (bath temperature) for 48 hr. The solvent was evaporated, the residue was taken up in ether, washed with water followed by saturated saline, and dried, and the solvent was removed to yield crude acidic product (0.533 g). The acidic residue was esterified with diazomethane to yield crude ester (0.62 g). Chromatographic separation yielded the pure product 19 (0.16 g): ν_{max} 1725, 1200–1150 cm^{-1}; nmr showed no terminal methyl, δ 2.6 (2 H, s) attributable to the methylene α to the newly created carbomethoxyl group, 3.65 (9 H, methoxyl); mass spectrum M$^+$ (m/e 356), M$^+$ − 31 (m/e 325), M$^+$ − (31 + 74) (m/e 251), M$^+$ − (31 + 143) (m/e 182, base peak).

Borohydride Reduction of 2-Oxo-5-(3-oxooctyl)cyclopentaneheptanoic Acid Ester. A.—To a solution of diketone 14 (0.42 g) in MeOH (6 ml) was added sodium borohydride (0.157 g). The reaction mixture was stirred at room temperature for 30 min. After diluting with ether, the mixture was washed with dilute hydrochloric acid, water, and saline. The organic liquor was dried and the solvent was removed. The residual oil (0.32 g) was chromatographed on silica gel to yield diol 20 (0.16 g) and 21 (0.06 g). The ir of both the products showed bands at 3400 and 1725 cm^{-1}. The nmr spectrum of the diol 20 showed a carbinolic proton (C-9)^{22} at δ 3.94 (m), and that of 21 was located at δ 4.29 (m). Both the spectra showed 4 H signals at δ 3.71–3.52. The mass spectrum of the diol 20 showed peaks at M$^+$ − 18 (m/e 338), M$^+$ − 18 × 2 (m/e 320), M$^+$ − (18 + 31) (m/e 307), M$^+$ − (36 + 71) (m/e 249). The alkaline hydrolysis of the methyl esters yielded the corresponding acids. The acid obtained from diol 21 was crystallized from acetone–hexane, mp 97–99°.

Anal. Calcd for $C_{20}H_{38}O_4$ (342): C, 70.13; H, 11.18. Found: C, 69.76; H, 11.13.

B.—A solution of diketone (3 g) in dimethoxyethane (18 ml) was cooled to −50°. Sodium borohydride (0.32 g) was added gradually to the solution. The reaction mixture was stirred for 1 hr, diluted with ether, washed with saturated ammonium chloride solution followed by water, and dried. The solvent was removed to yield crude product (3.21 g). Chromatography of the above residue on silicic acid (245 g) in ethyl acetate–benzene (2:8) yielded unchanged starting material (1.7 g). Further elution yielded 2α-hydroxy-5-(3-oxooctyl)cyclopentaneheptanoic acid methyl ester (24) (0.18 g): ν_{max} 3475, 1730, 1710 cm^{-1}; nmr δ 4.20 (1 H, carbinolic),^{22} 3.68 (3 H, carbomethoxy), and 0.91 (3 H, t, terminal methyl); mass spectrum M$^+$ − (31 + 18) (m/e 305), M$^+$ − (18 + 143) (m/e 193). Continued elution led to the isolation of 1 g of a product homogeneous by tlc but found to be a mixture of a major and a minor component by glc.^{29} The latter mixture (1.05 g) was treated with dihydropyran (1.2 g) in chloroform (18 ml) containing *p*-toluenesulfonic acid overnight. The tetrahydropyranyl ethers (2.6 g) were isolated in the usual manner. This was chromatographed on silica gel to separate the two derivatives. Subsequent hydrolysis of the faster moving (tlc) THP ether in methanol and Dowex 50W-X4 (1 g) yielded 2β-hydroxy-5-(3-oxooctyl)cyclopentaneheptanoic acid methyl ester (23) (0.115 g): ν_{max} 3425, 1730, 1710 cm^{-1}; nmr δ 3.89 (1 H, carbinolic),^{27} 3.68 (3 H, carbomethoxyl), 0.88 (3 H, t, terminal methyl).

Anal. Calcd for $C_{21}H_{38}O_4$ (354): C, 71.15; H, 10.8. Found: C, 71.14; H, 11.10.

The slower moving (tlc) pyranyl ether was eluted in later fractions and yielded upon hydrolysis in a similar manner as described above 2-oxo-5-(3-hydroxyoctyl)cyclopentaneheptanoic acid methyl ester (22) (0.84 g): ν_{max} 3425, 1730 cm^{-1}; nmr δ 3.68 (4 H, carbomethoxyl and carbinolic), 0.88 (3H, t, terminal methyl).

Anal. Calcd for $C_{21}H_{38}O_4$ (354): C, 71.15; H, 10.8. Found: C, 71.12; H, 10.85.

Methyl 2-Oxo-5-(3-hydroxy-1-octenyl)cyclopentaneheptanoate. Isomer A (31) and Isomer B (30).—Unsaturated ketone 25 described earlier^{27} was transformed to its THP ether by standard procedure. To a solution of enone 26 (30 g) in methanol (127 ml), cooled in ice bath, was added sodium borohydride (2.55 g) gradually. The mixture was stirred for 30 min and allowed to reach room temperature. Acetic acid (3 ml) was added and the solvent was evaporated. The residue was taken up in ether and washed with water until neutral, and the solvent was removed. The alcohol 27 (29.5 g) showed no absorption in ir or uv due to α,β-unsaturated ketone: ν_{max} 3460 cm^{-1}; nmr δ 5.5 (2 H, m, vinylic), 4.63 (1 H, doubly carbinolic).

Acetylation.—The above product was acetylated with acetic anhydride (85 ml) in dry pyridine (46 ml). After the usual work-up the crude acetate 28 (30.2 g) showed no OH absorption in the ir, ν_{max} 1735, 1240 cm^{-1}.

Hydrolysis.—The acetate was dissolved in acetic acid (288 ml) and mixed with water (144 ml) and tetrahydrofuran (24 ml). The solution was stirred at 55° overnight. The solvent was removed and the residue was taken up in ether and processed as usual to yield crude product (29.5 g). Chromatographic purification gave the pure mixture of isomeric hydroxy acetate 29 (21 g).

Oxidation.—The acetoxy alcohol 29 (23.27 g) was dissolved in acetone (250 ml) and the solution was cooled to 0°. The Jones reagent was added dropwise until the faint orange color persisted (22 ml). The stirring was continued until all starting material disappeared (tlc). Methanol was added to destroy the excess of the reagent. The solvent was removed, the residue was taken in ether, washed with water, and dried, and the solvent was removed to yield crude keto acetate (20.8 g).

Hydrolysis.—The keto acetate was dissolved in methanol (295 ml). A solution of sodium (1.35 g) in methanol (75 ml) was added to it, and the reaction mixture was stirred for 1 hr. The solution was neutralized with acetic acid (3 ml) and the solvent was removed. The residue was worked up in the usual manner to yield the mixture of crude alcohols 30 and 31 (18.9 g). Chromatography on silicic acid and elution with 20% ethyl acetate–benzene gave isomer A, 31^{23} (7.6 g): ν_{max} 3455, 1730 cm^{-1}; nmr δ 5.63 (2 H, m, vinylic), 4.13 (1 H, m, carbinolic), and 3.67 (3 H, s, carbomethoxy).

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(29) Gas chromatograms were done as TMS ethers, on XE-60 column (4.6%) at 215°. The retention times for **22**, **23**, and **24** were 20.5, 16.6, and 17.6 min, respectively.

Anal. Calcd for $C_{21}H_{36}O_4$ (352): C, 71.55; H, 10.3. Found: C, 71.40; H, 10.35.

Further elution yielded a mixture of alcohols of **30** and **31** (2.13 g) followed by isomer B, **30**[23] (4.84 g). The ir and nmr of this isomer were essentially identical with that of isomer A.

Anal. Calcd for $C_{21}H_{36}O_4$ (352): C, 71.55; H, 10.3. Found: C, 71.39; H, 10.04.

Methyl 5-(3-Hydroxyoctyl)-2-oxocyclopentaneheptanoate (32 and 33).—A solution of keto alcohol **30** (1.06 g) in methanol (25 ml) was hydrogenated with 10% palladium/charcoal (0.360 g). The catalyst was filtered and washed with hot methanol. The crude product was chromatographed to yield alcohol **32** (0.75 g): ν_{max} 3450, 1735 cm^{-1}; nmr δ 3.65 (4 H, s, carbomethoxyl).

Anal. Calcd for $C_{21}H_{38}O_4$ (354): C, 71.14; H, 10.80. Found: C, 71.11; H, 10.85.

In a similar manner as described above, alcohol **31** (2.5 g) was hydrogenated to yield keto alcohol **33** (1.32 g). The infrared and the nmr spectra were essentially identical with those of alcohol **32**.

Anal. Calcd for $C_{21}H_{38}O_4$ (354): C, 71.14; H, 10.80. Found: C, 71.13; H, 10.85.

The two alcohols **32** and **33** were indistinguishable by gc or by tlc in at least two different systems.

Hydrolysis of Alcohols 30, 31, 32, and 33.—Pure samples of the esters 30–33 were hydrolyzed in methanolic sodium hydroxide to yield the corresponding acids. The acids obtained from alcohols **31**, **32**, and **33** were oils, whereas that from alcohol **30** was a solid and crystallized from ether–hexane to yield an analytical sample, mp 85–86°. The ir showed characteristic acid

absorption: nmr δ 5.62 (2 H, m, vinylic), 4.3 (1 H, m, carbinolic), 0.92 (3 H, t, terminal methyl).

Anal. Calcd for $C_{20}H_{34}O_4$ (338.47): C, 70.97; H, 10.13. Found: C, 70.72; H, 10.19.

Registry No.—1, 34546-57-1; 5a, 34603-59-3; 5b, 34603-60-6; 6a, 34603-61-7; 6b, 34603-62-8; 7a, 34603-63-9; 7b, 34603-64-0; 8, 22973-15-5; 9, 34603-66-2; 10, 34603-67-3; 11, 34603-68-4; 13, 28764-52-5; 14, 22973-16-6; 16, 34546-58-2; 17, 34546-59-3; 18, 34647-02-4; 19, 34603-60-6; 20, 28764-72-9; 21, 28764-73-0; 21 free acid, 16887-10-8; 22, 28764-56-9; 23, 22973-17-7; 24, 28764-75-2; 27, 34603-78-6; 30, 34603-79-7; 30 free acid, 34603-80-0; 31, 34603-81-1; 32, 20592-62-5; 33, 34603-77-5; 1-carbomethoxy-2-oxocyclopentaneheptanoic acid Me ester, 34546-61-7; 2-oxocyclopentaneheptanoic acid 2,4-DNP, 34546-62-8; 5-oxo-1-cyclopentene-1-heptanoic acid, 5239-43-0.

General Methods of Alkaloid Synthesis. X. The Total Synthesis of the Sceletium Alkaloids (±)-Joubertiamine, (±)-*O*-Methyljoubertiamine, and (±)-Dihydrojoubertiamine

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An efficient synthesis of the pharmacologically interesting Sceletium alkaloid (±)-*O*-methyljoubertiamine (1a) and its conversion into (±)-joubertiamine (1b) and (±)-dihydrojoubertiamine (2) is described.

Renewed interest in the mesembrine alkaloids[2,3] has been catalyzed by the recent characterization[4–7] of several new bases found in various Sceletium species which are used by the natives of Southwest Africa in the preparation of a pharmacologically interesting drug known as "Channa" or "Koegoed." These include the seco-mesembrine alkaloids joubertiamine (1b),[4] dihydrojoubertiamine (2),[4] and dehydrojoubertiamine (3)[4] and the fused pyridine bases Alkaloid A$_4$ (4)[6,7] and tortuosamine (5).[7]

Inspection of the structural features of these new Sceletium alkaloids coupled with their potential physiological activity prompted the present investigation designed to test further two fundamental principles of

1a, R = CH$_3$
b, R = H
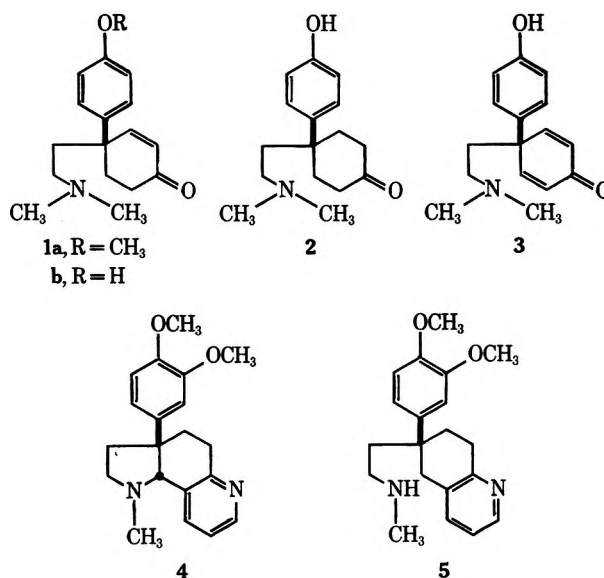
alkaloid synthesis which have found application in the synthesis of mesembrine (6) itself,[8] the closely related

(1) A. P. Sloan Fellow, 1969–1971.

(2) For a review see A. Popelak and G. Lettenbauer, "The Alkaloids," Vol. IX, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 467.

(3) In the older literature reference is made to the isolation of many of these alkaloids from the genus *Mesembryanthemum* Dill from which the names of several of these bases were derived. However, recently this classification has been revised to the genus *Sceletium* N. E. Brown (Ficoidaceae or Aizoaceae). Therefore, reference to these bases as mesembrine alkaloids is technically a misnomer.

(4) R. R. Arndt and P. E. J. Kruger, *Tetrahedron Lett.*, 3237 (1970).

(5) P. W. Jeffs, G. Ahmann, H. F. Campbell, D. S. Farrier, G. Ganguli, and R. L. Hawks, *J. Org. Chem.*, **35**, 3512 (1970).

(6) P. W. Jeffs, P. A. Luhan, A. T. McPhail, and N. H. Martin, *Chem. Commun.*, 1466 (1971).

(7) F. O. Snyckers, F. Strelow, and A. Wiechers, *ibid.*, 1467 (1971).

(8) (a) R. V. Stevens and M. P. Wentland, *J. Amer. Chem. Soc.*, **90**, 5580 (1968); (b) S. L. Keely, Jr., and F. C. Tahk, *ibid.*, **90**, 5584 (1968); (c) T. J. Curphey and H. L. Kim, *Tetrahedron Lett.*, 1441 (1968).

Amaryllidaceae alkaloid elwesine (**7**),[9] and other structurally diverse natural products such as the pyridine alkaloids myosmine and apoferrorosamine,[10] the Aspidosperma base aspidospermine,[11] and the parent skeletons of various Erythrina[12] and hasubanan[13] alkaloids.

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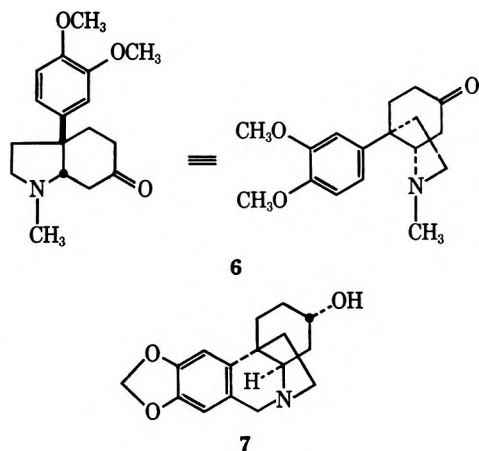
Key steps in each of these syntheses featured either the acid-catalyzed thermally induced rearrangement of a cyclopropyl imine as a general device for obtaining appropriately substituted 1- or 2-pyrrolines[8a,b,9,10,11b,13b] and/or methyl vinyl ketone annelation of these and other endocyclic enamines.[8,9,11a,12,13] We now report the application of both of these increasingly important general methods to the synthesis of the pharmacologically interesting Sceletium alkaloids (±)-*O*-methyljoubertiamine (**1a**), (±)-joubertiamine (**1b**), and (±)-dihydrojoubertiamine (**2**).

The present synthesis begins with *p*-methoxyphenyl acetonitrile (**8a**) whose cyclopropanation was achieved in 75% yield by means of ethylene dibromide and lithium amide base in glyme as solvent. These conditions followed from our previous studies[8a,9] in which the beneficial effect of employing the more covalent lithium salts in generating electronically destabilized carbanions of this type was established. Selective reduction of the resultant nitrile **8b** with diisobutylaluminum hydride in benzene provided an 86% yield of the corresponding aldehyde **8c**. Transformation of the latter intermediate into aldimine **9** was accomplished in 91% yield and simply required stirring a benzene solution of **8c** and excess methylamine for 2 days at room temperature in the presence of suspended magnesium sulfate.

The crucial rearrangement of imine **9** to pyrroline **10** proceeded in virtually quantitative yield at 140° by employing ammonium chloride as the acidic catalyst. Annelation of this endocyclic enamine with methyl vinyl ketone as described previously[8c,9] yielded exclusively the cis octahydroindolone **11** in 93% yield. The gross structural and stereochemical features of this intermediate were readily confirmed by comparison of its pmr spectrum with that of mesembrine (**6**).[8a] These

spectra were virtually identical in the highly diagnostic aliphatic region.

Conversion of the octahydroindolone **11** into (±)-*O*-methyljoubertiamine (**1a**)[14] required N-methylation and subsequent β elimination of the resultant quaternary ammonium salt **12**. This was accomplished in one operation by refluxing **11** in neat methyl iodide followed by work-up in aqueous base. The synthesis of racemic joubertiamine (**1b**) was completed by demethylation of **1a** in hot hydrobromic acid. Confirmation of the structural assignment was made by comparison of the infrared, ultraviolet, pmr, and mass spectra with those of the natural base and by catalytic hydrogenation to racemic dihydrojoubertiamine (**2**) and an identical comparison.[15]

8a, R = H; Z = CN
b, R = CH₂CH₂; Z = CN
c, R = CH₂CH₂; Z = CHO

(±)-**1a**   **12**   **11**

(±)-**1b**   (±)-**2**
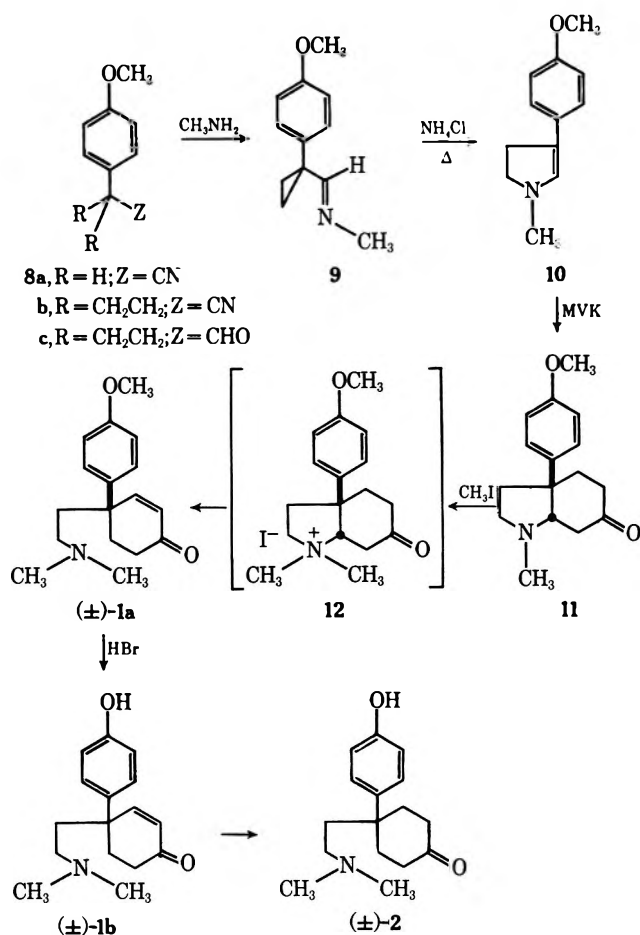
Experimental Section[16]

1-(*p*-Methoxyphenyl)cyclopropanecarbonitrile (**8b**).—*p*-Methoxybenzyl cyanide (1.38 g, 9.4 mmol), freshly prepared LiNH₂ (540 mg, 23.5 mmol), and 15 ml of dry glyme was placed in a 100-ml oven-dried jacketed flask equipped with N₂ flushing system, condenser, and magnetic stirrer. Ethylene dibromide (2.0 g, 10.6 mmol) was added over a 10-min period with cooling

(9) R. V. Stevens, L. E. DuPree, Jr., and P. L. Loewenstein, *J. Org. Chem.,* **37**, 977 (1972).

(10) R. V. Stevens, M. C. Ellis, and M. P. Wentland, *J. Amer. Chem. Soc.,* **90**, 5576 (1968).

(11) (a) R. V. Stevens, R. K. Mehre, and R. L. Zimmerman, *Chem. Commun.,* 877 (1968); (b) R. V. Stevens, J. M. Fitzpatrick, M. Kaplan, and R. L. Zimmerman, *ibid.,* 857 (1969).

(12) R. V. Stevens and M. P. Wentland, *ibid.,* 1104 (1968).

(13) (a) D. A. Evans, C. A. Bryan, and G. M. Wahl, *J. Org. Chem.,* **35**, 4122 (1970); (b) S. L. Keely, Jr., A. J. Martinez, and F. C. Tahk, *Tetrahedron,* **26**, 4729 (1970).

(14) Dr. A. Wiechers of the University of Pretoria, South Africa, has recently isolated *O*-methyljoubertiamine and *O*-methyldihydrojoubertiamine from *Sceletium spp.* and assigned the absolute configurations shown: private communications, Sept 10 and Nov 11, 1971.

(15) We are grateful to Professor Arndt and Dr. Kruger for providing us with this data.

(16) Infrared spectra were obtained on a Beckman IR-8 spectrometer. Uv spectra were secured in 95% ethanol solutions recorded on a Bausch and Lomb Spectronic 505 instrument and pmr spectra were obtained on a Varian A-56/60A spectrometer using tetramethylsilane as internal standard. Mass spectra were taken on a Consolidated Electrodynamics Corp. 21-110 high resolution spectrometer. Melting points and boiling points are uncorrected. Microanalyses were performed by the Elek Microanalytical Laboratory, Torrance, Calif.

after which steam was carefully admitted into the jacket. After the evolution of NH_3 had ceased, the dark brown solution was cooled and freed of solvent under reduced pressure, and water was cautiously added to the residue. Extraction with CH_2Cl_2, drying over Na_2SO_4, and distillation yielded 1.27 g (75%) of a colorless oil: bp 92–94° (0.25 mm); ir (neat) 2200 cm^{-1}; pmr δ 7.05 (symmetrical AA′BB′ q, 4 H), 3.80 (s, 3 H), 1.46 (symmetrical A_2B_2 m, 4 H).

Anal. Calcd for $C_{11}H_{11}NO$: C, 74.51; H, 6.88; mol wt, 173.21. Found: C, 74.21; H, 6.87; mol wt, 173 (mass spectrum).

1-(*p*-Methoxyphenyl)cyclopropanecarboxaldehyde (8c).—Nitrile 8b (1.28 g, 7.38 mmol) was dissolved in 13 ml of sodium-dried benzene in a flask equipped with N_2 flushing system, dropping funnel, and magnetic stirrer. Freshly prepared diisobutyl-aluminum hydride in benzene (0.0368 g/ml, 10.3 mmol) was added dropwise and the mixture was allowed to stir for 2 hr. The solution was then carefully poured into 200 ml of 5% H_2SO_4 and the mixture was stirred for 1 hr. The layers were separated and the aqueous phase was extracted with ether. The combined organic layers were dried over $MgSO_4$ and freed of solvent *in vacuo*, and the residue was distilled, providing 1.1 g (86%) of a colorless oil: bp 75.2–76.5° (0.3 mm); ir (neat) 1720 cm^{-1}; pmr δ 9.46 (s, 1 H), 7.03 (symmetrical AA′BB′ q, 4 H), 3.76 (s, 3 H), 1.40 (symmetrical A_2B_2 m, 4 H).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; mol wt, 176.21. Found: C, 74.75; mol wt, 176 (mass spectrum).

N-Methylaldimine (9).—Aldehyde 8c (9.2 g) was dissolved in 350 ml of sodium-dried benzene and 1 g of anhydrous $MgSO_4$ was added. The solution was cooled to 0–5° and saturated with dry methylamine gas. The mixture was stirred at room temperature for 48 hr, whereupon reaction was complete. Filtration and removal of the solvent *in vacuo* provided a light yellow oil which upon distillation gave 8.86 g (91%) of a colorless oil: bp 80–81° (0.3 mm); ir (neat) 1663 cm^{-1}; pmr δ 7.57 (t, 1 H), 7.03 (symmetrical AA′BB′ q, 4 H), 3.79 (s, 3 H), 3.23 (d, 3 H), 1.19 (symmetrical A_2B_2 m, 4 H); calcd mol wt, 189.25; found mol wt, 189 (mass spectrum).

N-Methyl-3-(*p*-methoxyphenyl)-2-pyrroline (10).—Aldimine 9 (141 mg) and 20 mg of NH_4Cl was heated under N_2 at 140° for 2 hr. The melt was cooled to 70° and extracted several times with hot hexane. Removal of the solvent provided yellow crystals which were sublimed at 65° (0.3 mm). In this manner 139 mg (98%) of white crystals of the pyrroline were obtained: mp 92–95°; ir (CHCl₃) 1680 cm^{-1}; uv (95% EtOH) 208 mμ (ε 1500), 222 (1500), 292 (3000); pmr δ 6.82 (symmetrical AA′BB′ q, 4 H), 6.12 (t, 1 H), 3.73 (s, 3 H), 2.68–3.30 (m, 4 H), 2.59 (s, 3 H); calcd mol wt, 189.25; found mol wt, 189 (mass spectrum).

cis-**Octahydroindolone (11).**—Pyrroline 10 (3.2 g) was dissolved in 200 ml of anhydrous ether and saturated with dry HCl. Removal of the ether provided a gummy hydrochloride salt which was dissolved in 20 ml of acetonitrile. Freshly distilled

methyl vinyl ketone (2 ml) was added to the solution and the solution was brought to reflux under N_2 for 9 hr. The mixture was cooled and then poured into 350 ml of 5% HCl and extracted with ether to remove neutral materials. The aqueous solution was basified with KOH pellets and extracted with ether. The organic layer was washed with saturated NaCl solution and dried over Na_2SO_4, and the solvent was removed *in vacuo*, yielding 4.09 g (93%) of essentially pure product. Kugelrohr bulb distillation at 110° (0.3 mm) provided analytically pure *cis*-octahydroindolone (11): ir (neat) 1715 cm^{-1}; pmr δ 7.10 (symmetrical AA′BB′ q, 4 H), 3.81 (s, 3 H), 2.81 (s, 3 H), 1.98–3.10 (m, 11 H); calcd mol wt, 259.34; found mol wt, 259 (mass spectrum).

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16. Found: C, 73.94; H, 8.30.

(±)-*O*-Methyljoubertiamine (1a).—Octahydroindolone 11 (951 mg) was dissolved in 15 ml of CH_3I and the solution was refluxed under N_2 for 24 hr. Removal of the solvent left a white solid 12, mp 135–138°, which was dissolved in 20 ml of 0.5 N KOH and extracted with ether. After drying over $MgSO_4$ the solvent was removed leaving 590 mg (62%) of essentially pure 1a. Kugelrohr bulb distillation at 120° (0.25 mm) provided an analytical sample of 1a as a colorless oil: ir (neat) 1680 cm^{-1}; pmr δ 7.22, 6.85 (dd, J = 7.50 cps, 4 H), 7.15, 6.05 (dd, J = 8.75 cps, 2 H), 3.81 (s, 3 H), 2.00–2.23 (m, 14 H); calcd mol wt, 273.36; found mol wt, 273 (mass spectrum).

(±)-Joubertiamine (1b).—*O*-Methyljoubertiamine (1a) was demethylated by heating in hot 48% HBr under N_2 for 3.5 hr. The resultant dark solution was cooled, basified with KOH solution, and extracted with ether to remove any neutral materials. The aqueous layer was then neutralized by addition of powdered NH_4Cl and extracted with ether. The ether extracts were combined, dried over $MgSO_4$, and freed of solvent, leaving yellow needles of 1b (80%), mp 126–130° dec. The ir, uv, pmr, and mass spectra of this material were identical with those recorded for natural joubertiamine.[4,15]

(±)-Dihydrojoubertiamine (2).—(±)-Joubertiamine (1b) was smoothly and quantitatively reduced over a 10% Pd/C catalyst in CH_3OH. The ir, uv, pmr, and mass spectra of this material were identical with those recorded for the natural product.[4,16]

The Synthesis of Methyl 2,4-Diacetamido-2,4,6-trideoxy Hexopyranosides[1]

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Received June 24, 1971

Acetylation of methyl 6-deoxy-3,4-*O*-isopropylidene-α-L-galactopyranoside gave methyl 2-*O*-acetyl-6-deoxy-3,4-*O*-isopropylidene-α-L-galactopyranoside (1). The isopropylidene residue could be selectively hydrolyzed by means of a weak acidic ion-exchange resin, leading to the formation of methyl 2-*O*-acetyl-6-deoxy-α-L-galactopyranoside (2). Reaction of compound 2 with methyl sulfonyl chloride in pyridine yielded methyl 2-*O*-acetyl-6-deoxy-3,4-di-*O*-methylsulfonyl-α-L-galactopyranoside (3) which was converted by treatment with sodium methylate into methyl 2,3-anhydro-6-deoxy-4-*O*-methylsulfonyl-α-L-gulopyranoside (4). Treatment of 4 with sodium azide in dimethylformamide followed by catalytic reduction and acetylation afforded a mixture of two products which could be separated by chromatography on alumina. One of these was shown by nmr to be methyl 3-*O*-acetyl-2,4-diacetamido-2,4,6-trideoxy-α-L-altropyranoside (5), the major product expected from trans-diaxial epoxide ring opening and methylsulfonate replacement in compound 4. The other product has been tentatively identified as methyl 3-*O*-acetyl-2,4-diacetamido-2,4,6-trideoxy-α-L-idopyranoside (6). It was assumed that it is formed as a result of an epoxide ring migration occurring during the treatment of compound 4 with sodium azide.

In 1959, Sharon and Jeanloz described the isolation from *Bacillus licheniformis* (then known as *Bacillus subtilis*) of an unusual diamino sugar, to which they ascribed the structure of a 4-acetamido-2-amino-2,4,6-trideoxyhexose[2] (*N*-acetylbacillosamine[3]). Since then, several other reports have appeared on the occurrence of derivatives of 2,4-diamino-2,4-dideoxyhexoses in natural products. Distler, Kaufman, and Roseman[4] isolated from extracts of *Diplococcus pneumoniae* a uridine diphosphate derivative of a 2,4-diamino-2,4,6-trideoxyhexose. Brundish and Baddiley[5] found a closely similar, or perhaps identical, diamino sugar in acid hydrolysates of the C-substance of *D. pneumoniae*. Another compound of this class, methyl 2,4-diamino-2,3,4,6-tetradeoxy-α-D-mannopyranoside, was isolated by Suhara, Maeda, and Umezawa following degradation of the antibiotic Kasugamycin.[6]

The first synthesis of a 2,4-diamino sugar was accomplished in 1963 by Jeanloz and Rapin, who prepared 2,4-diacetamido-2,4-dideoxy-D-glucose.[7] In 1964 we described in a preliminary note[1] the synthesis of two related 2,4-diamino hexose derivatives from methyl 6-deoxy-α-L-galactopyranoside. Here we present evidence that one of the compounds obtained is methyl 2,4-diacetamido-2,4,6-trideoxy-α-L-altropyranoside (5) and the other probably methyl 2,4-diacetamido-2,4,6-trideoxy-α-L-idopyranoside (6).

Results and Discussion

Methyl 6-deoxy-3,4-isopropylidene-α-L-galactopyranoside, prepared by a modification of the method of Percival and Percival,[8] was acetylated with acetic anhydride in pyridine, yielding crystalline methyl

2-*O*-acetyl-6-deoxy-3,4-*O*-isopropylidene-α-L-galactopyranoside (1). The isopropylidene residue was removed selectively by a weak acidic ion-exchange resin, since it was more sensitive to acid hydrolysis than the acetate or the methyl glycoside. The product, methyl 2-*O*-acetyl-6-deoxy-α-L-galactopyranoside (2), consumed 1 equiv of periodate[9] as expected from a vicinal diol system. The nmr and ir spectra were in agreement with the assigned structure. Compound 2 was treated with methylsulfonyl chloride in pyridine to yield the dimethylsulfonyl derivative 3 possessing the typical methylsulfonyl absorption at 1170 cm^{-1}.[10] The nmr spectrum was also in accordance with the proposed structure. Treatment of compound 3 with base gave the epoxide 4 which still exhibited the absorption at 1170 cm^{-1}.

The formation of an epoxide takes place readily when the groups participating in the elimination are trans diaxial[10] and is also known to occur in sugar derivatives where those groups are trans diequatorial in the most stable conformation.[11,12] In the latter case, however, a change in conformation to produce a trans-diaxial arrangement is presumed to precede the reaction. In the nmr spectrum of compound 4 (Figure 1) a satisfactory resolution of the ring protons was achieved except for H-2 and H-3 both in chloroform-*d* and in methyl sulfoxide-*d*. Double resonance experiments, carried out in chloroform-*d*, supported the assignment of the ring protons. Irradiation at the C-5 CH₃ signal caused the collapse of the H-5 octet to a narrow doublet ($J_{4,5}$ = 1.5 Hz) and irradiation at the center of the H-5 octet converged the C-5 CH₃ doublet to a singlet and the H-4 triplet to a narrow doublet ($J_{3,4}$ = 1.5 Hz). Irradiation in methyl sulfoxide-*d*, at the H-2,H-3 multiplet caused the collapse of H-1 to a singlet and H-4 to an apparent singlet. It is of interest to note that the nmr spectrum of compound 4 in chloroform-*d* differs from that in methyl sulfoxide-*d* in some of the chemical shifts. For instance, taking the spectrum in chloroform-*d* allows the separation of the methyl ether and the methylsulfonyl signals (τ 6.60 and 6.90, respectively) that do not separate in methyl sulfoxide-*d* (broad peak, centered at τ 6.66).

(1) Preliminary communications have appeared: U. Zehavi and N. Sharon, *Israel J. Chem.*, **2**, 322 (1964); Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 7C.

(2) N. Sharon, *Nature (London)*, **179**, 919 (1957); N. Sharon and R. W. Jeanloz, *Biochim. Biophys. Acta*, **31**, 277 (1959); N. Sharon and R. W. Jeanloz, *J. Biol. Chem.* **235**, 1 (1960).

(3) U. Zehavi and N. Sharon, *Israel J. Chem.*, **2**, 324 (1964); Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 7C.

(4) J. Distler, B. Kaufman, and R. Roseman, *Arch. Biochem. Biophys.*, **116**, 466 (1966).

(5) D. E. Brundish and J. Baddiley, *Biochem. J.*, **105**, 30c (1967); **110**, 573 (1968).

(6) Y. Suhara, K. Maeda, and H. Umezawa, *Tetrahedron Lett.*, 1239 (1966).

(7) R. W. Jeanloz and A. M. C. Rapin, *J. Org. Chem.*, **28**, 2978 (1963).

(8) E. E. Percival and E. G. V. Percival, *J. Chem. Soc.*, 690 (1950).

(9) G. O. Aspinall and R. J. Ferrier, *Chem. Ind. (London)*, 1216 (1957).

(10) E. J. Reist, R. R. Spencer, B. R. Baker, and L. Goodman, *ibid.*, 1794 (1962).

(11) F. H. Newth, *Quart. Rev., Chem. Soc.*, **13**, 30 (1959).

(12) G. J. Robertson and C. F. Griffith, *J. Chem. Soc.*, 1193 (1935).
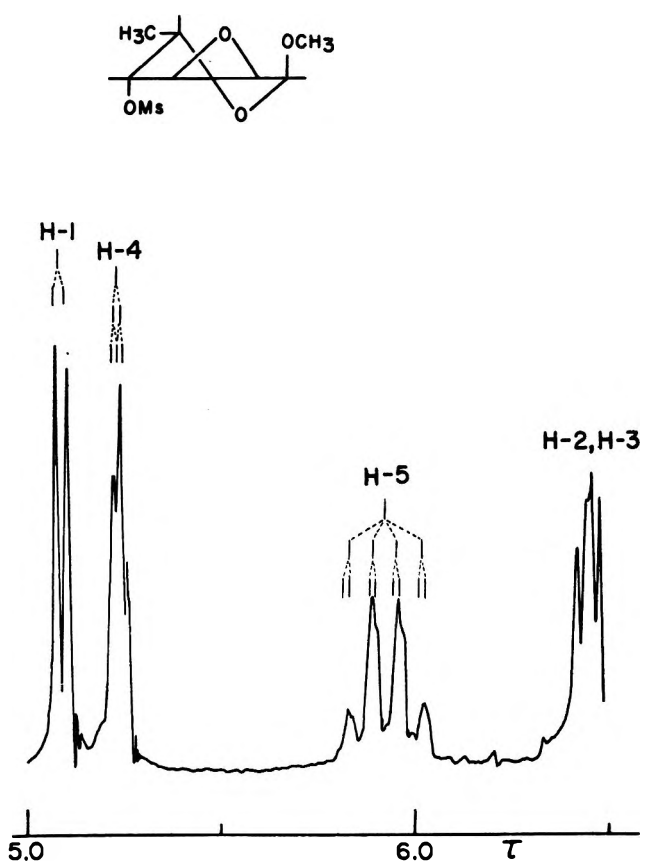
Figure 1.—The low-field portion of the 100-MHz spectrum of methyl 2,3-anhydro-6-deoxy-4-*O*-methylsulfonyl-α-L-gulopyranoside (4) in chloroform-*d*.

Compound 4 was treated with sodium azide in *N*,*N*-dimethylformamide at 130°, since extensive decomposition was observed to take place at reflux temperature. The products were not isolated at this stage. They were reduced with Adams platinum catalyst, acetylated, and then separated to give two major products, compounds 5 and 6. These compounds possess a rather limited solubility in many organic solvents, including chloroform. As a result, most nmr information was derived from spectra of saturated solutions of these products in methyl sulfoxide.

The use of azide ions for the opening of sugar epoxides was first described by Guthrie and Murphy.[13] In analogy to the opening of sugar epoxides with other nucleophiles the formation of two products can be envisaged, with the product of trans-diaxial opening of the more stable conformation of the sugar epoxide being the major one.[11] Since in our case the sugar derivative 4 contains also a methylsulfonyloxy group, another reaction can take place, namely the displacement of this group by azide ion that is known to be a bimolecular nucleophilic substitution occurring with Walden inversion.[10,13] The two products expected from epoxide opening and methylsulfonyloxy substitution in compound 4, followed by reduction and acetylation, are therefore methyl 3-*O*-acetyl-2,4-diacetamido-2,4,6-trideoxy-α-L-altropyranoside and methyl 2-*O*-acetyl-3,4-diacetamido-3,4,6-trideoxy-α-L-glucopyranoside. The nmr spectrum of compound 5 is in agreement with the first structure. The acetyl resonances are those of an axial acetate, and an axial and an equatorial acet-

amido group (τ 7.88, 8.04, and 8.07, respectively, in chloroform-*d*). The H-3 resonance deshielded by the acetate is moved downfield and the low coupling constants ($J_{1,2} = 3.0$, $J_{2,3} = 3.0$, $J_{3,4} = 3.0$ Hz) are in accordance with the altro *1C* conformation. Comparable data, although with lower $J_{1,2}$ values, were recorded by Coxon[14] for penta-*O*-acetyl-α-D-altropyranoside.
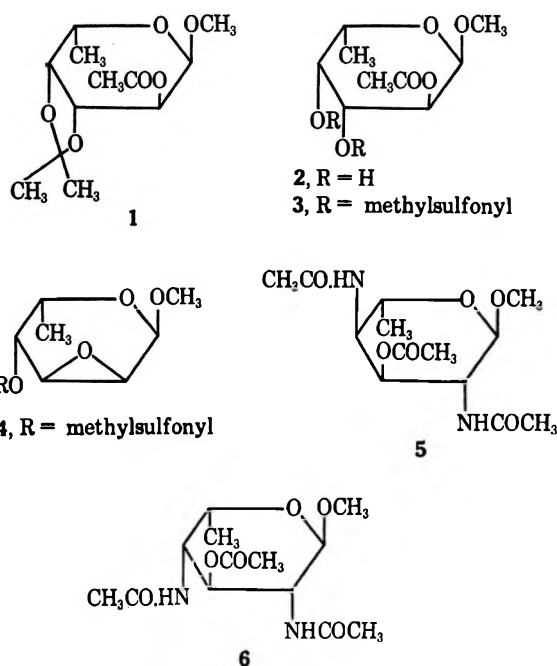
The structure of compound 6 was originally tentatively assigned as methyl 2-*O*-acetyl-3,4-diacetamido-3,4,6-trideoxy-α-L-glucopyranoside.[1] This was also suggested by the chemical shifts of the acetyl resonances measured in chloroform-*d* at 60 MHz which corresponded to those of an equatorial acetate and of two equatorial acetamido substituents. Since then, however, the study of the ring protons of compound 6 became possible from the 100-MHz nmr spectrum and the structure of methyl 3-*O*-acetyl-2,4-diacetamido-2,4,6-trideoxy-α-L-idopyranoside seems preferable. Double irradiation experiments on compound 6 in methyl sulfoxide-*d* supported the assignment of the ring protons. Irradiation at the H-2, H-4 multiplet caused the collapse of the H-1 and H-3 signals to singlets. Irradiation at the H-5 octet caused the collapse of the C-5 CH$_3$ doublet to a singlet and irradiation at the C-5 CH$_3$ resonance brought about the collapse of the H-5 octet to a doublet. The intermediate coupling constants for this compound probably represent a weighted time-average for the two chair conformers in rapid equilibrium with a larger proportion of the *C1* conformer. Such an equilibrium seems reasonable keeping in mind that, while energetic consideration supported the *1C* (D) conformation for α-D-idopyranose penta-acetate, it was actually found to favor the *C1* (D) conformation,[15] a fact that was attributed to polar factors whose importance is difficult to assess. The observed $J_{4,5} = 4.0$ Hz is somewhat high for axial–equatorial interactions while $J_{1,2} = 4.0$, $J_{2,3} = 6.0$, and $J_{3,4} = 6.0$ Hz are rather low for axial–axial interactions expected in the *C1* conformation.

(13) R. D. Guthrie and D. Murphy, *Chem. Ind. (London)*, 1473 (1962).

(14) B. Coxon, *Carbohyd. Res.*, 1, 357 (1966).

(15) N. S. Bhacca, D. Horton, and H. Paulsen, *J. Org. Chem.*, 33, 2484 (1968).

SCHEME I

4

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6
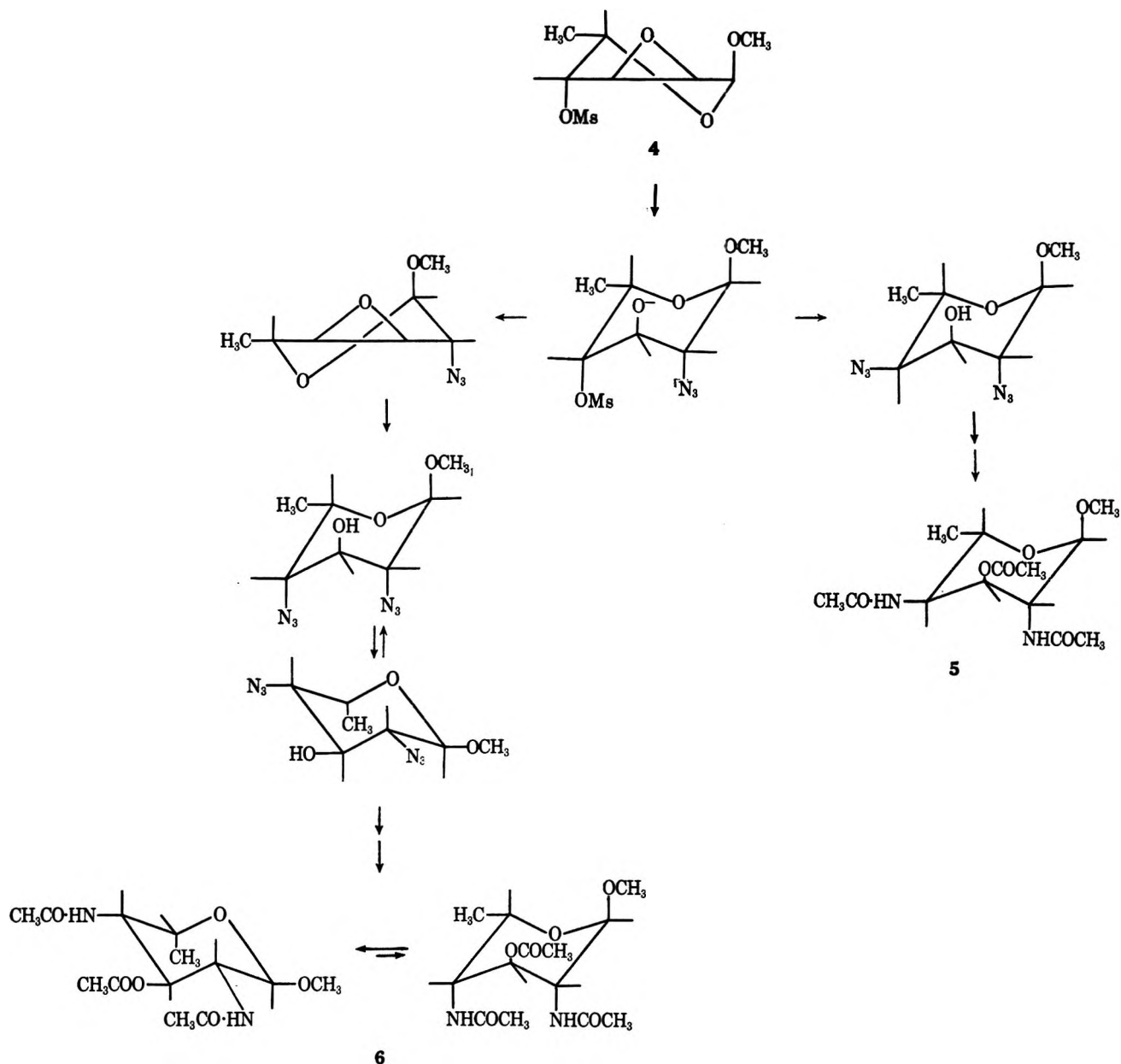
The ido configuration proposed for compound 6 may result from the reaction mechanism shown in Scheme I.

The epoxide ring in compound 4 is first attacked in a trans-diaxial fashion. This is followed by an intra-molecular displacement of the adjacent methyl sulfonate at C-4, thus forming the 3,4-altro-epoxide intermediate. Finally, nucleophilic attack at C-4 leads to the L-ido configuration with the nitrogen substituents at carbons 2 and 4.

Optical rotation considerations also support the assignment of the L-ido rather than the L-gluco configuration to compound 6 ([α]D $-60°$, MD -181). The specific rotation recorded for methyl 3-acetamido-2,4-di-O-acetyl-3,6-dideoxy-α-L-idopyranoside[16] is $-62°$ (MD -187). These values differ markedly from those recorded for related compounds of the gluco series: for methyl 4-acetamido-2,3-di-O-acetyl-4,6-dideoxy-α-D-glucopyranoside[17] ([α]D $+190°$, MD $+576$) and

for methyl 3-acetamido-2,4-di-O-acetyl-3,6-dideoxy-α-L-glucopyranoside[18] ([α]D $-128°$, MD -388). (All the above-cited rotations were taken in chloroform.)

Another support for the proposed structures of compounds 5 and 6 comes from the mass spectra of these compounds. The molecular peak (M, m/e 302) and M + 1 are present; the major fragmentation is through the loss of 31 and 32 mass units (methoxy radical and methanol) and through the elimination of 59 and 60 mass units (acetate and acetamide or acetic acid). No peak was detected at m/e 216, which would arise by the elimination of $CH_3CONHCHCH_3$[19] if ring contraction to a furanoside had occurred during the reaction with sodium azide.

Acid hydrolysis of compound 5 led to extensive degradation, probably as a result of the formation of a pyrrolidene derivative.[10] Repeated attempts to diminish the extent of degradation by modifying the conditions of hydrolysis had only limited success.

(16) J. Jarý, K. Čapak, and J. Kovac, *Collect. Czech. Chem. Commun.*, **28**, 2171 (1962).

(17) C. L. Stevens, P. Blumbergs, F. A. Daniher, D. H. Otterbach, and C. G. Taylor, *J. Org. Chem.*, **31**, 2822 (1966).

(18) A. C. Richardson and K. A. McLauchlan, *J. Chem. Soc.*, 2499 (1962).

(19) N. K. Kochetkov and O. S. Chizhov, *Advan. Carbohyd. Chem.*, **21**, 39 (1966).

Experimental Section

All melting points are corrected. Optical rotation was determined with a Bendix polarimeter. Spectra were measured with a Perkin-Elmer Infracord spectrometer in chloroform or in KBr discs. Nmr spectra were recorded on a Varian A-60 or HA-100 instrument with tetramethylsilane as an internal standard, unless otherwise mentioned. The uv spectra were taken on a Zeiss model PMQ II spectrometer. Mass spectra were measured on an Atlas CH4 mass spectrometer with 70 eV ionizing current. The samples were introduced through a direct inlet system and heating was applied until the vapor pressure was sufficient to obtain usable mass spectra. Column chromatography was routinely done on silica gel "Grace," Davison Chemical Corp., grade 950, 60–200 mesh. Thin layer chromatography was carried out on silica gel G (E. Merck, Germany); R_{SR} refers to mobility relative to sudan red, a component of the test mixture supplied by C. Desaga, Heidelberg, Germany. The plates were prepared using a Desaga applicator set for a thickness of 0.25 mm.

6-Deoxy-L-galactose (L-fucose) was purchased from Pfanstiehl Laboratories, Waukegan, Ill.

Methyl 6-Deoxy-α-L-galactopyranoside.—6-Deoxy-L-galactose (80 g) and methanol-washed Amberlite IR-120 resin (H⁺ form, 80 g) were refluxed in absolute methanol (800 ml) under a calcium chloride seal for 18 hr. The reaction mixture was filtered and evaporated *in vacuo*, and the solid residue was recrystallized from ethanol to yield 38 g (44%) of platelike crystals, mp 158°, $[\alpha]^{24}D$ −197.5 ± 0.3° (c 0.6, water).[20]
Anal. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.27; H, 7.86.

Methyl 6-Deoxy-3,4-O-isopropylidene-α-L-galactopyranoside.—Methyl 6-deoxy-α-L-galactopyranoside (27 g) was shaken at room temperature with anhydrous copper sulfate (300 g) in dry acetone for 18 hr.[8] The oil obtained, in quantitative yield, after filtration and evaporation was found by tlc to be chromatographically pure, R_{SR} 0.23 (benzene–ethyl acetate, 2:1) and R_{SR} 0.73 (ethyl acetate), and was used directly for the next reaction.

Methyl 2-O-Acetyl-6-deoxy-3,4-O-isopropylidene-α-L-galactopyranoside (1).—Methyl 6-deoxy-3,4-isopropylidene-α-L-galactopyranoside (10.7 g) was dissolved in dry pyridine (42 ml). Acetic anhydride (6.3 ml) was added to the solution and the reaction mixture was sealed and left at room temperature. Ice was added (4 g) and after 2 hr the solution was evaporated *in vacuo* from a bath of 40°. The residue was crystallized from petroleum ether (bp 30–60°), yielding 9.1 g (79%) of crystals, mp 100–101°, $[\alpha]^{25}D$ −230.1 ± 0.8° (c 0.62, benzene). The product moved as a single spot with R_{SR} 0.74 (benzene–ethyl acetate, 2:1) and R_{SR} 0.93 (ethyl acetate). The OH absorption present in the ir spectrum of the starting material has disappeared, and a carbonyl absorption was present at 1730 cm⁻¹: nmr (60 MHz, chloroform-d) τ 4.98 (1-proton doublet, H-1, $J_{1,2}$ = 3.4 Hz), 5.15 (1-proton quartet, H-2, $J_{2,3}$ = 4.8 Hz), 5.5–6.1 (multiplets, 3 protons, H-3,4,5), 6.61 (3-proton singlet, OCH₃), 7.86 (3-proton singlet, OCOCH₃), 8.45 and 8.64 [two 3-proton singlets, C(CH₃)₂], 8.62 (3-proton doublet, C-5 CH₃, $J_{5,6}$ = 6.5 Hz).
Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.54; H, 7.76.

Methyl 2-O-Acetyl-6-deoxy-α-L-galactopyranoside (2).—The isopropylidene derivative 1 (9.0 g) in water (1100 ml) was heated to boiling in the presence of Amberlite IRC 50 (H⁺ form, 5.6 g) for 2 hr. The resin was filtered off and the solution was evaporated *in vacuo* from a bath of 40° to give a syrup that solidified when placed in a desiccator. The material was recrystallized from benzene–petroleum ether, yielding 2.61 g (31%) of a chromatographically pure product, R_{SR} 0.47 (ethyl acetate), mp 82°. A second yield was obtained from the mother liquor after fractionation on a silica gel column (200 g, 4 cm diameter). The column was first washed with ethyl acetate (430 ml) and the product was subsequently removed by additional ethyl acetate (600 ml). The latter fraction was then evaporated and the solid residue was recrystallized as above, total yield 5.31 g (63%), mp 82–83°, $[\alpha]^{23}D$ −196 ± 0.3° (c 0.4, chloroform). The material, pure according to tlc, and giving as expected a positive color reaction for vicinal diols,[21] consumed 1.2 equiv of

(20) J. Minsaas, *Recl. Trav. Chim. Pays-Bas*, **51**, 475 (1932), reported mp 157.5–158.5°, $[\alpha]^{20}D$ −197.45°.
(21) A. Yoda, *J. Chem. Soc. Jap.*, **73**, 18 (1952); *Chem. Abstr.*, **47**, 3185 (1953).

periodate (5% NaIO₄, 37°, oxidation completed after 2 hr). In the ir it had a carbonyl absorption at 1730 cm⁻¹ and an OH absorption at 3450 cm⁻¹; nmr (60 MHz, chloroform-d) τ 4.88 (1-proton doublet, H-1, $J_{1,2}$ = 3.5 Hz), 5.10 (1-proton quartet, H-2, $J_{2,3}$ = 5.0 Hz), 5.8–6.2 (multiplets, 3 protons, H-3,4,5), 6.62 (3-proton singlet, OCH₃), 7.22 (2-proton singlet, disappears upon addition of deuterium oxide, OH), 7.87 (3-proton singlet, OCOCH₃), 8.70 (3-proton doublet, C-5 CH₃, $J_{5,6}$ = 6.5 Hz).
Anal. Calcd for $C_9H_{16}O_6$: C, 49.08; H, 7.32. Found: C, 49.08; H, 7.37.

Methyl 2-O-Acetyl-6-deoxy-3,4-di-O-methylsulfonyl-α-L-galactopyranoside (3).—A solution of compound 2 (13.5 g) in dry pyridine (130 ml) containing methylsulfonyl chloride (15.3 ml) was stirred overnight at 0° in a sealed tube. Ice water (100 ml) was added in small portions for 30 min and the stirring was continued for an additional 2 hr at 0°. Water (200 ml) was added and the mixture was extracted with chloroform (2 × 1 l.). The extracts were, in turn, washed with water (400 ml), combined, dried over sodium sulfate, and evaporated *in vacuo* to yield a chromatographically pure oil. The product was crystallized from benzene–petroleum ether, yielding 20.4 g (88.5%) of colorless crystals, mp 144°, $[\alpha]^{23}D$ −168 ± 0.4° (c 0.75, chloroform), R_{SR} 0.87 (ethyl acetate), 0.77 (benzene–ethyl acetate, 1:9). In the ir the material has a methylsulfonate band at 1170 cm⁻¹: nmr (60 MHz, chloroform-d) τ 4.8–5.1 (multiplets, 4 protons), 5.86 (1-proton multiplet), 6.59 (3-proton singlet, OCH₃), 6.79 and 6.88 (two 3-proton singlets, methylsulfonyl), 7.87 (3-proton singlet, OCOCH₃), 8.67 (3-proton doublet, C-5 CH₃, $J_{5,6}$ = 6.5 Hz).
Anal. Calcd for $C_{11}H_{20}O_{10}S_2$: C, 35.15; H, 5.33; S, 17.01. Found: C, 35.51; H, 5.13; S, 16.75.

Methyl 2,3-Anhydro-6-deoxy-4-O-methylsulfonyl-α-L-gulopyranoside (4).—Compound 3 (25 g) in 0.3 N sodium methoxide in methanol (250 ml) was refluxed for 45 min under a calcium chloride seal. The reaction mixture was cooled to room temperature and filtered, and the filtrate was passed through a column (2 cm diameter) containing methanol-washed Amberlite IR-120 (H⁺ form to a height of 30 cm) and below it Amberlite 4B (OH⁻ form, to a height of 30 cm). Methanol (600 ml) was then passed through the column and the combined eluates were evaporated *in vacuo*. The product, 15.9 g (100%), contained only traces of impurities (as determined by tlc). It was crystallized from methanol (mp 98°) and recrystallized from benzene–petroleum ether, mp 101–102°, $[\alpha]^{23}D$ −3.7 ± 0.8° (c 0.25, chloroform), R_{SR} 0.86 (ethyl acetate), 0.69 (benzene–ethyl acetate, 1:9). The material turned brownish-red immediately after the tlc plates were sprayed with sulfuric acid. No heating of the plates was required. In the ir it possessed a typical methylsulfonyl absorption at 1170 cm⁻¹; nmr (100 MHz, chloroform-d) τ 5.09 (1-proton doublet, H-1, $J_{1,2}$ = 3.0 Hz), 5.24 (1-proton triplet, H-4, $J_{3,4}$ = 1.5 Hz, $J_{4,5}$ = 1.5 Hz), 5.91 (1-proton octet, H-5, $J_{5,6}$ = 6.5 Hz), 6.41–6.55 (2-proton multiplet, H-2 and H-3), 6.60 (3-proton singlet, OCH₃), 6.90 (3-proton singlet, methylsulfonyl) 8.80 (3-proton doublet, C-5 CH₃); nmr (60 MHz, methyl sulfoxide-d, TMS as external standard) τ 5.01 (1-proton doublet, H-1, $J_{1,2}$ = 2.0 Hz), 5.11 (1-proton quartet, H-4, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 1.5 Hz), 6.06 (1-proton octet, H-5, $J_{5,6}$ = 6.5 Hz), 6.41–6.46 (2-proton multiplet, H-2,3), 6.66 (6-proton singlet, OCH₃ and methylsulfonyl), 8.87 (3-proton doublet, C-5-CH₃).
Anal. Calcd for $C_8H_{14}O_6S$: C, 40.34; H, 5.92; S, 13.45. Found: C, 40.44; H, 5.71; S, 13.55.

Methyl 3-O-Acetyl-2,4-diacetamido-2,4,6-trideoxy-α-L-altropyranoside (5) and Methyl 3-O-Acetyl-2,4-diacetamido-2,4,6-trideoxy-α-L-idopyranoside (6).—Compound 4 (1.9 g) and sodium azide (3.1 g) in absolute dimethylformamide (165 ml) were stirred mechanically in a three-necked flask equipped with a condenser and a calcium chloride tube. The reaction was carried out in an oil bath of 130° for 18 hr. The reaction mixture when analyzed by tlc gave three spots, R_{SR} 0.81, 0.97, 1.04 (ethyl acetate). The material migrating with R_{SR} 0.81 appeared as a bluish-gray spot immediately after spraying with sulfuric acid and without heating the plate.

The spot of R_{SR} 0.97 was fainter than the other two spots. The reaction mixture was then filtered and the precipitate was washed with a little dimethylformamide. The combined filtrates were evaporated *in vacuo*. The residue was extracted with ethyl acetate (50 ml) and filtered, and the filtrate was evaporated. The residue was dissolved in methanol (50 ml),

filtered, and reduced under pressure (38 psi) with Adams platinum catalyst (1.8 g of platinum oxide) for 4 hr. The catalyst was filtered off, and the basic solution obtained was then evaporated *in vacuo.*

The residue was examined by descending paper chromatography on Whatman No. 1 paper with *n*-butyl alcohol–acetic acid–water (25:6:25, upper phase), revealing two ninhydrin positive spots at $R_\text{2-Amino-2-deoxy-D-glucose}$ 1.57 (brown) and 2.38 (pink). When checked by high-voltage paper electrophoresis on Whatman No. 1 paper in 1.2 *M* pyridine adjusted to pH 6.5 with acetic acid at 60 V/cm for 20 min, the first spot had an $M_\text{2-Amino-2-deoxy-D-glucose}$ value of 1.24 and the second 1.02.

Dry pyridine (30 ml) was added to the residue and evaporated. The oily material was redissolved in pyridine (2 ml) and after cooling to 0° acetic anhydride (2 ml) was added. The acetylation mixture was left overnight at room temperature. Water (0.3 ml) was then added and the mixture was kept for an additional 2 hr at room temperature. The mixture was evaporated *in vacuo,* extracted with ethyl acetate (5 ml), filtered, and placed on an alumina column (Merck, acid washed, 30 g, 1.5 cm diameter). The column was monitored by tlc on alumina G using acetone as solvent. The column was washed with ethyl acetate (150 ml) and the first compound which emerged (0.12 g) was eluted with the first portion of 1% methanol in ethyl acetate (90 ml). It did not contain nitrogen and had a R_SR of 0.87. It was not further investigated. Compound 5, R_SR 0.67 (0.26 g, 10.8%), started to emerge after an additional volume (110 ml) of the same solvent, and its elution was completed with 200 ml of 2% methanol in ethyl acetate. The last fraction, compound 6, R_SR 0.56 (0.156 g, 6.5%), started to emerge after an additional volume (200 ml) of 2% methanol in ethyl acetate and was eluted with the same solvent (300 ml).

On a small scale the mixture of compounds 5 and 6 was obtained also through acetylation in pyridine of the material of $R_\text{2-Amino-2-deoxy-D-glucose}$ 1.57 isolated by preparative paper chromatography.

Compound 5 was obtained from ethyl acetate as an amorphous white solid, mp 272°, $[\alpha]^{24}\text{D}$ −168 ± 1.6° (*c* 0.29, chloroform). It had the expected ir spectrum; nmr (100 MHz, methyl sulfoxide-*d*, hexamethylsiloxane as an external standard) τ 5.09 (1-proton triplet, H-3, $J_{2,3} = 3.0$ Hz, $J_{3,4} = 3.0$ Hz), 5.23 (1-proton doublet, H-1, $J_{1,2} = 3.0$ Hz), 5.5–6.3 (3 protons, un-resolved multiplets), 6.50 (3-proton singlet, OCH_3), 7.82 (3-proton singlet, $OCOCH_3$), 8.04 and 8.06 (two 3-proton singlets, $NCOCH_3$), 8.74 (3-proton doublet, C-5 CH_3, $J_{5,6} = 6.0$ Hz); nmr (60 MHz, chloroform-*d*) τ 6.55 (3-proton singlet, OCH_3), 7.88 (3-proton singlet, $OCOCH_3$), 8.04 and 8.07 (two 3-proton singlets, $NCOCH_3$), 8.75 (3-proton doublet, C-5 CH_3).

Anal. Calcd for $C_{13}H_{22}N_2O_6$: C, 51.64; H, 7.34; N, 9.27. Found: C, 52.08; H, 7.61; N, 8.93.

Compound 6 was crystallized from ethyl acetate as colorless needles, mp 261° dec, $[\alpha]^{22}\text{D}$ −60 ± 1.3° (*c* 0.38, chloroform). It also had the expected ir spectrum; nmr (100 MHz, methyl sulfoxide-*d*, hexamethyl siloxane as an external standard) τ 5.05 (1-proton triplet, H-3, $J_{2,3} = 6.0$ Hz, $J_{3,4} = 6.0$ Hz), 5.19 (1-proton doublet, H-1, $J_{1,2} = 4.0$ Hz), 5.61 (1-proton octet, H-5, $J_{4,5} = 4.0$ Hz, $J_{5,6} = 6.5$ Hz), 5.8–6.1 (2-proton multiplet, H-2, H-4), 6.51 (3-proton singlet, OCH_3), 7.81 (3-proton singlet, $OCOCH_3$), 7.91 and 7.97 (two 3-proton singlets, $NCOCH_3$), 8.68 (3-proton doublet, C-5 CH_3); nmr (100 MHz, chloroform-*d*) τ 6.61 (3-proton singlet, OCH_3), 7.92 (3-proton singlet, $OCOCH_3$), 8.07 and 8.10 (two 3-proton singlets, $NCOCH_3$), 8.79 (3-proton doublet, C-5 CH_3).

Anal. Calcd for $C_{13}H_{22}N_2O_6$: C, 51.64; H, 7.34; N, 9.27. Found: C, 51.77; H, 7.64; N, 9.14.

Registry No.—1, 34388-70-0; **2**, 34388-71-1; **3**, 34402-58-9; **4**, 34388-72-2; **5**, 34388-73-3; **6**, 34388-74-4; methyl 6-deoxy-α-L-galactopyranoside, 14687-15-1.

The Crystal and Molecular Structure of (2S,3S)-1-Cyano-2-hydroxy-3,4-epithiobutane-α-naphthylurethane

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The constitution, relative configuration, and partial conformation proposed for (2S,3S)-1-cyano-2-hydroxy-3,4-epithiobutane and its acetate on the basis of spectral evidence were confirmed by an X-ray study on its α-naphthylurethane. The structure was solved by symbolic addition and refined to an R of 0.048. The shortness of the carbon–carbon single bond joining the episulfide ring to the other atoms supports the view that the carbons in an episulfide ring are between sp³ and sp² in hybridization. The naphthalene ring and urethane group form a dihedral angle of 55°; this unexpected lack of coplanarity probably occurs to allow intermolecular hydrogen bonding between N–H and carbonyl oxygen.

Enzymic hydrolysis of the thioglucosides progoitrin and epiprogoitrin produces four compounds formulated as the stereoisomeric 1-cyano-2-hydroxy-3,4-epithiobutanes; this unusual reaction probably involves episulfide formation by intramolecular transfer of thioglucoside sulfur to an isolated olefinic bond.[1] An ir–nmr study of these episulfides and their acetates permitted complete stereochemical assignments to be made, and further suggested that the hydrogens attached to the asymmetric carbons are trans to one another in the most stable conformation of each stereoisomer.[2] To check the constitution, relative configuration, and conformation of one of these substances and to gain further information about bond parameters in episulfide groups, we undertook an X-ray study on the title compound.[3]

(1) M. E. Daxenbichler, C. H. VanEtten, and I. A. Wolff, *Phytochemistry,* **7**, 989 (1968), and references cited therein.

(2) K. D. Carlson, D. Weisleder, and M. E. Daxenbichler, *J. Amer. Chem. Soc.,* **92**, 6232 (1970).

(3) This derivative, mp 134–136°, was kindly provided by M. E. Daxenbichler and I. A. Wolff. It was prepared by reacting episulfide B from epiprogoitrin with α-naphthyl isocyanate in the presence of dicyclohexylethylamine.
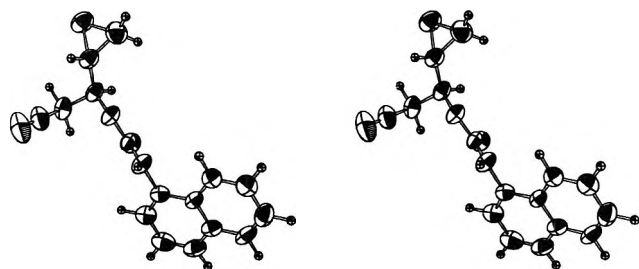
Figure 1.—Stereoscopic view of (2S,3S)-1-cyano-2-hydroxy-3,4-epithiobutane-α-naphthylurethane. Thermal ellipsoids enclose 50% probability. Hydrogen atoms are shown as spheres.
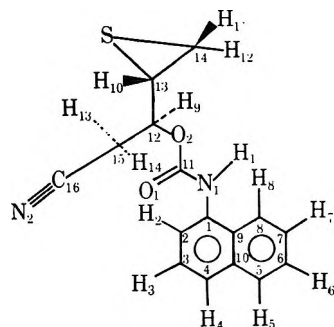
Figure 2.—Bond distances and angles in episulfides, with standard deviations in parentheses: (a) X-ray on the title compound; (b) microwave study on ethylene sulfide.[10]

Experimental Section

Collection and Reduction of the Data.—A slightly amber needle of dimensions 0.2 × 0.3 × 0.8 mm of (2S,3S)-1-cyano-2-hydroxy-3,4-epithiobutane-α-naphthylurethane was mounted for rotation about the needle axis (a). Oscillation and Weissenberg photographs indicated space group $P2_12_12_1$ or $P2_12_12$; the former was later definitely established by the full intensity data. The crystal was mounted on a Picker FACS-I four-circle automated diffractometer set for graphite-monochromatized Cu Kα radiation, λ = 1.54051 Å. The unit cell dimensions, determined by least-squares refinement of the angular settings of nine reflections, were a = 4.824(2), b = 10.803(7), and c = 28.679(16).

For data collection, the 2θ scan technique using a basic 2° scan width modified for radiation dispersion was employed. After scanning at 1°/min, 10 sec background counts were taken at both ends of the scan. Three standard reflections were measured 31 times during the data collection. The crystal decomposed approximately 4%. Of 1474 unique reflections measured up to 2θ = 125°, 935 were determined to be statistically significant on the basis $I \geqslant 2\sigma$.

Solution and Refinement.—The structure was solved by symbolic addition[4] using the MULTAN programs.[5] Using all 140 E's $\geqslant 1.50$, the program selected 103, 017, 036, and 108 as the origin- and enantiomorph-fixing reflections. An E map was constructed using the set of phases having the highest figure of merit (0.92). The largest peak on the E map corresponded to the sulfur position as determined by a sharpened Patterson. The positions of all 21 nonhydrogen atoms were found in the top 25 peaks in the E map. After four cycles of isotropic refinement, $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.105.$[6] The R was 0.074 after three cycles of anisotropic refinement. A difference map revealed all 14 hydrogens. Two additional cycles of anisotropic refinement including hydrogens (given the same anisotropic temperature factors as the atom to which they were attached)

dropped R to its final value, 0.0476. No corrections were made for extinction or absorption ($\mu = 19.1$ cm^{-1}).[7]

Results and Discussion

As can be seen from the ORTEP[8] plot in Figure 1, this study confirms the constitution, relative configuration, and trans arrangement of the protons attached to the asymmetric carbons. No attempt was made to verify the absolute configuration.

This is the first X-ray study of a substance containing an episulfide ring. Some bond distances and angles in the vicinity of this grouping are shown in Figure 2a;[9] they show geometry similar to that found for ethylene sulfide itself in a microwave study (Figure 2b).[10] The present study gives for the first time a value for the length of a carbon–carbon single bond between a carbon in an episulfide ring and another carbon: 1.468(11) Å, between C-12 and C-13. The shortness

Figure 3.—Stereoscopic view of the unit cell, a axis projection. The b axis is horizontal and the c axis vertical.

(4) J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849 (1966).

(5) G. Germain, P. Main, and M. M. Woolfson, *ibid.*, **26**, 274 (1970).

(6) Refinements were by full matrix least squares with the ORFLS program of W. R. Busing, K. O. Martin, and H. A. Levy, ORNL-TM-305, Oak Ridge National Laboratory, 1962. Unit weights were used. Form factors were obtained by graphical interpolation of those in the International Tables for X-Ray Crystallography, Vol. III, Table 3.3.1A, except for hydrogen, for which the form factors of R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965), were used.

(7) Listings of coordinates, temperature factors, bond distances and angles, least squares planes, and structure factors 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-72-2145. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche.

(8) C. K. Johnson, ORNL-3794, Oak Ridge National Laboratory, 1966.

(9) These values and their standard deviations were calculated using ORFFE, W. R. Busing, K. O. Martin, and H. A. Levy, ORNL-TM-306, Oak Ridge National Laboratory, 1964.

(10) G. L. Cunningham, Jr., A. W. Boyd, R. J. Myers, W. D. Gwinn, and W. I. Le Van, *J. Chem. Phys.*, **19**, 676 (1951).

of this bond might be considered to provide further evidence that the hybridization of the carbons in an episulfide ring is closer to sp² than sp³.[10,11]

The naphthalene ring and urethane group, normally expected to be planar to attain full p-orbital overlap, form a dihedral angle of 55.1°; C-11 is 1.05 Å out of the plane of the naphthalene ring. The disruption in p-orbital overlap is reflected in the relatively long bond [1.428(9) Å] between C-1 and N-1 as compared to the 1.325(9) Å bond between N-1 and C-11. The non-coplanarity may be partially caused by nonbonded steric interaction between H-2 and O-1; the energy lost by the disruption of p-orbital overlap is at least partially offset by that gained in the formation of an intermolecular hydrogen bond [2.24(9) Å] between

(11) D. R. Lide, Jr., *Tetrahedron*, **17**, 129 (1961). This sort of shortening has also been observed in substituted cyclopropanes: I. L. Karle, R. D. Gilardi, A. V. Fratini, and J. Karle, *Acta Crystallogr., Sect. B*, **25**, 1469 (1969).

H-1 and O-1 (perpendicular to the viewing axis in Figure 1 and in the packing diagram, Figure 3). This is the shortest intermolecular distance; the N-1–H-1 bond length is 0.74 Å, and the shortest intermolecular distance between nonhydrogen atoms (O-1 and N-1) is 2.89(8) Å.

Studies on a β-Keto Sulfone. Halogenation and Cyclization of γ-Methylsulfonyl-γ-benzoylbutyronitrile

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Received November 9, 1971

γ-Methylsulfonyl-γ-benzoylbutyronitrile (2) can be halogenated at the α position to the carbonyl group in weakly alkaline media. The halogen derivatives 3 are, however, unstable under alkaline conditions and split off the benzoyl group; therefore they are unable to undergo the Ramberg-Bäcklund rearrangement. Anhydrous acids cyclize compound 2 to 3,4-dihydro-5-methylsulfonyl-6-phenyl-2-pyridone (7), while with bromine 2 is converted into the 3-bromo derivative of 7. Photolysis of 2 proceeds either by a Norrish type II cleavage to ω-methylsulfonylacetophenone (12) or by rupture of the C–S bond to γ-benzoylbutyronitrile (13).

Addition of acrylonitrile to ω-methylsulfinylaceto-phenone yields the β-keto sulfoxide 1, which is oxidized by hydrogen peroxide to the corresponding β-keto sulfone, γ-methylsulfonyl-γ-benzoylbutyronitrile (2)[1] (see Scheme I). The reactions and properties of the latter form the subject of the present investigation.

SCHEME I

Halogenation of 2 with bromine in aqueous methanolic bicarbonate gave 3 (X = Br). Another successful

procedure was treatment of a chloroform solution of 2 with N-bromo- or N-chlorosuccinimide.

The halogen derivatives 3 proved unstable under a variety of conditions. (1) They easily underwent reduction to 2 when heated in THF or when treated with sodium azide or potassium cyanide in acetonitrile.[2] (2) Dilute (0.5 N) NaOH in 50% dioxane or NaHCO₃ in dilute methanol splits compounds 3 into benzoate and γ-halogeno-γ-methylsulfonylbutyronitrile (4) (see Scheme I), the bromo derivative reacting about twice as fast as the chloro compound. Similarly, the chloro derivative 3 (X = Cl) was decomposed by sodium methoxide in absolute methanol to 4 (X = Cl) and methyl benzoate.

Attempts to iodinate 2 at room temperature in methanolic solution, in the presence of NaHCO₃, directly led to the formation of 4 (X = I). Apparently, the sensitivity of 3 to alkaline fission increases in the order X = Cl < Br < I.

Compound 2 itself proved much more stable to alkali. Only contact with 1 N NaOH (2 equiv) at room temperature for 24 hr split this compound into benzoic acid and the known γ-methylsulfonylbutyronitrile.[3]

It should be noted that, in contrast to the behavior of 3-substituted pentane-2,4-diones,[4] enolization of

(1) F. Bergmann and D. Diller, *Israel J. Chem.*, **7**, 57 (1969).

(2) Similar reductions of α-halogenosulfones have been described by F. G. Bordwell and B. B. Jarvis, *J. Org. Chem.*, **33**, 1182 (1968).

(3) W. E. Truce, W. W. Bannister, and R. H. Knospe, *ibid.*, **27**, 2821 (1962).

(4) J. B. Conant and A. F. Thompson, *J. Amer. Chem. Soc.*, **54**, 4036 (1932).

·the tertiary hydrogen in 2 is lacking, as shown by ir and nmr spectra.[5]

The sensitivity of compounds 3 to alkaline cleavage may be responsible for the failure of the Ramberg–Bäcklund rearrangement,[6] which would require formation of an anion like 3a. As far as we are aware, only one similar case of a β-keto sulfone with a quaternary carbon has been studied: α-bromo-α-benzylsulfonyl-cyclohexanone did undergo the expected rearrangement.[7] However, in this derivative, the aromatic substituent facilitates anion formation in the CH_2 group, α to the phenyl and the sulfonyl group. It is well known that introduction of phenyl groups into dimethyl sulfone lowers the pK considerably (pK of dimethyl sulfone, 28; of dibenzyl sulfone, 22).[8]

Deuteration of 2.—In the presence of 1 equiv of 0.5 N NaOD in D_2O at room temperature, 2 was converted into the tetradeuterio derivative 2b. Upon heating in ethanol, 2b lost one deuterium atom to give the trideuterio derivative 2c. Thus exchange takes place first at the tertiary carbon (2a) and subsequently in the methylsulfonyl group (2b) (see Scheme II). In fact, the tertiary CH group exchanges even

SCHEME II
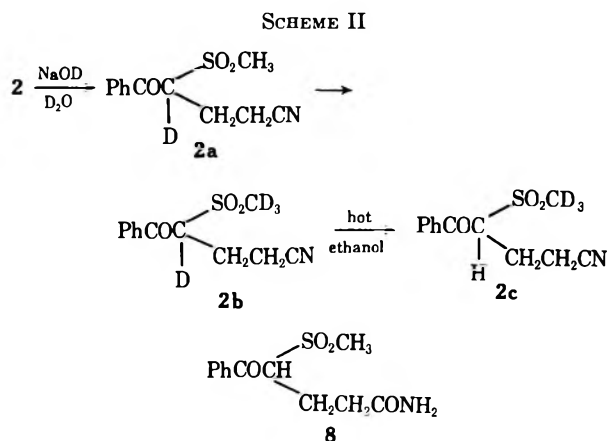
in acetonitrile–D_2O at neutral pH and room temperature to give 2a, while the methyl group is not attacked under these conditions. The methylene groups, α and β to the nitrile, do not participate in the exchange reactions. Localization of the deuterium atoms in 2a–c was achieved by means of nmr spectra.

Cyclization Reactions.—Treatment of the keto sulfone 2 with HBr in methylene chloride yielded 3,4-dihydro-5-methylsulfonyl-6-phenyl-2-pyridone (7). Cyclization of γ-keto nitriles has been studied previously by Kohler, *et al.*,[9] and by Allen and Ball,[10] who assumed the intermediate formation of the amide. We have, however, found that the amide 8, obtained from 2 by treatment with hydrochloric acid, is resistant to hydrogen bromide. Moreover, treatment of 7 with HBr in dilute acetic acid caused ring opening and gave a quantitative yield of amide 8. We suggest enolization of 2 and cyclization to the dihydropyran 6, which rearranges to 7 (see Scheme III). In samples with-

(5) G. Schwarzenbach and E. Felder, *Helv. Chim. Acta,* **27,** 1701 (1944).

(6) L. A. Paquette, *Accounts Chem. Res.*, **1,** 209 (1968).

(7) I. Shahak and E. D. Bergmann, *Israel J. Chem.*, **8,** 589 (1970).

(8) F. G. Bordwell, R. N. Imes, and E. C. Steiner, *J. Amer. Chem. Soc.*, **89,** 3905 (1967).

(9) E. P. Kohler, A. Graustein, and D. R. Merrill, *ibid.*, **44,** 2536 (1922).

(10) C. F. H. Allen and M. L. Ball, *ibid.*, **59,** 686 (1937).

SCHEME III
CYCLIZATION OF γ-METHYLSULFONYL-γ-BENZOYLBUTYRONITRILE (2)
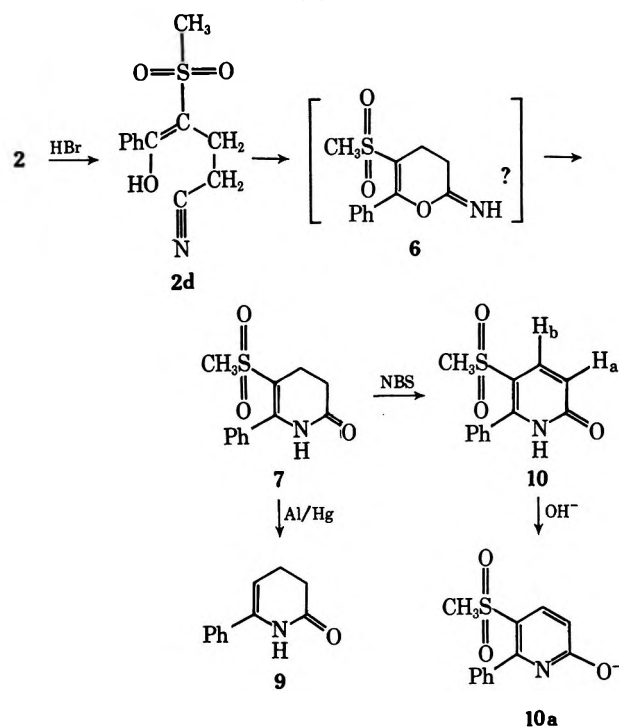
drawn during the reaction of 2 with HBr in methylene chloride, tlc showed the presence of a transient intermediate which may be 6, but this compound could not be isolated.

The methylsulfonyl group of 7 was removed by Al/Hg to give 3,4-dihydro-6-phenyl-2-pyridone (9), identical with the cylization product of γ-benzoyl-butyronitrile.[11] NBS dehydrogenated 7 to the 2-pyridone 10 (see Scheme III).

The structure of 7 is supported by the following observations. (1) In the ir spectrum of 7, the nitrile band of 2 (at 2250 cm^{-1}) has been replaced by two new bands at 3100 and 3200 cm^{-1}, characteristic for the NH stretching frequency of lactams.[12] (2) In the nmr spectrum of 7, bands of vinyl hydrogens are absent; *i.e.*, the double bond must be located at 5,6.

Structure 10 is based on the following data. Two doublets, H_a, δ 6.66, and H_b, δ 8.08, in CD_3CN–D_2O, characterize the two vinyl protons.[13] Assignment was possible by the nuclear Overhauser effect (15% increase in the intensity of H_b upon irradiation with the frequency of the methyl signal). A molecular model shows the close proximity of the hydrogen at C-4 to the methyl group of the 5-sulfonyl substituent.

In the anion of 10, the signal of H_a shifts upfield by 0.34 ppm, the one of H_b only by 0.15 ppm.[14]

The 3-Bromo Derivative of the Dihydropyridone 7.— When bromination of 2 was carried out in an aprotic solvent (methylene chloride) in the absence of base, again cyclization took place, but the reaction yielded a

(11) H. Krimm, DBP 1,092,919 (1961).

(12) K. Blaha, J. Smolikova, and K. Vitek, *Collect. Czech. Chem. Commun.*, **31,** 4296 (1966).

(13) Similarly, 6-phenyl-2-pyridone shows H_a, 6.51; H_b, 7.56; H_c, 6.69 (in DMSO–D_2O, 2:1). For related observations on 6,N-dimethyl-2-pyridone see J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

(14) Likewise, in the anion of 6-phenyl-2-pyridone the upfield shift for H_a is 0.30.

bromo derivative 11 of the dihydropyridone 7. The λ_{max} of 11 is 265 nm (λ_{max} of 7, 267 nm); its ir spectrum resembles closely that of 7, but the carbonyl stretching frequency is at 1700 cm^{-1}, while that of 7 is at 1680 cm^{-1}. α-Halogenation of ketones, by reducing the polarity of the C=O group, raises the carbonyl stretching frequency by 15–20 cm^{-1},[15] but such an effect is missing in α-halo amides. This difference has been explained by Bellamy and Williams[16] in the following way. The amide nitrogen, by virtue of its partial positive charge, attracts the halogen atom and thus brings it into a gauche position relative to the carbonyl oxygen. Furthermore, the partial negative charge at the oxygen atom repels the halogen atom and thus supports the gauche form in which the α halogen has no effect on the polarity of the carbonyl group, in contrast to α-halo ketones. The shift of the carbonyl band in the ir spectrum of 11, relative to that of 7, leads us therefore to ascribe to the cyclic amide 11 the following structure, where the bromine atom assumes preferen-

tially the equatorial conformation, thus coming into the plane of the carbonyl group. This may explain the elevation of the carbonyl stretching frequency in 11. In any case, this elevation is evidence for location of the bromine atom at position 3, i.e., α to the carbonyl; a β halogen would not influence the position of the carbonyl stretching band at all.
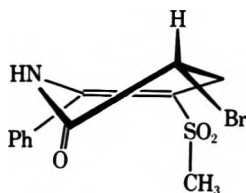
When 7 was exposed to bromine under the conditions used for 2, with or without hydrogen bromide, some degradation products were found, but 11 was not obtained. Therefore the latter is probably formed by bromination of an intermediate state, e.g., 6.

When 11 was heated in ethanol, it lost HBr to form 10 (see Scheme IV). Therefore, if isolation of 11 was not carried out under special precautions the compound was usually contaminated with the pyridone 10.

Treatment of 11 with hydrogen–Pd/C or with Zn–acetic acid gave the dihydropyridone 7. Under the same conditions, or by hydrogen–Raney nickel, 10 was not attacked. These observations made it possible to connect the structure of 11 and 10 in such a way as to confirm the point of attachment of the bromine atom in the former (see Scheme IV). Treatment of 11 with Zn/CH$_3$COOH gave the monodeuterio derivative 7a. In the nmr spectrum of the latter, the signal at δ 2.60–2.95 integrates for six instead of seven protons (three of the methyl group, two of the 4-methylene group, and one of the α hydrogen). Dehydrogenations of 7a with NBS in chloroform yielded a 1:1 mixture of 10 and its monodeuterio derivative 10b. In the nmr spectrum of this mixture, the doublet at δ 6.66 ($J = 10$ cps) has remained unchanged, but its area has been halved. Furthermore, instead of the doublet at δ 8.08, three lines are present. In addition to the two

SCHEME IV
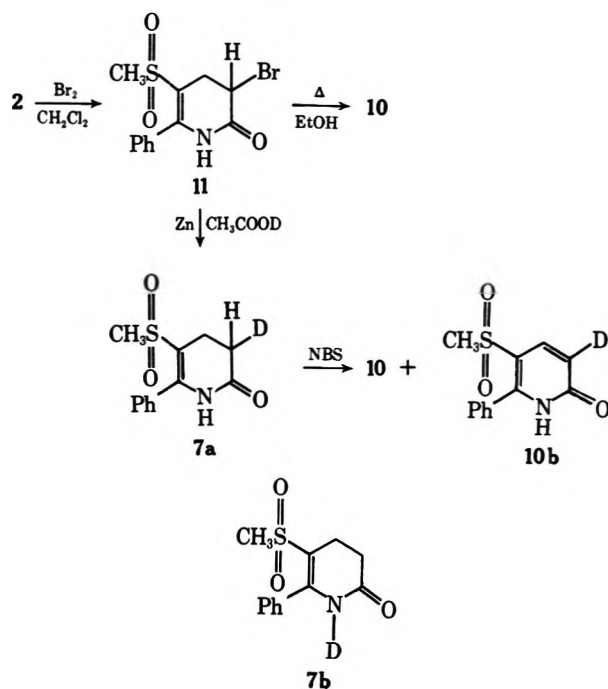
components of the doublet at δ 8.16 and 7.99, a signal appears in the middle, i.e., at δ 8.08. It is thus clear that only 50% of the 4-H signal, characterized by δ 8.08, is split by the neighboring vinyl proton, i.e., the latter has been partly replaced by deuterium.[17]

We may thus safely conclude that in 11 the bromine is attached to position 3. It should be recalled that in alkaline media, bromination of 2 takes place exclusively at the tertiary carbon, i.e., at that CH group which dissociates in alkali to form the anion. In contrast, in compound 11 the carbon atom, originally α to the nitrile group, has been halogenated.

Photochemical Fission of Compound 2.—Ultraviolet irradiation of 2 in benzene solution furnished two main fission products (see Scheme V): (a) ω-methylsulfonylacetophenone (12) (path 1) (Norrish type II cleavage[18]); and (b) γ-benzoylbutyronitrile (13) (path 2).

A third product was identified as acetophenone, which could be formed in two ways: (1) by Norrish type II reaction of γ-benzoylbutyronitrile; or (2) from 12, either by a process analogous to the splitting of γ-benzoylbutyronitrile, or by rupture of the C–S bond to form the radical C$_6$H$_5$COCH$_2$·. The latter would then stabilize itself by scavenging a hydrogen atom. In order to decide between these possibilities, both 12 and 13 were irradiated. Only the latter furnished acetophenone (yield practically quantitative), while this product was missing from the photolysis mixture of the β-keto sulfone.

γ-Benzoylbutyronitrile itself could also be formed from 2 in two ways: (1) by intramolecular hydrogen transfer from the methylsulfonyl group, followed by β fission; or (2) by rupture of the C–S bond and formation of radical 13b, which is then stabilized by abstraction of hydrogen from an external source. These

(15) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958.

(16) L. J. Bellamy and R. L. Williams, J. Chem. Soc., 4294 (1957).

(17) In accordance with these observations, in the anion of 10b the halved signal at δ 6.66 undergoes a large upfield shift of 0.34 ppm.

(18) C. H. Bamford and R. G. W. Norrish, J. Chem. Soc., 1504 (1935).

SCHEME V

PHOTOLYTIC REACTIONS OF
γ-METHYLSULFONYL-γ-BENZOYLBUTYRONITRILE (2)
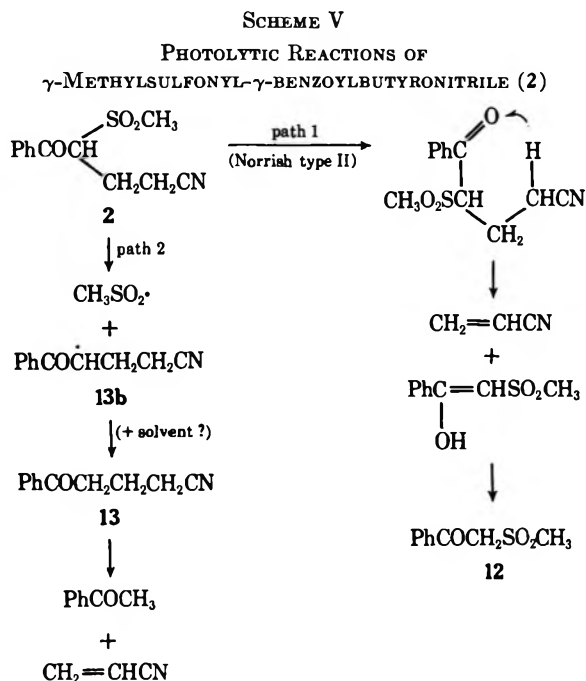
alternatives can be tested by the use of deuterated derivatives (see Scheme VI).

SCHEME VI

PHOTOLYSIS OF THE TETRADEUTERIO DERIVATIVE 2b
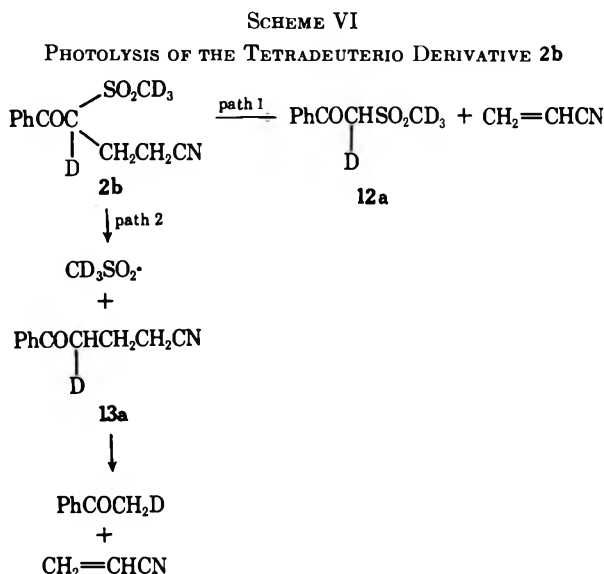
Photolysis of the tetradeuterio derivative **2b** yielded γ-benzoylbutyronitrile with a single deuterium atom at the γ position (**13a**). Likewise the acetophenone, resulting from further splitting, had the structure $C_6H_5COCH_2D$. These results exclude a Norrish type II reaction for the formation of **13** and show that the alternative pathway (2) is correct (see Scheme V). The radical **13b** is stabilized by abstraction of a hydrogen from an external source, e.g., from the solvent (benzene), but not from the methylsulfonyl radical. Abstraction of hydrogen from benzene during photochemical processes has been proposed by various authors.[19,20] Irradiation of **2** in CCl_4 yielded only **12**, while **13** and acetophenone were missing.

The photochemical reactions described provide two

examples in which a γ-CH group, connected to the carbonyl *via* a chain bearing a sulfonyl, e.g., $\overset{\gamma}{C}HSO_2$-CHCO, is unable to transfer its hydrogen to the CO group by a Norrish type II mechanism. This accords with the observations of McIntosh, *et al.*[21]

Experimental Section

All melting points are uncorrected. Microanalyses are by F. Strauss, Oxford. Uv spectra were measured in absolute ethanol on a Beckman DU spectrophotometer (ϵ_{max} values are given after the wavelength of the absorption maximum), and ir spectra were measured in KBr on a Perkin-Elmer Model 337 infrared spectrophotometer. Nmr spectra (TMS internal standard) were run on a Varian T-60 and a Jeol C-60-H instrument. pK values were determined in water from a plot of λ_{max} as a function of pH.

For tlc, fluorescent silica gel GF 254 was used. Three solvents served for separation: A, chloroform–methanol, 9:1 v/v; B, chloroform–tetrahydrofuran, 2:1 v/v; C, chloroform–ethyl acetate, 7:1 v/v. Spots were detected with the aid of a Mineralight short-wave lamp ($\lambda \sim 255$ nm) or by exposure to iodine vapor.

Bromination of γ-Benzoyl-γ-methylsulfonylbutyronitrile to 3 (X = Br).—To a mixture of γ-benzoyl-γ-methylsulfonylbutyronitrile (**2**)[1] (7.5 g, 0.03 mol) in methanol (180 ml) and sodium bicarbonate (5.8 g, 0.07 mol) in water (135 ml) was added a solution of bromine (5.5 g, 0.034 mol) in methanol (18 ml). The clear solution was stirred at room temperature for 15 min, when the color had disappeared and a colorless precipitate had formed. The solid was recrystallized from aqueous methanol as colorless rhombohedra: mp 91°; yield 6.3 g (64%); uv$_{max}$ 263–264 nm (ϵ 9870); R_f (A) 0.68; ir 1675 (C=O), 1150, 1320 (SO$_2$), 2250 cm^{-1} (CN); nmr (CDCl$_3$) δ 2.50–3.20 (m, 4, CH$_2$ β and γ to SO$_2$), 3.26 (s, 3, methyl), 7.55 (m, 3, meta and para hydrogens of phenyl), 8.16 (m, 2, ortho hydrogens).

Anal. Calcd for C$_{12}$H$_{12}$BrNO$_3$S: C, 43.6; H, 3.6; N, 4.2; Br, 24.2. Found: C, 43.9; H, 3.8; N, 4.2; Nr. 24.3.

Preparation of γ-Benzoyl-γ-chloro-γ-methylsulfonylbutyronitrile (3, X = Cl).—A solution of **2** (1.75 g) and N-chlorosuccinimide (1 g) in chloroform (14 ml) was refluxed for 45 min. The solution was chromatographed on 20 silica gel plates (0.75 mm thickness) in solvent A. The bands of **3** (X = Cl) were extracted with chloroform, the solvent was evaporated, and the residue was recrystallized from isopropyl alcohol as colorless prisms: mp 80–81°; yield 1.6 g (80%); uv$_{max}$ 261 nm (ϵ 9960); R_f (A) 0.72; ir 1675 (C=O), 1147, 1318 (SO$_2$), 2250 cm^{-1} (CN); nmr (CDCl$_3$) δ 2.50–3.05 (m, 4, CH$_2$ β and γ to SO$_2$), 3.20 (s, 3, CH$_3$), 7.83 (m, 3, meta and para protons of phenyl), 8.13 (m, 2, ortho hydrogens).

Anal. Calcd for C$_{12}$H$_{12}$ClNO$_3$S: C, 50.4; H, 4.2; N, 4.9; Cl, 12.4. Found: C, 50.2; H, 4.5; N, 4.9; Cl, 12.5.

γ-Halogeno-γ-methylsulfonylbutyronitriles (4). A. 4, X = Cl. —A solution of **3** (X = Cl) (0.6 g) in methanol (12 ml) was mixed with a solution of potassium carbonate (0.3 g) in water (6 ml). After standing at room temperature for 45 min, the solution was concentrated *in vacuo* and the residue was recrystallized from benzene–cyclohexane as colorless rods: mp 74°; yield 0.2 g (84%); no uv absorption above 220 nm; R_f (A) 0.50; ir 1140, 1315 (SO$_2$), 2250 cm^{-1} (CN); nmr (CDCl$_3$) δ 4.83 (m, 1, CH), 2.20–3.00 (m, 4, CH$_2$ β and γ to SO$_2$), 3.10 (s, 3, CH$_3$).

Anal. Calcd for C$_5$H$_6$ClNO$_2$S: C, 33.1; H, 4.4; Cl, 19.6. Found: C, 33.4; H, 4.3; Cl, 19.7.

The same compound was obtained in 50% yield by treatment of **3** (X = Cl) with 1 N NaOCH$_3$ in methanol.

B. 4, X = Br.—To a mixture of **2** (1 g) in methanol (24 ml) and of potassium carbonate (0.6 g) in water (12 ml) was added a solution of bromine (0.7 g) in methanol (3 ml). After standing for 30 min at room temperature, the solution was concentrated *in vacuo*. The residue was treated as described for the chloro derivative, and obtained as colorless rods: yield 0.8 g (89%); mp 89°; R_f 0.54; ir 1132, 1305 (SO$_2$), 2240 cm^{-1} (CN); nmr (CDCl$_3$) δ 4.85 (m, 1, CH), 2.25–3.00 (m, 4, CH$_2$ β and γ to SO$_2$), 3.15 (s, 3, CH$_3$).

(19) J. A. Bell and H. Linschitz, *J. Amer. Chem. Soc.*, **85**, 528 (1963).
(20) A. Beckett and G. Porter, *Trans. Faraday Soc.*, **59**, 2039 (1963).

(21) C. L. McIntosh, P. de Mayo, and R. W. Yip, *Tetrahedron Lett.*, **37** (1967).

Anal. Calcd for C₅H₈BrNO₂S: C, 26.6; H, 3.5; N, 6.2; S, 14.2. Found: C, 26.9; H, 3.9; N, 6.2; S, 14.1.

C. 4, X = I.—To a mixture of **2** (0.5 g) in methanol (15 ml) and sodium bicarbonate (0.4 g) in water (10 ml) was added a solution of iodine (0.6 g) in methanol (6 ml). After standing at room temperature for 24 hr, the methanol was removed *in vacuo* and the aqueous layer was extracted with chloroform. The organic layer was dried over sodium sulfate and brought to dryness *in vacuo*. The residue crystallized upon treatment with toluene. From benzene–cyclohexane colorless needles were obtained: mp 77°; yield 0.25 g (46%); uv$_{max}$ 256 nm (ϵ 725); R_f 0.54; ir 1137, 1307 (SO₂), 2240 cm⁻¹ (CN); nmr (CDCl₃) δ 4.95 (m, 1, CH), 2.20–2.95 (m, 4, CH₂ β and γ to SO₂), 3.20 (s, 3, CH₃).

Anal. Calcd for C₅H₈INO₂S: C, 22.0; H, 2.9; N, 5.1; I, 46.5. Found: C, 22.1; H, 3.0; N, 4.8; I, 46.6.

γ-Methylsulfonylbutyronitrile (4, X = H).—A suspension of **2** (5 g) in 1 N NaOH was stirred at room temperature for 24 hr, when a clear solution was obtained. Acidification with concentrated HCl precipitated a solid, mp 122°, identified as benzoic acid. The filtrate was extracted with chloroform and the solvent was evaporated *in vacuo*. The sirupy residue (0.45 g) was chromatographed on ten silica plates with the aid of solvent A. **4** (X = H) was localized by means of iodine vapor and extracted with chloroform. The chloroform residue crystallized spontaneously, mp 44°. It proved identical with the compound described by Truce, *et al.*[3]: R_f 0.38; ir 1130, 1305 (SO₂), 2250 cm⁻¹ (CN); nmr (CDCl₃) δ 3.19 (t, 2, CH₂ α to SO₂), 2.26 (m, 2, CH₂ β to SO₂), 2.65 (t, 2, CH₂ γ to SO₂), 2.97 (s, 3, CH₃).

Anal. Calcd for C₅H₉NO₂S: C, 40.8; H, 6.1; S, 21.8. Found: C, 40.8; H, 6.1; S, 22.0.

γ-Benzoyl-γ-methylsulfonylbutyramide (8).—A suspension of **2** (5 g) in concentrated HCl (50 ml) was stirred at room temperature for 4–5 hr, until a clear solution was obtained. The precipitate, resulting from neutralization with sodium bicarbonate, crystallized from methanol or THF–cyclohexane in rhomboids: mp 154°; yield 3.6 g (67%); uv$_{max}$ 254 nm (ϵ 26,000) R_f (A) 0.26; ir (Nujol) 1675 (C=O), 1122, 1310 (SO₂), 1650, 3175, 3300, 3410 cm⁻¹ (CONH₂); nmr (CD₃CN) δ 5.37 (t, 1, CH), 2.15–2.85 (m, 4, CH₂ β and γ to SO₂), 2.97 (s, 3, CH₃), 7.70 (m, 3, meta and para hydrogens of phenyl), 8.17 (m, 2, ortho hydrogens).

Anal. Calcd for C₁₂H₁₅NO₄S: C, 53.5; H, 5.6; N, 5.2; S, 11.9. Found: C, 53.3; H, 5.6; N, 5.5; S, 12.2.

Deuteration of 2.—**2** (10 g) was stirred with 1 equiv of 0.5 N NaOD in D₂O at room temperature for 24 hr. By addition of 1 equiv of CH₃COOD, a white precipitate (5.5 g) was formed; it was filtered off and washed with D₂O. It was identified as the tetradeuterio derivative **2b** by the nmr and mass spectra. A sample of **2b** was dissolved in hot absolute ethanol. From the cooled solution the trideuterio derivative **2c** was isolated.

Cyclization of 2 to 3,4-Dihydro-5-methylsulfonyl-6-phenyl-2-pyridone (7).—Through a solution of **2** (4 g) in methylene chloride (30 ml), cooled to 0°, was passed dry HBr gas until saturation. The solution was then kept at room temperature for 22 hr. The precipitate was removed and treated in warm methanol with solid sodium bicarbonate. From the filtrate, we obtained 1.8 g (45%) of solid **7** and from methanol long, colorless needles: mp 255°; uv$_{max}$ 227 nm (ϵ 8700), 267 (10,700); R_f (A) 0.49, (B) 0.40; pK_a 11.3; ir 1680 (C=O), 1140, 1302 (SO₂), 3100, 3200 cm⁻¹ (NH); nmr (CD₃COOD) δ 2.60–2.95 (m, 4, 3- and 4-CH₂), 2.95 (s, 3, CH₃), 7.55 (s, 5, aromatic).

Anal. Calcd for C₁₂H₁₃NO₃S: C, 57.4; H, 5.2; N, 5.6. Found: C, 57.4; H, 5.2; N, 5.7.

5-Methylsulfonyl-6-phenyl-2-pyridone (10).—A solution of the dihydropyridone **7** (2.5 g) and N-bromosuccinimide (3.6 g) in chloroform (150 ml) was refluxed for 3 hr. The solvent was removed *in vacuo* and the sirupy residue was dissolved in 15 ml of 60% ethanol. From the mixture, kept in the refrigerator for 24 hr, colorless crystals separated. From ethanol 1.5 g (60%) of colorless needles were obtained: mp 260–265°; uv$_{max}$ 207 nm (ϵ 16,600), 248 (14,500), 303 (6920); R_f (A) 0.43, (B) 0.26; pK 8.6; ir 1660 (C=O), 1128, 1303 (SO₂), 3040, 3110 cm⁻¹ (NH);[22] nmr (CD₃CN–D₂O, 2:1) 6.66 (d, 1, 3-H, $J_{3,4}$ =

10 Hz), 8.08 (d, 1, 4-H), 2.87 (s, 3, CH₃), 7.57 (s, 5, aromatic); nmr (DMSO-d₆) δ 6.46 (d, 1, 3-H, $J_{3,4}$ = 10 Hz), 7.86 (d, 1, 4-H), 2.85 (s, 3, CH₃), 7.48 (s, 5, aromatic).

Anal. Calcd for C₁₂H₁₁NO₃S: C, 57.8; H, 4.4; N, 5.6; S, 12.9. Found: C, 58.0; H, 4.4; N, 5.7; S, 12.9.

Conversion of Pyridone 10 into 3,4-Dihydro-6-phenyl-2-pyridone (9).—A solution of the pyridone **10** (4 g) in 240 ml of THF, containing 10% water and cooled to 4°, was stirred with aluminum amalgam (prepared from 12 g of aluminum foil according to Corey and Chaykovsky[23]). A sample, removed after 2 hr, showed on tlc the formation of the dihydro derivative **7**. The latter was identified by uv, ir, and nmr spectra. After 16 hr, a mixture of **7** and **9** was present, while after 24 hr only the latter derivative had been left. The conversion of **10** → **9** thus takes place in the following two steps: **10** → **7** → **9**. The reaction mixture was filtered and the filtrate was brought to dryness *in vacuo*. The mixture was chromatographed on 20 silica gel plates using solvent C. The product **9** was extracted with benzene and recrystallized first from benzene–cyclohexane, then from methanol as colorless plates (0.6 g), mp 155°. The substance proved identical with a sample of 3,4-dihydro-6-phenyl-2-pyridone prepared according to Krimm:[11] uv$_{max}$ 223 nm (ϵ 17,000), 270 (6300); R_f (A) 0.70, (B) 0.51; pK > 13.5; ir 1680 (C=O), 3100, 3200 cm⁻¹ (NH); nmr (CDCl₃) δ 2.45–2.75 (m, 4, 3- and 4-CH₂), 5.45 (t, 1, 5-CH), 7.38 (s, 5, aromatic).

3-Bromo-3,4-dihydro-5-methylsulfonyl-6-phenyl-2-pyridone (11).—A mixture of **2** (4 g) and bromine (2.8 g) in methylene chloride (40 ml) was kept at room temperature for 4 days, when the color of the halogen had disappeared. The precipitate was filtered off and dissolved at room temperature in tetrahydrofuran. Cautious addition of two volumes of cyclohexane caused crystallization of colorless needles: mp 259°; yield 3.3 g (62%); uv$_{max}$ (acetonitrile) 234 nm (ϵ 8900), 265 (7950); R_f (A) 0.59, (B), 0.56; ir 1700 (C=O), 1140, 1305 (SO₂), 3105, 3205 cm⁻¹ (NH); nmr (DMSO-d₆) δ 4.81 (t, 1, 3-H), 3.22 (d, 1) and 3.30 (d, 1, both for 4-CH₂), 2.86 (s, 3, CH₃), 7.40 (s, 5, aromatic).

Anal. Calcd for C₁₂H₁₂BrNO₃S: C, 43.6; H, 3.6; N, 4.2; Br, 24.2. Found: C, 43.8; H, 3.7; N, 3.8; Br, 24.5.

Reduction of 11 to 7.—A solution of **11** (0.8 g) in THF (50 ml) was shaken with 10% Pd/C (0.4 g) and MgO (0.4 g) under a hydrogen pressure of 2 atm at room temperature for 2 hr. The filtrate was brought to dryness and the solid residue was recrystallized from ethanol as long, colorless rods, yield 0.5 g (83%), mp 255°, identical with product **7** described above.

Reduction of 11 to 7a.—A solution of the bromo derivative **11** (165 mg) in CH₃COOD (12 ml) was mixed with zinc powder (100 mg) and refluxed for 2 hr. The residue, obtained after filtration and evaporation of the solvent, was recrystallized from absolute ethanol as colorless rods, mp 255°, yield 108 mg (86%), identical with **7**, but containing a single deuterium atom, as determined by nmr and mass spectra.

The 3-deuterio derivative **7a** was dehydrogenated with N-bromosuccinimide, as described before for the conversion of **7** → **10**. The product was a 1:1 mixture of **10** and **10b** (see Scheme IV).

Dehydrobromination of 11 to 10.—A suspension of the bromo derivative **11** (5 g) in ethanol (150 ml) was refluxed for 20 hr. When cooled, the solution deposited colorless crystals, yield 3 g (79%). From ethanol, colorless needles were obtained, mp 260–265°, identical with the pyridone **10** described before.

The same reaction could be effected by dissolving the bromo derivative **11** in 1 N NaOH.

Photochemical Reactions. A. Photolysis of 2.—A solution of **2** (1 g) in absolute benzene (225 ml) was stirred at room temperature and irradiated for 140 min under nitrogen. A brown turbidity was removed by filtration and the solvent was evaporated. The residue was dissolved in THF and chromatographed on 15 plates with solvent C. Five components were separated (Table I).

B. Photolysis of γ-Benzoylbutyronitrile (13).—γ-Benzoylbutyronitrile (0.5 g) in benzene (250 ml) was irradiated as above for 30 min. On tlc, only one product (acetophenone) was separated, in nearly quantitative yield.

C. Photolysis of ω-Methylsulfonylacetophenone (12).—This

(22) Since the NH band is found in the region where also the absorption due to stretching of aromatic CH bonds appears, the assignment was verified with the corresponding ND derivatives. In the latter, the bands at 3050, 3040, and 3110 cm⁻¹, respectively, are missing and a new band near 2250 cm⁻¹ has appeared; the ratio ν_{NH}/ν_{ND} is 1.37, as expected. See C. N. R. Rao in "Chemical Application of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 15.

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

TABLE I

R_f	Amount, mg	Identified as[a]
0.60	110	Acetophenone
0.52	350	γ-Benzoylbutyronitrile (13)
0.29	80	ω-Methylsulfonylacetophenone (12)
0.22	80	2
0.08	115	b

[a] Identification is based on ir and nmr spectra and on R_f values.
b Not identified.

compound was irradiated for 60 min under the same conditions as described above. A multitude of products was obtained on tlc, but acetophenone was not detected.

The Pyrolysis of 2H-Naphth[1,8-cd]isothiazole 1,1-Dioxide and Its 2-Phenyl Analog

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The pyrolytic reactions of 2H-naphth[1,8-cd]isothiazole 1,1-dioxide (2) and 2-phenylnaphth[1,8-cd]isothiazole 1,1-dioxide (3) are described. The major products from the pyrolysis of 2 were 2-cyanoindene (5) and 3-cyanoindene (6) (1.2/1, 68%). The major product from the pyrolysis of 3 was 7H-benz[k,l]acridine, in 43% yield. The mass spectra of 2 and 3 are discussed. Synthetic routes to 5 and 6 were developed in order to aid in their identification in the mixture obtained from the pyrolysis of 2.

We have reported the mass spectra and pyrolyses of o-phenylene sulfite,[2,3] o-phenylene carbonate,[4,5] 2-pyrone, and 2-pyridone.[6] This procedure has recently been used by Chapman to obtain cyclopentadienone on a low-temperature ir cell from o-benzoquinone, o-phenylene sulfite, and o-phenylene carbonate.[7]

As part of this project, we have pyrolyzed naphth-[1,8-cd]-1,2-oxathiole 2,2-dioxide (1).[8] The formation

of the products which are isolated can be rationalized in terms of loss of SO₂ from 1, followed by the trapping of the intermediate which results. We have also studied 2H-naphth[1,8-cd]isothiazole 1,1-dioxide (2) and 2-phenylnaphth[1,8-cd]isothiazole 1,1-dioxide (3) and describe our procedures and results in this article.

Results and Discussion

The major peaks in the mass spectrum of 2 arise from loss of SO₂ from the molecular ions, followed by H· or HCN (eq 1). The most intense fragment ion

$$m/e\ 205\ (100\%) \xrightarrow{-SO_2} m/e\ 141\ (52\%) \xrightarrow{-H \cdot} m/e\ 140\ (27\%)$$
$$\text{(M·}^+ \text{ from 2)} \qquad * \qquad \Big| \qquad -HCN \qquad \longrightarrow m/e\ 114\ (27.5\%) \tag{1}$$

is m/e 141, and a metastable peak is present for the loss of SO₂ from m/e 205. Similar behavior is observed from 3 (eq 2). However, in this case the most

$$m/e\ 281\ (100\%) \xrightarrow{-SO_2} m/e\ 217\ (55\%) \xrightarrow{-H \cdot} m/e\ 216\ (82\%)$$
$$\text{(M·}^+ \text{ from 3)} \quad * \quad \downarrow -HCN \qquad \qquad \downarrow -HCN \tag{2}$$
$$m/e\ 190\ (8\%) \qquad\qquad m/e\ 189\ (11\%)$$

intense fragment ion results from the elimination of SO₂ followed by H·. It is possible to postulate a stable structure (4) for m/e 216, which may explain its high relative intensity (eq 3). However, no evidence is

available to support these postulations.

On the basis of these facile losses of SO₂ from 2 and 3 in the mass spectrometer, we were encouraged to try to find products from similar losses of SO₂ pyrolytically.

Compound 2 was pyrolyzed in a stream of N₂ by sublimation into a pyrolysis zone containing a heated coil constructed from chromel wire. A series of cold traps condensed the products as they emerged from the pyrolysis zone. The highest yields were obtained when the temperature was 720–740° and when the pressure of N₂ was 3.0–3.5 mm. The ir spectrum of

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(2) (a) D. C. De Jongh and R. Y. Van Fossen, *J. Org. Chem.*, **37**, 1129 (1972); (b) D. C. De Jongh, R. Y. Van Fossen, and A. Dekovich, *Tetrahedron Lett.*, 5045 (1970).

(3) D. C. De Jongh, R. Y. Van Fossen, and C. F. Bourgeois, *ibid.*, 271 (1967).

(4) D. C. De Jongh and D. A. Brent, *J. Org. Chem.*, **35**, 4204 (1970).

(5) D. C. De Jongh, D. A. Brent, and R. Y. Van Fossen, *ibid.*, **36**, 1469 (1971).

(6) D. A. Brent, J. D. Hribar, and D. C. De Jongh, *ibid.*, **35**, 135 (1970).

(7) O. L. Chapman and C. L. McIntosh, *Chem. Commun.*, 770 (1971).

(8) D. C. De Jongh and G. N. Evenson, *Tetrahedron Lett.*, 4093 (1971).

the products showed the presence of a cyano group, and the mass spectrum gave a molecular ion at m/e 147, corresponding to a formula of $C_{10}H_7N$. These data can be explained by a loss of SO_2 from **2** upon pyrolysis, and rearrangement to a nitrile. The nmr spectrum could be interpreted in terms of a 1.2:1 mixture of 2-cyanoindene (**5**) and 3-cyanoindene (**6**). A yield
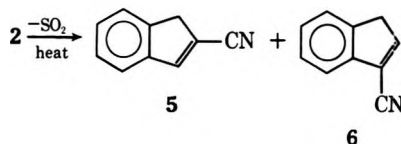
of 68% was determined. The isomers could not be separated by vacuum distillation, although there was separation by gas chromatography. It is possible that the cyanoindenes **5** and **6** form *via* a nitrene intermediate (**7**). Nitrenes similar to **7** undergo ring con-

traction to form nitriles, which at higher temperatures experience CN migrations.[9-11] For example, 3-cyanoindene (**6**) was the product from pyrolysis of 1,2-naphthotriazole, and 2-cyanoindene (**5**) was obtained from 2,3-naphthotriazole, at 500°.[11] At 1000° (0.25 mm), a ratio of 1.3:1 was obtained for **5**:**6**, when either pure **5** or **6** was pyrolyzed; at 800° (0.02 mm), the ratio of **5**:**6** was 1:1.5.[11] Thus, the two cyanoindenes are equilibrated at temperatures around 800°.
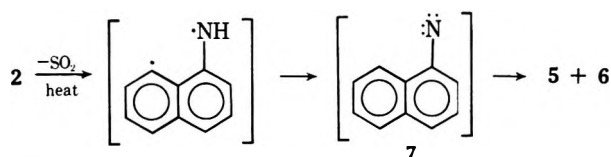
Our identification of the mixture of cyanoindenes **5** and **6** was verified by their syntheses and comparison of physical data obtained from the mixture with those from the authentic samples. 3-Cyanoindene (**6**) was synthesized from the known compound,[12] 1-cyano-2-indanone (**8**), as shown in eq 4. 2-Cyanoindene (**5**)
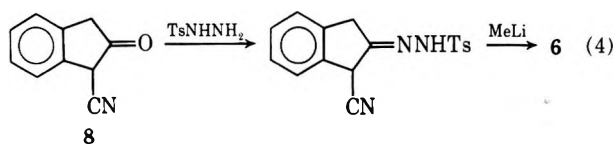
was synthesized by dehydration of the oxime **9**[13] of 2-indenal as shown in eq 5.
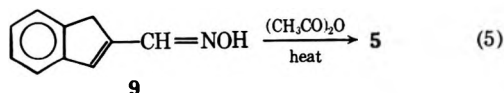
Pyrolysis of 2-phenylnaphth[1,8-cd]isothiazole 1,1-dioxide (**3**) also leads to a product resulting from initial loss of SO_2. Compound **3** was pyrolyzed at a temperature of 680° and a nitrogen pressure of 3.0–3.5 mm. The pyrolysis product was identified as 7H-benz-[k,l]acridine (**10**) and was isolated in 43% yield. Compound **10** can form by loss of SO_2 and intramolecular trapping of the intermediate which forms. The for-

mation of **10** resembles the process postulated in eq 3, leading to ion **4**.

Thus, **2** and **3** lose SO_2 upon pyrolysis, and the products which are isolated result from rearrangement to stable molecules. The fragmentation of their molecular ions proceeds *via* loss of SO_2 also, and this fact was used to predict their pyrolysis products. In attempts to trap intermediates which might form prior to formation of **5**, **6**, and **10**, we used methanol in the nitrogen stream in one experiment and substituted carbon dioxide for nitrogen in another experiment.[8] The results did not change in either case.

Experimental Section

Melting points were determined by the open-capillary method and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrometer; ultraviolet spectra were recorded on a Perkin-Elmer 202 spectrometer, in ethanol. Nuclear magnetic resonance spectra were determined on either a Varian A-60A spectrometer or a Varian T-60, using carbon tetrachloride or deuterioacetone as solvents and tetramethylsilane as the internal standard. Mass spectra were obtained from an Atlas CH4 or an AEI MS902 mass spectrometer; the ionizing energy was 70 eV. The MS902 was used for exact-mass measurements at high resolution.

Gas chromatographic studies were performed on a Hewlett-Packard 5750 research chromatograph with a thermal conductivity detector. The column used was 3.5 ft × 0.25 in., 5% Silicon Oil DC 550 on 60–80 Chromosorb W.

Elemental analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind.

The Pyrolysis Unit.—The pyrolysis unit utilizes an internal heating probe and thermocouple. The pyrolysis zone was made from 24-mm Vicor tubing, with Pyrex tubing used in the remainder of the unit. The heating and thermocouple probe was made from two 5-mm double-bore ceramic rods sealed wit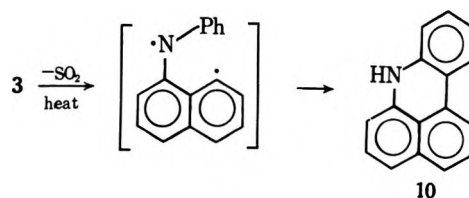h epoxy cement into a ₮ 24/40 inner joint. One rod houses the 16-gauge copper electrical leads, and the other, the 20-gauge Chromel-Alumel thermocouple. The heating element is a Chromel-wire coil, stretched between the two copper leads. The coil was made from 120 cm of 20 gauge wire and is 11 mm in diameter and 80 mm in length. The thermocouple head is centered within the heating coil. The pyrolysis zone is insulated from the surrounding environment with glass wool packing. The remainder of the unit is wrapped in a heating tape consisting of asbestos tape interwoven with Chromel wire and controlled with variacs. The tape consists of two sections, one controlling the sublimation chamber and the other the area leading to the pyrolysis zone. This latter tape is necessary in order to eliminate condensation of products along the walls. The unit is provided with a side arm which is used to introduce trapping agents.

The nitrogen-gas flow is controlled by a flow meter, and the nitrogen is dried (CaCl₂) before entering the sublimation chamber. The hot gases from the pyrolysis zone are condensed by an air trap followed by a series of liquid nitrogen traps. The vacuum line is connected to these traps and the pressure is measured with a mercury manometer and McLeod gauge.

Pyrolysis Procedure.—The starting material is placed into the sublimation chamber and the entire system is flushed with nitrogen. The vacuum is applied and the pressure is regulated with the nitrogen flow meter. The heating tapes are connected and the variacs are set at their specific voltages. The temperature within the pyrolysis zone is observed with a pyrometer, and the pyrolysis is started as soon as a constant temperature is achieved, by turning on the variac controlling the sublimation chamber. This tape is heated slowly, and pyrolysis, on the average, takes 1–1.5 hr for a 0.5-g sample.

(9) W. D. Crow and C. Wentrup, *Tetrahedron Lett.*, 5569 (1968).

(10) C. Wentrup and W. D. Crow, *Tetrahedron*, **27**, 361 (1971).

(11) C. Wentrup and W. D. Crow, *ibid.*, **26**, 3965 (1970).

(12) C. W. Moore and J. F. Thorpe, *J. Chem. Soc.*, 165 (1908).

(13) Z. Arnold, *Collect. Czech. Chem. Commun.*, **30**, 2783 (1965).

2H-Naphth[1,8-cd]isothiazole 1,1-Dioxide (2).—In the synthesis of **2**, 15.0 g (0.067 mol) of 1-amino-8-naphthalenesulfonic acid (J. T. Baker) was added to 58.4 g (0.38 mol) of POCl₃, and the solution was refluxed for 3 hr. The excess POCl₃ was vacuum distilled, and the residue was added to 350 g of ice. After this was allowed to stand at room temperature for 3 hr, the solid was filtered and dissolved in benzene. Recrystallization gave 4.3 g (31.3%) of pale yellow needles. Vacuum sublimation provided further purification and gave a white solid: mp 176–177° (lit.[14] mp 177–178°); ir (CH₂Cl₂) 3300, 1600, 1495, 1460, 1325, 1290, 1162, 1143, 818 cm⁻¹; mass spectrum, molecular ion at m/e 205 (base peak).

Anal. Calcd for C₁₀H₇NO₂S: C, 58.5; H, 3.44; N, 6.83. Found: C, 58.3; H, 3.52; N, 6.85.

2-Phenylnaphth[1,8-cd]isothiazole 1,1-Dioxide (3).—The sodium salt of 1-anilino-8-naphthalenesulfonic acid (J. T. Baker) (118 g, 0.37 mol) was added to 269 g (1.75 mol) of POCl₃ and refluxed for 20 hr. The excess POCl₃ was distilled and the solid was added to ice water; the solid was then filtered. Purification by means of column chromatography (silica gel with benzene) gave 46 g (44.2%) of a pale yellow solid: mp 163–165° (lit.[15] mp 165°); ir (CH₂Cl₂) 1590, 1490, 1375, 1320, 1179, 1160, 1145, 816 cm⁻¹.

Anal. Calcd for C₁₆H₁₁NO₂S: C, 68.1; H, 3.93; N, 4.96. Found: C, 68.3; H, 3.97; N, 4.97.

2-Cyanoindene (5).—The oxime **9** of 2-indenal was prepared by a known procedure, mp 127–129° (lit.[13] mp 128–130°). The oxime was dehydrated by a procedure analogous to the procedure developed by Mowry and Morner for formation of α,β-unsaturated nitriles from aldoximes.[16] Oxime **9** was added to an excess of acetic anhydride. The mixture was heated and the acetic anhydride was distilled under vacuum. Sublimation of the product gave a 58% yield of a white, crystalline solid, mp 40–42° (lit.[11] mp 39–40°). Nmr, ir, uv, and mass spectral data agree with those published for **5**.[11]

Anal. Calcd for C₁₀H₇N: C, 85.1; H, 5.00; N, 9.92. Found: C, 85.2; H, 5.10; N, 9.90.

3-Cyanoindene (6).—3-Cyanoindene (**6**) was prepared from 1-cyano-2-indanone (**8**). Compound **8** was synthesized by the method described by Moore and Thorpe,[12] mp 173–175° dec (lit.[12] mp 172° dec).

The tosylhydrazone of 1-cyano-2-indanone was prepared by adding an equimolar amount of **8** (6.75 g) to 8.0 g of tosylhydrazine in 100 ml of 1% EtOH–HCl. The solution was refluxed for 0.5 hr, the solution was cooled, and water was added. The tosylhydrazone of **8** was filtered and recrystallized from EtOH–H₂O, yield 7.78 g (55.7%), mp 202–203° dec.

The tosylhydrazone was reduced by a procedure reported by Shapiro and Heath.[17] The hydrazone (7.78 g) was dissolved in 100 ml of anhydrous ether and 25 ml of a 2.0 *M* solution of CH₃Li in ether was added slowly with stirring under an inert atmosphere. The slurry was stirred at room temperature for 1 hr, and then 20 ml of water was added. The ether layer was separated, washed with aqueous NaHCO₃, and then dried over Na₂SO₄. A dark oil was obtained upon evaporation of the ether. A small amount of 3-cyanoindene was obtained upon vacuum distillation of the oil; it was sufficient for identification, bp 36–37° (0.2 mm); ir, uv, nmr, and mass spectral data agreed with those published for **6**.[11] High-resolution mass spectrometry showed a molecular ion at m/e 141.0578 (calcd for C₁₀H₇N: 141.0594).

Pyrolysis of 2H-Naphth[1,8-cd]isothiazole 1,1-Dioxide (2).—A temperature of 720–740° was used along with a system pressure of 3.0–3.5 mm of nitrogen. Compound **2** was sublimed into the nitrogen stream and led through the pyrolysis zone, and products were condensed in the traps. A brown oil was isolated after the traps were washed with methylene chloride. Mass spectral, uv, ir, and nmr data indicated that the product was a mixture of 2- and 3-cyanoindene. The oil was purified by vacuum distillation and compared with the authentic samples of **5** and **6**, the syntheses of which are described above. In a typical experiment, a 1.2:1 ratio of **5**:**6** was obtained in a yield of 68% for the two products. No starting material was recovered.

Pyrolysis of 2-Phenylnaphth[1,8-cd]isothiazole 1,1-Dioxide (3).—Compound **3** was pyrolyzed by subliming it into a zone maintained at 680° in a nitrogen stream with a system pressure of 3.0–3.5 mm. The cold traps were washed with acetone, and the wash was concentrated to 10 ml. Water was added (400 ml), and the mixture was cooled and filtered. The product was 7H-benz[k,l]acridine (**10**), mp 123–125° dec (lit.[18] mp 125° dec). The yields for two experiments were 38.6 and 39.1% (42.9 and 43.5% if the unreacted starting material is accounted for in the calculations).

The 2,4,7-trinitro-9-fluorenone derivative had mp 183–185° dec. The spectrum of **10** (70 eV) showed m/e (rel intensity) 217 (100), 216 (37), 190 (4), 189 (6).

Registry No.—**2**, 603-72-5; **3**, 20027-18-3; **5**, 29005-25-2; **6**, 29872-81-9; **8** tosylhydrazone, 34414-22-7; **10** 2,4,7-trinitro-9-fluorenone derivative, 34414-23-8.

(14) F. Dannerth, *J. Amer. Chem. Soc.*, **29**, 1319 (1907).

(15) W. M. Cumming and G. D. Muir, *J. Roy. Tech. Coll.*, **3**, 562 (1936); *Chem. Abstr.*, **30**, 4491 (1936).

(16) D. T. Mowry and R. R. Morner, *J. Amer. Chem. Soc.*, **69**, 1831 (1947).

(17) R. H. Shapiro and M. J. Heath, *ibid.*, **89**, 5734 (1967).

(18) H. Sieper, *Chem. Ber.*, **100**, 1646 (1967).

Heterocyclic Ring-Closure Reactions. IV.[1] The Reaction of S,S'-Dialkyl Dithiooxaldiimidates with Thiocyanic Acid[2]

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Reaction of S,S'-dimethyl dithiooxaldiimidate (1a) with thiocyanic acid gives the 1:1 addition product, 4-amino-2-thioimidazole-2,5-dione 5-(dimethyl mercaptole), as determined by an X-ray crystallographic study. An intramolecular reaction mechanism is proposed for migration of the S-methyl substituent. A similar product is obtained with S,S'-dibenzyl dithiooxaldiimidate. S,S'-Diphenyl dithiooxaldiimidate does not yield a similar product.

We have investigated the reaction of S,S'-disubstituted dithiooxaldiimidates (1) with thiocyanic acid[3] as part of our study of heterocyclic ring-closure reactions. There appeared to be a variety of reaction modes open to these reactants, leading to both five- and six-membered ring systems.

When S,S'-dimethyl dithiooxaldiimidate (1a) was treated with 1 mol of thiocyanic acid or ammonium thiocyanate, the only isolated product was shown by elemental analysis and mass spectrometry to be a 1:1 adduct, disclosed by an X-ray crystallographic study (see below) to be 4-amino-2-thioimidazole-2,5-dione 5-(dimethyl mercaptole) (2a). This product did not provide spectral data in complete agreement with any of the possible products resulting from simple addition reactions.[4] Interpretation of the apparently contradictory spectral data was hampered by lack of appropriate model compounds. The nmr spectrum in deuterated DMSO showed three proton peaks in the ratio of 1:2:6 at δ 11.5, 8.83, and 1.95, respectively, thereby indicating that the two SMe groups are equivalent. The signal integrating for one proton at δ 11.5 is assigned to an NH rather than an SH (δ 1.5–3.5) proton, thereby indicating that the thioamide form of 2a exists in solution as well as in the crystal. The high resolution mass spectrum at m/e 47 showed the presence of both HNS and CH$_3$S ions, but studies at m/e 46 do not show the presence of SN$^+$ ion. There was no evidence for elimination of SH from the adduct. It appeared that a somewhat more involved reaction had occurred, so we turned to the X-ray crystallographic study to elucidate the structure of this substance. It was found to be 4-amino-2-thioimidazole-

2,5-dione 5-(dimethyl mercaptole) (2a), obtained apparently by migration of an alkylmercapto group[5] (Scheme I).

(1) Paper III: S. C. Mutha and R. Ketcham, *J. Org. Chem.*, **34**, 3661 (1969).

(2) Supported, in part, by Grant MH 08787, from the U. S. Public Health Service.

(3) G. M. Varshal and M. M. Senyavin, *Zh. Anal. Khim.*, **17**, 903 (1962).

(4) Addition of the NH substituents of 1a to the nitrile group of HSCN would give i, which could account for the equivalence of the SMe groups in the nmr. However, this structure should not be stable and does not agree with the mass spectrum (no loss of SH). The imidate might act as a heterodiene and the thiocyanate as a dienophile, in which case ii or iii or tautomers thereof would be obtained. However, among other objections, neither of these products have equivalent S-methyl substituents.

SCHEME I

The ir spectra of 2a shows a strong doublet at 1670 and 1640 cm^{-1} which can be attributed to C=S and C=N, and the marked enhancement in the uv spectrum from 1a [λ$_{max}$ 262 nm (ε 5200)] to 2a [λ$_{max}$ 292 nm (ε 33,100)] is in agreement with the extended chromophore which contains a C=S bond.

In order to investigate the possibility that the SR group might rearrange by an addition–elimination process, we carried out the reaction of the dimethyl diimidate 1a in the presence of benzyl mercaptan and of the dibenzyl diimidate 1b in the presence of methyl mercaptan. In neither case was a cross product obtained, indicating the rearrangement to be intramolecular as suggested in the mechanistic scheme. It is interesting to note that at no stage has the normally more nucleophilic sulfur atom of the thiocyanate acted as a nucleophile.[7]

(5) In response to a suggestion that we were not dealing with 1a,[6] but with an isomer, N=CC(SMe)$_2$NH$_2$, we reinvestigated its ir spectrum and found no evidence for either a nitrile or an amino function. A compound isomeric with 1a would not be expected to show any uv absorption. The fact that the diimidate shows a uv absorption, λ$_{max}$ 262 nm (ε 5200), further supports structure 1a.

(6) (a) H. M. Woodburn and C. E. Sroog, *J. Org. Chem.*, **17**, 371 (1952); (b) A. R. Martin and R. Ketcham, *ibid.*, **31**, 3612 (1966).

(7) In displacement reactions at saturated carbon the S atom is normally the nucleophile, whereas in displacement reactions in carboxylic acid derivatives the nitrogen atom is the nucleophile. See, e.g., M. Bögemann, S. Petersen, O. E. Schultz, and H. Soll, "Methoden der Organischen Chemie (Houben–Weyl)," Vol. 9, Georg Thieme Verlag, Stuttgart, 1955. p 773.

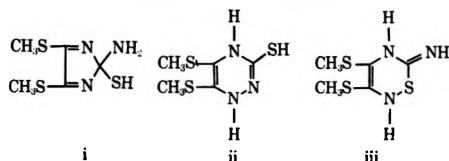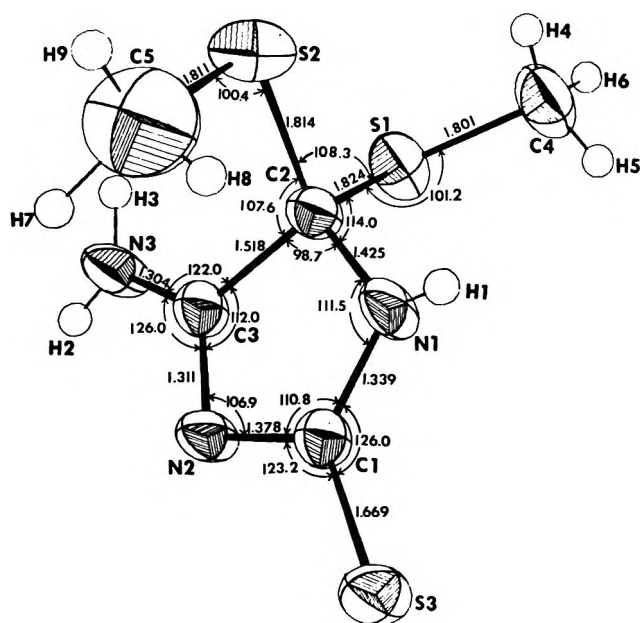Figure 1.—The atom numbering system used in the crystallographic part of the paper and the bond distances and bond angles between nonhydrogen atoms are shown. The angles S-2–C-2–N-1 and C-3–C-2–S-1 could not be conveniently illustrated; they are 114.0 and 107.6°, respectively.

As further representative reactants we selected S,S'-dibenzyl (**1b**) and S,S'-diphenyl dithiooxaldiimidates (**1c**). The former provided an analogous product using either ammonium thiocyanate or the free acid. With thiocyanic acid, **1c** gave a deeply colored substance of apparently different structure which has so far resisted purification. With ammonium thiocyanate, **1c** gave only diphenyl disulfide,[8,9] even when the reaction was carried out under nitrogen.

X-Ray Crystallographic Study.—The crystal structure determination proves that the molecule under investigation has a five-membered ring composed of three carbon and two nitrogen atoms. The two –SCH$_3$ groups are definitely bonded to the same ring carbon atom. The second ring carbon atom has a sulfur atom side chain while the third ring carbon atom has a –NH$_2$ side chain.

An Ortep[10] drawing of the molecule is shown in Figure 1. This figure also gives the atom numbering system used[11] and the interatomic distances and angles for all atoms except hydrogen. The estimated standard deviations are 0.004 Å for the distances, 0.3° for the angles between heavy atoms, and 3° for angles involving the hydrogen atom.

The stereoscopic view of the molecule, shown in Figure 2, illustrates the spatial arrangement of the atoms. In the crystal, each molecule forms four hydrogen bonds. Two of them, S-3–N-1, are to the same molecule and are related by a center of symmetry; the other two hydrogen bonds occur between the N-2

and N-3 atoms.[12] These bonds are related by a c glide plane and involve two other molecules. Each molecule is thus hydrogen bonded to three of its neighbors. The hydrogen bond distances and angles are listed in Table I. The primes differentiate the sym-

TABLE I

HYDROGEN BOND DISTANCES AND ANGLES

	Heavy atom distance, Å	Angle, deg
N-1–H-1---S'-3	3.326	175
S-3---H'-1-N'-1	3.326	175
N-3–H-3---N''-2	2.860	161
N-2---H'''-3-N'''-3	2.860	161

metry-related molecules which are hydrogen bonded to the unprimed molecule.

The C-1–S-3 bond distance of 1.67 Å falls between the single bond value of 1.81 Å and the double bond value of 1.61 Å.[13,14] This is in agreement with recent results[15,16] obtained on molecules which also contain the group >NCSN<. The C-2–N-1 and C-2–C-3 bond lengths rule out delocalized aromatic bonds for the ring system. The bond lengths and angles given in Figure 1 clearly indicate that structures such as **3a** and **3b** are important contributors to the resonance hybrid.
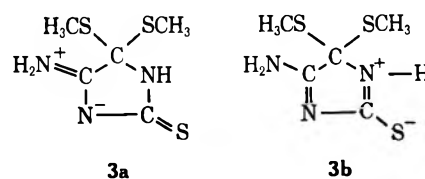
Experimental Section

Melting points are corrected and were measured on a Thomas-Hoover melting point apparatus. Ir spectra were taken on a Beckman IR 8 or a Perkin Elmer 457 spectrophotometer. Uv spectra were taken in 95% or 50% EtOH using a Cary Model 11 spectrophotometer. Nmr spectra were taken on a Varian A-60A or JEOLCO 100-H using TMS as an internal standard. Mass spectra were measured with an AEI MS9 high resolution mass spectrometer. Apparent pK_a values were determined in 50% EtOH using a Metrohm Herisau Potentiograph E 336. Elemental analyses were carried out by the Microanalytical Laboratory of the University of California at Berkeley, Calif.

S,S'-Disubstituted dithiooxaldiimidates were prepared by previously described procedures.[6]

4-Amino-2-thioimidazole-2,5-dione 5-(Dimethyl mercaptole) (2a). A. Ammonium Thiocyanate.—To 5 g (0.034 mol) of S,S'-dimethyl dithiooxaldiimidate (**1a**) dissolved in 30 ml of acetone, by warming, was added 2.6 g (0.034 mol) of ammonium thiocyanate. A blue color developed which disappeared on shaking. After 2 hr white crystals of the adduct precipitated

(8) "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1965, p 1279.

(9) The Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia, Pa., Spectrum No. 7389.

(10) C. K. Johnson, Oak Ridge National Laboratory, Report No. 3794.

(11) The numbering in the X-ray crystallographic portion of the paper conforms to the practice of such studies in giving each type of atom in the molecule sequential numbers. They are not related to the numbers in the system of chemical nomenclature.

(12) Tables of the final positional and thermal parameters and calculated and observed *F* values and a figure showing the projection of the structure on the (100) plane, which illustrates the intermolecular hydrogen bonds, 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-72-2155. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(13) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960.

(14) B. Krebs and P. F. Koenig, *Acta Crystallogr.*, **25**, 1022 (1965).

(15) G. B. Ansell, D. M. Forkey, and D. W. Moore, *Chem. Commun.*, 56 (1970).

(16) N. W. Isaacs and C. H. L. Kennard, *ibid.*, 631 (1970).
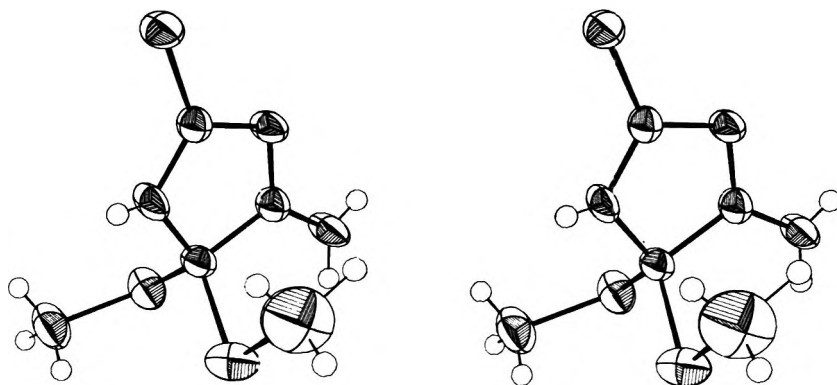
Figure 2.—A stereoscopic view of the molecule, with 50% probability ellipsoids.

and the maximum yield was obtained in about 3 hr. The product was collected and washed with acetone to give 2.5 g (36%) of white crystals, mp 136–145° dec. It was crystallized from ethanol, mp 165° dec.

The pK_a's of the compound were determined by titration in 50% aqueous alcohol, first with 1 N HCl and then with 1 N NaOH. The pK_a's were found to be 5.9 and 8.0. The uv measurements at different pH's showed two isosbestic points, thus confirming the pK_a studies: uv$_{max}$ 292 nm (ϵ 33,100); acidic λ_{max} 242 nm (ϵ 19,900), λ_{max} 296 (21,700); alkaline λ_{max} 290 nm (ϵ 20,900); nmr (CDCl$_3$) δ 1.67; nmr (DMSO-d_6) δ 11.5 (1 H), 8.83 (2 H), 1.95 (6 H).

Anal. Calcd for C$_5$H$_9$N$_3$S$_1$: C, 28.97; H, 4.37; N, 20.26; S, 46.40. Found: C, 28.97; H, 4.25; N, 20.09; S, 46.20.

To 200 mg (1.35 mmol) of S,S'-dimethyl dithiooxaldiimidate dissolved in 10 ml of acetone was added 100 mg of ammonium thiocyanate and 400 mg of benzyl mercaptan. After 2.5 hr white crystals, mp 138° dec, precipitated, which were crystallized from EtOH, mp 165° dec. Its ir spectrum was identical with that of the product obtained from ammonium thiocyanate and the dimethyl diimidate 1a alone.

**B. Thiocyanic Acid.**—Thiocyanic acid was generated from ammonium thiocyanate using a cation exchange resin by the procedure of Varshal and Senyavin.[3] The resin was first washed with 5 N HCl, and then with water. Ammonium thiocyanate (15 g) was dissolved in 300 ml of acetone and passed through the resin on a column. The column was further eluted with 200 ml of acetone. A total of 500 ml of the thiocyanic acid solution in acetone (ca. 0.1 M) was collected and stored in a refrigerator.

Dimethyl diimidate (1a, 2.5 g, 0.017 mol) was dissolved in 170 ml of acetone containing 0.017 mol of thiocyanic acid in acetone and allowed to stand at room temperature. In 2 hr white crystals separated in 40% yield which were identical with those obtained with ammonium thiocyanate. No addition product was isolated with potassium thiocyanate.

4-Amino-2-thioimidazole-2,5-dione 5-(Dibenzyl mercaptole) (2b).—Dibenzyl dithiooxaldiimidate (1b, 4 g, 0.013 mol) and 1 g (0.013 mol) of ammonium thiocyanate in acetone were allowed to stand for 17 hr at 25° and then poured over ice. The product was collected and crystallized from ethanol to give 2 g (40%) of white crystals, mp 164–165°.

Anal. Calcd for C$_{17}$H$_{17}$N$_3$S$_3$: C, 56.08; H, 4.77; N, 11.68; S, 26.76. Found: C, 56.23; H, 4.77; N, 11.49; S, 26.92.

When the above reaction was repeated using a solution of thiocyanic acid in acetone and dibenzyl diimidate 1b, an identical product was isolated in 40% yield.

To 400 mg (1.35 mmol) of dibenzyl diimidate 1b in 20 ml of acetone were added 100 mg of ammonium thiocyanate and 200 mg (1.35 mmol) of methyl mercaptan. The reaction mixture was allowed to stand for 17 hr at 25° and poured over ice. The product was collected and crystallized from ethanol. White crystals, mp 164–165°, with an ir spectrum identical with that of 2b, were obtained.

Reaction of S,S'-Diphenyl Dithiooxaldiimidate. A. With Ammonium Thiocyanate.—To 5.44 g (0.02 mol) of diphenyl diimidate 1c in 30 ml of acetone was added 1.52 g (0.02 mol) of ammonium thiocyanate. The reaction mixture turned dark red in 1 hr at 25°. The mixture was poured over ice, and the precipitate was collected by filtration and recrystallized from hexane, mp 60–62°.[8] Its ir spectrum was identical with that of diphenyl disulfide.[9]

When the above reaction was carried out at 5 or 25° under N$_2$ only diphenyl disulfide was identified besides starting material, as evidenced from tlc, melting point, and ir spectra.

B. With Thiocyanic Acid.—Diphenyl diimidate 1c (500 mg, 1.85 mmol) was added to 1.85 mmol of thiocyanic acid in 18.5 ml of acetone. The reaction mixture was kept at 15° for 1 hr and poured on ice. The brown precipitate was collected by filtration, mp 135° dec. It showed an ir spectrum different from that of the starting material. It was insoluble in petroleum ether, ether, and benzene and was soluble in acetone, chloroform, ethanol, and tetrahydrofuran. All attempts to purify this material, including column chromatography, have been unsuccessful.

X-Ray Determination of Structure.—Crystals suitable for X-ray diffraction analysis were crystallized from hot ethyl alcohol. The density of the crystals was measured by suspension in a mixture of xylene and ethylene bromide and found to be 1.429 g cm^{-3}. There are eight molecules in the unit cell, each occupying a general position. Weissenberg and precession photographs established the space group as *Pccn*. The lattice constants were obtained from high angle θ–2θ scans with the diffractometer set at a take-off angle of 1°. The crystal data are summarized in Table II.

TABLE II

CRYSTAL DATA

C$_5$N$_3$S$_3$H$_9$	Fw 207.34
Orthorhombic	Space group *Pccn*
$a = 11.250 (5)$ Å	$Z = 8$
$b = 19.90 (1)$ Å	$F(000) = 864$
$c = 8.734 (4)$ Å	$\rho_m = 1.429$ g cm^{-3}
λCu K$\alpha_1 = 1.54051$ Å	$\rho_c = 1.425$ g cm^{-3}

Intensity data were obtained from a small crystal, about 0.1 mm on a side, mounted on a computer-controlled four-circle diffractometer equipped with a full-circle goniostat. The Ni-filtered Cu radiation was detected by a scintillation counter coupled with a single-channel pulse height analyzer. Data were recorded for angles up to $2\theta = 125°$ using the θ–2θ scanning technique. The scan rate was 1°/min (in 2θ). Background was measured 0.5° on each side of the scan limits. Each background was counted for 20 sec. A total of 3804 reflections were measured, of which 1540 were independent; 42 of these were measured as zero.

Two reflections designated as standards were measured every 48 reflections. The intensity of these two standard reflections decreased with irradiation time, and these data were used to correct the observed intensities in a step-wise fashion.

A full-matrix least-squares program[17] was used to minimize the function $\Sigma w(\Delta F)^2/\Sigma wF_o^2$; $\Delta F = |F_o| - |F_c|$, where F_o and F_c are the observed and calculated structure factors, and w is a weighting factor taken equal to $1/\sigma^2(F)$. The value of $\sigma(F)$ was calculated by the expression $\sigma(F) = F_o - [F_o^2 - \sigma(F_o^2)]^{1/2}$ when $I > \sigma(I)$; w was set equal to zero when $I \leq \sigma(I)$.

Normalized structure factors $|E|$ were calculated by Wilson's

(17) The least-squares program was furnished by Dr. A. Zalkin, Lawrence Radiation Laboratory, Berkeley, Calif. 94720.

method by means of a computer program written by Maddox and Maddox.[18] These values were used to calculate phases by the symbolic addition procedure.[19] Origin determining signs were chosen for (058), (173), and (871) as all positive. Their E values are 3.38, 3.20, and 2.66, respectively. The 16 possible combinations of signs of four additional reflections were used to calculate probable phases for the remaining 110 reflections whose $|E|$ values were equal to or greater than 1.50. One combination of signs was clearly superior to the others. The four reflections chosen for iteration, their E values and correct phases are as follows (51 phases are plus and 66 are negative).

3	12	1	+2.72
3	2	1	−2.25
1	3	3	−2.46
1	6	1	−2.33

(18) H. S. Maddox and M. L. Maddox, private communication, 1965.

(19) J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849 (1966).

An E Fourier synthesis revealed the position of the heavy atoms. The positional parameters and an isotropic temperature factor for each of the 11 atoms were least-squares refined and resulted in an R index of 0.16, where R is defined as $\Sigma||F_o| - |F_c||/\Sigma|F_o|$. With anisotropic temperature factors, R was reduced to 0.060. A Fourier difference calculation revealed the approximate position of the nine hydrogen atoms. Three additional cycles of least-squares refinement, with anisotropic temperature factors for the heavy atoms, and isotropic temperature factors for the hydrogen atoms, gave a final R index of 0.046.[12]

1-Acyl-2,4,5-triphenyl-3-imidazolines[1]

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Condensation of hydrobenzamide with acid chlorides in the presence of triethylamine is shown to give 1-acyl-2,4,5-triphenyl-3-imidazolines. Synthesis of the isomeric 1-acyl-2-imidazolines and the hydrolysis of 1-acyl-2- and -3-imidazolines is also discussed.

A recent publication from these laboratories[2] reported the isolation of a compound postulated to be 1-azidoacetyl-2,4,5-triphenyl-2-imidazoline (1). We now wish to report further work which indicates that this compound is instead a mixture of *cis-* and *trans*-azidoacetyl-2,4,5-triphenyl-3-imidazoline (2a). We have also expanded the cyclization to other acid chlorides and trifluoroacetic anhydride.

The imidazoline 2a was produced by the reaction of hydrobenzamide (3) and azidoacetyl chloride in the

presence of triethylamine. Although other imines have been treated with acid chlorides or ketenes to give cycloaddition products,[3-5] there seem to have been no

(1) Abstracted from the Ph.D. Thesis of O. Reed Tarwater, Purdue University, Aug 1970.

(2) J. N. Wells and R. E. Lee, *J. Org. Chem.*, **34**, 1477 (1969).

(3) J. C. Sheehan and J. J. Ryan, *J. Amer. Chem. Soc.*, **73**, 1204 (1951).

(4) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967).

(5) J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Gott, and V. A. Hoyle, Jr., *J. Org. Chem.*, **36**, 2211 (1971).

reports of related electrophilic substitutions of hydrobenzamide in the literature. It was reported that the order of addition of the reactants played an important role in the course of this reaction. When 3 and triethylamine were combined and a solution of azidoacetyl chloride was added dropwise, 3-azido-4-phenyl-2-azetidinone was produced. If the order of addition was reversed, *i.e.*, if 3 and azidoacetyl chloride were combined and triethylamine was added, the imidazoline was obtained. Although 3 cyclizes on heating to 2-*cis*-4,5-triphenyl-2-imidazoline (4),[6] no reaction was observed with 3 and triethylamine in methylene chloride solution in the absence of acid chloride.

The two geometrical isomers of 1 have been prepared by an alternate method. 2-*cis*-4,5-Triphenyl-2-imidazoline (4) with acetyl chloride and trichloroacetyl chloride gave the corresponding 1-acyl-2-*cis*-4,5-triphenyl-2-imidazolines (5). Acylation with benzoyl chloride gave a compound whose physical data agreed with those of authentic 1-benzoyl-2-*cis*-4,5-triphenyl-2-imidazoline (5b).[7] Reaction with azidoacetyl chloride gave 1-azidoacetyl-2-*cis*-4,5-triphenyl-2-imidazoline (5d).
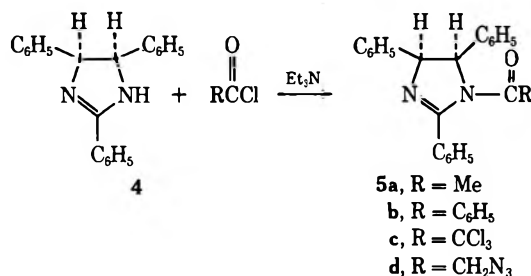
Conversion of 4 to 2-*trans*-4,5-triphenyl-2-imidazoline (6) occurs on heating to 170° in the presence of metallic

(6) R. J. Ferm and J. L. Riebsomer, *Chem. Rev.*, **54**, 593 (1954).

(7) A. Claus and L. Scherbel, *Ber.*, **18**, 3077 (1885).

sodium.[8] By this method **6** was prepared and treated with azidoacetyl chloride to give 1-azidoacetyl-2-*trans*-4,5-triphenyl-2-imidazoline (**7a**). Reaction of **6** with trichloroacetyl chloride gave 1-trichloroacetyl-2-*trans*-4,5-triphenyl-2-imidazoline (**7b**).
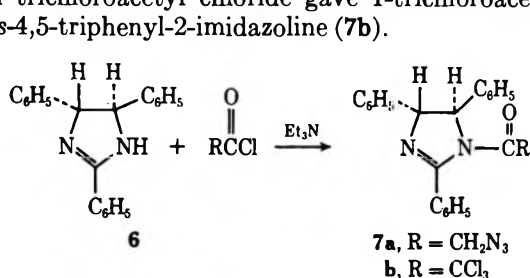
The imidazoline **2a** had a melting point of 218–219°.[2] Compounds **5d** and **7a** had melting points of 169–171 and 120.5–121.5°, respectively.

The hydrolysis of acylated 2-imidazolines has been shown to occur with cleavage at the 1,2 bond to give the corresponding diamide.[5] Hydrolysis of **5d** and **7a** produced *erythro*- and *threo*-N-benzoyl-N'-azidoacetyl-1,2-diphenylethylenediamine, respectively (8). There-

8 (erythro, threo)
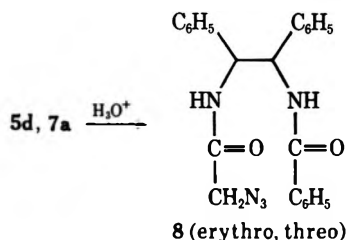
fore, both **5d** and **7a** are confirmed to be the 2-imidazolines.

Hydrolysis of acylated 3-imidazolines has been shown[9] to occur as follows.

Hydrolysis of **2a** gave two identifiable products. An aldehyde was isolated which was shown by comparison of ir spectra to be benzaldehyde (**9**, R⁴ = C₆H₅). An amino ketone was isolated whose mass spectrum was consistent with **10** (R¹ = R² = C₆H₅); the ir spectrum
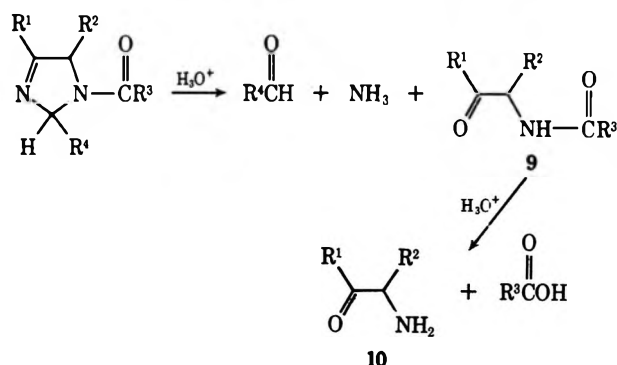
was identical with that of authentic **10** (R¹ = R² = C₆H₅).[10] Treatment of **2c** with potassium hydroxide in ethanol removed the trifluoroacetyl group. Migration of the double bond then gave the more stable amidine system, 2-*trans*-4,5-triphenyl- 2- imidazoline (**6**).

Several attempts were made to prepare 2,4,5-triphenyl-3-imidazoline (**11**) so that it could be acylated and provide an independent synthesis of the 1-acyl-3-imidazolines. α-Aminodeoxybenzoin[10] was treated

with benzaldehyde in the presence of ammonia. The only product isolated was tetraphenylpyrazine (**12**) formed by reaction of 2 mol of **10**.[11,12]
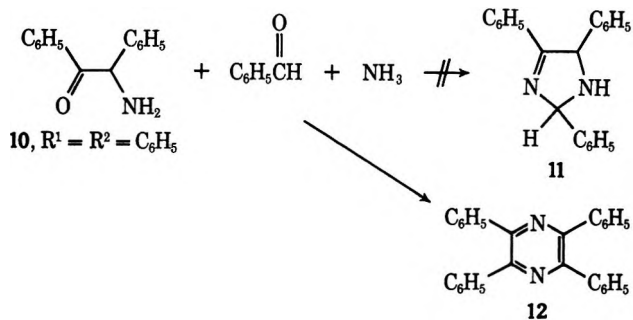
Spectral evidence strongly supports the 3-imidazoline assignment. The infrared spectra of the proposed 3-imidazolines (**2a–c**) showed a strong band between 5.95 and 6.02 μ assigned to a tertiary amide,[13] and a band of moderate intensity between 6.12 and 6.18 μ indicative of a conjugated C=N linkage.[14,15] These assignments are reinforced by the presence of similar bands in authentic 2-imidazolines (**4, 6**) and the C–N absorption at 6.16 μ in hydrobenzamide.

The ultraviolet spectrum of **2c** was measured in neutral and acidic solution. A solution in ethanol–hexane (8:2) exhibited λ_{max} 248 nm. This value compares favorably with those of other compounds containing the ArC=NR chromophore.[16] Addition of H_2SO_4 produces a bathochromic displacement of absorption to 268 nm. Protonation of the azomethine nitrogen is known to give similar shifts.[16,17] Similarly, the ultraviolet spectra of *cis*- and *trans*-2,4,5-triphenyl-2-imidazolines show a peak near 220 nm which is shifted to 245 nm upon acidification. A compound having the 4-imidazoline structure should show absorption characteristics of enamines, in which case a hypsochromic rather than bathochromic shift would be observed upon acidification.[18]

Confirmation of the structural assignment made from degradation studies and uv and ir spectra was sought from nmr studies of the 2- and 3-imidazolines. Both types show a two-proton multiplet near δ 7.75 which we assign to phenyl protons ortho to the point of attachment to the azine group. In the 2-imidazolines the chemical shift of this multiplet changes with the nature of the acyl groups; the most significant changes occur when the acyl group is trichloroacetyl (δ 7.91) or benzoyl (δ 7.68). In the 3-imidazolines (**2a–c**) this resonance is insensitive to acyl substitution, suggesting that the carbon bearing the phenyl group is not attached to the acyl-substituted nitrogen.

The 100-MHz spectrum of 1-azidoacetyl-2,4,5-triphenyl-3-imidazoline (**2a**) indicates the presence of cis and trans isomers. Two methylene signals of unequal

(8) F. R. Japp and J. Moir, *J. Chem. Soc.*, **77**, 608 (1900).

(9) F. Asinger, M. Thiel, and R. Sowada, *Monatsh. Chem.*, **90**, 402 (1959).

(10) R. Pschorr and F. Bruggeman, *Ber.*, **35**, 2740 (1902).

(11) E. Jassman and H. Schultz, *Pharmazie*, **18**, 461 (1963).

(12) G. Kirchner, *Justus Liebigs Ann. Chem.*, **625**, 98 (1959).

(13) A. D. Cross and R. A. Jones, "An Introduction to Practical Infra-red Spectroscopy," 3rd ed, Plenum Press, New York, N. Y., 1969, p 89.

(14) J. Fabian, V. Delaroff, and M. Legrand, *Bull. Soc. Chim. Fr.*, 287 (1956).

(15) J. Fabian, M. Legrand, and P. Poirier, *ibid.*, 1499 (1956).

(16) M. A. El-Bayoumi, M. El-Asser, and F. Abdel-Halim, *J. Amer. Chem. Soc.*, **93**, 586 (1971).

(17) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Macmillan, New York, N. Y., 1964, p 39.

(18) J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *J. Amer. Chem. Soc.*, **78**, 430 (1956).

intensity are noted for the azidoacetyl group, a singlet at δ 3.35 and an apparent doublet (separation 1 Hz) at δ 3.45, which corresponds to the inner lines of an AB quartet produced from nearly equivalent nuclei. The ratio of integrals of the "doublet" to the singlet is 3:4. The resonances of the C-2 and C-5 protons appear as two pairs of doublets located near δ 7.0 and 6.5, respectively. The ratio of integrals of the weaker pair of doublets (δ 6.32 and 7.15) to the stronger pair is the same as calculated for the azidoacetyl methylene signals. The resonances of the ring methine protons in **2b** and **2c** show a pattern similar to that described above in that a pair of doublets is located near δ 6.5. However, the multiplicity of the downfield signals is obscured by overlapping phenyl absorption. Chromatographic analysis of **2a–c** failed to show two isomers. The compounds were homogeneous by tlc. Glc of **2c** yielded one peak, while data for **2a,b** were equivocal. If the samples are homogeneous the nmr data are consistent with either a system undergoing slow (on the nmr time scale) inversion at the acylated nitrogen or one in which rotation about the nitrogen–carbonyl bond is restricted. It is noteworthy that for aziridines, in which nitrogen is substituted with acyl groups or bulky substituents, nonequivalence due to slow inversion is seen only at low temperatures.[19] This behavior need not be shown by **2a–c**, although they are acylated and molecular models indicate significant steric interaction among the 3- and 5-phenyl groups and the acyl group. The same steric interaction inhibits free rotation of the acyl group. Our data cannot exclude either the possibility of slow inversion or hindered rotation.

The coupling of 3.5–4 Hz between methine protons on C-2 and C-5 in **2a–c** indicates significant long-range interaction between these protons. Homoallylic coupling of this magnitude has been observed in other systems.[20] Recent studies[21] have shown long-range coupling (J = 0.3 Hz) between the same protons in imidazolidines.

Direct evidence against a 4-imidazoline structure was obtained from a deuterium-exchange experiment. The nmr spectrum (60 Hz) of **2a** was unchanged after shaking the sample with D₂O.

Experimental Section[22]

Acylation of 2-*cis*-4,5-Triphenyl-2-imidazoline (4) and 2-*trans*-4,5-Triphenyl-2-imidazoline (6).—2-*cis*-4,5-Triphenyl-2-imidazoline (4) or 2-*trans*-4,5-triphenyl-2-imidazoline (6) (5.0 g, 16.7 mmol) and triethylamine (1.7 g, 16.7 mmol) were combined in 150 ml of dry CH₂Cl₂ and stirred at 0° while 16.7 mmol of the appropriate acid chloride in 50 ml of CH₂Cl₂ was added over

(19) F. A. L. Anet and J. M. Osyany, *J. Amer. Chem. Soc.*, **89**, 352 (1967).

(20) P. Bladon, *Annu. Rev. NMR (Nucl. Magn. Resonance) Spectrosc.*, **2**, 11 (1969).

(21) J. P. Albrand, A. Cogne, D. Gagnaire and J. B. Robert, *Tetrahedron*, **27**, 2453 (1971).

(22) Melting points were determined using a Buchi Capillary Melting Point Apparatus with open capillary tubes and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer 21 or Model 237-B infrared spectrophotometer. Mass spectral data were obtained on a Perkin-Elmer Hitachi RMU-6-A mass spectrometer. A Varian Associates A-60A spectrometer was used at a sweep width of 500 cps using TMS as an internal standard to determine nmr spectra. Gas chromatographic data were obtained from a Beckman GC-5 instrument equipped with a hydrogen flame ionization detector. The column used was 3% OV-1 on Chromosorb G (AW-DMCS), 6 ft × 0.125 in., and helium carrier flow was 75 ml/min. Unless otherwise noted samples were dissolved in CDCl₃ (nmr) or CHCl₃ (ir). The high-resolution nmr spectra were determined on a Varian Associates HA-100 spectrometer. Elemental analysis were determined by Midwest Microlabs, Inc., Indianapolis, Ind. 46226.

1–2 hr. The reaction mixture was allowed to warm to room temperature and refluxed for 4 hr. After cooling to room temperature the reaction mixture was poured into 300 ml of water. The CH₂Cl₂ phase was separated and the aqueous phase was then extracted several times with CHCl₃. The CH₂Cl₂ and CHCl₃ extracts were combined and washed with cold dilute HCl and then with water. The organic extracts were dried and the solvent was removed *in vacuo*. The residue was recrystallized from EtOH.

Acylation of 4 with acetyl chloride gave 4.1 g (75% yield) of 1-acetyl-2-*cis*-4,5-triphenyl-2-imidazoline (5a): mp 153.5–154.5°; nmr δ 7.75 (m, 2, ArC=N), 7.40 (m, 3, Ar), 6.95 (s, 10, Ar), 5.63 (s, 2, C-4 and C-5), 1.85 (s, 3, COCH₃); ir 5.92 (C=O), and 6.15 μ (C=N); mass spectrum *m/e* 340 (M⁺).

Acylation of 4 with benzoyl chloride gave 2.40 g (36% yield) of 1-benzoyl-2-*cis*-4,5-triphenyl-2-imidazoline (5b): mp 181–183° (lit.[8] mp 180°); nmr δ 7.68 (m, 2, ArC=N), 6.67–7.50 (m, 18, Ar), 5.63 (AB quartet, J_{AB} = 8 Hz, 2, C-4 and C-5); ir 6.0 μ (C=O).

Acylation of 4 with trichloroacetyl chloride gave 6.55 g (88.5% yield) of 1-trichloroacetyl-2-*cis*-4,5-triphenyl-2-imidazoline (5c): mp 220–221°; nmr δ 7.91 (m, 1, ArC=N), 7.58 (m, 3, Ar), 7.05 (m, 10, Ar), 5.97 (AB quartet, J_{AB} = 7 Hz, 2, C-4 and C-5); ir 5.88 (C=O) and 6.12 μ (C=N); mass spectrum *m/e* 442 (M⁺).

Acylation of 4 with azidoacetyl chloride gave 4.30 g (68% yield) of 1-azidoacetyl-2-*cis*-4,5-triphenyl-2-imidazoline (5d): mp 169–171°; nmr δ 7.78 (m, 2, ArC=N), 7.51 (m, 3, Ar), 6.98 (s, 10, Ar), 5.67 (s, 2, C-4 and C-5), 3.60 (AB quartet, J_{AB} = 16 Hz, 2, CH₂N₃); ir (KBr) 4.75 (N₃), 5.9 (C=O), and 6.15 μ (C=N); mass spectrum *m/e* 381 (M⁺).

Acylation of 2-*trans*-4,5-triphenyl-2-imidazoline (6) with azidoacetyl chloride gave 6.3 g (98% yield) of 1-azidoacetyl-2-*trans*-4,5-triphenyl-2-imidazoline (7a): mp 120.5–121.5°; nmr δ 7.75 (m, 2, ArC=N), 7.2–7.6 (m, 13, Ar), 5.17 (s, 2, C-4 and C-5), 3.5 (AB quartet, J_{AB} = 17 Hz, 2, CH₂N₃); ir 4.75 (N₃), 5.9 (C=O), and 6.15 μ (C=N); mass spectrum *m/e* 381 (M⁺).

Acylation of 6 with trichloroacetyl chloride gave 6.9 g (92% yield) of 1-trichloroacetyl-2-*trans*-4,5-triphenyl-2-imidazoline (7b): mp 191–192°; nmr δ 7.96 (m, 2, ArC=N), 7.17–7.67 (m, 13, Ar), 5.80 (s, broad, 1, C-5), 5.30 (s, broad, 1, C-4); ir 5.85 (C=O) and 6.12 μ (C=N); mass spectrum *m/e* 442 (M⁺).

Anal. Calcd for C₂₃H₁₇N₂OCl₃: C, 62.25; H, 3.86. Found: C, 62.12; H, 4.10.

Hydrolysis of 1-Azidoacetyl-2-*cis*-4,5-triphenyl-2-imidazoline (5d).—1-Azidoacetyl-2-*cis*-4,5-triphenyl-2-imidazoline (5d) (1.0 g, 2.63 mmol) was dissolved in 80 ml of 95% EtOH, 2 ml of 3 *N* HCl was added, and the reaction mixture was refluxed for 16 hr. The reaction mixture was allowed to cool to room temperature and the white solid was removed by filtration. *erythro-N*-Benzoyl-*N'*-azidoacetyl-1,2-diphenylethylenediamine (8) (0.79 g, 75% yield) was obtained and was recrystallized from EtOH: mp 260–262°; nmr (DMSO-d₆) δ 8.7 (s, broad, 1, NH) 7.0–7.67 (m, 1, Ar and NH), 5.38 (apparent d, separation 4 Hz, C-1 and C-2), 3.43 (apparent d, separation 2 Hz, 2, CH₂N₃); ir 4.75 (N₃) and 6.1 μ (C=O); mass spectrum *m/e* 399 (M⁺), 342 (1), 300 (2), 236 (2), 210 (74), 105 (100), 77 (30).

Anal. Calcd for C₂₃H₂₁N₅O₂: C, 69.16; H, 5.30. Found: C, 69.00; H, 5.54.

Hydrolysis of 1-Azidoacetyl-2-*trans*-4,5-triphenyl-2-imidazoline (7a).—1-Azidoacetyl-2-*trans*-4,5-triphenyl-2-imidazoline (7a) (0.75 g, 1.97 mmol) was dissolved in 75 ml of 95% EtOH, 6 ml of 3 *N* HCl was added, and the mixture was refluxed for 24 hr. Upon cooling in an ice bath 0.45 g (57.5% yield) of *threo-N*-benzoyl-*N'*-azidoacetyl-1,2-diphenylethylenediamine (8) precipitated, which was isolated by filtration and recrystallized from EtOH: mp 234–234.5°; nmr (DMSO-d₆) δ 8.72 (s, broad, 1, NH), 6.8–7.8 (m, 16, Ar and NH), 5.4 (m, 2, C-1 and C-2), 3.75 (apparent d, separation 1 cps, 2, CH₂N₃); ir (KBr) 4.75 (N₃) and 6.11 μ (C=O); mass spectrum *m/e* 399 (M⁺), 342 (1), 300 (2), 236 (2), 210 (74), 105 (100), 77 (30).

Anal. Calcd for C₂₃H₂₁N₅O₂: C, 69.16; H, 5.30. Found: C, 68.93; H, 5.37.

Hydrolysis of 1-Azidoacetyl-2,4,5-triphenyl-3-imidazoline (2a).—1-Azidoacetyl-2,4,5-triphenyl-3-imidazoline (2a) (0.70 g, 1.84 mmol) was combined with 75 ml of 3 *N* HCl and refluxed for 20 hr. The reaction mixture was then allowed to cool to room temperature and extracted with chloroform to remove any nonbasic products. After drying, the chloroform was removed *in vacuo* to give an oil which was shown by ir to be benzaldehyde.

The aqueous phase was made basic with aqueous NaOH and then extracted with chloroform. Removal of the dried chloroform *in vacuo* gave a yellow oil, ir (neat) 5.95 μ (aryl ketone). This ir was identical with that of authentic α-aminodeoxybenzoin.[10] The hydrochloride was formed and recrystallized from EtOH-Et₂O: mp 240–244° (lit.[7] mp 244°); mass spectrum (as the free base) *m/e* 211 (M⁺, 3), 210 (7), 106 (11), 105 (100), 77 (44).

1-Trichloroacetyl-2,4,5-triphenyl-3-imidazoline (2b).—Hydrobenzamide (5.5 g, 18.5 mmol) and 1.87 g (18.5 mmol) of triethylamine were combined in 200 ml of CH₂Cl₂ at 0° and stirred while 3.4 g (18.5 mmol) of trichloroacetyl chloride dissolved in 50 ml of CH₂Cl₂ was added over a 2-hr period. The reaction mixture was allowed to warm to room temperature and stirred for 12 hr. The reaction mixture was treated with 100 ml of 1.5 N HCl, the CH₂Cl₂ phase was separated, and the aqueous phase was extracted several times with chloroform. The CH₂Cl₂ and CHCl₃ extracts were combined and washed twice with H₂O. After drying, the organic solvents were removed *in vacuo* to give a thick yellow oil which crystallized upon washing with Et₂O to give 1.77 g (21.6% yield) of white solid. Recrystallization from ethanol gave a solid: mp 207–209° dec; nmr δ 7.75 (m, 2, ArC=N), 7.16–7.55 (m, 14, Ar and C-2), 6.75 (d, *J* = 3.5 Hz, 1, C-5); ir 5.97 (C=O) and 6.12 μ (C=N); mass spectrum *m/e* 442 (M⁺). The nmr signal due to the C-5 proton was weak, and the presence of a small amount of a second isomer could not be ruled out on the basis of nmr integration alone. Glc analysis of 2b (column 228°, inlet 265°) showed two peaks, retention time 17.5 and 23.5 min. The major component always eluted first, but the ratio of minor to major peak varied from 0.05 to 0.40.

Anal. Calcd for C₂₃H₁₇OCl₃N₂: C, 62.25; H, 3.86. Found: C, 62.17; H, 4.11.

1-Trifluoroacetyl-2,4,5-triphenyl-3-imidazoline (2c).—Following the foregoing procedure, 18.5 mmol of hydrobenzamide was treated with 3.9 g (18.5 mmol) of trifluoroacetic anhydride to give 1.5 g (25% yield) of white solid: mp 192–193°; nmr δ 7.75 (m, 2, ArC=N), 7.2 (m, 14 Ar and C-2), 6.45 and 6.55 (two doublets, *J* = 3.5 Hz, 1 H, C-5); ir (KBr) 5.95 (C=O),

and 6.18 μ (C=N). Glc of 2c (column 210°, inlet 265°) gave one peak, retention time 12 min.

Anal. Calcd for C₂₃H₁₇N₂OF₃: C, 70.06; H, 4.34. Found: C, 70.46; H, 7.58.

Reaction of 1-Trifluoroacetyl-2,4,5-triphenyl-3-imidazoline (2c) with Alcoholic Potassium Hydroxide.—A mixture of 1-trifluoroacetyl-2,4,5-triphenyl-3-imidazoline (93 mg, 13.2 mmol), potassium hydroxide (132 mg, 13.2 mmol), and 25 ml of absolute ethanol was heated at reflux for 30 min. The ethanol was removed *in vacuo*, and 50 ml of water was added to the residue. The aqueous mixture was extracted with ether. Evaporation of the dried ether gave a solid which was recrystallized from aqueous ethanol to give 47.4 mg of white, crystalline solid, mp 201–203°. A mixture melting point with 2-*trans*-4,5-triphenyl-2-imidazoline was undepressed and the ir spectra were identical.

Nmr spectrum (100 MHz) of 1-azidoacetyl-2,4,5-triphenyl-3-imidazoline (2a)[2] showed peaks at δ 3.35 (s) and 3.44 (d, separation 1 Hz), total integration 2 H, CH₂N₃, 6.32 (d, *J* = 4 Hz) and 6.58 (d, *J* = 4 Hz), total integration 1 H, C-2, 6.90 (d, *J* = 4 Hz) and 7.15 (d, *J* = 4 Hz), C-5, 7.40 (m, 13 H, Ar), 7.80 (m, 2 H, ArC=N). Glc analysis (column 220°, inlet 265°) showed a major peak, retention time 25 min, and three minor ones, retention times 16, 17.5, and 32.5 min. The intensity of the minor peaks varied greatly; *e.g.*, repeated injections gave area ratios of retention times 16/25 that ranged from 0.07 to 0.17. To check for possible decomposition of the sample in the injection port the temperature was reduced to 235°. However, the sample was poorly vaporized at this temperature, and an extremely broad peak of low intensity was seen. Thin layer chromatography using several solvent systems indicated that 2a was homogeneous.

Registry No.—*cis*-2a, 34454-36-9; *trans*-2a, 34493-25-9; **2b,** 34454-37-0; **2c,** 34454-38-1; **5a,** 34454-39-2; **5b,** 34454-40-5; **5c,** 34454-41-6; **5d,** 34454-42-7; **7a,** 34454-43-8; **7b,** 34454-44-9; *erythro*-8, 34454-45-0; *threo*-8, 34454-46-1.

Synthesis and Thermodynamic Acidity of Dibenz[b,g]oxocin[1]

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The synthesis of dibenz[b,g]oxocin is reported. It is a slightly stronger carbon acid than xanthene. This fact is interpreted as evidence for the aromaticity of the 10-π-electron oxocinyl anion.

The influence of heteroatoms on potentially aromatic 10-π-electron systems has been the source of considerable interest.[2] Despite predictions of simple Hückel theory, there is little evidence that neutral or mononegatively charged heterocyclic π systems possess substantial resonance stabilization and a diamagnetic ring current. We report here the synthesis of dibenz[b,g]oxocin (1) and measurement of its acidity as a test of the aromaticity of the 10-π-electron oxocinyl anion 2 (eq 1).

Results and Discussion

The synthesis of 1 is outlined in Scheme I.

A. Homologation of Xanthylium Cation.—We have shown[3] that the reaction of diazoalkanes and their derivatives with stable carbonium ions is a useful method for preparing homoallyl and benzyl cations as transient intermediates. It was initially felt that reaction of xanthylium cation with excess ethyl diazoacetate should afford a direct entry into the dibenzoxocin ring systems *via* 6 (Scheme II).

Addition of ethyl diazoacetate to xanthylium perchlorate in dry acetonitrile at 0° led to rapid gas evolution. Two major products were isolated: 9-carboethoxydibenz[b,f]oxepin (3) and 9-carboethoxy-10-acetylamino-9,10-dihydrodibenz[b,f]oxepin (7). The structure of 3 follows from analogy with the diazomethane ring expansion of xanthylium perchlorate[3a] and from

(1) Abstracted from the Ph.D. thesis of H. S. K., 1969.

(2) (a) R. M. Coates and E. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 4016 (1971), and references contained therein; (b) N. L. Allinger and G. A. Youngdale, *ibid.*, **84**, 1020 (1962); (c) R. Breslow and E. Mohacsi, *ibid.*, **85**, 431 (1963); (d) L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Phillips, *ibid.*, **93**, 152 (1971); (e) L. B. Anderson, J. F. Hansesen, T. Kakihana, and L. A. Paquette, *ibid.*, **93**, 161 (1971); (f) A. P. Bindra, J. A. Elix, P. T. Garratt, and R. H. Mitchell, *ibid.*, **90**, 7372 (1968); (g) A. G. Anastassiou and J. H. Gebrian, *Tetrahedron Lett.*, 825 (1970); (h) A. G. Anastassiou and R. P. Cellura, *Chem. Commun.*, 903, 1521 (1969).

(3) (a) H. W. Whitlock, *Tetrahedron Lett.*, 593 (1961); (b) *J. Amer. Chem. Soc.*, **84**, 2807 (1962); (c) H. W. Whitlock and N. A. Carlson, *Tetrahedron*, **20**, 2101 (1964); (d) H. W. Whitlock and M. R. Pesce, *Tetrahedron Lett.*, 743 (1964).

SCHEME I
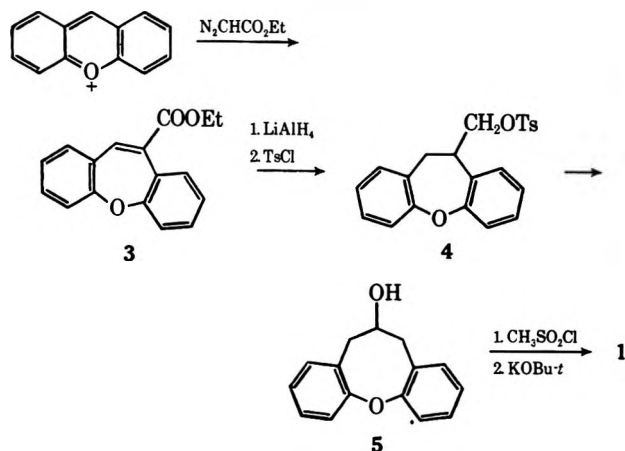
SCHEME II

its oxidation[4] to (diphenyl ether)-2,2'-dicarboxylic acid.[5] The isolation of this acid rules out the alternative structure 10 for the ring expansion product. This type of structure was the exclusive product found in the homologation of the 2,6-diphenylpyrrylium cation[3c] (eq 2).
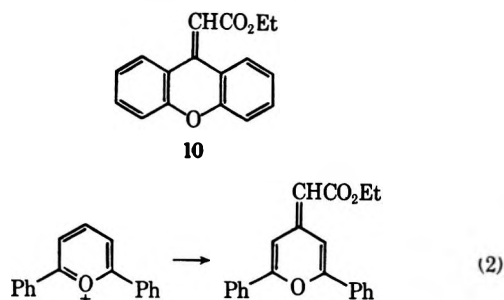
$$\tag{2}$$

Amide 7 was isolated as a single stereoisomer of unknown configuration. It presumably arises from a Ritter-type capture of the intermediate cation by acetonitrile, and its structure follows from its pyrolysis at 230° to 3. Small amounts of the 2:1 adduct 8 (see below) were also isolated. When dimethoxyethane was substituted as solvent for acetonitrile, no 7 was isolated and 3 could be obtained in up to 82% yield.

Inverse addition of xanthylium perchlorate to an excess of ethyl diazoacetate in dimethoxyethane afforded in addition to 3 a 2:1 diazo ester:cation adduct. That this adduct possesses the undesired seven-ring structure 8 rather than the sought-after oxocin 6 follows from these observations. Its nmr spectrum showed two singlets attributable to the aliphatic and vinyl hydrogens present. Brief treatment of 8 with alkali led to disappearance of its long-wavelength uv absorption at 313 mμ. Carried out preparatively, alkaline isomerization afforded as sole product an isomer 9 of 8 possessing a two-hydrogen singlet at δ 3.8 in its nmr spectrum. Its ultraviolet spectrum was consistent[6] with the presence of a dibenzo[b,f]oxepin chromophore. Saponification of 9 followed by treatment of the crude acid with acetic anhydride afforded a gummy material whose infrared spectrum (λmax 5.58 and 5.76 μ) was consistent with its being a glutaconic anhydride.[7] These data rule out structure 6 and other unlikely alternatives such as
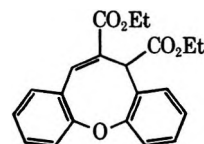
B. Conversion of 3 to Dibenz[b,g]oxocin.—Reduction of 3 with lithium aluminum hydride in refluxing tetrahydrofuran according to Jorgenson[8] resulted in reduction of the ester and double bond of 3.[9] Solvolysis of toluenesulfonate 4 in refluxing acetic acid followed by lithium aluminum hydride reduction of the resulting acetate afforded a single alcohol 5. Alcohol 5 was shown to be secondary and nonbenzylic by oxidation to a ketone, λmax 5.82 μ. The nmr of 5
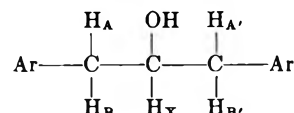
indicated the part structure with coupling constants $J_{AB} = 14$, $J_{AX} = 7$, $J_{BX} = 4.5$ Hz. Dehydration of 5 was effected by treatment of its methanesulfonate with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol. Attempted dehydration of 5 with *p*-toluenesulfonic acid in refluxing benzene afforded toluenesulfonate 4. A compound having the expected spec-

(4) (a) E. v. Rudloff, *Can. J. Chem.*, **34**, 1413 (1956); (b) E. E. Koemmel, *Anal. Chem.*, **36**, 426 (1964).

(5) (a) R. F. Manske and A. Ledingham, *J. Amer. Chem. Soc.*, **72**, 4797 (1950); (b) E. Bergman and M. Rabinowitz, *J. Org. Chem.*, **25**, 828 (1960); (c) O. V. Schickh, *Chem. Ber.*, **698**, 242 (1936); (d) F. Fujikawa and Y. Miyoshi, *J. Pharm. Soc. Jap.*, **8A**, 19 (1944).

(6) F. A. Anet and P. M. G. Bavin, *Can. J. Chem.*, **35**, 1084 (1957).

(7) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 45.

(8) M. J. Jorgenson and A. W. Friend, *J. Amer. Chem. Soc.*, **87**, 1815 (1965).

(9) Extended reduction in refluxing dioxane afforded i, mp 55–56°, which
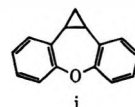
could also be prepared from dibenz[b,f]oxepin[3a] and iodomethylzinc iodide.

tral properties of the toluenesulfonate of **5** was detected on short reaction periods.

Acidity of Dibenzo[b,g]oxocin.—The acidity of **1** relative to xanthene, fluorene, and 1,3-bis(p-anisyl)propene was measured by equilibration of the butyllithium prepared salts in tetrahydrofuran.[10] It was initially shown that treatment of the above carbon acids with 1.05–1.1 equiv of n-butyllithium in tetrahydrofuran at −80° followed by 25° produced in good yield the monolithium salts (Table I). In all cases the nmr spec-

TABLE I

REACTION OF HYDROCARBONS WITH BUTYLLITHIUM IN
TETRAHYDROFURAN FOLLOWED BY DEUTERIUM
OXIDE QUENCHING

		Deuterium content		
RH	BuLi:RH	% d_0	% d_1	% d_2
Dibenz[b,g]-oxocin	1.05	11.5	82	6.5
Xanthene	1.05	5	92.5	2.5
Fluorene	1.05	8.5	86.5	5
Di(p-anisyl)-propene	1.09	9	88	3

tra of the deuterated species isolated on quenching of the anions with deuterium oxide showed the deuterium present to be localized on the allylic (or benzylic) carbons.

Acid–base equilibration of pairs of the above carbon acids was performed by allowing a 1:1 mixture of one acid and the lithium salt of another to equilibrate followed by deuterium oxide quenching[1c] and low-voltage mass spectrometry of the deuterated acid mixture. Analysis by mass spectrometry of the separated components of the deuterated mixture was in agreement with that of the mixture itself, as was analysis by nmr. Where necessary (dibenz[b,g]oxocin–xanthene) equilibrium was approached from both directions.

The results (Table II) allow one to place the acidity of these four carbon acids in the order
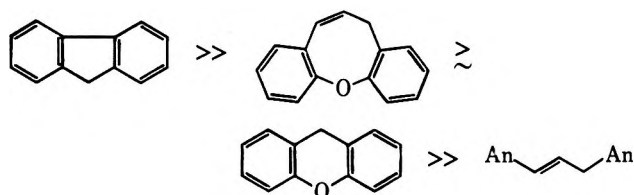
From the data in Table II one may calculate that dibenz[b,g]oxocin is an approximately 1.90 pK units stronger acid than xanthene. Assuming the pK_a of xanthene to be 29,[11] this affords 27 as the pK_a of dibenz[b,g]oxocin. This number may be compared with the pK_a of fluorene, 23.[11] Employing the Streitwieser[12] correlation, $pK_a = 48{-}15.5\Delta M$, where ΔM is the change in delocalization energy in units of β on ionization of a carbon acid, one calculates by simple Hückel theory a pK_a for dibenz[b,g]oxocin of 24.9 ($\Delta M = 1.4924\beta$).

The significance of the acidity of dibenz[b,g]oxocin hinges on a number of imponderables, principal of which is the appreciable (but hard to evaluate) increase in strain energy on going from **1** to **2**. We feel that considering the ring strain involved in ionization of **1** (assuming that anion **2** is planar), the experimental pK_a is in satisfactory agreement with that calculated and hence the dibenz[b,g]oxocinyl anion shows a property consistent with "aromaticity."[13]

Experimental Section[14]

Xanthylium perchlorate[15] was prepared by reaction of xanthydrol with 60% perchloric acid in acetic acid at 5°, and was recrystallized from acetonitrile–ether, mp 230° dec (lit.[15] mp 235° dec).

Xanthylium fluoroborate, mp 179° dec, was prepared similarly from xanthydrol and 50% fluoboric acid in acetic acid.

Xanthylium Perchlorate and Ethyl Diazoacetate in Acetonitrile. —Ethyl diazoacetate (1.95 g, 17 mmol) was added over 2 hr to a stirred solution of 3.10 g (11 mmol) of xanthylium perchlorate in 275 ml of acetonitrile maintained at 2°. At the end of addition, 455 ml (calculated, 381 ml) of gas had been evolved. The brown reaction mixture was poured into 1 l. of water and worked up to afford 3.33 g of a semicrystalline oil. Repeated chromatography of this oil on silica gel afforded the following substances in order of elution.

(1) 10-Carboethoxydibenz[b,f]oxepin (**3**), 330 mg (11.3% yield), had mp 72.5–73° (hexane); $\lambda_{max}^{CCl_4}$ 5.84 (COOC$_2$H$_5$), 6.19 μ (C=C); λ_{max}^{EtOH} 230 mμ (ϵ 2.3 × 10^4), 293 (1.07 × 10^4); nmr (CCl$_4$) δ 7.77 (singlet, 1 H, ArCH=C), 7.6–6.85 (multiplet, 8 H, ArH), 4.3 and 1.35 (quartet and triplet, 5 H, OCH$_2$CH$_3$); mass spectrum m/e 266 (parent, base).

Anal. Calcd for C$_{17}$H$_{14}$O$_3$: C, 76.67; H, 5.29. Found: C, 76.44; H, 5.26.

A mixture of 104 mg (0.39 mmol) of **3** and 0.4 g of potassium permanganate in 8 ml of water and 0.1 ml of 10% sodium hydroxide was refluxed with stirring for 4.5 hr. The mixture was cooled and acidified, and sufficient sodium bisulfite was added to dissolve the manganese dioxide. Xanthone, 15 mg, mp 177–178°, was removed by filtration and the filtrate was extracted with ether to afford 40 mg (40% yield) of (diphenyl ether)-2,2′-dicarboxylic acid, mp 232–233° (lit.[5a] mp 231°), identical with a sample prepared from dibenz[b,f]oxepin. Oxidation by the procedure of Kuemmel[6b] afforded (diphenyl ether)-2,2′-dicarboxylic acid only, in 63% yield.

(2) Xanthone, 65 mg (3% yield), was identified by comparison with an authentic sample.

(3) Diester **8**, 241 mg (6.3% yield), was obtained as cubes: mp 105–106.5° (benzene–hexane); $\lambda_{max}^{CHCl_3}$ 5.78, 5.85 (COOC$_2$H$_5$), 6.16 μ (C=C); λ_{max}^{EtOH} 234 mμ (ϵ 1.67 × 10^4), 273 (1.32 × 10^4), 313 (8.35 × 10^3); nmr (CDCl$_3$) δ 7.7–6.93 (multiplet, 8 H, ArH), 6.9 (singlet, 1 H, C=CHCO$_2$C$_2$H$_5$), 6.23 (singlet, 1 H, C=CCHArCO$_2$C$_2$H$_5$), 4.27 and 4.04 (quartets, 2 H each, OCH$_2$CH$_3$), 1.32 and 0.94 (triplets, 3 H each, OCH$_2$CH$_3$); mass spectrum m/e 352 (parent), 250 [base, parent − (C$_2$H$_5$OH + CO + C$_2$H$_4$)].

Anal. Calcd for C$_{21}$H$_{20}$O$_5$: C, 71.56; H, 5.72. Found: C, 71.22; H, 5.63.

Base-Catalyzed Isomerization of 8.—A solution of 100 mg of **8** and 0.5 g of sodium in 20 ml of dry ethanol was allowed to stand at room temperature. There was rapid (~1 min) loss of the absorption at 313 mμ characteristic of **8**. After 2 hr the reaction mixture was worked up to afford 75 mg of **9**: mp 156–158° (benzene–hexane); λ_{max}^{EtOH} 226 mμ (ϵ 1.29 × 10^4), 278 (6.58 × 10^3); $\lambda_{max}^{CHCl_3}$ 5.82 (COOC$_2$H$_5$), 6.22 μ (C=C); nmr (CDCl$_3$) δ 7.23 (8 H, multiplet, ArH), 4.34 and 4.16 (quartets, 2 H each,

(10) *I.e.*, as the solvent separated ion pairs: T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 207 (1966).

(11) (a) W. K. McEwen, *ibid.*, **58**, 1124 (1936); (b) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 4.

(12) A. Streitwieser, *Tetrahedron Lett.*, 23 (1960).

(13) A number of attempts to observe the nmr spectrum of **2** were unsuccessful.

(14) "Work-up" entailed: (1) partitioning diluted reaction mixtures between water and ether; (2) washing the ether layer with saturated sodium bicarbonate solution and then with saturated salt solution; (3) drying of the ether layer over anhydrous sodium sulfate followed by filtration and evaporation. Isotopic analyses of deuterated compounds were performed at 7 eV nominal ionization voltage on a CEC-103C mass spectrometer.

(15) K. A. Hofmann, R. Roth, K. Hobold, and A. Hetzler, *Chem. Ber.*, **43**, 2624 (1910).

TABLE II

ADDITION OF 1.0 EQUIV OF RH TO R'Li (PREPARED FROM R'H AND n-C$_4$H$_9$Li) IN TETRAHYDROFURAN

$$R'Li + RH \rightleftarrows R'H + RLi$$

R'H derived R'Li	RH	Recovered R'H			Recovered RH		
		% d_0	% d_1	% d_2	% d_0	% d_1	% d_2
Dibenz[b,g]oxocin[a]	Xanthene	18.5	78.5	3	92	8	e
Xanthene[b,c]	Dibenz[b,g]oxocin	91	9	e	16	81.5	2.5
Xanthene[b,d]	Dibenz[b,g]oxocin	91.5	8.5	e	20	77.5	2.5
Fluorene[b]	Dibenz[b,g]oxocin	10	86	4	98.5	1.5	
1,3-Bis(p-anisyl)-propene[b]	Dibenz[b,g]oxocin	97	3		26.5	71.5	2

[a] 0.5 mM R'H and 0.5 mM n-C$_4$H$_9$Li. [b] 1.0 mM R'H and 1.05 mM n-C$_4$H$_9$Li. [c] 30 min equilibration time. [d] 75 min equilibration time. [e] The low voltage mass spectrum of dibenz[b,g]oxocin exhibits weak fragment peaks at m/e 181–183 (xanthylium cations). As a result these peaks were corrected for both isotopic natural abundance and contribution from the deuterated oxocin.

OCH$_2$CH$_3$), 3.83 (singlet, 2 H, C=CCH$_2$COOC$_2$H$_5$), 1.31 and 1.2 (triplets, 3 H each, OCH$_2$CH$_3$); mass spectrum m/e 352 (parent).

Saponification of 80 mg of 9 in refluxing aqueous ethanolic sodium hydroxide afforded 78 mg of an acidic material: λ_{max}^{EtOH} 227 mμ (ϵ 1.33 × 10^4), 278 (6.82 × 10^3); $\lambda_{max}^{CHCl_3}$ 5.85 μ; mp 154–157°. A solution of this material in 2 ml of acetic anhydride was heated under reflux for 1.5 hr, and solvent was removed *in vacuo* to afford 50 mg of a gum: $\lambda_{max}^{CHCl_3}$ 5.58, 5.76 μ (cyclic anhydride[7]); mass spectrum m/e 278 (parent).

(4) Acetamide 7, 1.44 g (40.3% yield), was obtained as needles: mp 171–172.5° (benzene–hexane); $\lambda_{max}^{CHCl_3}$ 2.92 (NH), 5.77 (COOC$_2$H$_5$), 5.98 μ (CONHR); λ_{max}^{EtOH} 270 mμ (ϵ 1650); mass spectrum m/e 325 (parent), 2.66 (base, parent − CH$_3$CONH$_2$); nmr (CDCl$_3$) δ 7.18 (multiplet, 8 H, ArH), 5.82 (doublet, J = 5 Hz, superimposed on a broad singlet, 2 H, NH and CHCO$_2$-C$_2$H$_5$), 4.26 (triplet, J = 5 Hz, 1 H, CHNHAc), 4.03 (quartet, 2 H, OCH$_2$CH$_3$), 1.82 (singlet, 3 H, CH$_3$CONH–), 1.06 (triplet, 3 H, OCH$_2$CH$_3$). Addition of deuterium oxide to the nmr sample led to slow exchange of the NH to produce ϵ 4.24 (doublet, J = 5 Hz, 1 H) and 5.84 (doublet, J = 5 Hz, 1 H).

Anal. Calcd for C$_{19}$H$_{19}$O$_4$N: C, 70.12; H, 5.98; N, 4.30. Found: C, 69.91; H, 5.88; N, 4.38.

Pyrolysis of 150 mg of 7 at 250° under nitrogen followed by sublimation and chromatography of the sublimate afforded 23 mg of 3, identified by comparison with an authentic sample, and 89 mg (60% recovery) of 7.

Addition of xanthylium perchlorate to a threefold excess of ethyl diazoacetate in acetonitrile afforded a 31% yield of the 2:1 adduct 8 and a 39% yield of the Ritter product 7.

Xanthylium Perchlorate and Ethyl Diazoacetate in Dimethoxyethane.—To a stirred slurry of 3 g (10.7 mmol) of xanthylium perchlorate in 50 ml of dry dimethoxyethane at 0° was added over 1.5 hr a solution of 1.35 ml (1.46 g, 12.8 mmol) of ethyl diazoacetate in 20 ml of dimethoxyethane. Gas (360 ml, calculated 336 ml) was evolved. The brown-red reaction mixture was poured into water and worked up to afford 3.27 g of a dark solid. Chromatography of this on silica gel afforded, in order of elution, 40 mg (2% yield) of xanthene, 1.37 g (48% yield) of 9-carbethoxydibenz[b,f]oxepin (3), mp 70–71.5°, and 453 mg (22% yield) of xanthone, identified by comparison with an authentic sample.

Xanthylium Fluoroborate and Ethyl Diazoacetate.—Addition of ethyl diazoacetate (16.74 g, 0.165 mol) over 4 hr to xanthylium fluoroborate (33.5 g, 0.125 mol) in dimethoxyethane (300 ml) containing γ-collidine (9.17 g, 0.76 mol) at −13° afforded on chromatography 27.2 g (82% yield) of oxepin 3, mp 71–72°.

10-p-Toluenesulfonyloxymethyl-10,11-dihydrodibenz[b,f]oxepin (4).—A mixture of 300 mg (1.13 mmol) of 3 and 400 mg of lithium aluminum hydride in 50 ml of dry tetrahydrofuran was refluxed with stirring under nitrogen for 16 hr.[8] Excess hydride was decomposed with water and the reaction mixture was worked up to afford 250 mg (98% yield) of 9-hydroxymethyl-9,10-dihydrodibenz[b,f]oxepin as an oil: λ_{max}^{EtOH} 270 mμ (ϵ 1580); nmr (CCl$_4$) δ 7.0 (multiplet, 8 H, ArH), 3.76–2.9 (multiplet, 5 H, ArCH$_2$CHArCH$_2$OH), 2.8 (broad singlet, D$_2$O-exchangeable, 1 H, OH). The same compound (nmr, ir, conversion to p-toluenesulfonate 4 below) was obtained by sequential hydrogenation (Pd/C, atmospheric pressure) and lithium aluminum hydride reduction of 3. The crude alcohol was converted to its toluenesulfonate 4 by the procedure of Tipson[16] in 72% yield as

needles: mp 76–77° (hexane–benzene); λ_{max}^{EtOH} 269 mμ (ϵ 1360); nmr (CDCl$_3$) δ 7.7 and 7.23 (AB quartet, J = 8 Hz, 4 H, sulfonate ring protons), 7.05 (multiplet, 8 H, oxepine ring protons), 4.37–2.73 (multiplet, 5 H, CH$_2$CHCH$_2$OTs), 2.41 (singlet, 3 H, CH$_3$Ar).

Anal. Calcd for C$_{22}$H$_{20}$O$_4$S: C, 69.46; H, 5.30; S, 8.41. Found: C, 69.27; H, 5.33; S, 8.43.

Acetolysis of 4. 11-Hydroxydibenzoxocin (5).—A solution of 8.05 g of 4 in 150 ml of dry acetic acid was refluxed under nitrogen for 15 hr. The reaction mixture was worked up and the crude product was allowed to react with a solution of 1 g of lithium aluminum hydride in 50 ml of ether at 25° for 2 hr. Excess hydride was destroyed with water and the reaction mixture was worked up to afford 4.0 g (85% yield) of 5 as needles: mp 104–105° (benzene–hexane); $\lambda_{max}^{CHCl_3}$ 2.79 and 2.90 μ (OH); nmr (CDCl$_3$) δ 7.14 (multiplet, 8 H, ArH), 4.05 [broad singlet, 1 H, (ArCH$_2$)$_2$CHOH], 2.83 (AB part of ABX, J_{AB} = 14 Hz, J_{AX} = 7 Hz, J_{BX} = 4.5 Hz, 4 H, ArCH$_2$CHOH), 1.57 (singlet, 1 H, OH); λ_{max}^{EtOH} 237 mμ (ϵ 6353), 272 (1732).

Anal. Calcd for C$_{15}$H$_{14}$O$_2$: C, 69.71; H, 6.24. Found: C, 79.75; H, 6.23.

Oxidation of 5 with Jones[17] reagent afforded a 63% yield of the ketone 10-oxo-9,10-dihydrodibenz[b,g]oxocin: mp 74–75° (hexane); $\lambda_{max}^{CHCl_3}$ 5.82 μ; nmr (CDCl$_3$) δ 7.2 (multiplet, 8 H, ArH), 3.65 (singlet, 4 H, ArCH$_2$CO). Reaction of 5 with methanesulfonyl chloride in pyridine at 5° afforded the corresponding methanesulfonate as unstable needles: mp 124–126.5° dec (ether); nmr (CDCl$_3$) δ 7.13 (multiplet, 8 H, ArH), 5.06 [pentet, J = 6 Hz, 1 H, (ArCH$_2$)$_2$CHOMs], 3.05 (doublet, J = 7 Hz, 4 H, ArCH$_2$), 3.0 (singlet, 3 H, CH$_2$SO$_2$).

Dibenz[b,g]oxocin.—A solution of the above methanesulfonate, 265 mg (0.90 mmol), and 0.5 g of potassium in 15 ml of *tert*-butyl alcohol was refluxed under nitrogen for 8 hr. The reaction mixture was worked up to afford 150 mg (93% yield) of an oil shown by glpc (20% SE-30 on Chromosorb P at 235°) to be an 80:20 mixture of two compounds. Two evaporative distillations afforded 106 mg (66% yield) of the more abundant compound (pure by glpc) as a colorless oil: $\lambda_{max}^{CHCl_3}$ 6.14, 14.03, 14.48 μ (cis CH=CH); λ_{max}^{EtOH} 261 mμ (ϵ 5350); nmr (CDCl$_3$) δ 7.15 (multiplet, 8 H, ArH), 6.55 (A part of ABX$_2$, J_{AB} = 11, J_{AX} = 1 Hz, 1 H, ArCH=CHCH), 5.99 (B part of ABX$_2$, J_{BA} = 11, J_{BX} = 7 Hz, 1 H, ArCH=CHCH$_2$Ar), 3.34 (X part of ABX$_2$, J_{BX} = 7 Hz, 2 H, ArCH=CHCH$_2$Ar); mass spectrum m/e 208 (parent), 181 (base, parent − C$_2$H$_3$, xanthylium cation).

Anal. Calcd for C$_{15}$H$_{12}$O: C, 86.50; H, 5.81. Found: C, 86.47; H, 5.81.

The minor component was isolated by glpc and identified as 10-methylene-10,11-dihydrodibenz[b,f]oxepin by comparison with a sample prepared by treatment of toluenesulfonate 4 with refluxing collidine.

Attempted dehydration of 5 with *p*-toluenesulfonic acid in benzene at 25° afforded a mixture of 4 and an unstable toluenesulfonate whose nmr spectrum [(CDCl$_3$) δ 4.81 (pentet, J = 5.5 Hz, 1 H relative to the toluenesulfonate methyl singlet, ArCH$_2$-CHOTsCH$_2$Ar)] was consistent with the presence of 11-toluenesulfonyloxydibenz[b,g]oxocin. The proportion of the two depended on the toluenesulfonic acid:5 ratio and reaction time. On reflux with toluenesulfonic acid in benzene the unstable tosylate disappeared and 4, mp 72–74°, mmp 72.5–74°, was isolated in 70% yield.

(16) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(17) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 258 (1953).

1,3-Bis(p-anisyl)propene.—1,3-Bis(p-anisyl)-2-propanone was prepared from p-anisylacetic acid and lead carbonate.[18] Reduction of the above ketone with lithium aluminum hydride in tetrahydrofuran at 25° afforded 1,3-bis(p-anisyl)-2-propanol in 91% yield as needles, mp 56.5–57.5°.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.96; H, 7.41. Found: C, 74.60; H, 7.24.

Reaction of the above alcohol with p-toluenesulfonyl chloride in pyridine[16] afforded 1,3-bis(p-anisyl)-2-propanol p-toluenesulfonate in 85% yield as needles, mp 99–99.5° (methanol).

Anal. Calcd for $C_{21}H_{26}O_5S$: C, 67.59; H, 6.15; S, 7.50. Found: C, 67.85; H, 6.19; S, 6.48.

The above toluenesulfonate was refluxed in *tert*-butyl alcohol containing excess potassium *tert*-butoxide to afford 1,3-bis(p-anisyl)propene in 84% yield as needles: mp 66.5–67° (methanol); nmr (CDCl$_3$) δ 6.4 (A part of ABX$_2$, J_{AB} = 15.5 Hz, 1 H, ArCH=CHCH$_2$Ar), 6.18 (B part of ABX$_2$, J_{AP} = 15.5 Hz, J_{BX} = 5.5 Hz, 1 H, ArCH=CHCH$_2$Ar), 3.4 (X part of ABX$_2$, J_{BX} = 5.5 Hz, 2 H, ArCH=CHCH$_2$Ar).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.27; H, 7.14. Found: C, 80.29; H, 6.90.

Formation of Lithium Salts of Carbon Acids.—The following procedure is typical. To a stirred solution of 208 mg (1.0 mmol) of dibenz[b,g]oxocin in 5 ml of dry tetrahydrofuran at −80° (Dry Ice–acetone) under nitrogen was added 0.5 ml (1.05 mmol) of 2.1 *M* butyllithium in hexane. A red precipitate was formed. The mixture was stirred for 10 min, the cooling bath was removed, and the now homogeneous solution was allowed to stand at 25° for 4.5 hr. The red solution was added dropwise to a rapidly stirred solution of 4 ml of deuterium oxide (99.77% isotopic purity) in 2.5 ml of tetrahydrofuran. Work-up afforded 204 mg of an oil that was distilled at 55° (0.5 mm) to afford 177 mg of a

clear oil. Low-voltage mass spectrometry afforded the isotopic content: 12% d_0, 82% d_1, 6% d_2. The area of the nmr peak at ϵ 3.34 corresponded to 1 H and the splitting pattern to the part structure ArCH=CHCHDAr.

Equilibration of Anions.—The following experiment is typical. To a solution of 127 mg (0.50 mmol) of 1,3-bis(p-anisyl)propene in 2.5 ml of dry tetrahydrofuran at −80° was added 0.235 ml (0.50 mmol) of 2.13 *M* butyllithium in hexane. The pink reaction mixture was stirred at −80° for 10 min and allowed to stand at 25° for 3.5 hr. A solution of 104 mg (0.50 mmol) of dibenz[b,g]oxocin in 1.5 ml of tetrahydrofuran was added, and the mixture was stirred for 25 min and then added to a mixture of 3 ml of deuterium oxide and 2.5 ml of tetrahydrofuran. Work-up afforded 227 mg of a sticky solid. Low-voltage mass spectrometry of this mixture afforded the following results: dianisylpropene (m/e 254–256), 97% d_0, 3% d_1; dibenzoxocin (m/e 208–212), 24% d_0, 74% d_1, 2% d_2. Recrystallization and distillation of this mixture allowed separation of the two olefins, low-voltage mass spectra of which indicated the same isotopic distribution as above. The results for the series of experiments are in Table II.

(18) S. Chiavarelli, G. Setlimj, and H. M. Alves, *Gazz. Chim. Ital.*, **87**, 109 (1957).

Aminoethylation of Some Pyrimidine Derivatives[1]

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Ethylenimine alkylated readily and exclusively the N[1] and N[3] positions of 2,4-dioxopyrimidine derivatives. Substitution of ethylenimine by 2-chloroethylamine produced lower yields. The reactivity of several other nucleic acid building blocks was investigated. The structures were assigned on the basis of spectral data and on the results of hydrolysis.

In aqueous ethylenimine, HN(CH$_2$)$_2$, 4-thiouridine is the most readily modified base[2] at pH 8 but the modification is not absolutely specific in that a slower alkylation of guanine residues in *E. coli* B tRNA is also detectable.[3]

This paper presents the evidence that under more drastic conditions HN(CH$_2$)$_2$ alkylates readily and exclusively the N[1] and N[3] positions of 2,4-dioxopyrimidine derivatives. The highest yields were obtained when pyrimidines were directly dissolved in HN(CH$_2$)$_2$; dilution with water or with organic solvents decreased yields considerably.

Compounds 3-(2-aminoethyl)uridine (5) and 3-(2-aminoethyl)thymidine (9) were isolated from the reaction mixture of uridine (1) or thymidine (3) in yields of over 70%; less than 10% of nucleosides were recovered unchanged; the rest comprised a mixture of higher alkylated derivatives.

The presence of alkyl at the N[3] position of 5 and 9 was indicated by the uv spectra; comparison was made with spectra of known 3-alkyl nucleosides. The presence of two strong bands in the carbonyl region in the ir spectra of aminoethylated derivatives excluded O-alkylation. The assigned structures were confirmed by acidic hydrolysis of 5 and 9 to 3-(2-aminoethyl)-uracil (6) and 3-(2-aminoethyl)thymine (10), respectively. No unsubstituted pyrimidines were obtained after hydrolysis. This would have been the case if the O-alkylation of sugar moiety or the acid-labile O-alkylation on the heterocyclic ring had occurred.[4]

Deoxyuridine, 2′,3′-O-isopropylideneuridine, and 5′-O-tritylthymidine reacted like the corresponding parent compounds, whereas 3-methyluridine and 3-methylthymidine were, as expected, quantitatively recovered from the reaction mixture.

A small amount of higher alkylated derivatives was present in all reaction products. It was proven by chemical and spectroscopic means that these compounds are oligomers of HN(CH$_2$)$_2$ attached to the N[3] position of nucleosides. Some polymerization of HN(CH$_2$)$_2$

(1) Presented in part at the 6th Middle Atlantic Regional Meeting of the American Chemical Society, Baltimore, Md., Feb 1971.

(2) (a) B. R. Reid, *Biochem. Biophys. Res. Commun.*, **33**, 627 (1968); (b) K. H. Sheit, *Biochim. Biophys. Acta*, **195**, 294 (1969); (c) B. R. Reid, *Biochemistry*, **9**, 2852 (1970).

(3) B. R. Reid, *Methods Enzymol.*, **20**, 168 (1971).

(4) G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 4489 (1930).

to low molecular weight products was catalyzed by 2,4-dioxopyrimidine derivatives, and hence freshly distilled reagent decreased only moderately the formation of 3-oligoethylenimino derivatives.

The N-alkylation of pyrimidine bases was complicated by the fact that these systems possess two ionizable protons. Thus, uracil (2) (pK_a N^1 = 9.43; pK_a N^3 > 13[5]) gave rise to approximately equal amounts of 1-(2-aminoethyl)uracil (7) and 1,3-di(2-aminoethyl)-uracil (8), whereas the 3-alkylated derivative 6 was isolated as a minor product. It is not possible to obtain N^1-substituted product selectively, since in the N^1-monosubstituted product the acidity of the N^3 proton is increased sufficiently (pK_a = 9.71[6]) to give a competitive dialkylation reaction, namely, formation of 8. Corresponding derivatives (11, 12, and 10) were synthesized from thymine (4). The relatively low yields encountered in both cases were caused by the extensive polymerization of $HN(CH_2)_2$.

Two pairs of structural isomers (13, 14 and 15, 16) of the single site dialkylated pyrimidines are possible, and both were isolated and tentatively identified by uv spectroscopy and correct analysis for N, and corroborated by the following chemical properties. In line with the findings of Rogers, *et al.*,[7] the N^1- and N^3-alkylated uracils (6, 7, 13, 14) were found to be stable when heated with dilute NaOH. Under the same reaction conditions, the 1,3-dialkylated uracil (8), the 3-alkylated uridine (5), and the model compound 3-methyluridine were partly degraded. This is in accord with the reported instability of 1,3-dialkyluracils in alkali.[8] Under the above conditions, all derivatives of thymine (9, 10, 11, 12, 15, 16) and the model com-

	R_1	R_2	R_3
1	Ribosyl	H	
2	H	H	
3	2-Deoxyribosyl	Me	
4	H	Me	
5	Ribosyl	H	$H_2NCH_2CH_2$
6	H	H	$H_2NCH_2CH_2$
7	$H_2NCH_2CH_2$	H	H
8	$H_2NCH_2CH_2$	H	$H_2NCH_2CH_2$
9	2-Deoxyribosyl	Me	$H_2NCH_2CH_2$
10	H	Me	$H_2NCH_2CH_2$
11	$H_2NCH_2CH_2$	Me	H
12	$H_2NCH_2CH_2$	Me	$H_2NCH_2CH_2$
13	$H(NHCH_2CH_2)_2$	H	H
14	H	H	$H(NHCH_2CH_2)_2$
15	$H(NHCH_2CH_2)_2$	Me	H
16	H	Me	$H(NHCH_2CH_2)_2$

pound, 3-methylthymidine, were stable in alkali. This is in agreement with the known fact that 3-methylthymidine is stable,[9] while the O^2- and O^4-glucosides of thymine and uracil are hydrolyzed completely when

heated with 0.2 *N* NaOH at 100° for 10 min to give thymine and uracil, respectively.[7]

The additional and definite proof of structure of 1,3-dialkylated pyrimidines 8 and 12 has involved the unambiguous primary synthesis starting with 1- and 3-monoalkylated pyrimidines 6, 7, 10, and 11.

In all four cases the isolated dialkylated compounds were identical by mixture melting point, uv spectroscopy, and paper and ion-exchange chromatography with 8 or 12 synthesized from unsubstituted pyrimidines 2 or 4.

In line with expectation, preliminary experiments indicated that 2'-deoxyuridine, pseudouridine, and inosine reacted very readily with $HN(CH_2)_2$, whereas cytidine resisted alkylation. Adenosine and deoxyadenosine were quantitatively recovered unchanged from the reaction mixture, and the bases cytosine, adenine, and guanine remained insoluble in $HN(CH_2)_2$.

Aminoethylation of pyrimidines with a 2-mol excess of 2-chloroethylamine in a basic aqueous solution produced lower yields. This is to be expected, since the reaction proceeds through the ethylenimine intermediate.[10] A large excess of $ClCH_2CH_2NH_2$ did not significantly increase the yield owing to a ready polymerization of this reagent in an aqueous basic solution.

In all cases the products have been *N*-alkylpyrimidine derivatives; this is based on the analytical and spectroscopic data, and on the results of base and acid hydrolysis.

Alkylation with $ClCH_2CH_2NH_2$ in DMSO under anhydrous reaction conditions was unsuccessful. Condensation of 2-aminoethanol with uracil in the presence or in the absence of a condensing agent[11] led to an unidentified compound.

Experimental Section[12]

The ion-exchange resins used were Dowex 1 × 8 and Dowex 50W × 8, both 200–400 mesh, and Duolite C-20, 20–50 mesh.

Purity of the compounds was checked by descending chromatography on Whatman No. 1 paper. Solvent systems used were (A) *i*-PrOH–HCl–H₂O (680:164:156, v/v); (B) *n*-BuOH–AcOH–H₂O (4:1:1, v/v); (C) *n*-BuOH–H₂O (86:14, v/v); (D) *i*-PrOH–NH₄OH–H₂O (7:1:2, v/v). The compounds were located by their absorption of uv light, or were visualized as purple spots on paper chromatograms with ninhydrin spray.

General Procedure for Aminoethylation of Pyrimidines with Ethylenimine.—A solution of 1.0 g of pyrimidine derivative in 10 ml of $HN(CH_2)_2$ was incubated at 37° for 2 days and then it was concentrated to a gum over H_2SO_4 *in vacuo*. The crude aminoethylated derivative, contaminated with starting material, polyethylenimines, and polyethyleniminopyrimidines, was purified as indicated below.

3-(2-Aminoethyl)uridine (5). Method A.—The reaction product of $HN(CH_2)_2$ and uridine (1) was dissolved in about 50 ml of water and applied on a 0.9 × 65 cm column of Dowex 50W (NH₄⁺) resin. Elution was carried out with 0.05 *M* NH₄OH, and optical density of the effluent was measured at 260 nm. Unreacted 1 (40 mg, 4%) was eluted in the first 150 ml. The fractions containing 5 (800–1800 ml) were concentrated to dryness and NH₄HCO₃ was removed by repeated coevaporation with small amounts of water. The slightly colored residue was redissolved in about 50 ml of water and passed through a column of

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(8) (a) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952); (b) Y. Kondo, J. L. Fourrey, and B. Witkop, *J. Amer. Chem. Soc.*, **93**, 3527 (1971).

(9) C. Janion and D. Shugar, *Acta Biochim. Pol.*, **7**, 309 (1960).

(10) (a) H. Freudlich and W. Neumann, *Z. Phys. Chem. (Leipzig)*, **87**, 69 (1914); (b) H. Freudlich and H. Kroepelin, *ibid.*, **122**, 39 (1926).

(11) R. T. Markiw and E. S. Canellakis, *J. Org. Chem.*, **34**, 3707 (1969).

(12) Melting points were determined on the hot stage and are corrected. Ir data were recorded on a Beckman IR 4 spectrophotometer and nmr data on a Varian Associates A-60A spectrometer (TMS). Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

0.5 ml of Dowex 1 (HCO_3^-). The colorless effluent was concentrated to dryness and the residue was crystallized from 95% EtOH to give 0.89 g (76%). At least eight small peaks of 3-polyethyleniminouridines could still be eluted from the column with 1.5 M NH_4OH.

When starting with 200 mg of uridine, the purification was conveniently performed on a 1 × 3 cm column of Dowex 50W (H^+) resin. The unreacted 1 was washed out with 20 ml of H_2O, and then 5 was eluted with 15 ml of 1.5 M NH_4OH. The eluate was concentrated to dryness and the residue was crystallized consecutively from 95, 50, and 95% EtOH as needles: yield 100 mg (43%); decomposition above 170°; R_f (A) 0.34; uv max (pH 2) 262 nm, min 232 nm, max (pH 12) 262 nm, min 233 nm; ir (KBr) 1710 and 1670 cm^{-1} (CO). *Anal.* Calcd for $C_{11}H_{17}N_3O_6$: C, 45.99; H, 5.96; N, 14.63. Found: C, 45.85; H, 6.16; N, 14.63. Compound 5 in supernatant fractions can be conveniently separated from polyethyleniminouridines by paper chromatography (Whatman 3MM) in solvent A.

Method B.—The reaction product of $HN(CH_2)_2$ and 2′,3′-O-isopropylideneuridine, 3-(2-aminoethyl)-2′,3′-O-isopropylideneuridine, was hydrolyzed in 1 N HCl at 80° for 10 min. The resulting compound, after being purified, was found to be identical with 5 by chromatographic properties, uv spectra, melting point, and mixture melting point.

3-(2-Aminoethyl)uracil (6).—Compound 5 (300 mg) was hydrolyzed in 5 ml of 70% $HClO_4$ for 2 hr at 100°, diluted with 10 ml of H_2O, and centrifuged off the tar. The supernate and washings (2 × 10 ml) were neutralized with 6.0 g of KOAc, and the precipitated $KClO_4$ was removed by filtration. The filtrate was concentrated to dryness *in vacuo* and 6 was extracted from the residue with 95% EtOH. After concentration to dryness, the residue was dissolved in about 30 ml of H_2O and applied on a 3 × 1 cm column of Dowex 50W (H^+) resin. Impurities were washed out with H_2O, 6 was eluted with 0.05 M NH_4OH, and eluate was passed through 1-ml Dowex 1 (HCO_3^-) resin. Concentration of effluent to dryness and crystallization from EtOH gave 147 mg (91%) of 6 as an amorphous powder, mp 162–165°, R_f (A) 0.30.

6·HCl was obtained as off-white crystals (90% EtOH): mp 234–235° dec; uv max (pH 2) 260 nm, min 230 nm, max (pH 12) 284 nm, min 245 nm; ir (KBr) 1620 and 1600 cm^{-1} (CO); nmr (D_2O) δ 7.64 (d, 1, $J = 8$ Hz, C_6H), 5.95 (d, 1, $J = 8$ Hz, C_5H), 4.33 (t, 2, $J = 6$ Hz, N_3CH_2), 3.43 (t, 2, $J = 6$ Hz, CH_2NH_2). *Anal.* Calcd for $C_6H_9N_3O_2 \cdot HCl$: C, 37.61; H, 5.26; N, 21.93; Cl, 18.50. Found: C, 37.66; H, 5.35; N, 21.64; Cl, 18.45.

1-(2-Aminoethyl)uracil (7) and 1,3-Di(2-aminoethyl)uracil (8).—The concentrated reaction product of uracil (2) and $HN(CH_2)_2$ was dissolved in about 50 ml of 0.5 M HOAc, applied on a 1.4 × 68 cm column of Dowex 50 (H^+) resin, and eluted with 6 l. of a linear gradient from 0 to 3 N HCl. Unreacted 2 was eluted in the first peak (fractions 4–21, 20 ml/fraction), followed by 7 (fractions 75–102), 8 (fractions 187–227), and polyethyleniminouridines (fractions 267–300). Peaks were concentrated to dryness, the residues were discolored by passage of aqueous solutions through columns of 0.5 ml Dowex 1 (Cl^-) resin, and the effluents were concentrated to dryness. The isolated hydrochlorides were crystallized from 90% EtOH: yield of 7·HCl 186 mg (10.9%), off-white crystals, decomposition above 220°; R_f (A) 0.28; uv max (pH 2) 262 nm, min 230 nm, max (pH 12) 265 nm, min 242 nm; ir (KBr) 1730 and 1680 cm^{-1} (CO); nmr (D_2O) δ 7.77 (d, 1, $J = 8$ Hz, C_6H), 5.93 (d, 1, $J = 8$ Hz, C_5H), 4.23 (t, 2, $J = 6$ Hz, N_1CH_2), 3.48 (t, 2, $J = 6$ Gz, CH_2NH_2). *Anal.* Calcd for $C_6H_9N_3O_2 \cdot HCl$: C, 37.61; H, 5.26; N, 21.93; Cl, 18.50. Found: C, 37.54; H, 5.37; N, 21.65; Cl, 18.34. The HCl-free 7, mp 170–172° (EtOH), was obtained by elution from Dowex 50W (NH_4^+) resin with 0.1 M NH_4OH: yield of 8·2HCl 261 mg (10.8%), decomposition above 250°; R_f (A) 0.19; uv max (pH 2) 264 nm, min 232 nm, max (pH 12) 268 nm, min 236 nm; ir (KBr) 1710 and 1670 cm^{-1} (CO); nmr (D_2O) δ 7.73 (d, 1, $J = 8$ Hz, C_6H), 6.01 (d, 1, $J = 8$ Hz, C_5H), 4.28 (m, 4, N_1-CH_2 and N_3CH_2), 3.44 (m, 4, two CH_2NH_2). *Anal.* Calcd for $C_8H_{14}N_4O_2 \cdot 2HCl$: C, 35.44; H, 5.95; N, 20.66; Cl, 26.15. Found: C, 35.35; H, 6.08; N, 20.38; Cl, 25.92. The HCl-free 8 was isolated by means of ion-exchange resin in the form of noncrystallizable gum. The mother liquor from 7·HCl contained 6. This mixture was resolved on a 1.4 × 68 cm column of Dowex 50W (NH_4^+) resin using for elution 6 l. of linear gradient from 0 to 0.15 M NH_4OH. Compound 7 was eluted in the first peak; the second peak contained 18 mg (1.3%) of 6.

3-(2-Aminoethyl)thymidine (9). Method A.—The reaction product of $HN(CH_2)_2$ and thymidine (3) was purified by the procedure described for the preparation of 5, except that the first crystallization was from acetone–EtOH, then from EtOH, as needles, yield 0.95 g (72%, calculated as ·$^1/_2C_3H_8$[13]).

Method B.—The reaction product of $HN(CH_2)_2$ and 5′-O-tritylthymidine was washed with H_2O, and then the water-insoluble 3-(2-aminoethyl)-5′-O-tritylthymidine was extracted with MeOH and detritylated by heating for 10 min at 100° in 80% HOAc. The isolated compound, identical with 9 prepared above, was obtained as needles: decomposition above 160°; R_f (A) 0.53; uv max (pH 2) 268 nm, min 237 nm, max (pH 12) 268 nm, min 238 nm; ir (KBr) 1690 and 1670 cm^{-1} (CO). *Anal.* Calcd for $C_{12}H_{19}N_3O_5 \cdot ^1/_2C_3H_8$: C, 54.53; H, 7.26; N, 13.16. Found: C, 54.55; H, 7.28; N, 13.23.

3-(2-Aminoethyl)thymine (10).—Compound 9 (300 mg) was hydrolyzed in 5 ml of HOAc–HCl (2:1, v/v) at 100° for 1 hr, then concentrated to dryness over NaOH *in vacuo*. The residue was freed from decomposition products by passage of the aqueous solution through 0.5 ml of Dowex 1 (Cl^-) resin and the effluent was applied on 1 ml of Dowex 50 (H^+) resin. The derivative was eluted with 1 N HCl, concentrated to dryness, and crystallized from 95% EtOH to give 186 mg (96%) of 10·HCl: mp 221–223°; R_f (A) 0.41; uv max (pH 2) 265 nm, min 235 nm, max (pH 12) 291 nm, min 249 nm; ir (KBr) 1720 and 1670 cm^{-1} (CO); nmr (D_2O) δ 7.49 (s, 1, C_6H), 4.34 (t, 2, $J = 6$ Hz, N_3CH_2), 3.41 (t, 2, $J = 6$ Hz, CH_2NH_2), 1.95 (s, 3, C_5CH_1). *Anal.* Calcd for $C_7H_{11}N_3O_2 \cdot HCl$: C, 40.88; H, 5.88; N, 20.43; Cl, 17.24. Found: C, 40.88; H, 5.90; N, 20.14; Cl, 17.22. The HCl-free 10 was obtained by means of cation-exchange resin as needles from EtOH–acetone, mp 171–172°.

1-(2-Aminoethyl)thymine (11) and 1,3-Di(2-aminoethyl)-thymine (12).—Compounds 11 and 12 were isolated from the reaction mixture of thymine and $HN(CH_2)_2$ by the procedure described for the preparation of 7 and 8, yield of 11·HCl 283 mg (17.4%). The supernatant contained 40 mg of 11·HCl and 35 mg (2.2%) of 10·HCl. Compound 11·HCl decomposed above 200°: R_f (A) 0.35; uv max (pH 2) 269 nm, min 235 nm, max (pH 12) 270 nm, min 245 nm; ir (KBr) 1700 and 1680 cm^{-1} (shoulder, CO); nmr (D_2O) δ 7.63 (s, 1, C_6H), 4.23 (t, 2, $J = 6$ Hz, N_1CH_2), 3.51 (t, 2, $J = 6$ Hz, CH_2NH_2), 1.93 (s, 3, C_5-CH_3). *Anal.* Calcd for $C_7H_{11}N_3O_2 \cdot HCl$: C, 40.88; H, 5.88; N, 20.43; Cl, 17.24. Found: C, 40.98; H, 5.80; N, 20.14; Cl, 17.15. The HCl-free 11, obtained as needles (EtOH), mp 191–192°, sublimed at higher temperature. They yield of 12·2HCl was 575 mg (25.4%): decomposition above 250°; R_f (A) 0.29; uv max (pH 2) 269 nm, min 236 nm, max (pH 12) 272 nm, min 240 nm; ir (KBr) 1700 and 1670 cm^{-1} (CO); nmr (D_2O) δ 7.58 (s, 1, C_6H), 4.27 (m, 4, N_1CH_2 and N_3CH_2), 3.42 (m, 4, two CH_2NH_2), 1.96 (s, 3, C_5CH_3). *Anal.* Calcd for $C_9H_{16}N_4O_2 \cdot 2HCl$: C, 37.91; H, 6.36; N, 19.65; Cl, 24.86. Found: C, 38.09; H, 6.40; N, 19.44; Cl, 24.71. The HCl-free 12 was isolated as a gum; all attempts to crystallize it failed.

Small-scale separations of 10, 11, and 12 as well as 5, 7, and 8 could be conveniently performed by paper chromatography (solvent A, 80 hr).

Reaction of Other Pyrimidines and Purines with Ethylenimine.—The same reaction conditions were used except that the amounts were scaled down. The reaction progress was followed by means of paper and ion-exchange chromatography.

Reaction of N^1- and N^3-Monoaminoethylated Pyrimidines with Ethylenimine.—Compounds 6, 7, 10, and 11 were treated with $HN(CH_2)_2$ under reaction conditions specified by the general procedure and the concentrated reaction products were applied on columns of Duolite C-20 (H^+) resin (1 × 25 cm). The unreacted monoalkylated compounds were eluted with 0.1 M NH_4OH and then the 1,3-dialkylated pyrimidines (8, 12), with traces of trialkylated derivatives, were eluted with 1.5 M NH_4OH and purified by paper chromatography in solvent A: yields, 8, 75–80%; 12, 60–65%.

Aminoethylation of Uracil (2) and Thymine (4) with 2-Chloroethylamine.—To a boiling solution of 10 ml of 1 N NaOH, 100 mg of KI, 2 ml of Et_3N, and 1.12 g (10 mmol) of 2 or 1.26 g (10 mmol) of 4, was added dropwise in a 4-hr period a solution of 2.32 g (20 mmol) of $ClCH_2CH_2NH_2 \cdot HCl$ in 20 ml of 1 N NaOH. The cooled reaction mixture was applied on a 1.5 × 28 cm column of Duolite C-20 (H^+) resin. The unreacted pyrimidine (0.81 g of 2, 0.69 g of 4) was washed out with H_2O and the derivatives

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(13) C_3H_8 was eluted from the new Dowex 50W resin with NH_4OH.

were eluted with 0.1 M NH$_4$OH. After a concentration to dryness the residue was extracted with H$_2$O and the soluble fraction was applied on a 1.4 × 68 cm column of Dowex 50W (NH$_4$$^+$) resin. The derivatives were eluted with 6 l. of a linear gradient from 0 to 0.15 M NH$_4$OH. Compound 7, 85 mg, was eluted in fractions 46–71, followed by a mixture of 6, 57 mg, and 1-(β-aminoethyl-N-β-aminoethyl)uracil[14] (13), 56 mg, in fractions 114–140, separable by paper chromatography in solvent A. Fractions 180–190 contained 10 mg of 3-(β-aminoethyl-N-β-aminoethyl)uracil[14] (14), followed by 13 mg of 8 in fractions 242–252. Higher alkylated derivatives were identified in fractions 253–300. Thymine derivatives were eluted in the following fractions: 11, 120 mg, in 85–110; 1-(β-aminoethyl-N-β-amino-

(14) Tentatively identified by uv spectra, chromatographic properties, and correct analysis for N.

ethyl)thymine[14] (15), 55 mg, in 180–200; 10, 53 mg, in 206–222, followed by 3-(β-aminoethyl-N-β-aminoethyl)thymine[14] (16) and by 12.

Reaction of Alkylated Derivatives with Sodium Hydroxide.— The alkylated derivatives (10 mg) and 0.2 N NaOH (0.5 ml) were heated at 100° for 10 min. The reaction products were chromatographed on paper and the uv spots were examined.

Nucleophilic Substitution at an Acetylenic Carbon.   A Mechanistic and Synthetic Study of the Reactions of Phosphines with Haloacetylenes[1]

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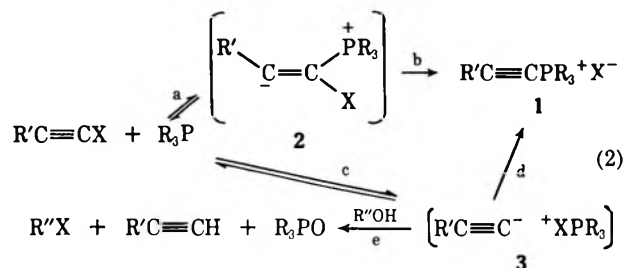
Received December 9, 1971

A synthetic route to ethynylphosphonium salts from haloacetylenes, phenylhaloacetylenes, but not alkylhaloacetylenes is described. These salts are electrophiles; when phenylethynyltriphenylphosphonium bromide is treated with tributylphosphine in acetonitrile, the α,β-bis(tributylphosphonium)styrene dibromide is formed. Rate data for the second-order reactions of several systems in DMF are (ΔH^+, kcal/mol; ΔS^+, eu; k, M^{-1} sec^{-1} at 36°): C$_6$H$_5$C≡CBr-(C$_6$H$_5$)$_3$P (16.8; 23; 8.45 × 10^{-5}); C$_6$H$_5$C≡CCl-(C$_6$H$_5$)$_2$P (14.5; 29; 1.75 × 10^{-4}); C$_6$H$_5$C≡CBr-(n-C$_4$H$_9$)$_2$P (5.4; 44; 2.20 × 10^{-1}); C$_6$H$_5$C≡CCl-(n-C$_4$H$_9$)$_3$P (11.5; 27; 5.92 × 10^{-2}); CH$_3$Br-(C$_6$H$_5$)$_3$P (11.8; 31; 2.88 × 10^{-3}). Both the element effect, k(Cl) > k(Br), and the results of scavenging experiments with methanol provide evidence for mechanistic alternatives. Although tributylphosphine attacks the bromine of phenylbromoacetylene exclusively, attacks on halogen and the terminal carbon atom appear to be competitive in the other systems. The general order of reactivity in substitution at carbon by phosphine nucleophiles is sp^3 ∼ sp > sp^2.

Nucleophilic displacement at an acetylenic carbon

$$R'C{\equiv}CX + Nuc \longrightarrow R'C{\equiv}C\text{-}Nuc + X \qquad (1)$$

has come of age only within the last few years.[2–7] Substitution attacks on haloalkynes have now been reported for organometallics,[5,7] amines,[2a,e,j,3] phosphites,[2g,3e,6] thiolates,[2b,c,3c] phosphides,[5] alkoxides,[2h,i] etc. Kinetic data in this area are still rare.[2a–c,f–h,j,3e] Our work was undertaken to find out first whether

(1) (a) Research supported by National Institutes of Health Grant GM07021. This work was presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., 1963. (b) Taken from the Ph.D. Thesis of J. I. D., Illinois Institute of Technology, 1970.

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ethynylphosphonium salts could be prepared by process 2, and second to develop a deeper understanding of a still new and relatively unexplored process.

$$
\begin{array}{c}
R'C{\equiv}CX + R_3P \xrightarrow{\ a\ }
\left[
\begin{array}{c}
R' \\ \diagdown \\ C{=}C \diagup \overset{+}{P}R_3 \\ \diagup \qquad \diagdown X
\end{array}
\right]
\xrightarrow{\ b\ } R'C{\equiv}CPR_3{}^+X^- \\
2 \qquad\qquad\qquad 1
\end{array}
$$

$$R''X + R'C{\equiv}CH + R_3PO \xleftarrow[e]{R''OH} \left[R'C{\equiv}C^- \ ^+XPR_3\right] \qquad (2)$$
$$3$$

1a, R′ = R = C$_6$H$_5$; X = Br
 b, R′ = R = C$_6$H$_5$; X = Cl
 c, R′ = C$_6$H$_5$; R = n-C$_4$H$_9$; X = Br
 d, R′ = C$_6$H$_5$; R = n-C$_4$H$_9$; X = Cl
 e, R′ = H; R = C$_6$H$_5$; X = Cl
 f, R′ = H; R = C$_6$H$_5$; X = Br
 g, R′ = H; R = n-C$_4$H$_9$; X = Cl

The first ethynylphosphonium salts were prepared in aprotic solvents.[2b,3d,4] In the presence of a proton donor, the formation of 1 *may* fail, because of diversion of the ion pair 3 along path e. This was found in the system phenylbromoacetylene–triphenylphosphine.[4] For this reason, Hoffmann and Förster suggested that steps c and d in eq 2 were appropriate for this process, and this conclusion has been accepted by workers in the field.[2f] In this paper, we show that all of the options of eq 2 must be retained and describe some of its synthetic applications.

Experimental Section[1b]

Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and A. Bernhardt, Mulheim (Ruhr). Melting points were taken on a Mel-Temp melting point apparatus and are uncorrected. Infrared (ir) spectra were obtained on Perkin-Elmer Model 21 and Infracord Model 137 spectrometers and calibrated against several polystyrene bands. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian A-60 instrument and referred to tetramethylsilane (TMS), which was used as an internal standard. Neat liquids were used for the spectra, except as indicated.

The identities and purities of reactants, products, and solvents were checked routinely by gas chromatography (gc) (Table I).

Table I

Conditions Employed for Gas Chromatographic Analyses

Compd	Instrument[a]	Column	Temp, °C[b]
$C_6H_5C \equiv CBr$, $C_6H_5C \equiv CCl$	BC10	Apiezon L (6 ft × 0.25 in.)[d] Ar (25 psi)	160, 140, 200
$C_6H_5C \equiv CH$	A700	20% QF-1 (6 ft × 0.25 in.)[c] He (10 psi)	90, 130, 200
CH_3Br	A350	Apiezon L (6 ft × 0.25 in.) He (5 psi)	0, 25, 25
$(C_6H_5)_3P$ $(C_4H_9)_3P$ $(C_6H_5)_3PO$ $(C_4H_9)_3PO$	BC10	20% Apiezon L (6 ft × 0.25 in)[d] Ar (30 psi)	275, 200, 350
DMF	BC10	Diethylene glycol succinate (DEGS) (6 ft × 0.25 in.) Ar (15 psi)	120, 90, 150

[a] Barber Coleman Model 10; Aerograph Models 350 and 700. [b] Column, detector, inlet. [c] An aluminum column containing 20% by weight QF-1 on 40–60 mesh acid-washed firebrick. [d] A glass column containing 20% Apiezon L on 40–60 mesh acid-washed firebrick.

Materials.—Commercially available compounds were purified, if need be, by distillation or recrystallization. The properties of known compounds that we synthesized will be summarized, while the properties of certain materials, e.g., those used in the kinetic studies, will be given in more detail.

The solvent for our kinetics was dimethylformamide (DMF). Reagent grade material was stored over sodium hydroxide for 1 week and filtered directly into a fractional distillation apparatus. The second of three fractions was used; it had bp 63° (30 mm), n^{25}D 1.4270, and one gc peak [lit.[8] bp 63° (30 mm), n^{25}D 1.4269]; its ir spectrum revealed no trace of water.

Triphenylphosphine was recrystallized from 50% ethanol–ether to mp 80–81° (lit.[9] mp 80°); it had one gc peak. Tributylphosphine was fractionally distilled; the middle fraction had bp 151° (50 mm), n^{20}D 1.4625, one gc peak, and no ir (P=O) band (lit.[10] bp 149.5° (50 mm), n^{20}D 1.4634). Methyl bromide was purified by fractional condensation in U traps at 0, −45, and −78°. The middle fraction had a minimum purity of 99% by gc.

Most of the 1-haloalkynes were prepared by shaking the 1-alkyne, chlorine or bromine, and potassium hydroxide in water. The 1-haloalkynes were purified by fractional distillation and stored under nitrogen in a refrigerator.[11] Phenylbromoacetylene had bp 55–56° (1.5 mm), n^{25}D 1.6102, ir 4.71 μ (C≡C).[11] Phenyl-

chloroacetylene had bp 70–71° (16 mm), n^{25}D 1.5732, ir 4.65 μ (C≡C).[12] 1-Bromo-1-hexyne had bp 41–42° (11 mm), n^{25}D 1.4698, ir 4.62 μ (C≡C).[13] 1-Chloro-1-hexyne, prepared from 1-sodio-1-hexyne and benzenesulfonyl chloride, had bp 45–46° (5 mm), ir 4.51 μ (C≡C).[12] A number of haloacetylenic alcohols and/or their 2′-tetrahydropyranyl ethers were also used: 1-(chloroethynyl)cyclohexanol and ether,[14] 1-(bromoethynyl)cyclohexanol,[15] 1-chloro-3-methyl-1-pentyn-3-ol and ether,[16] and 2′-(1-chloro-3-methylbutyn-3-oxy)tetrahydropyran.[14]

Chloroacetylene (Hazardous! On contact with air this substance may explode and burn) was generated by refluxing a solution of 1,2-dichloroethylene (48 g, 0.5 mol) and potassium hydroxide (40 g, 0.7 mol) in 1,2-dimethoxyethane (300 ml) under nitrogen. Chloroacetylene was swept out of solution by a nitrogen stream through calcium chloride and phosphorus pentoxide tubes and condensed in a liquid nitrogen cooled trap. High vacuum fractionation through U traps at −94, −120, and −196° yielded material of vapor pressure 416 mm at −45° (lit.[17] 414.7 mm at −44.9°).

Bromoacetylene (Hazardous! On contact with air this substance may explode and burn) was prepared from 1,2-dibromoethene (37.2 g, 0.2 mol) and potassium hydroxide (40 g, 0.7 mol) by the method described for chloroacetylene. Bromoacetylene was passed slowly through a train containing cold baths at −45, −94, and −196°. The center fraction had a vapor pressure of 72 mm at −45° (lit.[17] 74.3 mm at −43.6°).

Preparation of Ethynylphosphonium Salts.—A mixture of the phosphine (0.1 mol) and the haloalkyne (0.1 mol) in 500 ml of ether at ca. 25° deposited phosphonium salt in several days. Purification was accomplished by repeated solution of the salt in absolute ethanol followed by slow precipitation with ether. Since some of the phosphonium salts, especially the chlorides, were very hygroscopic, these compounds had to be analyzed as chloroplatinates and tetraphenylborates. We prepared the chloroplatinates from aqueous chloroplatinic acid and the borates from sodium tetraphenylboron in water. The solids were recrystallized from ethanol or acetone–water.

In several cases, e.g., ethynyltributylphosphonium chloride [ir (CHCl₃) 3.2 (≡CH) and 4.60 μ (C≡C)] and its derivative (chloroplatinate, mp 224–226°), the expected structures were probably obtained, but the elementary analyses were unsatisfactory. In addition, the alkylhaloalkynes of the preceding section led to products and/or derivatives of uncertain structure. The properties of these unknown materials, e.g., elemental analyses, spectra, melting points, and some speculations concerning their structure, are found in the thesis.[1b]

Phenylethynyltriphenylphosphonium Bromide.—This salt was prepared from phenylbromoethyne (18.1 g, 0.1 mol) and triphenylphosphine (26.2 g, 0.1 mol) in 90% yield, mp 209–211°, ir (CHCl₃) 4.55 μ (C≡C) [lit.[4] mp 206°, ir (CHCl₃) 4.60 μ (C≡C)].

Anal. Calcd for $C_{26}H_{20}BrP$: C, 70.27; H, 4.50; Br, 17.61. Found: C, 69.87; H, 4.50; Br, 18.02.

The chloroplatinate derivative had mp 208–211°, ir (KBr) 4.67 μ (C≡C).

Anal. Calcd for $C_{52}H_{40}P_2PtCl_6$: C, 55.03; H, 3.52. Found: C, 54.54; H, 3.54.

The bromide (8.8 g) was hydrolyzed in 25% aqueous sodium hydroxide in 2 hr at ~100°; triphenylphosphine oxide (2.7 g), mp 153° from ethanol, and phenylacetylene (0.5 g) were isolated and identified.

Phenylethynyltriphenylphosphonium Chloride.—Phenylchloroacetylene (13.7 g, 0.1 mol) and triphenylphosphine gave a hygroscopic oil in 86% yield, ir (CHCl₃) 4.65 μ (C≡C) [lit.[3d] ir (CHCl₃) 4.62 μ (C≡C)]. Its ir spectrum was identical with that of phenylethynyltriphenylphosphonium bromide. The chloroplatinate had mp 208–211° and showed no depression in melting point upon admixture with the chloroplatinate of phenylethynyltriphenylphosphonium bromide. The tetraphenylboron derivative had mp 133–136° dec from acetone–water (70:30).

Anal. Calcd for $C_{50}H_{40}BP$: C, 87.97; H, 5.91. Found: C, 87.42; H, 6.27.

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Phenylethynyltributylphosphonium Bromide.—Phenylbromo-ethyne (18.1 g, 0.1 mol) and tributylphosphine (20.2 g, 0.1 mol) gave an oil in 92% yield. Repeated solution–precipitation yielded white crystals: mp 57–59°; ir (CHCl₃) 4.59 μ (C≡C); nmr (DCCl₃) 7.55 (m, 5, ArH), 2.32 (6, CH₂), 1.49 (12, CH₂), and 0.9 ppm (9, CH₃).

Anal. Calcd for C₂₀H₃₂BrP: C, 62.66; H, 8.30. Found: C, 62.72; H, 8.26.

The chloroplatinate had mp 149–152°.

Anal. Calcd for C₄₀H₆₄P₂PtCl₆: C, 47.34; H, 6.28. Found: C, 47.10; H, 6.29.

Phenylethynyltributylphosphonium Chloride.—Phenylchloro-ethyne (13.7 g, 0.1 mol) and tributylphosphine (20.2 g, 0.1 mol) produced a viscous oil in 83% yield, ir (CHCl₃) 4.65 μ (C≡C). The infrared and nmr spectrum of this salt was identical with that of phenylethynyltributylphosphonium bromide. The chloroplatinate had mp 149–152°, ir (KBr) 4.60 μ (C≡C).

Anal. Calcd for C₄₀H₆₄P₂PtCl₆: C, 47.34; H, 6.36. Found: C, 46.94; H, 6.28.

Ethynyltriphenylphosphonium Chloride.—Chloroethyne (3.3 g, 0.055 mol) and triphenylphosphine (13.1 g, 0.05 mol) gave 3.1 g of a hygroscopic solid, ir (CHCl₃) 3.23 (≡CH) and 4.55 μ (C≡C) [lit.³ᵈ ir (CHCl₃) 3.02 μ (≡CH)], nmr (D₂O) 7.9–8.3 (ArH) and 4.47 ppm (d, *J* = 28 Hz, HC≡)]. The chloroplatinate had mp 205–207°, ir (KBr) 3.20 μ (≡CH), and an unsatisfactory analysis. The tetraphenylboron derivative had mp 172° dec.

Anal. Calcd for C₄₄H₃₆BP: C, 87.13; H, 5.98. Found: C, 86.92; H, 6.28.

Ethynyltriphenylphosphonium Bromide.—Bromoethyne (5.3 g, 0.05 mol) and triphenylphosphine (13.1 g, 0.05 mol) gave 4.3 g of a hygroscopic solid which had an ir spectrum identical with that of ethynyltriphenylphosphonium chloride.

α-(Triphenylphosphonium)-β-(tributylphosphonium)styrene Dibromide.—The reaction between phenylethynyltributylphosphonium bromide (7.6 g, 0.02 mol) and triphenylphosphine (10.5 g, 0.04 mol) was carried out in boiling acetonitrile. After 24 hr, 3.8 g of product was precipitated by the addition of ether and recrystallized several times from acetonitrile–ether: mp 239–241°; ir (CHCl₃) 6.15 μ (C=C); nmr (CDCl₃) 7.50–8.28 (20, ArH) and 0.65–3.0 ppm (27, alkyl H).

Anal. Calcd for C₃₈H₄₈P₂Br₂: C, 62.80; H, 6.66. Found: C, 62.73; H, 6.29.

α,β-Bis(tributylphosphonium)styrene Dibromide.—By the procedure described in the preceding section, phenylethynyltriphenylphosphonium bromide (8.8 g, 0.02 mol) and tributylphosphine (8.1 g, 0.04 mol) gave 3.1 g of the solid product: mp 211–212°; ir (CHCl₃) 6.10 μ (C=C); nmr (CDCl₃) 7.50–7.99 (5, ArH) and 1.59–3.15 ppm (54, alkyl H).

Anal. Calcd for C₃₂H₆₀P₂Br₂: C, 57.65; H, 9.07. Found: C, 57.71; H, 9.15.

Analytical Procedures.¹ᵇ Halide Analysis.—A Precision Scientific Titrometer equipped with glass and silver electrodes was used for potentiometric bromide titrations. The silver nitrate solution, which was standardized potentiometrically, was checked by the eosin (0.1%) adsorption indicator method; the two methods agreed to within 0.3%. The bromide in benzyltriphenylphosphonium bromide, a typical salt, was determined to within 0.2% of the calculated value by potentiometric titration. In the kinetic studies, triphenylphosphine appeared to interfere with the bromide analysis. After removal of triphenylphosphine with two ether extractions, 0.5 ml of concentrated nitric acid was added to the aqueous layer and the bromide was estimated by potentiometric titration. DMF, acetone, and phenylbromoethyne did not interfere with the halide titration. In DMF solutions containing triphenylphosphine or phenylbromoacetylene and phenylethynyltriphenylphosphonium bromide in concentration ranges similar to the kinetic experiments, the bromide ion content could be estimated to ±0.25%.

In the kinetic study of phenylchloroethyne with triphenylphosphine in DMF, the amount of ionic chloride could not be determined potentiometrically because of insensitivity at the end point. After removal of the organic compounds with ether, the chloride in the aqueous layer was determined in a Volhard titration. The accuracy of this procedure was established to be 0.5%.

Kinetic Procedures.—The identity of the products under kinetic and synthetic conditions was established, *e.g.*, by ir and melting point. The disappearance of organic halide or nucleophile was followed by gc and paralleled the production of ionic

halide. In the first method, aliquots (5 or 10 ml) at 20–25° were distributed among nitrogen-flushed ampoules, which were capped, cooled at −78°, and sealed. In the case of methyl bromide, aliquots (5 ml) of the reaction mixture were distributed with an automatic overflow pipet, which minimized losses by evaporation. For a kinetic run, an ampoule was brought to *ca.* 25° and then immersed quickly, with vigorous shaking, in a constant-temperature bath. After a known interval, the ampoule was removed from the bath, shaken in Dry Ice–acetone, and stored at −78°. For analysis, the ampoules were washed out with several portions of water and acetone and the halide ion was determined.

Because we corrected for the warm-up period (0.5–2.5 min), the uncertainty in the time was usually <2%. Normally, no significant amounts of halide were formed during preparation of the runs or storage of the ampoules. Methyl bromide did, however, show 3–4% reaction blanks. The concentration of our stock methyl bromide solution was found by treating aliquots of it with excess sodium hydroxide until reaction was complete. The amount of blank reaction was found by analyzing the contents of the first and last ampoules of the set to be used in the kinetic run. The mean concentration of unreacted methyl bromide at *t* = 0 was taken as [CH₃Br]₀.

Blank experiments on organic halide and solvent indicated that no ionic halide was formed under the reaction conditions. The presence of *ca.* 1% of water had no effect on the rate constants. In the triphenylphosphine reactions, a few ampoules were analyzed to determine whether oxidation had occurred; no triphenylphosphine oxide was detected by gc.

Each kinetic run was followed to at least 75% conversion. The rate constants are defined by the standard second-order expression.¹ᵇ All of the rate constants were corrected for thermal expansion (or contraction). The necessary factors (°C) follow: 0.951 (−25.0), 0.960 (−15.0), 0.970 (−5.0), 0.987 (12.5), 0.974 (0.0), 1.011 (36.3), 1.015 (40.2), 1.021 (46.05), 1.025 (50.0), 1.037 (60.4), 1.037 (60.8), 1.05 (72.2), and 1.065 (86.0).⁸ Activation parameters were obtained from Arrhenius plots and the standard expressions

$$\Delta H^{\pm} = E_A - RT$$
$$\Delta S^{\pm} = 2.303R(\log k - \log kT/h) + \Delta H^{\pm}/T \quad (3)$$

In the conductance method, we followed the change in resistance (*R*) of solutions contained in Freas-type cells by means of a General Radio Impedance Bridge, Model 1650A, operated at 1000 cps. The same results were obtained whether the electrodes were platinized or not. To prevent evaporation of the solutions, the ground stoppers in the cells were greased and held in place by springs. Apiezon N grease was used below 25° and Apiezon T above 25°. We made certain that 1/*R* of the products (salts) were linear functions of their concentrations in the appropriate solvents. Moreover, *R* of the solutions containing any one reactant or product remained unchanged under the conditions of reaction.

A typical procedure follows. A stock solution (20 ml) of tributylphosphine (10⁻³–10⁻² *M*) was pipetted into a nitrogen-flushed cell. This was immersed to within 0.5 in. of the stopper in a constant-temperature bath. After the solution reached bath temperature, a stock solution (0.1 ml) of the haloalkyne was added to the cell, while it was shaken vigorously. *R* was followed for at least 3 half-lives. The *R*'s of the reactants in DMF were *ca.* 2–4 × 10⁵ Ω; the changes in *R* during any one run were as low as 18,000 Ω and as high as 120,000 Ω. In all ranges, *R* could be measured to three significant figures. With a temperature variation of ±0.05°, the accuracy of *R* was ∼±0.02%.

Since pseudo-first-order conditions were used, the rate law took a simple form (eq 4). *R∞* was determined after 15–20 half-lives. *kψ* was calculated from the slopes of linear plots of log

$$k[\text{Nuc}]t \equiv k_{\psi}t = 2.303 \log R(R_0 - R_\infty)/(R - R_\infty)R_0 \quad (4)$$

(*R* − *R∞*)/*RR∞* *vs. t*. Duplicate runs never varied by more than 2% (in *kψ*). The *k*'s were determined from plots of *kψ vs.* [Nuc]. Several runs in which the haloalkyne was in large excess led to the same *k* value. These data are collected in Tables II–VII.

Product Analysis in Some Mechanistically Interesting Systems.—Ampoules containing the phosphine (1.0 *M*) and the haloalkyne (0.5 *M*) in 30 ml of methanol–DMF were sealed and placed in constant-temperature baths. At appropriate times the ampoules were removed from the baths, opened, and analyzed. Products

Table II
The Reaction of Phenylbromoethyne with Triphenylphosphine in DMF

Temp, °C	$C_6H_5C\equiv CBr$, $M \times 10^3$	$(C_6H_5)_3P$, $M \times 10^3$	$k \times 10^4$,[a] $M^{-1} sec^{-1}$
86.00 ± 0.03	24.84	55.97	40.8 ± 0.7
	9.033	67.84	41.5 ± 0.8
	90.33	6.784	40.3 ± 0.7
	6.210	69.96	40.7 ± 0.8
		k_{corr}	43.5 ± 0.8
72.20 ± 0.03	24.84	55.97	15.5 ± 0.1
	9.033	67.84	15.5 ± 0.3
	90.33	6.784[b]	15.6 ± 0.3
	6.210	69.96	15.7 ± 0.3
		k_{corr}	16.3 ± 0.3
60.80 ± 0.03	24.84	55.97	6.72 ± 0.08
	9.033	67.84	6.65 ± 0.13
	90.33	6.784	6.60 ± 0.10
	6.210	69.96	6.70 ± 0.12
		k_{corr}	6.91 ± 0.12

[a] k_{corr} is the mean rate constant corrected for solvent expansion. The average deviation of k_{corr} for the four runs is shown while average deviations for the points of an individual run are also given. [b] 0.1% water was added.

Table III
The Reaction of Phenylchloroethyne with Triphenylphosphine in DMF

Temp, °C	$C_6H_5C\equiv CCl$, $M \times 10^2$	$(C_6H_5)_3P$, $M \times 10^3$	$k \times 10^6$,[a] $M^{-1} sec^{-1}$
60.40 ± 0.05	2.463	7.718	102 ± 2
	7.390	2.573	101 ± 1
	6.569	1.372	104 ± 2
	3.284	6.860	101 ± 2
		k_{corr}	106 ± 2
50.00 ± 0.05	2.463	7.718	50.2 ± 1.8
	7.390	2.573[b]	49.3 ± 0.7
	6.569	1.372	50.7 ± 0.9
	3.284	6.860	48.8 ± 1.3
		k_{corr}	51.0 ± 1.2
40.20 ± 0.03	2.463	7.718	23.8 ± 0.5
	7.390	2.573	23.5 ± 0.8
	6.569	1.372	23.5 ± 0.7
	3.284	6.860	22.3 ± 0.5
		k_{corr}	23.6 ± 0.6

[a] k_{corr} is the mean rate constant corrected for solvent expansion. The average deviation of k_{corr} for the four runs is shown while average deviations for the points of an individual run are also given. [b] 0.1% water was added.

Table IV
The Reaction of Phenylbromoethyne (8.016×10^{-4} M) with Tributylphosphine in DMF

Temp, °C	$(C_4H_9)_3P$, $M \times 10^3$	$k_\psi \times 10^4$, sec^{-1}	$k \times 10^2$,[a] $M^{-1} sec^{-1}$
-25.00 ± 0.05	8.115	1.82	2.23
	17.58	3.87	2.20
	26.38[b]	5.73	2.17
	47.48	10.22	2.15
	k_{corr}		2.03 ± 0.03
-15.00 ± 0.05	10.55	3.87	3.67
	20.57	7.02	3.42
	28.49	9.77	3.43
	37.67	12.92	3.43
	k_{corr}		3.23 ± 0.09
-5.00 ± 0.05	8.245	4.43	5.38
	17.11	9.07	5.30
	23.98	12.62	5.27
	32.98	17.00	5.15
	k_{corr}		5.00 ± 0.06

[a] k_{corr}, which is corrected for solvent contraction, is based on a graph of k_ψ vs. $[(C_4H_9)_3P]$. The average deviation is from the precision of a mean k for the four runs. The corrected k_{mean} values for the three temperatures are 2.08, 3.35, and 5.12 × 10^{-2}, respectively. [b] 0.1% water was added.

Table V
The Reaction of Phenylchloroethyne (7.785×10^{-4} M) with Tributylphosphine in DMF

Temp, °C	$(C_4H_9)_3P$, $M \times 10^3$	$k_\psi \times 10^5$, sec^{-1}	$k \times 10^3$,[a] $M^{-1} sec^{-1}$
0.00 ± 0.03	6.24	2.90	4.65
	11.32	5.00	4.42
	24.51	10.82	4.42
	50.88	23.00	4.52
	k_{corr}		4.42 ± 0.08
12.50 ± 0.03	67.36	7.65	11.4
	11.75	13.58	11.6
	24.90	29.00	11.7
	50.49	58.83	11.7
	k_{corr}		11.5 ± 0.1
25.00 ± 0.03	7.215[b]	20.83	28.8
	12.29	34.33	28.0
	25.11	71.83	28.7
	36.78	105.50	28.7
	k_{corr}		28.6 ± 0.3

[a] k_{corr}, which is corrected for solvent contraction, is based on a graph of k_ψ vs. $[(C_4H_9)_3P]$. The average deviation is derived from the precision of a mean k for the four runs. The corrected k_{mean} values for the three temperatures are 4.38, 11.4, and 28.6 × 10^{-3}, respectively. [b] 0.1% water was added.

were identified by their ir spectra and their gc retention times (Table I). For quantitative work, samples containing known amounts of *tert*-butylbenzene, an internal standard, and phenylacetylene were made up to 5 ml in DMF-CH$_3$OH. The accuracy of plots of the ratio of the peak areas of phenylacetylene to *tert*-butylbenzene vs. the concentration of phenylacetylene was ca. 4–5%. In blank experiments, no phenylacetylene could be detected in solutions of bromo- or chlorophenylacetylene (0.5 *M*) and methanol (12.4 *M*) in DMF which were kept for 4 days at 77°. When phenylethynyltriphenylphosphonium bromide (0.5 *M*) was heated in the same solvent mixture, 3.7% phenylacetylene was produced after 3 days.

The product ratio PR is defined in eq 5. Since we measured [X$^-$] and [R'C≡CH], we could only obtain a lower limit to PR

$$PR = \frac{[R'C\equiv CPR_3{}^+X^-]}{[R'C\equiv CH]} = \frac{[X^-] - [R'C\equiv CH] + [CH_3X]}{[R'C\equiv CH]} \quad (5)$$

by neglecting [CH$_3$X] in eq 5. Because of their high reactivity (Table VII), the methyl halides would eventually be consumed and our calculated PR's would approach the true values in long-

term ampoules. The expected increase and leveling off of PR can be seen in Tables VIII and IX. For subsequent discussion, we shall use our highest observed values of PR.

Unless a series was run for a certain solution for varying times, all of the single PR values of Tables VIII–X are based on at least two determinations. Where we did have a series we could also estimate crude second-order rate constants based on halide production. The scatter in these k's (and perhaps in PR too) can be ascribed to the fact that, at the high concentrations used, the time for temperature equilibration of the ampoules was comparable to the total reaction time.

Results and Discussion

Syntheses.—Most alkynylphosphonium compounds have been prepared from a phosphorus halide and an acetylide.[5,18,19] The syntheses of ethynylphosphonium

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TABLE VI

THE REACTION OF METHYL BROMIDE
WITH TRIPHENYLPHOSPHINE IN DMF

Temp, °C	CH_3Br, $M \times 10^3$	$(C_6H_5)_3P$, $M \times 10^2$	$k \times 10^4$,[a] $M^{-1} sec^{-1}$
46.05 ± 0.03	32.38	4.523	5.43 ± 0.10
	9.338	6.167	5.22 ± 0.20
	83.00	1.131	5.43 ± 0.15
	66.00	2.035	5.40 ± 0.12
		k_{corr}	5.48 ± 0.15
36.30 ± 0.03	32.38	4.523	2.82 ± 0.15
	9.338	6.167	2.82 ± 0.12
	83.00	1.131	2.88 ± 0.11
	66.00	2.035	2.92 ± 0.15
		k_{corr}	2.89 ± 0.13
25.03 ± 0.03	32.38	4.523	1.38 ± 0.01
	9.338	6.167	1.38 ± 0.01
	83.00	1.131	1.38 ± 0.01
	66.00	2.035	1.36 ± 0.01
		k_{corr}	1.38 ± 0.01

[a] k_{corr} is the mean rate constant corrected for solvent expansion. The average deviation of k_{corr} for the four runs is shown, while average deviations for the points of an individual run are also given.

TABLE VII

RATE DATA FOR PHOSPHINE DISPLACEMENT REACTIONS

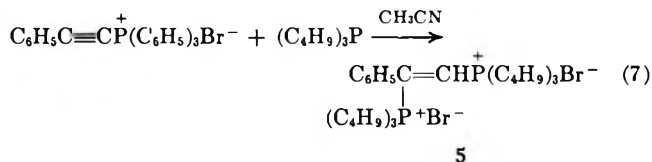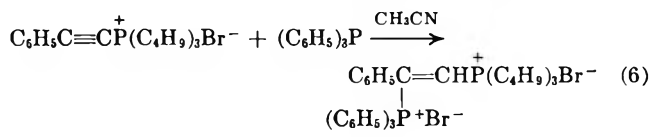| Reaction	k, $M^{-1} sec^{-1}$ at 36°	$\Delta H^{\ddagger}$,[a] kcal/ mol	$-\Delta S^{\ddagger}$,[b] eu
$C_6H_5C \equiv CBr-(C_6H_5)_3P$	8.45×10^{-5}	16.8[c]	23[c]
$C_6H_5C \equiv CCl-(C_6H_5)_3P$	1.75×10^{-4}	14.5[d]	29[d]
$C_6H_5C \equiv CBr-(n-C_4H_9)_3P$	2.20×10^{-1}	5.4[e]	44[e]
$C_6H_5C \equiv CCl-(n-C_4H_9)_3P$	5.92×10^{-2}	11.5[f]	27[f]
$CH_3Br-(C_6H_5)_3P$	2.88×10^{-3}	11.8[g]	31[g]
$n-C_3H_7Br-(n-C_4H_9)_3P$	6.0×10^{-5}[h]		
$n-C_3H_7Cl-(n-C_4H_9)_3P$	2.4×10^{-7}[h]		

[a] Uncertainty <1 kcal/mol. [b] Uncertainty <3 eu. [c] At 72.20°. [d] At 60.40°. [e] At −15.00°. [f] At 12.50°. [g] At 36.30°. [h] Reference 24. k was determined at 34.97°. The solvent was acetone.

salts from 1-haloalkynes, as in eq 2, is at least as direct and convenient. The first reports mention fluoroacetylene, chloroacetylene, phenylbromo- and phenylchloroacetylene.[2b,3d,4] In our work, high yields of 1a–d were obtained in 2–3 days in ether at 25° according to eq 2. For salts 1e–g, longer reaction times were required and lower yields were obtained.

Like typical phosphonium compounds, the bromides were generally solids while the chlorides were obtained as oils. These could be converted into solid chloroplatinate and tetraphenylboron derivatives which were used for elemental analysis. These salts exhibit a moderately strong ir $C \equiv C$ stretching band at 2150–2200 cm^{-1} and the ethynylphosphonium compounds also show the characteristic CH band at *ca.* 3200 cm^{-1}. The nmr spectrum of 1b shows an H–P coupling constant of 28 Hz. Compounds 1 are relatively stable toward heat and oxygen: salts kept for 1 year in contact with atmosphere showed no change in their ir spectra; only at temperatures above 250° is there any appreciable decomposition. In the presence of aqueous refluxing base, however, 1a decomposed to triphenylphosphine oxide and phenylacetylene. Other nucleophiles, *e.g.*, amines and alkoxides, attack the carbon β to phosphorus, giving vinylphosphonium salts;[4] for example, when 1a is heated in water, phenacyltriphenylphosphonium bromide is obtained.[4]

Unlike the haloacetylenes and phenylhaloacetylenes, the applicability of process 1 to the alkylhaloacetylenes has not yet been established. This is not because the latter are inert to triphenyl- or tributylphosphine, for we have been able to obtain products (or derivatives) from several of them. At present, we tentatively ascribe the unsatisfactory elementary analyses of these products to the fact that they consisted of mixtures deriving from nucleophilic attack at halogen, at carbon α and at carbon β, as well as from further conversion of the initial products (see below). Judging by our difficulties with the ethynylphosphonium salts, we suggest that the mere observation of salt formation and an ir peak in the $C \equiv C$ region[3d] is not really a structure proof for 1.

We have examined the reactions of phenylethynyltributylphosphonium bromide with triphenylphosphine and phenylethynyltriphenylphosphonium bromide with tributylphosphine in acetonitrile. Nmr and elemental analysis indicated that α,β-diphosphonium salts 4 and 5 were formed in 20–25% yield. The overall processes given by eq 6 and 7 do not specify the

$$C_6H_5C \equiv \overset{+}{C}P(C_4H_9)_3Br^- + (C_6H_5)_3P \xrightarrow{CH_3CN}$$

$$C_6H_5C = CH\overset{+}{P}(C_4H_9)_3Br^- \quad (6)$$
$$\underset{(C_6H_5)_3\overset{+}{P}Br^-}{|}$$

4

$$C_6H_5C \equiv \overset{+}{C}P(C_6H_5)_3Br^- + (C_4H_9)_3P \xrightarrow{CH_3CN}$$

$$C_6H_5C = CH\overset{+}{P}(C_4H_9)_3Br^- \quad (7)$$
$$\underset{(C_4H_9)_3\overset{+}{P}Br^-}{|}$$

5

origin(s) of the "extra" hydrogen and bromine atoms, but these presumably derive from the reactants and the medium. Since ethynylphosphonium salts (1) are activated acetylenes, initial attack by bromine ion or phosphine on 1 is plausible and has precedent.[4,20] The following observations provide support for this idea: triphenylphosphine hydrobromide adds to 1a in acetonitrile to yield the α,β-bis[triphenylphosphonium]-styrene dibromide[4] or to other alkynes to give vinylphosphonium salts;[21,22] triphenylphosphine reacts with β-bromoacrylic acid in benzene to give α,β-bis[triphenylphosphonium]ethylene dibromide. The formation of 5 involves the substitution of tributylphosphine for triphenylphosphine, the weaker base and nucleophile;[23,24] whether phosphine exchange precedes or follows addition is not determined by our data.

The reactions of phenylbromoethyne with other Group V nucleophiles, triphenylantimony, triphenylbismuth, and triphenylarsenic in boiling xylene (10 hr), failed to produce salts analogous to 1, although such compounds are known.[19] Since trialkylamines do react,[2a] it appears that basicity may be an important

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Table VIII
The Reaction of $C_6H_5C{\equiv}CBr$ with $(C_6H_5)_3P$ (1.0 M) in DMF and Varying Concentrations of Methanol at 77°

[CH₃OH], M	[C₆H₅C≡CBr], $M \times 10$	Time, min	[C₆H₅C≡CH], $M \times 10^2$	[Br⁻],[a] $M \times 10$	PR'[b]	$k \times 10^3$,[c] M^{-1} sec⁻¹
0	3.98	2880	0	3.975		2.2
1.00	5.0	2.0	1.23	0.9915	7.1	2.0
		5.0	1.62	2.439	14	2.7
		15.0	1.59	3.827	23	2.2
		27.0	1.99	3.996	19	1.3
2.47	5.0	25.0	3.92	4.422	10.3	2.1
4.94	5.0	3.0	2.75	1.011	2.7	1.3
		7.0	3.93	2.121	4.4	1.5
		13.5	4.49	4.283	8.5	3.5
		60.0	4.91	4.898	9.0	1.8
6.20[d]	4.02	2880	6.35	4.015	5.3	
8.65	5.0	2.6	6.18	2.115	2.4	4.0
		3.0	6.11	1.983	2.3	3.2
		7.1	8.43	3.351	3.0	3.3
		13.0	9.61	4.402	3.6	4.0
12.4[d]	3.95	2880	13.2	3.950	2.0	
19.8[d]	4.5	2880	29.1	4.470	0.54	

[a] [Br⁻] = [C₆H₅C≡CP(C₆H₅)₃⁺] + [CH₃P(C₆H₅)₃⁺]. [b] PR' = ([Br⁻] − [C₆H₅C≡CH])/[C₆H₅C≡CH]; this ratio is a lower limit to PR; see eq 7. [c] These k's are based on the bromide analyses. They are crude values (see text). [d] Run at 70°.

Table IX
The Reaction of $C_6H_5C{\equiv}CCl$ (0.5 M) with $(C_6H_5)_3P$ (1.0 M) in DMF and Varying Concentrations of Methanol at 77°

[CH₃OH], M	Time, min	[C₆H₅C≡CH], $M \times 10^2$	[Cl⁻],[a] $M \times 10$	PR'[b]	$k \times 10^3$,[c] M^{-1} sec⁻¹
0	2880	0	5.0		3.1
2.47	5.0	2.98	3.143	9.5	4.1
	9.0	2.30	3.907	16	3.8
	22.5	3.33	4.670	13	3.2
7.41	3.0	1.48	1.210	7.2	1.7
	8.0	2.43	2.717	10.2	1.9
	13.5	3.78	4.343	10.5	3.6
12.4	3.0	0.843	0.7139	7.4	0.9
	6.0	2.26	2.320	9.3	2.0
	13.0	2.93	3.966	12.5	2.7
	16.2	3.02	3.708	11.3	1.8

[a] [Cl⁻] = [C₆H₅C≡CP(C₆H₅)₃⁺] + [CH₃P(C₆H₅)₃⁺]. [b] PR' = ([Cl⁻] − [C₆H₅C≡CH])/[C₆H₅C≡CH]; this is a lower limit to PR; see eq 7. [c] These k's are based on chloride analyses. They are crude values (see text).

Table X
The Phosphine–Phenylhaloacetylene (R_3P–$R'X$) Reactions in 12.4 M Methanol in Dimethylformamide at 70°

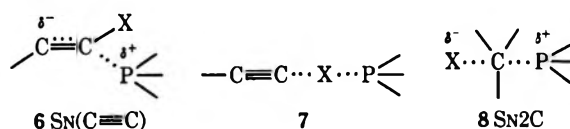| R[a]	X	[R'X], $M \times 10$	[C₆H₅C≡CH], $M \times 10^2$	PR'[b]	R'R₃P⁺X⁻[c]
n-C₄H₉	Br	4.030	27.1	~0	—
C₆H₅	Br	3.825	11.7	2.3	+
n-C₄H₉	Cl	4.300	22.5	0.91	+
C₆H₅	Cl	4.195	6.0	6.0	+

[a] [(C₄H₉)₃P] = [(C₆H₅)₃P] = 1.0 M. [b] PR' = ([C₆H₅C≡CP-(C₆H₅)₃⁺X⁻] + [CH₃P(CH₃)₃⁺X⁻] − [C₆H₅C≡CH])/[C₆H₅-C≡CH]. Reactions were allowed to proceed to 100% completion. [c] Ethynylphosphonium salts were isolated as chloroplatinates. Analysis by gc showed that R₃PO was also produced in these reactions. At low conversion CH₃X was found by gc.

factor in determining the reactivity of nucleophiles with haloalkynes.

Kinetics.—All of the reactions of haloalkynes and phosphines in DMF proceeded according to eq 1 and produced 1, as in eq 2. The processes were first order in each reagent. The rate data are given in Tables II–V and VII. Two features of the activation parameters stand out. The negative entropies of activation are comparable to others found for reactions of molecules which produce ions.[25] The $\Delta H^{\ddagger}$ = 5.4 kcal/mol and $\Delta S^{\ddagger}$ = −44 eu are unusually low for substitution of an organic halide and may indicate a mechanistic discontinuity, a point to which we shall return shortly.

In order to compare reactivities at different carbon sites, we included methyl bromide[26] in our work (Tables VI, VII). At 36°, k (CH₃Br)/k (C₆H₅C≡CBr) = 34 for triphenylphosphine. If, however, we compare Henderson and Buckler's kinetic data for tributylphosphine and the 1-propyl bromide or chloride in acetone[24] with the corresponding data for the phenylhaloacetylenes, the rate ratio k (sp) > k (sp³). (DMF and acetone are similar solvents for molecule–molecule reactions.[27]) Such comparisons are given here to dispel a general impression about the inertness of haloalkynes in process 1 but they can be misleading for two reasons. The "standard" n-alkyl halide presumably reacts by concerted displacement, while halounsaturates react by stepwise processes. As between halounsaturates and haloalkanes the transition states to be compared are different (6 or 7 vs. 8). Secondly, broad generaliza-

6 S_N(C≡C)   7   8 S_N2C

tions based on specific unreactive systems, e.g., haloalkyne–nucleophile in proton solvents or phenylchloroacetylene–iodide in acetone,[28] simply do not stand up.

To compare reactivities at an unsaturated carbon, we ran the reaction of tributylphosphine with β-bromo-p-nitrostyrene (0.1 mol) in benzene at ca. 80°. No ionic bromide (<5%) was found after several days. Pattenden and Walker recently found that activated

(25) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1965, p 138.

(26) The first standard we tried was n-butyl bromide, triphenylphosphine in DMF, but elimination rather than displacement occurred.

(27) (a) M. H. Abraham, *Chem. Commun.*, 1307 (1969); (b) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

(28) (a) J. A. Nieuwland and R. R. Vogt, "The Chemistry of Acetylene," Reinhold, New York, N. Y., 1945, p 71; (b) M. J. Murray, *J. Amer. Chem. Soc.*, **60**, 2662 (1938).

haloalkenes, *e.g.*, β-haloacrylic acids, reacted readily with tributyl- or triphenylphosphine in benzene but that α- or β-alkyl-β-haloacrylic acids or β-chlorovinyl ketones did not react under forcing conditions.[22] With 1-bromo- and 1-chloro-2,4-dinitrobenzene and phosphines, facile displacement has been found.[1b] Taking into account the activation by substituents, we can set up the following tentative rate sequence for phosphine nucleophiles at an unsaturated carbon site in DMF: k (sp) $\gg k$ (sp^2) $\sim k$ (sp$^{2.5}$).

The effect of methanol in phenylhaloacetylene–triphenylphosphine systems may seem puzzling at first glance (Tables VIII, IX). For phenylchloroacetylene, both the rate constants and the PR are roughly constant, *i.e.*, PR $\cong$ 12.5 ± 1.5 in 2.5–12.4 *M* methanol; for phenylbromoacetylene, the rate constant does not vary much, but the PR changes markedly, *i.e.*, PR = 0.54–19 in 1–19.8 *M* methanol. In the next section, we shall argue that if a single process were involved, one might expect roughly parallel effects, but if two competing processes, a and c of eq 2, are involved and their weights are different for the two substrates, one could expect to find a differentiating medium effect.

Mechanisms.—Detailed mechanisms for *two* alternatives in eq 2, namely attack on the terminal carbon (a) *vs.* attack on halogen (c), will be considered here. Both steps may be rate determining and reversible. Second-order kinetics do not distinguish between them. We must resort, therefore, to other means to establish the competitive nature of process 1.

Consider our "element" effect. It will be recalled that in substitution reactions of organic halides, k (Cl) $\ll k$ (Br), when carbon–halogen bond breaking *is* involved; but k (Cl) $\gtrsim k$ (Br), when carbon–halogen bond breaking *is not* involved in the rate-determining step. The former reactivity order is found in the S$_N$2C reaction of the tributylphosphine and propyl halides (Table VII)[24] and the S$_N$2Hal reaction of triethyl phosphite and 1-halo-3-methylbut-1-yn-3-ols;[28] the latter reactivity order is found in substitutions at aryl and vinyl carbons.[29] Both orders are found in the phenylhaloacetylenes: with triphenylphosphine k (Cl) $> k$ (Br) and with tributylphosphine k (Cl) $< k$ (Br) (see Table VII). On this basis, we would favor step a for triphenylphosphine and step c for tributylphosphine. Another plausible "arrangement," in which the pattern of activation parameters is taken into account, would assign only the system phenylbromoacetylene–tributylphosphine to path c in eq 2. An interesting situation involves the syntheses triphenylphosphine with fluoro- or chloroacetylene to give 1;[3d] the fact that fluoroacetylene reacts much more rapidly indicates a strong preference for path a in eq 2.

More direct insight into the mechanism is afforded by those systems in which a trapping agent such as methanol is present. The appearance of parent acetylene with or without product 1 is compelling evidence for the existence of steps c and e in eq 2. The product ratio as defined in eq 5 may now be used to set limits on the competition in eq 2, *i.e.*, PR $\leq k_a/k_c$. Although such an approach is probably oversimplified here, it appears to apply to the reaction of phenylbromoacetylene with

methoxide[2b] and it does convey the essential notion that the substitution process 1 may be more complex than it seems.

If the steady-state assumption is applied to the intermediates 2 and 3 of eq 2, one can derive the product ratio expression eq 8 for a given concentration of methanol. The steady-state assumption would appear to

$$\text{PR} = \frac{k_a k_b(k_c + k_d + k_e[\text{CH}_3\text{OH}])}{k_c k_e(k_{-a} + k_b)[\text{CH}_3\text{OH}]} + \frac{k_d}{k_e[\text{CH}_3\text{OH}]} \quad (8)$$

be sound, but the possible medium dependence of each k limits the utility of eq 8 to limited regions of solvent composition. For our purposes, it will suffice to outline two of the numerous mechanistic variations following from the kinetic analysis.

In our trapping experiments with methanol (Tables VIII–X), we found that one system was unique; *i.e.*, tributylphosphine and phenylbromoacetylene gave methyl halide, tributylphosphine oxide, phenylacetylene, and none of 1 (Table X). On this basis, we can say that $k_a \simeq 0$ and $k_d \ll k_e[\text{CH}_3\text{OH}]$; only the second term on the right hand side of eq 8 survives! By way of contrast, tributylphosphine and phenylchloroacetylene gave these products as well as 1 (Table X). We do not believe that the relatively rapid partitioning of 3 in eq 2 should be highly sensitive to structure. (The possibility that the chloro ion pair is diverted to the substitution product 1 more readily than the ion pair formed from the bromoalkyne is unlikely; phosphorochloridates, for example, undergo nucleophilic displacement at a faster rate than the corresponding fluoridates.[30]) We can conclude that k_d and the second term of eq 8 can be neglected, except when [CH$_3$OH] → 0. It thus appears that the reaction of tributylphosphine with phenylbromoacetylene follows step c and with phenylchloroacetylene follows both steps a and c.

We turn to the three remaining systems in which both 1 and phenylacetylene are produced in methanol–DMF. If nucleophilic attack on halogen were exclusive or $k_a \simeq 0$, a plot (eq 8) of PR *vs.* 1/[CH$_3$OH] should be linear, have a slope of k_d/k_e, and pass through the origin. Unfortunately, there is sufficient uncertainty both in the estimated PR values and in the long extrapolation to 1/[CH$_3$OH] = 0 to leave open the question of the limiting slope and intercept. As we have indicated above, it does not appear necessary to include step d in any of our systems when [CH$_3$OH] is moderate or high; thus, we *must* accept a contribution from step a. Further support of the notion of competition between steps a and c comes from the high PR values in 0–8 *M* methanol. Finally, if the data for phenylchloroacetylene–triphenylphosphine (Table IX) are plotted to test eq 8,[1b] one obtains results which are quite decisive: the intercept of a linear plot is substantial at *ca.* 12 and the slope is zero or negative. We take this as strong evidence for the operation of both steps a and c.

Based on the preceding interpretation, the rate constant for the formation of product 1 in the absence of proton donor would have the form of eq 9. In the case

$$k_{\text{obsd}} = \frac{k_a k_b}{k_b + k_{-a}} + \frac{k_c k_d}{k_d + k_{-c}} \quad (9)$$

(29) (a) Z. Rappoport, *Advan. Phys. Org. Chem.*, **7**, 1 (1969); (b) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, Amsterdam, 1968, Chapter 5; (c) S. D. Ross, *Progr. Phys. Org. Chem.*, **1**, 31 (1963).

(30) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, p 274.

of tributylphosphine–phenylbromoacetylene, the first term is small, if not negligible; in the three other phosphine–haloalkyne systems, both terms contribute, the first being more important than the second. Equation 9 does not lend itself to facile interpretation of rate data, *e.g.*, activation parameters, element effects, solvent variations, etc. With some plausible, but *ad hoc* assumptions, we can obtain the more tractable form, eq 10, and refine our rationalizations: the "abnormal"

$$k_{obsd} \simeq k_a + k_c k_d / k_{-c} \qquad (10)$$

activation energy and entropy for tributylphosphine–phenylbromoacetylene (Table VII) is associated with a composite rate constant $k_c k_d / k_{-c}$; the element effect and the activation parameters for the reactions of triphenylphosphine and the phenylhaloacetylenes appear to derive from different mixes of the two terms in eq 10 (or eq 9); the rates of formation of 2, a dipole, and 3, an ion pair, in eq 2 have different susceptibilities to added methanol, hence the different behavior of the phenylhaloacetylenes (Tables VIII, IX), etc.

In summary, we have suggested that phenylbromoacetylene tends to favor step c of eq 2 and phenylchloroacetylene takes both branches a and c. The methanol scavenging results, the element effect, and perhaps the activation parameters support this approach. Certainly, the rejection of step a by some chemists was premature. It is clear, however, that careful kinetic and product studies over the whole

DMF–CH₃OH solvent range will be necessary before eq 8 can be fully exploited and the mechanistic details filled in. Variations on the mechanisms of process 1 appear in the companion paper.[2a]

Nucleophilic Substitution at an Acetylenic Carbon. Kinetics, Mechanism, and Syntheses with Tertiary Amines[1]
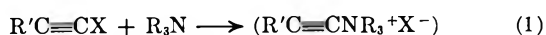
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Haloalkynes cleave one bond at the amine bridgehead to produce ynamines 9 or amides 10. A number of new substitution products have been obtained with phenylbromo- or phenylchloroacetylene and 1,4-diazobicyclo[2.2.2]octane (Dabco), brucine, dihydrobrucine, quinuclidine, as well as with 2′-(3-chloro-1,1-dimethyl-2-propynyloxy)tetrahydropyran and Dabco. Rate data for the second-order reactions of several halides with Dabco in acetonitrile are ($\Delta H^{\ddagger}$, kcal/mol; $-\Delta S^{\ddagger}$, eu; $10^4 k$, M^{-1} sec^{-1} at 60°): C₆H₅C≡CBr (14.2, 30, 7.95); C₆H₅C≡CCl (10.7, 40, 10.6); n-C₄H₉Cl (13.8, 34, 1.82). Toward Dabco, the electrophilic order of carbon sites is k (sp) ⩾ k (sp³) > k (sp²·⁵). Although Dabco does appear to abstract halogen from the phenylhaloacetylenes, this appears to be far less important than attack on the terminal carbon, which leads to ynamines 2.

As a part of our interest in nucleophilic displacement reactions at the triple bond, we studied both the synthetic and mechanistic aspects of process 1.[2] When this work was begun, the sp carbon to nitrogen bond system, $-C≡CN<$, was essentially unknown. In

$$R'C≡CX + R_3N \longrightarrow (R'C≡CNR_3^+X^-) \qquad (1)$$

the meantime, alkynylamines or ynamines have been prepared by several routes and shown to be interesting

and useful synthetic intermediates.[3,4] Our present contribution emphasizes the kinetics, mechanism, and some synthetic applications of bridgehead amines in process 1.

Certain complications in reaction 1 are worth attention.[3a] A haloalkyne may form charge transfer complexes, *e.g.*, C₆H₅C≡CI·H₂NC₆H₅.[5] Alternatively, the "positive" halogen may be abstracted by the nu-

(1) Research supported by National Institutes of Health Grant GM 07021. This work was taken from the Ph.D. thesis of J. I. D., Illinois Institute of Technology, 1970.

(2) (a) J. I. Dickstein and S. I. Miller, *J. Org. Chem.*, **37**, 2168 (1972); (b) H. G. Viehe, S. I. Miller, and J. I. Dickstein, *Angew. Chem., Int. Ed. Engl.*, **3**, 582 (1964); (c) A. Fujii, J. I. Dickstein, and S. I. Miller, *Tetrahedron Lett.*, 3435 (1970); (d) R. Tanaka and S. I. Miller, *J. Org. Chem.*, **36**, 3856 (1971); (e) A. Fujii and S. I. Miller, *J. Amer. Chem. Soc.*, **93**, 3694 (1971); (f) A. K. Kuriakose and S. I. Miller, *Tetrahedron Lett.*, 905 (1962); (g) R. Tanaka, M. Rodgers, R. Simonaitis, and S. I. Miller, *Tetrahedron*, **27**, 2651 (1971).

(3) (a) H. G. Viehe in "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 12; (b) S. Y. Delavarenne and H. G. Viehe, Chapter 10; (c) H. G. Viehe, U. S. Patent 3,520,942 (1970); *Chem. Abstr.*, **73**, 98490 (1970); (d) S. Y. Delavarenne and H. G. Viehe, *Chem. Ber.*, **103**, 1198, 1209 (1970); (e) A. Halleux, H. Reimlinger, and H. G. Viehe, *Tetrahedron Lett.*, 3141 (1970).

(4) (a) L. I. Peterson, U. S. Patent 3,499,928 (1970); *Tetrahedron Lett.*, 5357 (1968); (b) T. Sasaki and A. Kojima, *J. Chem. Soc. C*, 476 (1970); (c) J. Freear and A. E. Tipping, *ibid.*, 411 (1969); (d) J. Ficini and C. Barbara, *Bull. Soc. Chim. Fr.*, 2787 (1965); (e) W. G. Galesloot, M. J. A. De Bie, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **89**, 575 (1970).

(5) R. H. Baughman, *J. Org. Chem.*, **29**, 964 (1964).

$$-C\equiv CH \xleftarrow{R_2NH} -C\equiv CX \xrightarrow{R_2NH} -CH=CXNR_2 \xrightarrow{H_2O} -CH_2CONR_2$$

$$\mathbf{7} \qquad\qquad\qquad \mathbf{3} \qquad\qquad \mathbf{6}$$

$$-C\equiv CNHR_2^+X^- \underset{R_2NH}{\overset{R_2NH}{\rightleftarrows}} -C\equiv CNR_2 \xrightarrow{R_2NH} -CH=C(NR_2)_2 \longrightarrow -CHC=NR$$

$$\mathbf{1} \qquad\qquad \mathbf{2} \qquad\qquad \mathbf{4} \qquad\qquad\qquad \underset{NR_2}{|}$$

$$\mathbf{5}$$

(2)

cleophile to produce an ion pair, which in the presence of a proton source (solvent or nucleophile) may give an acetylenic hydrocarbon, *e.g.*, 7.[6a-c] Moreover, the substitution process as such may be masked if the amine contains mobile protons: any ynamines formed in these reactions will tautomerize to give nitriles or imines, *e.g.*, 5; addition–elimination sequences can also intrude and give 4.[3a,6d,7] Because an ynamine is a weak base, alkyl or hydrogen interchange normally takes place,[2b,6] and the isolation of the initial displacement product, an ethynylammonium salt, is rare.[2d,3a] An additional problem which can prevent the recovery of an ynamine is its facile hydration.[3a,6,7] Thus, the products of reactions of dialkylamines with dichloroacetylene were 3–6,[7a] with phenylbromoacetylene were 4, 6, and 7,[6b] and with 1-bromo-3-methyl-1-pentyn-3-ol were 6, 7, and some decomposition products. Some of these problems are alleviated when haloalkynes are treated with alkali metal dialkylamides or trialkylamines in aprotic solvents, and successful replacements have been effected.[2b,d,3a-d]

Experimental Section

Certain analyses, instruments, procedures, compounds, etc., employed here have been described in the accompanying paper.[2a]

Materials.—Anhydrous acetonitrile was distilled from anhydrous sodium carbonate, bp 82° (760 mm), n^{20}D 1.3440 [lit.[8] bp 81–82° (760 mm), n^{20}D 1.3442], no trace of water by infrared spectra (ir), and one peak by gas chromatography (gc). Liquid amines were distilled over KOH and stored under nitrogen. 1,4-Diazobicyclo[2.2.2]octane (Dabco) was recrystallized from methanol–ether (1:1) to mp 155–157° (lit.[9] mp 155–157°); it was water-free, as judged by its ir spectrum. Quinuclidine was distilled under high vacuum at *ca.* 25° into a trap (−78°), taken up in ether, and dried overnight with sodium sulfate. On evaporation of the ether, quinuclidine was recovered, mp 157–158° (lit.[8] mp 158°).

Brucine was recrystallized from acetone–water, mp 176–178°, $[\alpha]^{25}$D −113° (*c* 0.8520, CHCl₃) [lit.[10,11] mp 178°, $[\alpha]^{30}$D −117° (CHCl₃)]. Dihydrobrucine was prepared by the hydrogenation of brucine (5.23 g, 0.0133 mol) in ethanol over platinum(IV) oxide (0.5 g) and recrystallized from ethyl acetate. After drying at 100° (1 mm), it had mp 181–182° and $[\alpha]^{25}$D 5.2° (*c* 2.3114, CHCl₃) [lit.[11] mp 182°, $[\alpha]^{30}$D 7.6° (CHCl₃)].

n-Butyl chloride was fractionally distilled, and had bp 79°, n^{20}D 1.4010, and one gc peak [lit.[10] bp 78.5°, n^{20}D 1.4016].

N-Phenylethynyl-N-2-(4-aza-1-azoniabicyclo[2.2.2]octane)-ethylpiperazine Bromide.—Phenylbromoacetylene (18.1 g, 0.1 mol) was mixed with Dabco (22.4 g, 0.2 mol) in ether and left for several days at *ca.* 25°. The quaternary salt which

(6) (a) V. Wolf and W. Block, *Justus Liebigs Ann. Chem.*, **637**, 119 (1960); (b) V. Wolf and F. Kowitz, *ibid.*, **638**, 33 (1960); (c) V. Wolf, W. Block, and H. Piater, *ibid.*, **682**, 112 (1965); (d) V. Wolf and H. Piater, *ibid.*, **696**, 90 (1966).

(7) (a) E. Ott and G. Dittus, *Chem. Ber.*, **76**, 80 (1943); (b) R. Truchet, *Ann. Chim. (Paris)*, **16**, 309 (1931).

(8) "Handbook of Tables for Organic Compound Identification," Z. Rappoport, Ed., Chemical Rubber Co., Cleveland, Ohio, 1967.

(9) S. D. Ross, J. J. Bruno, and R. C. Petersen, *J. Amer. Chem. Soc.*, **85**, 3999 (1963).

(10) I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, London, 1965.

(11) H. Wieland and W. Munster, *Justus Liebigs Ann. Chem.*, **480**, 39 (1930).

separated was filtered, dissolved in chloroform, and reprecipitated by the addition of ether. This procedure often gave an oil, but after several cycles a solid could be obtained in *ca.* 85% yield: mp 144° dec; ir (CHCl₃) 4.51 (C≡C) and 6.07 μ (C=O); nmr (DCCl₃) δ 7.3–7.4 (5 ArH) and 2.5–4.0 (24 CH₂, m).

Anal. Calcd for C₂₀H₂₉BrN₄: C, 59.25; H, 7.21; Br, 19.71. Calcd for C₂₀H₂₉BrN₄·H₂O: C, 56.73; H, 6.86; Br, 18.87. Found: C, 58.35; H, 7.23; Br, 19.43.

Acidic hydrolysis (25% sulfuric acid) of this compound (10 g, 0.025 mol) gave phenylacetic acid (1 g), mp 76–77°, identical by ir and mixture melting point comparison with an authentic sample.

N-Phenylethynyl-N-2-(4-aza-1-azoniabicyclo[2.2.2]octane)-ethylpiperazine Chloride.—This compound was prepared by the procedure described above for the bromide. The chloride was very hygroscopic and the oil which was isolated in *ca.* 70% yield could not be crystallized. The ir spectrum of the oil was identical with that of N-phenylethynyl-N-2-(4-aza-1-azoniabicyclo[2.2.2]octane)ethylpiperazine bromide, ir (CHCl₃) 4.51 (C≡C) and 6.05 μ (C=O).

Anal. Calcd for C₂₀H₂₉ClN₄: Cl, 9.85. Calcd for C₂₀H₂₉ClN₄·H₂O: Cl, 9.38. Found: Cl, 9.52.

Reaction of 2'-(3-Chloro-1,1-dimethyl-2-propynyloxy)tetrahydropyran with Dabco.—The pyranyl ether (10.2 g, 0.05 mol) was heated with Dabco (11.2 g, 0.1 mole) in 250 ml of ether for *ca.* 1 month. The crude product (9.0 g, 40% yield) was removed from the reaction mixture by filtration. The quaternary chloride salt showed an amide band at 6.11 μ and no C≡C absorption in the infrared. This material was dissolved in water and treated with sodium tetraphenylboron to give a quantitative amount of the tetraphenylboron salt. The tetraphenylboron compound was recrystallized in ethanol–water (80:20, v/v) and had mp 65° dec.

Anal. Calcd for C₄₆H₆₁BO₃N₄: C, 75.80; H, 8.44. Found: C, 75.58; H, 7.75.

N-Phenylethynyl-2-(1-azabicyclo[2.2.2]octane)ethylpiperidine Bromide.—Phenylbromoacetylene (1.81 g, 0.01 mol) and quinuclidine (2.22 g, 0.02 mol) were dissolved in ether (100 ml) and allowed to stand at *ca.* 25° for 1 week. The insoluble product (2.56 g, 64% yield) was isolated by filtering the reaction mixture. The crude mixture exhibited a C≡C absorption at 4.50 μ and an amide carbonyl band at 6.11 μ. Treatment of this material with water completely removed the C≡C linkage. An nmr proton countr evealed that 1 mol of phenylbromoacetylene had reacted with 2 mol of quinuclidine to form the product. The amide salt was dissolved in water and treated with sodium tetraphenylboron. A quantitative yield of the tetraphenylboron derivative was obtained. This material was recrystallized from ethanol–water (80:20, v/v): mp 77–80° dec; ir (KBr) 6.10 μ (C=O); nmr (CHCl₃) δ 6.6–7.4 (25 ArH) and 0.8–4.2 (28 alkyl H).

Anal. Calcd for C₄₆H₅₃BON₂: C, 83.61; H, 8.08. Found: C, 83.91; H, 8.04.

18-Bromo-19-(phenylacetyl)-18,19-secobrucine and 20-Bromo-19-(phenylacetyl)-19,20-secobrucine.—Phenylbromoethyne (9.0 g, 0.05 mol) and brucine (13.0 g, 0.033 mol) were dissolved in 200 ml of benzene and left at *ca.* 25° for several days. The products precipitated out of the benzene solution and 18 g (crude yield 92%) was isolated from the reaction mixture by filtration. Fractional crystallization in absolute ethanol resulted in the separation of two isomers. Neither isomer showed C≡C absorption in the ir. Since brucine contains an amide grouping (ring C), the hydration of the phenylethynyl moiety attached to the nitrogen of brucine could not be established by ir. Nmr proton counts indicated that both products resulted from the union of 1 mol of phenylbromoacetylene with 1 mol of brucine.

Isomer A had mp 186° dec, $[\alpha]^{25}$D +23.62° (*c* 0.7430, CHCl₃), nmr (DCCl₃) δ 5.5–8.3 (ArH, 7 =CH, broad) and 0.8–5.0 (25 alkyl H, broad).

Anal. Calcd for $C_{31}H_{33}O_5N_2Br$: C, 62.73; H, 5.60. Found: C, 62.36; H, 5.84.

Isomer B had mp 216° dec, $[\alpha]^{25}D$ +106.12° (*c* 0.8745, CHCl₃), nmr (DCCl₃) δ 5.5–8.3 (7 ArH, 1 =CH, broad) and 0.8–5.0 (25 alkyl H, broad).

Anal. Calcd for $C_{31}H_{33}O_5N_2Br$: C, 62.73; H, 5.60. Found: C, 62.31; H, 5.75.

Isomer B (0.77 g, 0.0013 mol) was dissolved in 120 ml of absolute ethanol containing PtO₂ (0.188 g) and hydrogenated. The dihydrobrucine product had mp 215° dec, $[\alpha]^{25}D$ +82.34° (*c* 1.0069, CHCl₃).

Anal. Calcd for $C_{31}H_{33}O_5N_2Br$: C, 62.52; H, 5.92. Found: C, 63.22; H, 6.59.

Reaction of Phenylbromoacetylene with Dihydrobrucine.—Dihydrobrucine (1.98 g, 0.005 mol) and phenylbromoacetylene (1.4 g, 0.0075 mol) were heated in benzene (100 ml) for *ca.* 2 days. The crude product (1.76 g, 50% yield) was isolated from the reaction mixture by filtration. This material was recrystallized from ethanol, mp 270° dec, $[\alpha]^{25}D$ +73.7° (*c* 1.4380, CHCl₃).

Anal. Calcd for $C_{31}H_{35}O_5N_2Br$: C, 62.52; H, 5.92. Found: C, 62.38; H, 5.76.

18-Chloro-19-(phenylacetyl)-18,19-secobrucine and 20-Chloro-19-(phenylacetyl)-18,19-secobrucine.—Phenylchloroacetylene (4.1 g, 0.03 mol) and brucine (7.5 g, 0.019 mol) were dissolved in benzene (100 ml). The reaction mixture was allowed to stand at *ca.* 25° for 1 week and 6.0 g (58% yield) of the crude products was isolated by filtration. The ir spectrum of this material was identical with that of phenylbromoethyne–brucine crude product. Isomers C and D, obtained by fractional crystallization of crude material in absolute ethanol, are obvious as analogs of compounds A and B. Therefore, we include D, despite a poor analysis.

Isomer C had mp 174–177° dec.

Anal. ' Calcd for $C_{31}H_{33}O_5N_2Cl$: C, 67.81; H, 6.06. Found: C, 67.34; H, 6.20.

Isomer D had mp 208–210° dec.

Anal. Calcd for $C_{31}H_{33}O_5N_2Cl$: C, 67.81; H, 6.06. Found: C, 66.71; H, 6.04.

Reactions of Phenylbromoacetylene with Trialkyl Amines and Amides.—Phenylbromoethyne (18.1 g, 0.1 mol) and triethylamine (20.2 g, 0.2 mol) in ether or toluene (200 ml) were kept at *ca.* 25°. (Higher temperatures led to lower product yields.) Tetraethylammonium bromide precipitated; this was filtered off and purified by repeated solution in chloroform followed by ether precipitation. The yield was 71%. Identification was made with an authentic sample by ir and elemental analysis. The final work-up of the second product was a short-path distillation of an oil at 50° (10⁻³ mm). This gave *N,N*-diethylphenylacetamide (4.1 g, 21%), ir (neat) 6.20 μ (C=O), $n^{22}D$ 1.5323, identical with an authentic sample by ir and elemental analysis.

The general procedure just outlined, except for variations in details, *e.g.*, solvent, temperature, etc., was used with other nitrogen nucleophiles. The haloalkyne and amine or lithium amide in anhydrous ether, toluene, or DMF were kept at ~25° for several days. Work-up of the mixtures yielded salts and intractable tarry residues. As a synthesis of ynamines from phenylbromoacetylene, our experiments were negative; the fact that trimethyl- and tri-*n*-propylamine yielded tetraalkylammonium salts just as with triethylamine indicates that ynamines probably had formed.[3a-c] From secondary amines, *e.g.*, piperidine, di-*n*-butylamine, and di-*tert*-butylamine, the corresponding ammonium hydrobromides were isolated. No isolable products could be obtained with tri-*n*-hexylamine, *N*-methylpyrrolidine, pyridine, quinoline, acridine, lithium piperidide, lithium diethylamide, and lithium dibutylamide, although reaction with ionic halide and tar formation were observed.

Kinetics.—The methods of the companion paper were used.[2a] In each case, the identity of the products and stoichiometry of the reactions (see eq 5) were verified under the conditions used in the rate studies. For the reaction of phenylbromoacetylene with Dabco, rate law 3 was used. Where appropriate, the conductances of the product salts were shown to be linear functions of their concentrations. All of the rate constants have been corrected for the thermal expansion of the solvent (CH_3CN)

$$kt = 2.303(2a - b)^{-1}\log b(a - x)/a(b - 2x) \qquad (3)$$

with the following factors:[12] 1.020 at 39.6°, 1.028 at 45.0°, 1.035 at 49.7°, 1.035 at 49.8°, 1.046 at 57.6°, 1.050 at 60.3°, 1.064 at 70.0°, and 1.066 at 70.3°. Details are given in the thesis;[1b] the rate data are collected in Tables I–IV.

TABLE I

TITRIMETRIC RATE DATA FOR THE REACTION OF
1-PHENYLBROMOACETYLENE WITH DABCO IN ACETONITRILE

Temp, °C	$C_6H_5C\equiv CBr$, M	Dabco, M	$k^a \times 10^4$, $M^{-1}\,sec^{-1}$
70.00 ± 0.03	0.02500	0.07523	14.3 ± 0.1
	0.08000	0.2006	14.6 ± 0.2
	0.008108	0.09217	14.3 ± 0.1
	0.06875	0.03134	14.3 ± 0.1
		k_{corr}	15.3 ± 0.1
57.63 ± 0.03	0.02500	0.07523	6.30 ± 0.20
	0.08000	0.02006	6.42 ± 0.17
	0.008108	0.09217	6.47 ± 0.12
	0.06875	0.03134	6.33 ± 0.28
		k_{corr}	6.67 ± 0.20
45.00 ± 0.03	0.02500	0.07523	2.65 ± 0.15
	0.08000	0.02006	2.62 ± 0.06
	0.008108	0.09217	2.72 ± 0.07
	0.06875	0.03134	2.67 ± 0.10
		k_{corr}	2.74 ± 0.10

a These are mean values; k_{corr} are final values obtained by correcting the *k*'s for solvent expansion.

TABLE II

CONDUCTOMETRIC RATE DATA FOR THE REACTION
OF $C_6H_5C\equiv CCl$ WITH DABCO IN CH_3CN

Temp, °C	Dabco, M	$k\psi \times 10^4$, sec^{-1}	$k^a \times 10^4$, $M^{-1}\,sec^{-1}$
60.30 ± 0.05	0.1613	1.62	10.6
	0.2292	2.30	
	0.4419	4.43	
	0.6193	6.25	
49.80 ± 0.05	0.2131	1.25	6.05
	0.5313	3.12	
	0.7143	4.17	
	0.9938	5.80	
39.00 ± 0.05	0.1582	0.530	3.40
	0.2584	0.870	
	0.4658	1.55	
	0.4715	1.57	

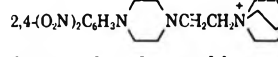*a* The rate constants are corrected for solvent expansion.

TABLE III

CONDUCTOMETRIC RATE DATA FOR THE REACTION OF
n-BUTYL CHLORIDE WITH DABCO IN CH_3CN

Temp, °C	Dabco, M	$k\psi \times 10^5$, sec^{-1}	$k^a \times 10^5$, $M^{-1}\,sec^{-1}$
49.70 ± 0.03	0.3026	2.52	8.58
	0.5964	4.95	
	0.9860	8.22	
60.30 ± 0.03	0.1125	2.00	18.2
	0.2987	5.28	
	0.5762	9.77	
	0.8143	13.9	
70.30 ± 0.03	0.2190	7.08	34.3
	0.4100	13.2	
	0.5635	18.8	
	0.7998	25.5	

a The rate constants are corrected for solvent expansion.

(12) "International Critical Tables," Vol. 3, E. W. Washburn, Ed., McGraw-Hill, New York, N. Y., 1928, p 28.

TABLE IV
RATE DATA FOR DISPLACEMENT REACTIONS WITH DABCO IN ACETONITRILE AT 60°

Halide	Product	$k \times 10^4$, M^{-1} sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
$C_6H_5C{\equiv}CBr$	$C_6H_5C{\equiv}CN$⬡NCH$_2$CH$_2$N̈⬡N Br$^-$	7.95	14.2 ± 0.5	30 ± 2
$C_6H_5C{\equiv}CCl$	$C_6H_5C{\equiv}CN$⬡NCH$_2$CH$_2$N⬡N Cl$^-$	10.6	10.7 ± 0.5	40 ± 2
$n\text{-}C_4H_9Cl$	$n\text{-}C_4H_9N$⬡NCl$^-$	1.82	13.8 ± 1.0	34 ± 3
$2,4\text{-}(O_2N)_2C_6H_3Cl^a$	$2,4\text{-}(O_2N)_2C_6H_3N$⬡NCH$_2CH_2$N⬡NCl$^-$	1.13^b		

^{a} Reference 9. The predominant first product has β-chloroethyl as the 4-substituent; the chlorine atom is eventually replaced by another Dabco molecule. ^{b} Determined at 50.8°.

Results and Discussion

Syntheses.—In most areas involving displacement at carbon, there was a firm synthetic base on which to launch mechanism studies. None existed for haloalkynes in the early 1960's, although contributions by several workers have since made them accessible.[3,4] We can, however, report progress with bridgehead nitrogen compounds. Of these, Dabco has proved useful for kinetic and mechanism studies.

Our reactions of trialkylamines with phenylbromoacetylene in aprotic solvents are consistent with eq 4.

$$-C{\equiv}CX \xrightarrow[a]{R_3N} (-C{\equiv}CNR_3^+X^-) \quad -CH_2CONR_2$$

$$X^- \Big\downarrow c \qquad R_3N \Big\downarrow b \qquad e \Big\uparrow H_2O \qquad (4)$$

$$-C{\equiv}CNR_2 + RX \xrightarrow{R_3N}_{d} R_4N^+X^- + -C{\equiv}CNR_2 \xrightarrow{f} polymer$$

Although we isolated only *N,N*-diethylphenylacetamide and several alkyl quaternary salts, Viehe[3a] has recently given directions for the preparation of dimethylaminophenylacetylene from phenylbromoacetylene and trimethylamine. Since several ethynylammonium salts and the corresponding ynamines have been prepared from other haloalkynes,[2d,3] it would appear that the synthetic problem of preparing ynamines *via* eq 4 has been solved. Nevertheless, the high reactivity of ynamines as electrophiles, nucleophiles, dipolarophiles, etc.,[3,4] provides a rationale for the troublesome diversions e and f in eq 4, and indicate that care in their preparation is essential.

With respect to ethynylammonium salts, several examples in the older literature have been discredited,[13] while several new ones have been reported.[2d,14] *In this study*, at least, the yields (>50%) of quaternary ammonium salts indicate $k_a < k_b$ in eq 4. The presence of the alkyl quaternary salts which turned up routinely is mechanistically significant. Because of the electron-withdrawing character of the ethynyl group, an ynamine is a weaker base than most corresponding alkylamines. Hence the conversion of the ethynylammonium salt either by excess amine or halide is favored thermodynamically. Judging from our mild reaction conditions, *e.g.*, 1–3 days at ~25°, and the low rate constant for reaction between triethylamine and ethyl bromide, *i.e.*, $5.5 \times 10^{-4}\ M^{-1}$ sec^{-1} in acetone at 100°,[15] we believe that step b is generally favored over c in eq 4.

The characteristics of the reactions of trialkylamines show up to some degree with Dabco. The expected salts from phenylbromo- and phenylchloroacetylene form ynamine **9a,b** either by step c or by processes a and b of eq 5. In the latter pathway, excess Dabco

$$RC{\equiv}CX + N\overset{+}{\curvearrowright}Q \longrightarrow (RC{\equiv}CN\overset{+}{\curvearrowright}QX^-)$$

$$X^- \Big\diagup a \qquad\qquad \mathbf{8} \qquad c \Big| Dabco$$

$$(RC{\equiv}CN\overset{}{\curvearrowright}Q\overset{}{\curvearrowright}X) \xrightarrow[b]{Dabco} RC{\equiv}CN\overset{}{\curvearrowright}Q\overset{+}{N\curvearrowright}QX^-$$

$$\mathbf{10a,b} \qquad\qquad\qquad \mathbf{9a, b, d}$$

$$\Big\downarrow H_2O$$

$$RCH_2CON\overset{}{\curvearrowright}Q\overset{+}{N\curvearrowright}QX^-$$

$$\mathbf{11c, d, e} \qquad\qquad\qquad (5)$$

a, R = C_6H_5; X = Cl; Q = N
b, R = C_6H_5; X = Br; Q = N
c, R = $(CH_3)_2CO$⬡O; X = Cl; Q = N
d, R = C_6H_5; X = Br; Q = C
e, R = C_6H_5; X = B(C_6H_5)$_4$; Q = C

was used and consequently **10a,b** were not isolated. Ynamines **9a,b** are demonstrably hygroscopic, form amides in water,[2b] and yield phenylacetic acid in concentrated acid. Perhaps because of the long heating period (~1 month), the only product obtained in the reaction of 2'-(3-chloro-1,1-dimethyl-2-propynyloxy)-tetrahydropyran with excess Dabco was the amide **10c**.

It is interesting that process 5 is closely similar to von Braun's cyanogen bromide reaction with tertiary amines.[16] Furthermore, analogous products have been reported for 2,4-dinitrochlorobenzene and Dabco as well as from 2-iodocyclohepta-2,4,6-trienone and quinuclidine, in which analogs of **8–10** were isolated.[17] In all of these examples, the rationale proposed for transalkylation, as in step 5c, or the retro Menschutkin reaction, as in step 5a,[9,17] is analogous to that given for ynamines, namely, that there is a conjugative interaction between the lone pair on nitrogen and the unsaturated system, which stabilizes the base and lowers its base strength.

The action of excess quinuclidine on phenylbromoacetylene gave a mixture of products, **9d** and **11d**.

(13) F. Klages and E. Drerup, *Justus Liebigs Ann. Chem.*, **547**, 65 (1941).
(14) (a) J. Dumont, *C. R. Acad. Sci.*, **261**, 1710 (1965); (b) B. I. Ionin and A. A. Petrov, *Zh. Obshch. Khim.*, **35**, 2255 (1965).
(15) N. Menschutkin, *Z. Phys. Chem. (Leipzig)*, **5**, 589 (1890); **6**, 41 (1890).
(16) H. A. Hageman, *Org. React.*, **7**, 198 (1953).
(17) F. Pietra and F. D. Cima, *J. Chem Soc. B*, 2224 (1971).

Upon treatment with water, **9d** was easily converted to the amide salt **11d**.

Facile reactions occurred between brucine, which contains a bridgehead nitrogen in ring C, and bromo- and chlorophenylacetylene, which were initially present in excess. Two isomers result from different cleavage modes at the bridgehead: attack by the halide ion at C-18 and C-20 produces 18-halo-19-(phenylacetyl)-18,19-secobrucine (**12**) and 20-halo-19-(phenylacetyl)-18,19-secobrucine (**13**), respectively.

12a, X = Br
b, X = Cl

13a, X = Br
b, X = Cl

Although we do not assign structures **12** cr **13**, similar scission products have been previously established for strychnine and brucine with cyanogen bromide.[18] In the reaction of dihydrobrucine with cyanogen bromide, it has been demonstrated that bromide ion attacks C-18 exclusively to form a single product. For brucine, SN2 displacement at C-18 appears to compete with the normally more facile allylic cleavage at C-20; in dihydrobrucine, no N–C-20 breakage occurs at all. It has been suggested that this can be taken as a measure of the greater steric accessibility of C-18 over C-20 to the attack of external reagents.[19] Accordingly, the product from the reaction of phenyl-bromoacetylene with dihydrobrucine is assigned structure **12a**, but without the double bond. An indication of the greater reactivity of C-20 over C-18 in brucine is reflected by the reaction conditions employed for brucine and dihyrobrucine. With brucine and phenyl-bromoacetylene in benzene, high conversion is obtained at *ca.* 25°, while with dihydrobrucine moderate quantities of product are obtained at 80°.

Kinetics and Mechanism.—The kinetics of the reactions of phenylbromo- and phenylchloroacetylene and *n*-butyl chloride with Dabco in acetonitrile were studied. These systems showed second-order kinetics, first order in Dabco and first order in halide (Tables I–IV). The large negative values for $\Delta S^{\ddagger}$ are in accord with other molecule–molecule reactions in which ion pairs are initially formed.[2d,e] However, the activation parameters for the haloalkynes showed large differences (Table IV): although the rate constants for phenylchloro- and phenylbromoacetylene are sim-

(18) H. G. Boit, *Chem. Ber.*, **86**, 133 (1953).
(19) J. B. Hendrickson in "The Alkaloids," Vol. 6, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, Chapter 6.

ilar at 60°, the former is favored by a factor of *ca.* 200 in the energy of activation while the latter is favored by a factor of *ca.* 160 in the entropy of activation. The more negative value of $\Delta S^{\ddagger}$ for the chloro compound is also found in the analogous molecule–molecule reactions of triphenylphosphine with phenylchloro- and phenylbromoacetylene in DMF.[2a] To understand the detailed pattern of activation parameters, we believe that more data are required on solvent and substrate variation in which analogous charge-dispersed but neutral transition states are involved.

Halounsaturates, *e.g.*, vinyl, aryl, and ethynyl, have traditionally been regarded as relatively indifferent to nucleophiles by comparison with haloalkanes. The data in Table IV indicate that phenylchloroacetylene is more reactive than 1-chlorobutane, "standard" for SN2 processes,[20] and is even more reactive than an activated chlorobenzene:[9] k (sp) $\geqslant k$ (sp^3) $> k$ (sp$^{2.5}$). Among unsaturates, a partial rationalization of the high reactivity of the acetylenic carbon towards amines may be attributed to the fact that the sp carbon is more electronegative than aryl or vinyl carbon.

Among the three major mechanisms currently considered for process 1, we favor steps a (slow) and b (fast) of eq 6 for the particular haloalkynes used in this study. Evidence for terminal carbon (α) attack (a, b), halogen abstraction (c, d), and internal carbon

$$(6)$$

(β) attack (e) followed by rearrangement has been produced for different systems.[2,3] (Note that "α- and β-attack" are positions relative to halogen.) All can be consistent with second-order kinetics. This means that the generation of any one of the intermediates, *e.g.*, from an alkene, and subsequent isolation of the ynamine is not conclusive as to the mechanism, for any of the intermediates can revert to the starting materials. Thus, there is an inherent uncertainty about any mechanism which can only be settled by specific consideration of actual systems.

With respect to β attack (on the internal carbon) followed by rearrangement, the 1,2-sigmatropic shift of R_2N- is known,[3d] but that of R_3N^+- or alkyl (R') is forbidden,[21] as well as unprecedented.[22] 1,2-Aryl migrations, however, do occur in the analogous Fritsch-Buttenburg–Weichell (FBW) rearrangement, but the bases used are generally more powerful and the reaction conditions more forcing than those we employed here.[3d,23] For all of these reasons, we believe the FBW sequence e and f in eq 6 to be improbable.

To attempt to find evidence for halogen abstraction

(20) A. Streitwieser, *Chem. Rev.*, **56**, 571 (1956).
(21) S. I. Miller, *Advan. Phys. Org. Chem.*, **6**, 185 (1968).
(22) D. V. Banthrope in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, Chapter 10.
(23) G. Köbrich, *Angew. Chem.*, **79**, 15 (1967).

(c) in eq 6, we used methanol in trapping experiments. Now, both phenylacetylene and ynamine are produced. If one allows for the uncertainties of the product analyses at low conversions, it appears that halogen abstraction is a minor competing process in our systems (Table V). In passing, it is interesting that we observe less

halogen abstraction with tertiary amine than with tertiary phosphine; *i.e.*, Dabco < $(C_6H_5)_3$P < (n-C$_4$H$_9$)$_3$P.[2a] This may be attributed to the greater polarizability of the phosphorus atom and to the more energetically favorable P–X bond formation.

Although the production of phenylacetylene is positively diagnostic for step c of eq 6, it provides no information on whether the ynamine is also produced after step c. As a route to the ynamine salt, step d seems plausible on paper, but is, in fact, improbably complex. Consider the ion pairs **14,15a,b**. The formation of the substitution product *via* step d pre-

15a   **15b**

sumably requires backside attack of the acetylide ion on nitrogen. In view of the fact that the nitrogen in **14** is a bridgehead atom, such a process cannot take place. Since the bicyclic ring is opened in these reactions, back-side attack could be salvaged by having **15a** rearrange to **15b**, *within* the solvent cage. But in order to form **15a**, Dabco molecules must penetrate the solvent cage in preference to the smaller and more abundant methanol molecules, which seems unlikely. Furthermore, the phenylacetylide ion would presumably move from the original displacement center (N–X) to the new charged site. With all of this relative

motion taking place, the acetylide ion is unlikely to survive in the presence of a proton source to give ynamine **9**. All of this suggests that k_d = 0, and that the ynamine salt and the acetylene are formed on independent paths in eq 6; halogen abstraction from haloalkynes can occur but it appears to be a dead end, off the route from haloalkyne to ynamine!

We are left with a and b of eq 6 as the dominant sequence for the amine–haloalkyne systems that we studied. However, this mechanism does have real support. The element effect, k (Cl)/k (Br) > 1, is significant in that this is consistent with predominant rate-determining attack on carbon rather than on halogen (Table IV). This order has now been found with the nucleophiles thiolate,[2f] phosphite,[2e] phosphine,[2a] and alkoxide[2g] in process 1; but where nucleophilic attack is on halogen, the order has been shown to be k (Br) ≫ k (Cl).[2c,e,g] There is also product evidence in the reaction of phenylbromoacetylene with diethylamine, which yields β,β-bis(dialkylamino)styrene, presumably *via* the appropriate ynamine.[6a,d] The absence of α-dialkylamino-β-bromostyrene or its derivatives, which were found with alkylhaloalkynes, would also appear to indicate against β attack.[6]

If attack on the terminal carbon is accepted, there is still the problem of obtaining our final product **9**; the alternatives are laid out in eq 5. Our rate constants were determined by following the production of salt by conductance for phenylchloroacetylene and by potentiometric titration for phenylbromoacetylene. If the concentration of the neutral molecule **10** in eq 5 were significant, these methods would not give "constant" rate constants. For 2,4-dinitrochlorobenzene-Dabco, satisfactory kinetic data have been reported for the conditions of amine in large excess over halide; here the concentration of the haloethylpiperazine was negligible.[9] Our rate constants for phenylchloroacetylene were determined by making measurements with the haloalkyne at low concentration and the amine in *ca.* 20–100-fold excess. In fact, for phenylbromoacetylene–Dabco, we obtained identical k values with either reagent in excess. This suggests that step c of eq 5 is relatively fast and there is little or no storage of **10b** during the course of the reaction. This completes our mechanistic proposals for the processes given in eq 5 and 6.

Orientation in 1,3-Dipolar Cycloadditions According to the Diradical Mechanism. Partial Formal Charges in the Linnett Structures of the Diradical Intermediates[1,2]

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Received November 2, 1971

The question of regioselectivity in 1,3-dipolar cycloadditions is taken up in detail from the viewpoints of both diradical and concerted mechanisms. The predominant unidirectionality of orientation exhibited by most 1,3 dipoles toward both electron-rich and electron-poor dipolarophiles is a natural consequence of the diradical mechanism but conflicts with the concerted one, as seen by analysis of both transition-state structure and prereaction complexes. Steric effects also favor the diradical theory. Linnett structures for the diradical intermediates possess partial formal charges, which account for (1) the nature of the favored diradicals, (2) the dual orientation of azides, and (3) the competition between cyclo and extended conformations of diradicals in reactions that exhibit concurrent cycloaddition and condensation with hydrogen transfer. Parallels with the Diels–Alder reaction and with free-radical additions are drawn.

Orientation, or regiospecificity, is an important criterion of mechanism in the field of cycloaddition reactions. For the Diels–Alder reaction, whatever its mechanism may be, it has long been recognized that the orientational phenomena are those that would be expected for a diradical mechanism.[3] On the other hand, regiospecificity in the closely related 1,3-dipolar cycloaddition reaction has been interpreted as favoring both diradical[4] and concerted[5-8] mechanisms. A detailed analysis of the latter field will be presented here, which will attempt to show that for this reaction, too, the orientational facts are in accord with the diradical mechanism.

The Concerted Mechanism.—In its simplest form, the concerted transition state for the cycloaddition of 1,3 dipole a=b$^+$–c$^-$ to dipolarophile d=e is **1**, with the formation of the two new bonds equally well advanced and synchronized with the dissolution of the two old bonds. However, when the dipolarophile bears a substituent with appreciable conjugation energy, which is lost in the product, **1** implies that part of this energy is lost in the transition state, which would retard the reaction relative to one with an unsubstituted dipolarophile. Yet the opposite seems to be an invariable rule, *i.e.*, all substituents in the dipolarophile (relative to H) strongly accelerate 1,3-dipolar cycloadditions. For this reason, the concerted mechanism has been described as "concerted but not synchronous,"[5] with transition state **2** rather than **1**. The six electrons of interest in **2** move together but do not march precisely

in step, creating a surplus or deficiency of electrons in the dipolarophile which conjugates with the substituent

more strongly than did the original double bond. Control over orientation has been assigned[5] to two factors: (1) the σ-bond energy factor, active only when the two atoms d and e in the dipolarophile are different, and (2) steric effects. The first factor is not operative for C=C and C≡C dipolarophiles, which are the most numerous that have been studied, and will be the only types to be discussed herein; thus the σ-bond energy factor requires no further consideration. Steric effects will be discussed later on in the paper.

It is not possible to predict, for any 1,3-dipole, what sort of unbalanced charge distribution in **2** is preferred, but it is apparent that any particular 1,3-dipole will tend to prefer the same nonsynchronous pattern in all its reactions. This pattern should affect orientation by guiding the β carbon of a monosubstituted ethylene with an electron-withdrawing substituent to that end of the 1,3-dipole which tends to be electron-rich in the transition state, and the β carbon of an electron-rich olefin in the opposite fashion. Thus regiospecificity for electron-poor and electron-rich olefins should be opposite for each 1,3-dipole. The same remarks apply, incidentally, to the Diels–Alder reaction.[9]

There is another reason why olefins of opposite polarities should orient oppositely toward the same 1,3-dipole by a concerted mechanism. The approach of two polar molecules must be governed by electrostatic forces until the distance between them is small enough for covalent interaction to begin. In a concerted cycloaddition, the two partners must approach the transition state in a parallel position, with no solvent molecules in between. The electrostatic energy of this

(1) Application of the Linnett Electronic Theory to Organic Chemistry, Part V. Part IV: R. A. Firestone, *J. Org. Chem.*, **36**, 702 (1971).

(2) Presented in part at the IUPAC Symposium on Cycloadditions, Munich, Sept 1970.

(3) C. Walling, *J. Amer. Chem. Soc.*, **71**, 1930 (1949); E. C. Coyner and W. S. Hillman, *ibid.*, **71**, 324 (1949); G. Stork, S. S. Wagle, and P. C. Mukharji, *ibid.*, **75**, 3197 (1953); R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(4) R. A. Firestone, *J. Org. Chem.*, **33**, 2285 (1968).

(5) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963).

(6) A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, **100**, 2192 (1967).

(7) R. Huisgen, G. Szeimies, and L. Möbius, *ibid.*, **100**, 2494 (1967).

(8) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968).

(9) Numerous theoretical studies based on the concerted mechanism support these statements. For the Diels–Alder reaction, where the substituents in diene and dienophile are of opposite polarities, preferential ortho-para orientation is predicted by PMO calculations.[10] However, exactly the same method predicts *meta* orientation when both *substituents are electron withdrawing*.[11] Another study reaches similar conclusions.[12] Only calculations aimed at predicting *which σ bond is formed first* have claimed complete success in accounting for orientation;[13] of course, this picture is identical with the diradical mechanism. For 1,3-dipolar cycloadditions, recent Hückel calculations of frontier orbital amplitudes, assuming a concerted mechanism, predict that all of a variety of common 1,3-dipoles should add in the opposite sense to electron-rich and electron-poor olefins.[14]

(10) J. Feuer, W. C. Herndon, and L. H. Hall, *Tetrahedron*, **24**, 2575 (1968).

(11) T. Inukai and T. Kojima, *J. Org. Chem.*, **36**, 924 (1971).

(12) J. Bertran, R. Carbo, and T. Moret, *An. Quim.*, **67**, 489 (1971).

(13) O. Eisenstein, J. Lefour, and N. T. Anh, *Chem. Commun.*, 969 (1971).

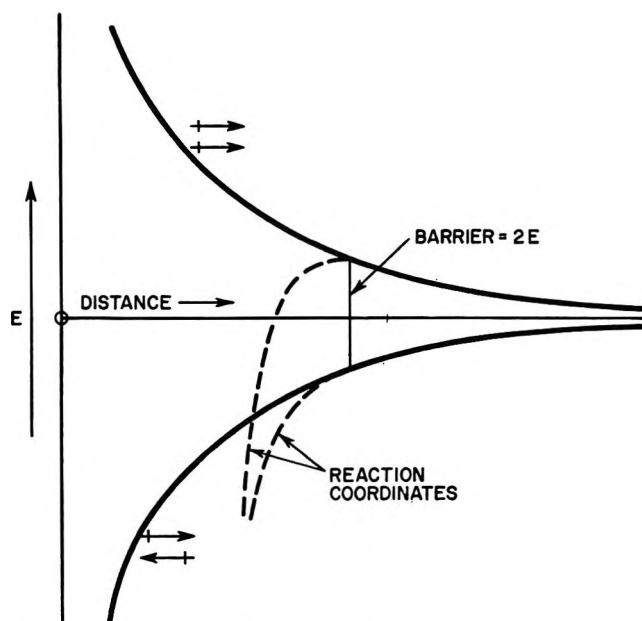(14) Independent, unpublished study by Dr. B. G. Christensen of these laboratories.

Figure 1.—Parallel approach of dipoles.

array is expressed[15] by eq 1, where E is in kcal/mol, μ is in Debye units, and a is the distance of separation in

$$E = \pm \frac{14.4\mu_A\mu_B}{a^3} \qquad (1)$$

Å. Interaction is favorable when the dipoles line up in antiparallel fashion, and unfavorable when they are parallel. Thus, the orientation of the 1,3-dipole toward the two classes of olefins should be opposite *as they approach* the transition state. Both cycloadditions are symmetry allowed, and consequently the transition state's orientation ought to be governed by the mode of approach.

It is recognized that, once covalent bond reorganization has become appreciable in the transition state, the dipole moments of the two partners prior to reaction are no longer of paramount importance. At this point, another factor *not yet identified* might conceivably cause certain transition states to be lower in energy than their orientational opposites, even in defiance of the electrostatically governed mode of approach. If such a factor exists, it is not orbital symmetry, nor, as will be seen later, is it steric. If no such factor exists, then the above prediction must hold.

Typical single bonds are about 1.5 Å in length, and since the Morse function that describes covalent bonding falls off with distance much faster than do electrostatic forces, which obey Coulomb's law, it is apparent that eq 1 governs the situation until the molecules are within a few A of each other. As an example of the magnitude of the interaction, when $\mu_A = \mu_B = 3.5$ D and $a = 4$ Å, $E = 2.8$ kcal/mol, an appreciable number for a reaction whose activation energy is typically about 15 kcal/mol. Furthermore, for those examples in which the observed orientation is incorrect by this criterion, the energy difference, or "barrier," between the observed and the electrostatically preferred mode of approach is $2E$, or 5.5 kcal/mol,

(15) E. A. Moelwyn-Hughes, "Physical Chemistry," 2nd ed, Pergamon Press, Oxford, 1961, p 306. Strictly speaking, eq 1 applies only at the larger distances.

in the above example. Figure 1 expresses the situation graphically. An actual case will be presented subsequently.

The Diradical Mechanism.—In contrast with the concerted mechanism, the diradical mechanism predicts that the regiospecificity observed with both electron-poor and electron-rich olefins should be the same toward any given 1,3-dipole. Diradicals, as high-energy intermediates, lie close on the reaction coordinate to their transition states of formation, and therefore energy differences among them are taken as approximately equal to energy differences among the transition states. For any combination of 1,3-dipole and dipolarophile four diradical intermediates are possible. Only two of these need be considered when the dipolarophile is a monosubstituted carbon–carbon multiple bond, because relative to hydrogen all substituents stabilize a radical center, and the σ-bond energy factor is absent. In the generalized eq 2, the two possible regioisomeric products **5** and **6** arise from the diradicals **3** and **4**, respectively. Diradicals **7** and **8** are obviously poorer than **3** and **4** because they do not utilize the radical-stabilizing power of the substituent X, and therefore need not be considered further.

For any individual 1,3-dipole, a preference for either **3** or **4** is expected, and this preference should be the same whether the substituent X in the dipolarophile is electron-attracting or electron-releasing. The preference need not be large, and it has been calculated[16] that, for most 1,3-dipoles, **3** and **4** differ little in bond energy, in accord with the fact that regioselectivity in 1,3-dipolar cycloadditions is seldom total. Nevertheless, the diradical mechanism clearly predicts that each 1,3-dipole should exhibit an orientational preference of the same kind for both electron-rich and electron-poor olefins. This prediction is exactly the opposite of that for the concerted mechanism.

Patterns of Orientation.—The most important fact concerning orientation in 1,3-dipolar cycloadditions is that there is a strong tendency for each 1,3-dipole (with one exception) to add in the same direction to both electron-rich and electron-poor olefins. This fact contradicts the concerted mechanism, and supports the diradical mechanism.

(16) R. A. Firestone, *J. Chem. Soc. A*, 1570 (1970).

Inasmuch as orientational patterns have already been discussed at length in a previous paper,[4] the remarks herein concerning this point will be kept to a minimum. The most extensively studied 1,3-dipoles are nitrile oxides, nitrile imines, nitrones, diazoalkanes, azomethine imines, sydnones, and azides. Only carbon–carbon dipolarophiles whose preferred modes of radical addition are unmistakable will be considered. In order to save space, for each 1,3-dipole only the most typical products will be shown, without equations; the dashed lines depict the mode of union of dipole and dipolarophile. Each regioisomer illustrated is the major one reported, and is frequently accompanied by lesser amounts of the other regioisomer.

The vast majority of adducts of nitrile oxides arise from diradicals of type **9**.[17] The variety of dipolarophiles which add in this fashion is exceptionally great, and only a small portion of the literature is summarized here.[22-33] Mesitonitrile oxide is a special case of great

interest which will be discussed separately, under "steric effects."

Nitrile imines have also been extensively studied, and their preferred orientation arises from diradicals **10**.[34-39]

10

X = COOR, C_6H_5, CN, alkyl.[34]
NR_2,[6] OR,[35] C≡CSiMe$_3$,[29]
P(O)(OMe)$_2$,[28] vinyl[34]

X = Y = CH_3,[36] C_6H_5,[37] OEt[34]
X = CH_3; Y = COOMe,[38] OEt[35]

X = C_6H_5, COOMe, CH(OPr)$_2$,[34]
p-C_6H_4Y, where Y = NMe_2,[39]
OMe, NO$_2$[37]

9

X = C_6H_5,[22] CN,[23] COOEt,[24] CH_3,[25]
n-alkyl,[22] OAc,[23] OR,[26]
CH=CH$_2$NMe$_2$,[27] P(O)(OMe)$_2$,[28]
C≡CSiMe$_3$[29]

X = Y = CH_3,[25] OEt[30]

X = C_6H_5, OMe, OEt,[30]
COOMe[31]

COOMe[32]

X = C_6H_5, COOMe,[32] CH$_2$OH,[33]
CMe$_2$OH[33]

11

R, R' = C_6H_5, Alkyl
X = C_6H_5,[40] COOEt,[41] CONH$_2$,[42] CN,[41]
2-Py,[43] P(O)(OMe)$_2$,[28] C≡CSiMe$_3$,[29]
CH$_2$OH,[41] OEt,[35] OBu,[43] alk,[24]
N-pyrrolidinyl[44]

X = H; Y = CN, COOMe
X = CH_3; Y = COOMe

X = Y = OEt, C_6H_5[43]
X = CH_3; Y = C_6H_5,[43] COOMe[41]
X = C_6H_5; Y = N-pyrrolidinyl[46]

(17) Independent evidence for the existence of diradicals **9** are the observations of U-shaped Hammett plots for the addition of nitrile oxides to olefins CH$_2$=CHC$_6$H$_4$X[18] and acetylenes CH≡CC$_6$H$_4$X.[19-21] All X groups conjugated to an unsaturated radical center stabilize it relative to H. Substituents Y in YC$_6$H$_4$CNO, which are not conjugated with an unsaturated radical center in **9**, give normal Hammett plots stemming from purely ground-state effects.[18-19]

(18) A. Battaglia and A. Dondoni, *Ric. Sci.*, **38**, 201 (1968).
(19) A. Dondoni, *Tetrahedron Lett.*, 2397 (1967).
(20) P. Beltrame, C. Veglio, and M. Simonetta, *J. Chem. Soc. B*, 867 (1967).
(21) P. Beltrame, P. Sartirana, and C. Vintani, *ibid.*, 814 (1971).
(22) P. Grünanger, *Gazz. Chim. Ital.*, **84**, 359 (1954).
(23) G. Stagno d'Alcontres and P. Grünanger, *ibid.*, **88**, 741 (1950).
(24) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).
(25) G. Stagno d'Alcontres, *Gazz. Chim. Ital.*, **82**, 627 (1952).
(26) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 2215 (1962).
(27) P. Caramella and P. Bianchessi, *Tetrahedron*, **26**, 5773 (1970).
(28) I. G. Kolokol'tseva, V. N. Chistokletov, B. I. Ionin, and A. A. Petrov, *J. Gen. Chem. USSR*, **38**, 1203 (1968).
(29) I. G. Kolokol'tseva, V. N. Chistokletov, M. D. Stadnichuk, and A. A. Petrov, *ibid.*, **38**, 1771 (1968).
(30) P. Grünanger and M. R. Langella, *Gazz. Chim. Ital.*, **89**, 1784 (1959).
(31) M. Christl and R. Huisgen, *Tetrahedron Lett.*, 5209 (1968).
(32) R. Huisgen and M. Christl, *Angew. Chem., Int. Ed. Engl.*, **6**, 456 (1967).
(33) A. Quilico and G. Stagno d'Alcontres, *Gazz. Chim. Ital.*, **79**, 654, 703 (1949).

(34) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).
(35) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 4179 (1967).
(36) R. Huisgen, H. Knupfer, R. Sustmann, G. Wallbillich, and V. Weberndorfer, *Chem. Ber.*, **100**, 1580 (1967).
(37) J. S. Clovis, A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, and V. Webernodorfer, *ibid.*, **100**, 1593 (1967).
(38) R. Huisgen, R. Sustmann, and G. Wallbillich, *ibid.*, **100**, 1786 (1967).
(39) S. Morrocchi, A. Ricca, and A. Zanarotti, *Tetrahedron Lett.*, 3215 (1970).

Nitrones react *via* diradicals of type **11**.[40-47] Methyl propiolate does not fit the rule, but there are very few such exceptions in the nitrone field.

The best diradicals from diazoalkanes look like **12**. Doubt has been cast on the ability of structures $RN_2\cdot$ to do anything except lose nitrogen,[8] but evidence from a variety of sources establishes that radicals $RN_2\cdot$, while unstable, can indeed enjoy finite existence.[48] Alkoxy-acetylenes, alone in this large group, add in exceptional fashion. (See ref 49-66.)

12 $X = COOR,$[24] $CHO, Ac,$[49] $C_6H_5, m\text{-}O_2NC_6H_4,$[50] $p\text{-}MeOC_6H_4,$[50] $CH=CH_2,$[51] $C\equiv CH,$[52]
$^+P(C_6H_5)_3Br^-,$[53] $CH\begin{smallmatrix}O\\O\end{smallmatrix},$[49] SEt[54]

$R = Ar; X = Ar$[55]
$R = X = COOMe$[56]
$R = CF_3; X = CF_3, CH_3$[57]

$X = COOMe,$[58]
$^+P(C_6H_5)_3Br^-$[53]

$OEt(i\text{-}Pr)$

$X = CH_2OH,$[59] $SnEt_3,$[60] $CHO,$[61]
$CH=CHOMe$[62]

$R = CH_2=CH_2; X = Ac, COC_6H_5$[63]
$R = CF_3; X = CF_3, Br$[57]
$R = COOEt; X = CHO$[61]

$R = C_6H_5; X = CHO,$[64] $COOMe,$[64,65] $C(CH_3)=CH_2$[66]
$R = CH_3; X = CH=CHOMe$[62]

For azomethine imines, the best diradical is normally **13**. At one time[4] it seemed that disobedience to the best diradical rule on the part of azomethine imines was widespread; however, their behavior appears less ambiguous in the light of recent evidence. Thus, diradical **13** prevails without exception with weakly substituted carbon, *i.e.*, when the carbon atom of the 1,3-dipole bears no strongly radical-stabilizing substituent.[67]

13 $X = $ aryl, vinyl, $COOEt, CN$

On the other hand, with strongly substituted carbon, orientations arising from diradical **14** account for a significant, though still minor, portion of the total.

$Fl \equiv 9\text{-fluorenyl}$

(40) R. Huisgen, R. Grashey, H. Hauck, and H. Seidl, *Chem. Ber.*, **101**, 2548 (1968).

(41) R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *ibid.*, **101**, 2568 (1968).

(42) B. G. Murray and A. F. Turner, *J. Chem. Soc. C*, 1338 (1966).

(43) R. Huisgen, R. Grashey, H. Seidl, and H. Hauck, *Chem. Ber.*, **101**, 2559 (1968).

(44) O. Tsuge, M. Tashiro, and Y. Nishihara, *J. Chem. Soc. Jap.*, **92**, 72 (1971).

(45) M. Ochiai, M. Obayashi, and K. Morita, *Tetrahedron*, **23**, 2641 (1967).

(46) O. Tsuge, M. Tashiro, and Y. Nishihara, *Tetrahedron Lett.*, 3769 (1967).

(47) H. Seidl, R. Huisgen, and R. Knorr, *Chem. Ber.*, **102**, 904 (1969).

(48) (a) S. Seltzer and F. T. Dunne, *J. Amer. Chem. Soc.*, **87**, 2628 (1965); (b) W. R. Roth and M. Martin, *Justus Liebigs Ann. Chem.*, **702**, 1 (1967); *Tetrahedron Lett.*, 4695 (1967); (c) W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, **89**, 1741 (1967); **92**, 5403 (1970); (d) J. Hollaender and W. P. Neumann, *Angew. Chem., Int. Ed. Engl.*, **9**, 804 (1970); (e) P. B. Condit and R. G. Bergman, *Chem. Commun.*, **4** (1971); (f) N. A. Porter, M. E. Landis, and L. J. Marnett, *J. Amer. Chem. Soc.*, **93**, 795 (1971); (g) N. A. Porter and P. M. Iloff, Jr., *Chem. Commun.*, 1575 (1971).

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(53) E. E. Schweizer, C. S. Kim, and R. A. Jones, *Chem. Commun.*, **39**, 1584 (1970).

(54) S. H. Groen and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **80**, 879 (1961).

(55) C. G. Overberger, N. Weinshenker, and J. Anselme, *J. Amer. Chem. Soc.*, **87**, 4119 (1965).

(56) E. Buchner, *Ber.*, **21**, 2637 (1888); **23**, 701 (1890); E. Buchner and A. Papendieck, *Justus Liebigs Ann. Chem.*, **273**, 232 (1893).

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(60) L. G. Sharanina, V. S. Zavgorodnyi, and A. A. Petrov, *J. Gen. Chem. USSR*, **38**, 1099 (1968).

(61) R. Hüttel, *Ber.*, **74**, 1680 (1941).

(62) M. Noel, Y. Vo-Quang, and L. Vo-Quang, *C. R. Acad. Sci.*, **270**, 80 (1970).

(63) G. Manecke and H. U. Schenk, *Tetrahedron Lett.*, 617 (1969).

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(65) J. van Alphen, *Recl. Trav. Chim. Pays-Bas*, **62**, 485 (1943).

(66) L. Vo-Quang, *C. R. Acad. Sci.*, **266**, 642 (1968).

(67) W. Oppolzer, *Tetrahedron Lett.*, 2199 (1970).

Exceptions[24] are shown below.

14

X = C₆H₅, CN

Sydnones are azomethine imines which are unusually stable owing to the special circumstance of their aromaticity. They cycloadd according to diradical **15**,[68-71] the counterpart of **13**.

15

X = C₆H₅,[24] CN,[68] CH₃, CH₂—⟨⟩[69]

CH₃OAc,[70] C≡CSiMe₃[29]

X = C₆H₅, COOMe, CH₂OH

X = Y = CH₃, C₆H₅[70]

X = CH₃; Y = CN[68]

Up to this point, the unidirectionality of orientation exhibited by each individual 1,3-dipole clearly bespeaks a two-step mechanism with a diradical intermediate. Were the cycloadditions concerted, for each type the orientation would be incorrect for dipolarophiles of one or the other polarity. In azides, we now encounter for the first time a 1,3-dipole that orients in opposite fashion with olefins of opposite polarity. With electron-poor olefins, diradical **16** is preferred,[72,73] and with electron-rich olefins, diradical **17**.[74]

Nevertheless, even azides' orientations provide no support for the concerted mechanism, because not even half the dipolarophiles orient properly. Azides are polarized with the outer nitrogen negative,[24] and conse-

(68) R. Huisgen, R. Grashey, and H. Gotthardt, *Chem. Ber.*, **101**, 829 (1968).

(69) H. Gotthardt and R. Huisgen, *ibid.*, **101**, 552 (1968).

(70) R. Huisgen and H. Gotthardt, *ibid.*, **101**, 839 (1968).

(71) R. Huisgen, H. Gotthardt, and R. Grashey, *ibid.*, **101**, 536 (1968).

(72) R. Huisgen, G. Szeimies, and L. Möbius, *ibid.*, **99**, 475 (1966).

(73) R. Huisgen, R. Knorr, L. Möbius, and G. Szeimies, *ibid.*, **98**, 4014 (1965).

(74) R. Huisgen, L. Möbius, and G. Szeimies, *ibid.*, **98**, 1138 (1965).

16   X = COOR, Ac, CN   X = COOH, COOMe,[73] CHO[61]

17   X = C₆H₅,[24] OR[74]

X = OMe, OEt, OBu
Y = H, CH₃, C₆H₅

quently regioselectivity with both electron-rich and electron-poor olefins is incorrect for the concerted mechanism. Although at first glance the pattern seems no better for the diradical mechanism, it will be shown that diradicals actually work quite well for azides.

Electrostatic Forces and the Concerted Mechanism.—With the survey of orientational facts now completed, it is instructive to evaluate quantitatively the electrostatic "barrier," shown earlier to be $2E$ where E is defined by eq 1, for an actual case where the orientation is known to be incorrect for the concerted mechanism. The reaction of eq 3 occurs with a high degree of regiospecificity,[41] despite the antagonistic lineup of the molecular dipoles[75] as they approach. Table I lists the Coulombic interaction energies, or

TABLE I
COULOMBIC INTERACTIONS FOR EQUATION 3

Separation, Å	E, kcal/mol	Barrier ($2E$)
2	23.9	47.8
3	7.1	14.2
4	3.0	6.0
5	1.5	3.0
6	0.89	1.8
7	0.56	1.1
8	0.38	0.75

barrier, between the observed alignment and its opposite.

$$(3)$$

It is certain that for a concerted mechanism, in which the two partners must enter the transition state with their dipoles either parallel or antiparallel, before covalent interaction has begun *the 1,3-dipole and dipolar-*

(75) V. Baliah and V. Chandrasekharan, *Indian J. Chem.*, **8**, 1096 (1970).

ophile must be oriented in opposite fashion from that shown in eq 3. At this point—we know not precisely where, but 4–5 Å seems reasonable—a barrier must be invoked which raises the energy of the unobserved transition state by at least $2E$. The barrier is not orbital symmetry, since both orientations are symmetry allowed, and it is difficult to imagine the source of an effect so large in relation to the total activation energy, typically 16–18 kcal/mol for nitrones.

For a two-step mechanism, the electrostatic requirements for approach are much more relaxed, since not only may the alignment be less precise to form one new bond than two, but also, solvent molecules are not necessarily excluded from between the two ends of the developing diradical that are to later form the second bond. However, once the diradical has been formed, the radical centers are held rather close together, and electrostatic interactions between them become large enough to influence the formation of the second bond, as will be shown subsequently.

Regiospecificity in the Addition of Free Radicals.—The orientational rules found for the formation of diradicals from 1,3-dipoles also govern the addition of free radicals, which attack at the same site that dipolarophiles do in forming the first bond. In the examples below, to save space only the first intermediates are shown. (See ref 76–79.)

$$(C_6H_5)_3C\cdot + CH_2N_2 \longrightarrow (C_6H_5)_3CCH_2N_2\cdot{}^{77}$$

$$R\cdot + ArCNO \longrightarrow Ar\dot{C}=NO\cdot{}^{79}$$

Interpretation of Regioselectivity in Cycloadditions.—Heretofore, orientational patterns have been presented as indicating that they fit the *idea* of best-diradical intermediates, and not the concerted mechanism. However, the diradical mechanism goes deeper than that, and accounts for the *nature* of the best diradicals as well.

The situation is simpler for the closely related Diels–Alder reaction. The predominant regioisomer from the reaction of a monosubstituted dienophile with 1- and 2-substituted butadienes is always the ortho and para isomer, respectively. This rule holds whether the activating groups in the diene and dienophile are of the same or the opposite electronic type. The nature

(76) A. Rieker, R. Renner, and E. Müller, *Justus Liebigs Ann. Chem.*, **730**, 67 (1969).

(77) (a) W. Schlenk and C. Bonhardt, *ibid.*, **394**, 183 (1912); (b) E. Müller, A. Moosmayer, and C. Bonhardt, *Z. Naturforsch.*, **18b**, 983 (1963); (c) D. B. Denney and N. F. Newman, *J. Amer. Chem. Soc.*, **89**, 4692 (1967).

(78) M. Iwamura and N. Inamoto, *Bull. Chem. Soc. Jap.*, **40**, 702, 703 (1967); **43**, 856, 860, 3638 (1970).

(79) (a) T. Caronna, A. Quilico, and F. Minisci, *Tetrahedron Lett.*, 3633 (1970); (b) B. C. Gilbert, V. Malatesta, and R. O. C. Norman, *J. Amer. Chem. Soc.*, **93**, 3290 (1971).

of the best diradical for each case is easily discerned here; **18** and **19** clearly account for the orientations.

The observation is already well known.[3,80] If the mechanism were concerted, the orientation with any given diene should be opposite for dienophiles of opposite electronic type, for the reasons already given.[9]

The nature of the best diradicals for 1,3-dipolar cycloadditions is not as obvious owing to their more complicated electronic structures, but a method of analysis is now proposed.

Bond Energies of Regioisomeric Diradicals.—In a reaction involving an unstable intermediate, the transition state lies close to the intermediate on the reaction coordinate, and hence the activation energy will be but slightly greater than the difference in energy between the intermediate and reactants. For a wide variety of 1,3-dipolar cycloadditions, it has been shown that the bond energy changes from reactants and diradicals can be used to estimate activation energies to within a few kcal/mol.[16] Of importance to the question of orientation was the finding that, for many cases, the calculated change in bond energy is approximately the same for both regioisomeric diradicals. Thus, in eq 4, the losses in bond energy attending the formation of **20** and **21** are 14 and 15 kcal/mol, respectively. Within the accuracy of the method, these numbers are the same. A similar result was obtained with the majority of examples. Bond energy analysis thus accounts for the fact that *regioselectivity* rather than 100% *regiospecificity* is observed in most 1,3-dipolar cycloadditions, but does not yet explain the orientational patterns.

$$(4)$$

Partial Formal Charges in Diradicals.—In eq 4 the 1,3-dipole and diradicals are depicted as Linnett structures because the more conventional Lewis structures give erroneous results,[8] owing to their failure to take into account the stabilization of radical centers

(80) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).

(81) M. Christl, Diploma Thesis, University of Munich, 1966.

adjacent to heteroatoms by partial bonding. Another attribute of the Linnett forms, heretofore ignored in our work but now to be featured, is their possession of partial formal charges. These exist at both ends of each diradical, but let us first focus our attention only on the end originating with the 1,3-dipole.

A simplified form of the analysis in ref 16 has been devised, which considers only those bond changes that are relevant to the question of orientation. Chart I illustrates the analysis for nitrile oxides.

CHART I

SIMPLIFIED ORIENTATION WITH NITRILE OXIDES[a]

$$R—C{=}N{-}\ddot{O}: \qquad R—\ddot{C}{=}\dot{N}{-}\dot{O}:$$

with charges: $^{1/2+}$ $^{1/2-}$ over 22, and $^{-}$ $^{1/2+}$ $^{1/2+}$ over 23

	22		23
C=N	143	C=N	143
N≟O	99	N≟O	99
C–C	83	C–O	86
5 pairs	20	4 pairs	16
C=N≟	−3[b]	C=N≟	−3[b]
	342		341
Advantage	1		

[a] In kcal/mol; for explanation see text. [b] L strain.

Diradicals **22** and **23** are the same as **20** and **21**, but with the elimination of all elements they hold in common. Thus the residue from the dipolarophile CH₂CHCOOMe is now depicted simply as D, and the phenyl group as R. The differences in electronic array are kept to the smallest possible compass, and only the central bonds and unshared electrons of the 1,3-dipoles are included in the analysis. Otherwise, the method is exactly the same as before. Bond energies are taken from standard sources, with odd-electron bond energies obtained by interpolation. Electron correlation is taken into account by listing, for each structure, the number of electrons not close-paired, an advantage of 4 kcal/mol per electron pair. L-Strain values are listed.

In the summation for each diradical, the *absolute* values obviously have no meaning, but the difference for each pair of regioisomers reflects their *relative* bond energies. These differences are the same as those derived from the more complicated analyses in ref 16 except that conjugation with R is neglected here. In all cases, whenever more than one Linnett structure could possibly be written, that structure was chosen which maximized the bond energy.

It is immediately seen that, although the bond energies of **22** and **23** are, within error, the same, the distribution of formal charges is not. They differ in that **22** has a half negative charge on oxygen while **23** has a full negative charge on carbon and a half positive charge on oxygen. These high values are doubtless mitigated by polarization of the valence shells, but the charge distribution unquestionably favors **22** over **23**, since oxygen, more electronegative than carbon, bears negative charge more easily and positive charge more reluctantly.

Thus diradical **22** is expected to prevail over **23**, in accord with observation. It will be seen that the interplay of formal charge distribution and electronegativity in the intermediate diradicals is the key to orientation for many 1,3-dipoles.

Chart II presents the results from simplified analyses

CHART II

SIMPLIFIED ORIENTATION WITH FOUR 1,3-DIPOLES

Nitrile imines

$$R—C{=}N{-}N—R \qquad R—C{=}N{-}N—R$$

24 (Advantage 4) 25

Nitrones

$$R_2C—N{-}\ddot{O}: \qquad R_2\ddot{C}—\dot{N}{-}\dot{O}:$$

26 (Advantage 1) 27

Azomethine imines

$$R_2C—N{-}N—R \qquad R_2\ddot{C}{-}\dot{N}—N—R$$

28 (Advantage 7) 29

Diazoalkanes

$$R_2C—N{=}N: \qquad R_2\ddot{C}—\dot{N}{=}\dot{N}$$

30 (Advantage 17) 31

of four other well-studied 1,3-dipoles. In the cases of nitrile imines and nitrones, the advantages in bond energy for the better diradicals are considered within the error of the method; for azomethine imines the advantage is considered of borderline significance; and for diazoalkanes, especially with nonconjugating R, significant. With each type of 1,3-dipole, the experimentally observed better diradical (**24, 26, 28,** and **30**) is that with the better charge distribution, in that the most electronegative atoms bear the most negative and the least positive charge. In addition, **28** has a slight, and **30** a significant, bond energy advantage over **29** and **31**.

The orientational patterns for the majority of 1,3-dipoles are thus seen to be explained by the diradical mechanism. The method of analysis, while not as simple as that for the Diels–Alder reaction shown earlier, is nevertheless consistent and unambiguous.
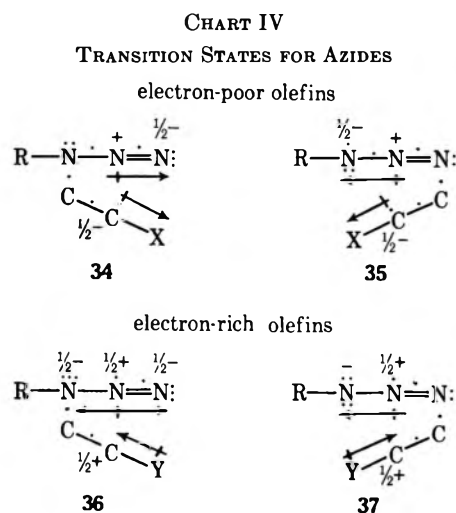
The only important 1,3-dipole whose orientation is not unidirectional is the azide function. Nevertheless, azides do fit the diradical mechanism (and not the concerted; *vide supra*). Chart III gives the results of
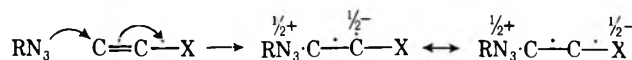
CHART III

SIMPLIFIED ORIENTATION WITH AZIDES

$$R—\ddot{N}—N{=}N: \qquad R—\ddot{N}—\dot{N}{=}\dot{N}$$

32 (Advantage 1) 33

simplified analysis for azides. Both orientations have essentially the same bond energy, and since both terminal atoms are nitrogens, the electronegativity criterion cannot be used here, as with the other 1,3-dipoles. A minor distinction is that **33** has the greater
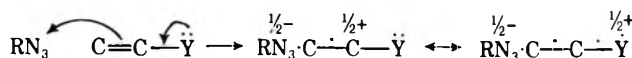
charge separation of the two,[82] which, other things being equal, should give an edge to **32**. However, extending our scrutiny backwards along the reaction coordinate to the transition states,[84] we find that electron-poor and electron-rich olefins give rise to quite different charge distributions. Chart IV depicts the

CHART IV
TRANSITION STATES FOR AZIDES

electron-poor olefins

34   **35**

electron-rich olefins

36   **37**

transition states for both orientations with each type of dipolarophile. All structures have been adjusted for the maximum possible bond energies. The arrows denote localized dipoles created by partial formal charges. It is assumed that electron-poor dipolarophiles prefer to be electrophilic in the transition state, reacting in the sense

and that electron-rich dipolarophiles act as nucleophiles, *viz.*

Electron-poor olefins give rise to transition states **34** and **35**, which have identical juxtapositions of localized dipoles. Therefore, the only remaining distinction between the regioisomeric diradicals **32** and **33** lies in their charge distributions, which, as observed earlier, favor **32**. The orientation of azides with electron-poor olefins, then, should fit in with diradical **16** as observed.

Electron-rich olefins, in contrast, lead to transition states **36** and **37**, whose localized dipoles face each other in markedly different ways. The electrostatic array in **37** is clearly lower in energy than that in **36**,[85] which might be sufficient to tip the balance toward the opposite orientation, represented by diradical **17** (or **33**). This is indeed the preferred diradical for electron-rich dipolarophiles.

If this explanation is correct, then the difference between **32** and **33** in charge distribution ought to cause a large difference in rates with olefins of opposite polarity when the group R is varied. In particular, electron-withdrawing substituents in R should promote reaction with electron-rich but not electron-poor dipolarophiles; or in other words, the reactivity of the azide should be most sensitive to olefin polarity when R is a good electron sink, and least when it is not.

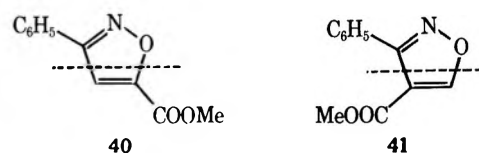These expectations are amply fulfilled, as shown in Table II. The diradical mechanism is supported in

TABLE II
SOME REACTION RATES WITH AZIDES[a]

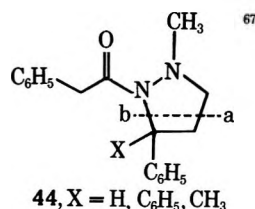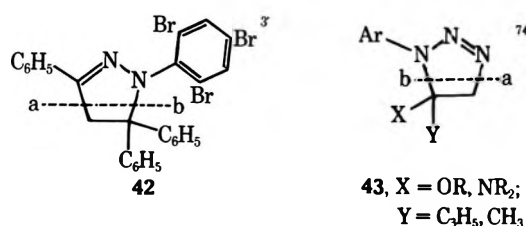|	Maleic anhydride	1-Pyrrolidino-cyclohexene	Relative rate, enamine/ anhydride
$p\text{-MeOC}_6\text{H}_4\text{N}_3$ (**38**)	20.8	3.15×10^3	151
$p\text{-O}_2\text{NC}_6\text{H}_4\text{N}_3$ (**39**)	1.28	1.42×10^6	1.1×10^6
Rel rate, 38/39	16	1/450	
Hammett ρ	-1.1	2.54	

[a] $10^7 k_2$, benzene, 25°. See ref 7.

every detail by (1) the much greater sensitivity of **39** than **38** to type of dipolarophile, (2) greater sensitivity of electron-rich than electron-poor olefins to substitution in R, and (3) the very large difference in Hammett ρ constants between maleic anhydride and 1-pyrrolidino-cyclohexene. Although a difference in ρ might be anticipated for a concerted mechanism also, the observed difference is far too great. The facts summarized in Table II have heretofore never been satisfactorily explained.
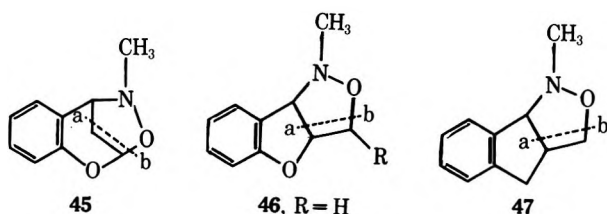
Steric Effects on Orientation.—One of the cornerstones of the interpretation of orientation according to the concerted mechanism has been steric effects.[5] Thus for example, **40** is obtained rather than **41**, supposedly because it is less crowded, and the two regioisomeric concerted transition states reflect in part **40**'s steric advantage.

40   **41**

We shall present here only a few key examples which illustrate that steric effects actually favor the diradical, and not the concerted, mechanism. Compound **42** is highly crowded, and a concerted transition state with partial bonding at both a and b looks poorer than its regioisomer. There is no bar, however, to a transition state with only bond a being formed, leading to normal orientation *via* a diradical of type **10**. Exactly the same remarks apply to **43**. It embodies, in extreme form, all adducts of azides and electron-rich olefins, which now are seen to orient incorrectly for the concerted mechanism on both steric *and* electronic (*vide supra*) grounds. In **44** also, formation of unhindered bond a to the azomethine imine, leading to diradical **13**, is not inhibited because the more difficult linkage b is made only afterwards.

(82) This greater charge separation is responsible for the fact that alkyl azides show greater regioselectivity than phenyl azide with electron-poor olefins.[83] Diradical **33** is less disfavored when R is phenyl because the inner nitrogen's negative charge can be better delocalized.

(83) W. Broeckx, N. Overbergh, C. Samyn, G. Smets, and G. L'abbe, *Tetrahedron*, **27**, 3527 (1971).

(84) More accurately, to the midpoints of the reaction coordinates. The true transition states lie farther along but before the diradical intermediates.

(85) For a similar example of conformational effects caused by the interaction of localized dipoles, see D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **36**, 1314 (1971).

42

43, X = OR, NR$_2$;
Y = C$_7$H$_5$, CH$_3$

44, X = H, C$_6$H$_5$, CH$_3$

Compound **45** illustrates another sort of steric effect. It is clearly more strained than its regioisomer **46**, the minor product, and indeed the opposite orientation **47** *is* found when the dipolarophile is weakly sub-
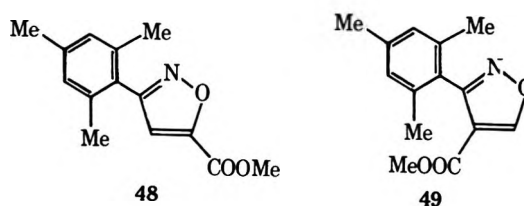

45   **46**, R = H   **47**

stituted.[86] Thus, the site of bond a in **45** is controlled by the strong substituent RO despite the strain created later in bond b, while the lack of a strong substituent in the latter case allows a to form at the other site, leading to **47**. In the absence of unusual influences, preferential formation of five-membered rather than six-membered rings is typical of free-radical cyclizations.[87] Failure to form **46** instead of **45** is thus incompatible with the concerted mechanism, but in harmony with the diradical mechanism.

We now come to the most striking example of steric effects. If the preference for **40** over **41** truly arises from steric interactions in concerted transition states, one would expect the degree of regiospecificity to diminish when the phenyl in benzonitrile oxide is replaced by a smaller group, and to increase when it is replaced by a larger one. *Yet exactly the opposite behavior is observed.* The regioselectivity for **40** is 72%, *i.e.*, **40:41** = 72:28. Replacement of the phenyl by the much smaller hydrogen *increases* the regioselectivity to 84%,[32] while replacement by the much larger mesityl group *lowers* it to 28%,[31] with the result that the sterically more crowded **49** is now favored over the "normal" isomer **48** by the ratio 49:48 = 72:28. Toward the dipolarophile acrylic ester, the situation is the same,

but in a less dramatic way; the per cents of "normal" isomer formed with benzonitrile oxide, fulminic acid, and mesitonitrile oxide are 96, 100, and 93, respectively.[31]
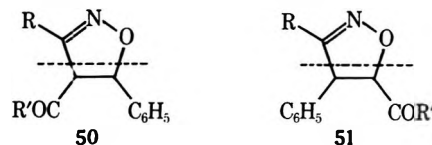
Further examples of the preference of the more bulky mesityl group over phenyl for the sterically more demanding position in the adduct are provided in Table III.[88] It is clear that these facts can in no way be

48   **49**

TABLE III
REGIOISOMERS FROM BENZO- AND MESITONITRILE OXIDES[a]

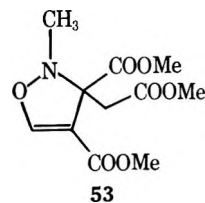| R	R'	50:51
Phenyl	CH$_3$	58:42
Mesityl	CH$_3$	28:72
Phenyl	α-C$_4$H$_3$S	44:56
Mesityl	α-C$_4$H$_3$S	14:86

[a] See ref 88.

accommodated by the concerted mechanism.

50   **51**

The diradical interpretation stems from the discussion given earlier about eq 4. The dipolarophile, *e.g.*, acrylic or propiolic ester, always prefers attack at the β carbon. The 1,3-dipole benzonitrile oxide prefers attack on carbon rather than oxygen (leading to a diradical of type **20**) but only by a small factor.[16] When the phenyl group grows to mesityl, steric hindrance to carbon attack increases, but not to oxygen attack, leading to an increase in the ratio 21:20.

Example **53**[39] fits in with the foregoing discussion.[90]

53

(86) W. Oppolzer and K. Keller, *Tetrahedron Lett.*, 1117 (1970). When R is a radical-stabilizing substituent such as OR or COOEt, **46** becomes the major product.

(87) For just a few of the many reported examples, see (a) N. O. Brace, *J. Amer. Chem. Soc.*, **86**, 524 (1964); *J. Org. Chem.*, **31**, 2879 (1966); **32**, 2711 (1967); (b) C. Walling and M. S. Pearson, *J. Amer. Chem. Soc.*, **86**, 2262 (1964); (c) R. C. Lamb, J. G. Pacifici, and P. W. Ayers, *J. Org. Chem.*, **30**, 3099 (1965); (d) R. D. Rieke and N. A. Moore, *Tetrahedron Lett.*, 2035 (1969); (e) Y. L. Chow, R. A. Perry, B. C. Menon, and S. C. Chen, *Tetrahedron Lett.*, 1545 (1971); (f) P. Piccardi and M. Modena, *Chem. Commun.*, 1041 (1971). The preference for five-membered rings is kinetic, not thermodynamic: M. Julia, *Pure Appl. Chem.*, **15**, 167 (1967); M. Julia and M. Maumy, *Bull. Soc. Chim. Fr.*, 2415, 2427 (1969).

(88) C. J. Grundmann and P. Grünanger, "The Nitrile Oxides," Springer-Verlag, Heidelberg, 1971, p 104. We thank Professor Grünanger for a preprint of these data, and for several additional unpublished examples, all of a similar nature except one (in which phenyl and mesityl both give 87:13).
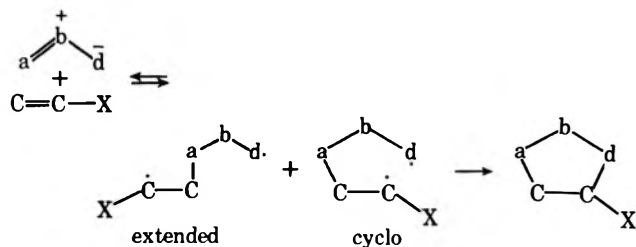
(89) E. Winterfeldt, W. Krohn, and H. Stracke, *Chem. Ber.*, **102**, 2346 (1969).

(90) Just as there exist analogies in free-radical chemistry for addition to 1,3-dipoles with the same orientation as that found for the favored diradicals in 1,3-dipolar cycloadditions (*vide supra*), an example has also been recently observed[91] of steric reversal of free-radical addition to C-phenyl-N-tert-butyl nitrone, in a manner exactly analogous to that described above for **48-53**. Thus, phenyl radical adds normally at carbon (hfc's, mT: a_N = 1.452, a_H = 0.221) but the hindered 2,4,6-trichlorophenyl radical adds principally at oxygen (minor isomer: a_N = 1.446, a_H = 0.227; major isomer: a_N = 1.436, a_H = 0.698). The esr of the latter radical is consistent with a highly delocalized benzyl radical.[92]

(91) R. A. W. Johnstone, A. F. Neville, and P. J. Russell, *J. Chem. Soc. B*, 1187 (1971); our interpretation, not the authors'.

(92) We thank Dr. Alan Douglas of these laboratories for his assistance in interpreting the esr spectra.

Partial Formal Charges and Diradical Conformation.—There remains to be discussed another aspect of the orientation of the 1,3-dipole toward the dipolarophile in the transition state, concerned with conformation rather than regioisomerism. An important corollary of the diradical theory is the possibility that the first new bond is formed at any dihedral angle between the reactants. The many possible conformations of the diradical are here idealized as the two extremes, the cyclo and extended conformations. Only the cyclo form may cyclize to product, and since single-

bond rotation is slower than either cyclization or reversion to reactants,[93] the extended form cannot achieve the cyclo form by rotation, but only by separation into reactants and then recombination. On this account it has heretofore been impossible to detect extended forms except through their effect on the entropy of activation (by lowering the per cent of effective collisions).[4] However, new discoveries, made since the first exposition of the diradical theory, have brought diradicals of extended form out of the shadow.[94]

It was first reported in 1969[95] that cycloaddition of nitrile oxides to arylacetylenes is accompanied by hydrogen transfer, forming oximes (eq 5). In corresponding fashion, nitrilimines afford hydrazones *via* hydrogen transfer, alongside normal cycloadducts (eq 6).[39] Ox-

RCNO + ArC≡CH →

$$\text{(5)}$$

RCNNR' + ArC≡CH →

$$\text{(6)}$$
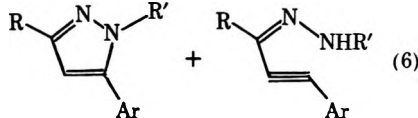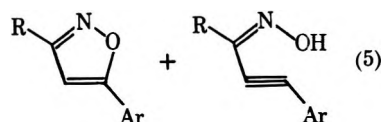
imes syn to the acetylene residue are formed exclusively.[96] Isoxazoles and oximes are formed independently (*i.e.*, not from each other) by second-order processes, both solvent independent and both with the same activation energy.[21,95,97,98] Hydrogen and deuterium are transferred at the same rate.[21]

These facts are best interpreted as arising from concurrent cyclization of cyclo diradicals (eq 2) and hydrogen transfer in extended diradicals 54 and 55[99], and establish the correctness of the diradical mechanism beyond a resonable doubt.[100]

→ oxime   → hydrazone

54   55

The competition between cyclo and extended diradicals, just as that between regioisomeric diradicals, is governed by partial formal charges. These were discussed earlier for the 1,3-dipoles' but not the dipolarophiles' portion of the diradicals. For an understanding of the latter, it is important to realize that even nominally neutral delocalized radicals have charge separation. This is not apparent from the Lewis structures, *e.g.*, 56 and 57, but becomes evident in the Linnett forms[101] 58, 59, and 60. Both canonical forms of the Lewis hybrids 56 and 57 have no charge

56   57

58   59   60
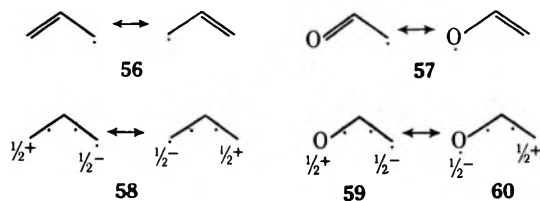
separation, and therefore even with unequal weighting of the forms of 57, no extra polarity is imposed by delocalization of the radical beyond that already inherent in the carbonyl group. On the other hand, it is obvious from the Linnett structures that, although 58 remains dipole-free overall,[102] 60 is better than 59, showing that delocalization definitely shifts negative charge toward carbonyl oxygen. Thus, delocalization of a radical into carbonyl, cyano, nitro, and the like imposes a partial positive charge on the radical center. Stabilizing groups of the opposite type—amino, ether, halogen, etc.—impose partial negative charge on the radical center, as in 61.[105]

61
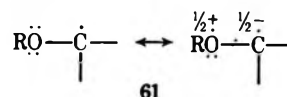
The complete array, then, of formal charges for diradicals arising from nitrile oxides and arylacetylenes bearing electron-withdrawing substituents X is summarized in 62, and with electron-releasing substituents

(93) This is required by the stereospecificity of cycloadditions to cis and trans olefins.[4]

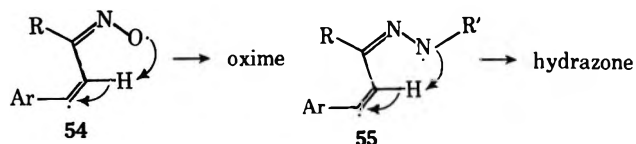(94) Not all the authors cited in this connection have endorsed the diradical interpretation.

(95) S. Morrocchi, A. Ricca, A. Zanarotti, G. Bianchi, R. Gandolfi, and P. Grünanger, *Tetrahedron Lett.*, 3329 (1969).

(96) P. Grünanger, personal communication.

(97) A. Battaglia and A. Dondoni, *Tetrahedron Lett.*, 1221 (1970).

(98) A. Battaglia, A. Dondoni, and A. Mangini, *J. Chem. Soc. B*, 554 (1971).

(99) The importance of hydrogen transfer in proving the existence of diradicals has also been recognized by Huisgen.[8]

(100) They do not thereby establish the incorrectness of the concerted mechanism, but the likelihood of two so dissimilar processes occurring simultaneously seems to us rather small.

(101) J. W. Linnett, *J. Amer. Chem. Soc.*, **83**, 2643 (1961); "The Electronic Structure of Molecules," Methuen, London, 1964.

(102) Yet the charges in forms 58 are not without consequence. They give rise to an excess of odd-electron spin on the terminal atoms, and an equal excess of the opposite spin on the central atom,[103] observed by esr.[104] The simple valence picture 56 shows none of this.

(103) D. M. Hirst and J. W. Linnett, *J. Chem. Soc.*, 1035 (1962); 1068 (1963).

(104) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).

(105) R. A. Firestone, *Tetrahedron Lett.*, 971 (1968); *J. Org. Chem.*, **34**, 2621 (1969).

Y in **63**. For nitrile imines, the corresponding diradicals are **64** and **65**.
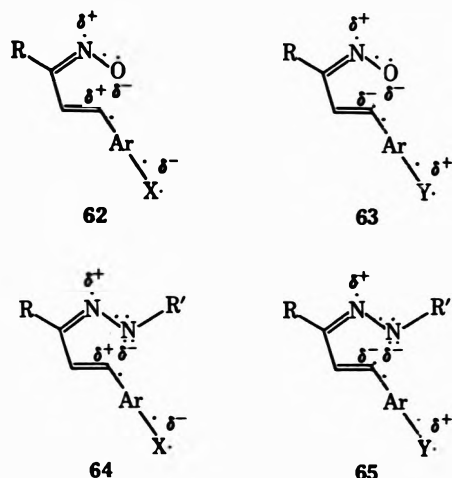
In **62** and **64**, the atoms which are to unite in cyclization bear opposite charges, while in **63** and **65** they bear like charges. A tendency is therefore anticipated for electron-withdrawing substituents to assist cyclization *via* cyclo forms **62** and **64**. Electron-releasing substituents, by creating repulsive interactions in **63** and **65**, must encourage reaction *via* extended diradicals such as **54** and **55**, *i.e.*, hydrogen transfer.[106]

The experimental results are in complete accord with this discussion. Tables IV[107] and V show data for nitrile oxides and nitrilimines which establish that both 1,3-dipoles exhibit the expected trend.

There is a clear shift toward hydrogen transfer and away from cyclization as the electron-donor power of the acetylenic substituent increases, as expected from the charge distribution in the diradicals **62–65**. Many more data, not reproduced here for lack of space, show exactly the same trend.[21,39,107] In addition, it is noteworthy that substituents in the nitrile oxide have, in contrast, almost no influence because their effect on the charge distribution in the diradicals is minor.

(106) We believe that this interpretation is sensibly the same as that offered in ref 21. Much the same argument was used by N. J. Turro and D. R. Morton, *J. Amer. Chem. Soc.*, **93**, 2569 (1971), to explain cyclization *vs.* cleavage ratios of various photochemically generated diradicals.

(107) S. Morrocchi, A. Ricca, A. Selva, and A. Zanarotti, *Atti Acad. Naz. Lincei*, **48**, 231 (1970), and personal communication from Dr. Ricca.
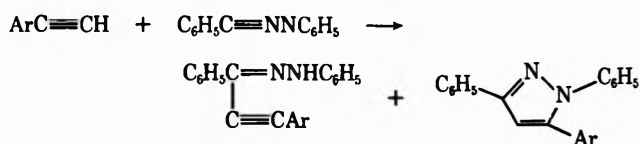
TABLE IV
PERCENTAGE OF OXIME FROM ARYLACETYLENES AND NITRILE OXIDES[a]

$ArC{\equiv}CH \ + \ Ar'C{\equiv}NO \ \longrightarrow$

Ar	Ar'			
	p-MeOC₆N₄	C₆H₅	*p*-ClC₆N₄	*p*-O₂NC₆N₄
p-O₂NC₆H₄	0	0	0	*ca.* 5
p-ClC₆H₄	7	7	9	11
C₆H₅	10	12	15	18
p-MeOC₆H₄	24	28	32	34
p-Me₂NC₆H₄	52	53	65	74

[a] Oxime/(oxime + isoxazole) × 100. See ref 107.

TABLE V
PERCENTAGE OF HYDRAZONE FROM ARYLACETYLENES AND NITRILIMINES[a]

$ArC{\equiv}CH \ + \ C_6H_5C{\equiv}NNC_6H_5 \ \longrightarrow$

Ar	Hydrazone, %
p-O₂NC₆H₄	<17
C₆H₅	23
p-MeOC₆H₄	32
p-Me₂NC₆H₄	50

[a] Hydrazone/(hydrazone + pyrazole) × 100. See ref 39.

If the mechanism were concerted, one would have expected the results to be sensitive to substituents in both partners.

Conclusion.—The principal facts of orientation in 1,3-dipolar cycloadditions have been shown to be in accord with the diradical mechanism. Previous papers have dealt with energetics,[16] stereospecificity, solvent effects, and the question of acetylenic dipolarophiles.[4] Among these topics, the only one that is fully reconcilable with the concerted mechanism is stereospecificity, which is accommodated by both mechanisms. The weight of evidence at the present time therefore favors the diradical mechanism.

Heterogeneous Catalytic Deuteration of Substituted Benzenes in Acetic Acid-d_1[1]

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Series of mono- and polyalkylbenzenes and methyl benzoate were reduced in acetic acid-d_1 using hydrogen and deuterium and the amounts and distributions of deuterium incorporated into the cyclohexane derivative were determined. Platinum was used as the catalyst in all cases except one in which rhodium on alumina was used. Extensive hydrogen–deuterium exchange which results in the formation of almost all possible deuterated species of the cyclohexane products is reported. It is concluded that the use of acetic acid-d_1 and hydrogen gas is an effective means of adding deuterium to aromatic hydrocarbons and that the hydrogen–deuterium exchange is relatively insensitive to the presence of α-hydrogen atoms and to the kind, number, and substitution patterns of substituents on the benzene ring.

The benzene nucleus of most aromatic hydrocarbons is readily reduced by hydrogen at low pressures in acetic acid using platinum as a catalyst.[2] In this paper, we report the results of a study of the deuteration of

cis and trans isomers
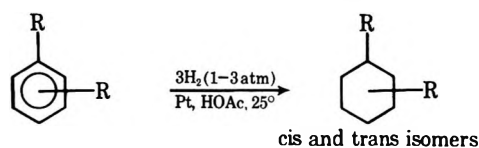
series of mono- and polyalkylbenzenes in acetic acid-d_1 using hydrogen and deuterium. One of our first objectives was to determine the effectiveness of acetic acid-d_1 and hydrogen compared to acetic acid-d_1 and deuterium as a means of introducing deuterium into organic compounds. Other major goals of this study were to determine the effects of the structure of the alkyl groups, the number of α-hydrogen atoms, and the alkyl substitution pattern on the amount and distribution of deuterium incorporation.

The generally accepted mechanism for the catalytic hydrogenation of benzene has been reviewed by Bond and Wells.[3] The initial step involves the reversible formation of a π complex of the benzene with the catalyst surface in some way, possibly with a single catalyst atom. The adsorbed benzene then picks up hydrogen atoms which have been previously united with the catalyst through a series of reversible steps until an adsorbed cyclohexene is formed.[3,4] There is some question as to whether the adsorbed cyclohexene is a π complex or a σ-1,2 dicomplex.[3,5] The olefin complex then picks up a single hydrogen atom to form a monoadsorbed complex. This process can reverse or another

hydrogen atom can be picked up to form the unadsorbed cycloalkane. The reversibility of the formation of the monoadsorbed species accounts for the hydrogen–deuterium exchange reaction of olefins.[3,5,6] This mechanism for the hydrogenation of olefins is the classic Horiuti–Polyanyi mechanism.[7]

Results

About 1 mmol of the aromatic compound in 5 ml of acetic acid at room temperature was hydrogenated at atmospheric pressure using *ca.* 20 mg of platinum oxide in a standard apparatus. The time required to complete the hydrogenation depended on the compound and ranged from 40 to 1700 min except for 1,3,5-tri-*tert*-butylbenzene, which was not reduced.[8] After the the hydrogenation, the alkane was extracted with ether and the acetic acid was removed by a normal work-up procedure. Usually most of the ether was removed by distillation and the alkane was purified by glpc and analyzed by nmr and mass spectral analyses. The nmr analysis involved the use of a standard, naphthalene. In general, the total amount of deuterium in the alkanes was found to be higher by nmr analysis than mass spectral analysis, but the numbers were always reasonably close. We attribute the difference between the nmr and mass spectral values to error involved in the integration of the nmr signals.

The initial point to be established was the effectiveness of acetic acid-d_1 and hydrogen gas as a deuterium source. The reduction of three alkylbenzenes was carried out in acetic acid-d_1 using hydrogen or deuterium. The results of these experiments are listed in Tables I and II.

TABLE I

NUMBER OF DEUTERIUM ATOMS PER MOLE OF
ALKYLCYCLOHEXANE PRODUCED IN ACETIC
ACID-d_1 USING HYDROGEN OR DEUTERIUM

Alkyl group	D/mol, hydrogen gas		D/mol, deuterium gas	
	Mass spectrum	Nmr	Mass spectrum	Nmr
Methyl	5.3	6.2	6.5	7.7
Isopropyl	5.1	5.7	6.3	6.6
tert-Butyl	4.6	5.9	5.7	6.2

(1) (a) This work was partially supported by Public Health Service Grant GM 13799 from the National Institute of General Medical Sciences and Grant GP-18031 from the National Science Foundation. We thank these organizations for their support. (b) Based on work by D. H. B. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Iowa State University. (c) Alfred P. Sloan Research Fellow, 1970–1972. (d) National Science Foundation Summer Fellow, 1968, and National Institutes of Health Special Fellow, 1968–1971.

(2) (a) R. Willstätter and E. Waldschmidt-Leitz, *Chem. Ber.*, **54**, 113 (1921); (b) A. Skita and W. A. Meyer, *ibid.*, **45**, 3589 (1912); (c) A. Skita and A. Schneck, *ibid.*, **55**, 144 (1922); (d) R. Adams and J. R. Marshall, *J. Amer. Chem. Soc.*, **50**, 1970 (1928).

(3) G. C. Bond and P. B. Wells, *Advan. Catal.*, **15**, 91 (1964).

(4) (a) S. Siegel and M. Dunkel, *ibid.*, **9**, 15 (1957); (b) S. Siegel and G. V. Smith, *J. Amer. Chem. Soc.*, **82**, 6082 (1960); (c) *ibid.*, **82**, 6087 (1960); (d) S. Siegel, G. V. Smith, B. Dmuchovsky, D. Dubbell, and W. Halpern, *ibid.*, **84**, 3136 (1962); (e) S. Siegel and B. Dmuchovsky, *ibid.*, **84**, 3132 (1962); (f) F. Hartog and P. Zwietering, *J. Catal.*, **2**, 79 (1963); (g) S. Siegel, V. Ku, and W. Halpern, *ibid.*, **2**, 348 (1963); (h) S. Siegel and V. Ku, *Proc. Int. Congr. Catal.*, *3rd*, **2**, 1199 (1965).

(5) (a) K. Schrage and R. L. Burwell, Jr., *J. Amer. Chem. Soc.*, **88**, 4555 (1966); (b) R. L. Burwell, Jr., *Chem. Eng. News*, **44**, 56 (August 22, 1966); (c) R. L. Burwell, Jr., *Accounts Chem. Res.*, **2**, 289 (1969), and references cited therein.

(6) J. J. Philipson and R. L. Burwell, Jr., *J. Amer. Chem. Soc.*, **92**, 6125 (1970).

(7) I. Horiuti and M. Polyanyi, *Trans. Faraday Soc.*, **30**, 1164 (1934).

(8) It is not clear why we failed to hydrogenate 1,3,5-tri-*tert*-butylbenzene, since it is reported to be reduced fairly readily under conditions similar to ours.[9] Possibly the large substituents retarded the rate of complexation of the aromatic nucleus with the catalyst more effectively under our conditions.

(9) H. Van Bekkum, H. M. A. Buurmans, G. Van Minnen-Pathuis, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **88**, 779 (1969).

Table II

Deuterated Species of the Alkylcyclohexanes Produced in Acetic Acid-d_1 Using Hydrogen or Deuterium[a]

Alkyl group	Gas	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}	d_{11}	d_{12}	d_{13}	d_{14}
Methyl	H₂	0.1	1.1	3.9	10.2	18.5	22.1	18.1	12.0	7.5	3.8	1.7	0.6	0.1	0.1	0.2
	D₂	0.1	0.1	0.7	3.3	10.0	19.2	21.8	16.0	:2.7	8.7	4.0	2.0	0.8	0.4	0.2
Isopropyl	H₂	0.2	0.8	3.3	10.1	21.0	26.5	21.1	10.4	3.9	1.6	0.7	0.4			
	D₂			0.5	2.3	8.6	19.6	27.4	22.0	:1.4	4.8	2.0	0.8	0.4	0.1	0.1
tert-Butyl	H₂	1.4	1.6	5.3	13.5	25.2	26.4	17.5	5.9	1.9	1.0	0.3				
	D₂	0.6	0.5	1.3	3.4	11.6	26.7	31.2	16.1	6.0	2.0	0.4	0.2			

[a] The values reported in this and other tables are corrected normalized values obtained from the partial mass spectra of the alkanes.

Table III

Deuterated Species and the Number of Deuterium Atoms per Mole of Alkylcyclohexanes Produced in Acetic Acid-d_1 Using Hydrogen

Registry no.	Alkyl group	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}	d_{11}	d_{12}	d_{13}	d_{13}	D/mol Mass spectrum	D/mol Nmr
110-82-7	Hydrogen	0.4	1.8	6.2	15.0	22.6	22.3	14.7	7.3	4.3	2.7	1.7	0.8	0.2			4.9	5.8
108-87-2	Methyl	0.1	1.1	3.9	10.2	18.5	22.1	18.1	12.0	7.5	3.8	1.7	0.6	0.1	0.1	0.2	5.3	6.2
1678-91-7	Ethyl	0.6	0.7	3.3	9.4	18.4	23.4	20.2	12.6	6.4	2.6	1.4	0.6	0.3	0.1		5.4	5.5
696-29-7	Isopropyl	0.2	0.8	3.3	10.1	21.0	26.5	21.1	10.4	3.9	1.6	0.7	0.4				5.1	5.7
3178-22-1	*tert*-Butyl	1.4	1.6	5.3	13.5	25.2	26.4	17.5	5.9	1.9	1.0	0.3					4.6	5.2

The deuterium per mole values, the average numbers of deuterium atoms incorporated into the cyclohexane molecules, indicate that the deuterium incorporation into a cyclohexane derivative increases by about one deuterium atom per mole when deuterium is used in place of hydrogen (Table I). The distribution pattern of the deuterated isomers, d_n, was shifted by one unit when deuterium was used in place of hydrogen (Table II); e.g., the most prominent peak in the mass spectrum of methyl-, isopropyl-, and *tert*-butylcyclohexane is d_5 when hydrogen was used and d_6 when deuterium was used. Notice that the amounts of deuterium per mole and the exchange patterns of the cyclohexane derivatives given in Tables I and II (and subsequent tables) indicate that some of the exchanged hydrogen atoms of the hydrocarbon are being incorporated into other molecules of the product. Some of the hydrogen atoms liberated in the exchange of the aromatic hydrocarbon are apparently not exchanging with the solvent but are remaining on the catalyst and are then incorporated into other product molecules. Since only 1 mmol of hydrocarbon was reduced in the presence of 82 mmol (5 ml) of acetic acid-d_1 if all of the liberated hydrogen atoms exchanged with the solvent, one would expect a much larger incorporation of deuterium in the absence of a very large isotope effect for the hydrogenation step. Of course, an alternative explanation for the large amount of incorporation of hydrogen is that complete randomization of hydrogen and deuterium atoms occurs but there is a large isotope effect on the step which transfers hydrogen atoms from the catalyst to the hydrocarbon.

The results of the deuteration of benzene, toluene, ethylbenzene, isopropylbenzene, and *tert*-butylbenzene are presented in Table III. The nmr spectra of the methyl-, ethyl-, and isopropylcyclohexanes indicate that some deuterium is incorporated into the alkyl groups. The methyl signal of the three alkyl groups shows some splitting by geminal or vicinal deuterium atoms.

The results of the deuteration of polyalkylbenzenes are listed in Table IV. Hydrogenation of the *o*-, *m*-,

and *p*-xylenes give 90, 77, and 74% of the *cis*-dimethyl-cyclohexanes, respectively.

To check if aromatic hydrogen exchange prior to reduction was important, benzene, toluene, and *p*-xylene were half hydrogenated, and the products and starting materials were separated by glpc and analyzed for deuterium incorporation by mass spectroscopy. These results are presented in Table V.

During our study, it was reported that the catalytic deuteration of methyl benzoate in acetic acid-d_1 involved little hydrogen–deuterium exchange.[10] Since this result was surprising considering the extensive exchange that we found with the mono- and polyalkylbenzenes, we reduced methyl benzoate over reduced platinum oxide using hydrogen and deuterium and 5% rhodium on alumina in acetic acid-d_1 using deuterium. The results of these reductions are given in Table VI.

Our results disagree with those reported, since we find extensive exchange similar to that observed with the alkylbenzenes whereas the dominant peak in the mass spectrum of methyl cyclohexanecarboxylate was reported to be that of the d_6 isomer using deuterium and 5% rhodium on alumina. Moreover, hydrogenation of methyl benzoate-d_5 using 5% platinum on alumina and hydrogen in acetic acid was reported to give predominantly methyl cyclohexanecarboxylate-d_5. Again, this result conflicts with our results obtained with platinum, deuterium, and acetic acid-d_1, assuming that the extent of exchange on platinum and platinum on alumina would be similar.

The published nmr spectrum of the material reported to be methyl cyclohexanecarboxylate-d_6 gave two broad peaks at δ 1.3 and 1.7 for the cyclohexyl hydrogen atoms which integrated for 4.6 hydrogen atoms relative to the methoxy group. The nmr spectrum of our methyl cyclohexanecarboxylate produced by use of deuterium and platinum in acetic acid-d_1 also showed two broad peaks at δ 1.33 and 1.75 for the cyclohexyl hydrogen atoms which integrated relative to the methoxy group for 6.4 hydrogen atoms. The two spectra

(10) C. C. Price and C. D. Beard, *J. Amer. Chem. Soc.*, **92**, 5921 (1970).

TABLE IV

DEUTERATED SPECIES AND THE NUMBER OF DEUTERIUM ATOMS PER MOLE OF POLYALKYLCYCLOHEXANES PRODUCED IN ACETIC ACID-d_1 USING DEUTERIUM[a]

Registry no.	Polyalkyl groups	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}	d_{11}	d_{12}	d_{13}	d_{14}	d_{15}	d_{16}	d_{17}	d_{18}	D/mol Mass spectrum	D/mol Nmr
583-57-3	1,2-Dimethyl	0.2		0.6	2.4	7.8	15.1	17.1	14.0	12.2	10.5	8.0	6.0	3.7	1.8	0.6	0.2	0.1			7.4	6.8
591-21-9	1,3-Dimethyl		0.1	0.6	2.5	6.7	12.4	15.2	14.6	13.6	12.0	9.4	6.9	4.0	1.3	0.4	0.1				7.5	8.6
589-90-2	1,4-Dimethyl		0.2	0.5	2.4	7.4	14.6	17.2	14.0	12.3	10.4	8.2	6.5	3.9	1.5	0.6	0.2	0.1			7.4	8.0
1678-97-3	1,2,3-Trimethyl	0.1	0.1	0.2	1.4	4.0	8.2	11.4	11.8	12.6	12.4	11.4	9.8	7.2	4.8	2.8	1.3	0.4	0.1		8.6	9.5
1839-63-0	1,3,5-Trimethyl			0.1	0.7	2.8	6.6	11.2	13.2	13.4	12.0	9.5	9.0	7.7	6.6	5.0	2.0	0.2			9.0	10.7
2090-38-2	1,2,4,5-Tetramethyl			0.4	0.6	2.4	5.8	9.2	10.4	11.8	11.8	11.0	8.2	7.4	5.8	4.9	4.0	3.3	2.2	0.8	9.7	10.6
34386-82-8	1,4-Di-tert-butyl	0.2	1.4	6.2	14.4	22.0	25.4	15.7	11.4	2.3	0.6	0.3	0.1								4.7	6.8
34387-60-5	1,3,5-Triisopropyl		5.0	2.7	1.5	1.5	2.3	7.6	11.6	16.1	16.2	12.3	8.9	5.7	3.9	2.5	1.6	0.6			8.4	6.6
91-17-8	1,2-Tetramethylene	0.4	0.1	0.3	0.4	1.6	3.8	7.4	13.2	20.6	23.4	17.3	7.9	2.6	0.8	0.2					8.4	8.9

[a] These data are for the mixtures of stereoisomers that were obtained from the reductions.

are very similar and yet our sample was certainly not predominantly the d_6 species.

Discussion

The times required for the hydrogenation of the various arenes fit the generalizations[11] that the rates of hydrogenation decrease as the number of substituents increase and increase as the symmetry of the substitution pattern of the benzene ring increases, even when the higher symmetry leads to a greater degree of substitution.[8,9]

The results shown in Tables I and II clearly show that acetic acid-d_1 and hydrogen are a very effective means of adding deuterium to aromatic hydrocarbons. Evidently the adsorbed hydrogen exchanges very rapidly with the acidic deuterium atoms of the solvent and so deuterium atoms are incorporated into the hydrocarbon almost to the same extent as when deuterium is used. Our observation is consistent with the results of Eidinoff and coworkers,[12] who found that the deuteration of olefins in acetic acid over platinum resulted in *ca.* 1% deuterium incorporation.

These results suggest that acetic acid-t_1 and hydrogen should be a convenient way to introduce tritium into molecules.

Philipson and Burwell studied the reduction of cyclic olefins in the liquid phase using deuterium in acetic acid-d_1 and a number of d_1 alcohols.[6] The use of acetic acid-d_1 resulted in the most incorporation of deuterium through reduction and exchange; acetic acid-d_1 exhibited the highest rate of exchange between solvent hydrogen atoms and adsorbed hydrogen atoms.

From the results presented in Tables III and IV, it is seen that extensive exchange takes place during the reduction of the benzene ring so that no single deuterated species predominates and, in fact, virtually all possible deuterated species are obtained. Moreover, this hydrogen–deuterium exchange is relatively insensitive to the presence of α-hydrogen atoms or the kind, number, and substitution patterns of alkyl substituents on the benzene ring. The data in Table III show that the number of deuterium atoms incorporated into cyclohexane and its alkyl derivatives is about 5.0 and the distribution of the deuterium is approximately the same, even in those compounds which possess α-hydrogen atoms. The absence of α-hydrogen atoms does not seem to prevent the ring from exchanging hydrogen atoms on both of its sides, since even cyclohexane and *tert*-butylcyclohexane contain species with >6 deuterium atoms. The hydrocarbons which possess α-hydrogen atoms do show a slightly higher fraction of species that contain >6 deuterium atoms, and this is consistent with exchange of the α-hydrogen atoms. The incorporation of deuterium into the α positions of the methyl-, ethyl-, and isopropylcyclohexanes is confirmed by their nmr spectra, and the nmr spectra of the ethyl- and isopropylcyclohexanes indicate that exchange of the β-hydrogen atoms may also have occurred. The lack of deuterium incorporation into the *tert*-butyl group of the *tert*-butylcy-

(11) H. A. Smith in "Catalysis," Vol. V, P. H. Emmett, Ed., Reinhold, New York, N. Y., 1957, pp 175–256.
(12) M. L. Eidinoff, J. E. Knoll, D. K. Fukushima, and T. F. Gallagher, *J. Amer. Chem. Soc.*, **74**, 5280 (1952).

TABLE V

DEUTERATED SPECIES AND THE NUMBER OF DEUTERIUM ATOMS PER MOLE OF HYDROCARBON PRODUCED IN ACETIC ACID-d_1 STOPPING THE REACTION AFTER 50% REACTION

Registry no.	Hydrocarbon	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}	d_{11}	d_{12}	d_{13}	d_{14}	D/mol
71-43-2	Benzene[a]	83.2	10.9	2.9	1.4	0.9	0.7										0.3
	Cyclohexane[a]	0.3	1.8	7.2	17.2	26.2	24.5	12.7	4.8	2.4	1.5	0.9	0.4	0.1			4.5
108-88-3	Toluene[a]	64.3	20.7	9.1	4.8	0.9	0.2										0.6
	Methylcyclohexane[a]	0.0	0.5	1.9	7.0	16.3	23.7	22.6	14.0	7.2	3.9	1.6	0.7	0.4	0.2		5.7
106-42-3	p-Xylene[b]	69.2	12.2	5.2	4.2	2.6	3.0	3.4	0.2								0.8
	1,4-Dimethylcyclohexane[b]	0.0	0.2	1.1	4.8	13.1	22.9	21.3	12.8	9.7	6.6	3.5	2.2	1.3	0.4	0.1	6.2

[a] Hydrogen was used.   [b] Deuterium was used.

TABLE VI

DEUTERATED SPECIES AND THE NUMBER OF DEUTERIUM ATOMS PER MOLE OF THE METHYL CYCLOHEXANECARBOXYLATE PRODUCED BY THE REDUCTION OF METHYL BENZOATE IN ACETIC ACID-d_1

Group	Gas	Catalyst	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}	d_{11}	D/mol
Methoxycarbonyl	H_2	Pt	1.2	5.5	14.3	23.8	25.4	17.6	8.0	2.8	0.8	0.3	0.2		3.7
Methoxycarbonyl	D_2	Pt	0.5	1.9	6.7	16.3	24.7	24.9	15.2	6.7	2.3	0.8			4.5
Methoxycarbonyl	D_2	Rh/Al$_2$O$_3$		0.2	1.4	6.1	17.1	30.0	26.0	10.7	5.1	2.4	0.9	0.2	5.4

clohexane is consistent with the requirement that only 1,2-, not 1,3-diadsorbed species, can form.[5]

From the results presented in Table IV, it is seen that the substitution patterns of dimethyl- and trimethylbenzenes have little effect on the deuterium incorporation. The amount of deuterium incorporated per mole and its distribution are very similar for all three xylenes. The results of the 1,2,3- and 1,3,5-trimethylbenzenes are also very similar. The slight differences which exist show that more deuterium was incorporated into the 1,3,5 compound, the more symmetrical isomer. 1,2,4,5-Tetramethylbenzene leads to the same sort of results obtained with the di- and trimethyl derivatives. There is, in fact, a gradual increase in the total amount of deuterium incorporated in going from the dimethyl (7.4 D/mol) to the trimethyl (8.8 D/mol) to the tetramethyl (9.7 D/mol) compounds, and this is expected since the number of α-hydrogen atoms which can undergo exchange is also increasing in this series.

The 1,4-di-*tert*-butylbenzene leads to species containing greater than six deuterium atoms and so deuterium atoms must be incorporated on both sides of the ring despite the bulky substituents. 1,3,5-Triisopropylbenzene gives comparable results; however, the interpretation of the results is a little more ambiguous since the α- and β-hydrogen atoms of the isopropyl groups can undergo exchange. 1,2-Tetramethylenebenzene does lead to a greater amount of deuterium incorporation than o-xylene, which is expected since an additional ring is present.

The insensitivity of the hydrogen–deuterium exchange to the kind, number, and substitution patterns of alkyl groups on the benzene ring is further seen from comparison of the numbers of deuterium atoms incorporated per exchangeable hydrogen atom for the various cyclohexanes. These numbers are presented in Table VII for the methyl-, polymethyl-, *tert*-butyl-, 1,4-di-*tert*-butyl-, and 1,2-tetramethylenecyclohexanes (decalin) and indicate that ca. 0.5 deuterium atom is

TABLE VII

AVERAGE NUMBER OF DEUTERIUM ATOMS INCORPORATED PER EXCHANGEABLE HYDROGEN ATOM IN THE ALKYLCYCLOHEXANES PRODUCED WITH DEUTERIUM AND ACETIC ACID-d_1

Alkyl group	Average D/H
Methyl	0.46
1,4-Dimethyl	0.46
1,3,5-Trimethyl	0.50
1,2,4,5-Tetramethyl	0.49
tert-Butyl	0.52
1,4-Di-tert-butyl	0.47
Isopropyl	0.35
1,3,5-Triisopropyl	0.28
1,2-Tetramethylene	0.47

incorporated per hydrogen atom irrespective of the kind, number, and substitution patterns of the alkyl groups.

Both isopropyl derivatives show slightly lower numbers of deuterium atoms incorporated per exchangeable hydrogen atom than the other compounds, but these low values are probably a result of the inclusion of the six hydrogen atoms on the β-methyl groups as exchangeable hydrogens. Probably not all of these hydrogens are subject to exchange during one period of residence on the catalytic surface.

The extensive hydrogen–deuterium exchange which is reported in this study demands that hydrogen exchange can occur on both sides of the ring of a given molecule. Several published results also demand exchange on both sides of the ring. For example, the hydrogenation of the xylenes and 1,2-dimethylcyclohexane leads to a considerable amount of the *trans*-dimethylcyclohexanes.[4,13] Also, extensive hydrogen–deuterium exchange occurs during the reduction of some cycloalkenes[6] and the hydrogen–deuterium exchange of some cycloalkanes.[5] Moreover, *trans*-1,2-dimethylcyclopentane is partially converted to its cis isomer

(13) S. Siegel, *Advan. Catal.*, **16**, 123 (1966).

during the hydrogen–deuterium exchange reactions.[5,14]

One possible explanation for the extensive hydrogen–deuterium exchange observed in this study, and its relative insensitivity to the presence of α-hydrogen atoms or the kind, number, or substitution patterns of substituents, is that exchange of the hydrogen atoms of the starting arene occurs. The results shown in Table V indicate that some exchange of the hydrogen atoms had occurred after 50% deuteration. This explanation requires that the rate of prior exchange relative to the rate of reduction of a given arene is relatively insensitive to substituents, which is not an expected condition, but not an impossible one.

Another mechanism which accounts for the data in Tables III and IV involves the intermediate formation of a trans 1,2-diadsorbed complex. The essential point in this mechanism is that the ring can be flipped by going through a trans 1,2-diadsorbed state without ever leaving the catalyst surface. The ring could, of course, still contain unsaturation. The insensitivity of the hydrogen–deuterium exchange reaction to the kind, number, and substitution patterns of alkyl groups on the benzene ring is readily explained if the mono-adsorbed complex can go to either a cis or trans 1,2-diadsorbed complex with comparable ease and with ring substituents having very little effect on this process.

cis 1,2-diadsorbed complex

trans 1,2-diadsorbed complex
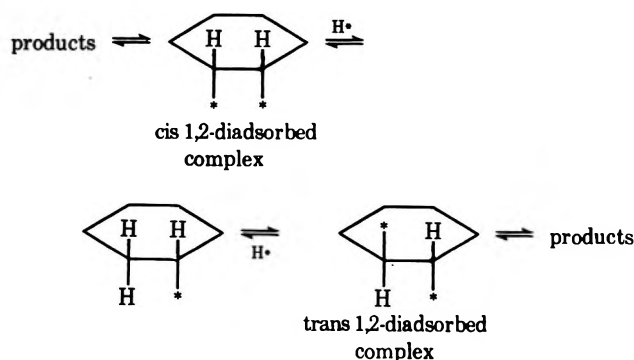
A trans 1,2-diadsorbed alkene has been postulated to explain the trans products from the reduction of xylenes,[15] but is not a readily acceptable mechanism since exchange experiments indicate that olefins are either π adsorbed to the catalyst or if diadsorbed by 1,2 σ bonds, the σ bonds prefer to be eclipsed.[5,6,16] However, evidence that the hydrocarbon–catalyst bonds of the 1,2-diadsorbed complex must be eclipsed comes mainly from hydrogen–deuterium exchange experiments with adamantane, bicyclo[2.2.1]heptane, and cyclopentane.[5,6] With these systems, it is difficult or impossible for hydrocarbon–catalyst bonds of a trans 1,2-diadsorbed complex to have a dihedral angle of <60°. From the inspection of Dreiding models, one can see that the flexibility of the cyclohexane ring permits the dihedral angle between 1,2-trans carbon–hydrogen bonds to be as low as *ca.* 30°. Thus, we feel that trans 1,2-diadsorbed complexes of cyclohexane rings are not out of the question and we are unaware of any evidence which rigorously excludes their existence.

The extensive hydrogen–deuterium exchange found in the substituted cyclohexanes could also result from the desorption of a cyclohexene intermediate followed by readsorption of the cyclohexene, on either side of the ring, and reduction to give the cyclohexane. The desorption mechanism has been proposed to explain the formation of *trans*-dialkylcyclohexanes from the dimethylcyclohexenes and xylenes,[4,9,13,17] and cyclohexenes have been produced during the reduction of aromatic compounds[4,9,18] but in most cases they have been isolated in only low yields. Arguments have been presented that indicate that cyclohexene formation is only a side reaction.[14,19]

No support is obtained from the results in Table IV for mechanisms of hydrogen–deuterium exchange which go through "dissociatively adsorbed olefins" (σ-bonded olefins),[19,20] or involve "rolling over" of the cycloalkane from one side to the other.[5a,c] The deuterium incorporation by either one of these mechanisms would be expected to be quite sensitive to the substitution patterns of the polyalkylbenzenes.

The results presented in Table VI clearly show that the same sort of hydrogen–deuterium exchange occurs during the reduction of a benzene ring that contains a methoxycarbonyl group as occurs during the reduction of alkyl-substituted benzene rings. The report[10] that the deuteration of methyl benzoate gave exclusively the d_6 isomer and the hydrogenation of methyl benzoate-d_5 gave exclusively the d_5 isomer is difficult to explain considering our results. Possibly subtle differences in the catalyst or reaction conditions account for the disagreement of our results.

Experimental Section

Methods and Materials.—Most equipment has been previously described.[21] For glpc analysis, a 6 ft $\times$ 0.25 in. 15% SE-30 on Chromosorb W and a 6 ft $\times$ 0.25 in. 10% QF-1 on Chromosorb P column were used. The mass spectra of the cyclohexane derivatives were measured with an ionization voltage of 20 eV. The calculations needed to correct the peak intensities for natural isotope abundance were carried out on the Iowa State University IBM Series 360 Model 65 computer.

All hydrogenations were carried out using an atmospheric pressure hydrogenation apparatus which consisted of three gas burets, capacities of 10, 50, and 100 ml, connected to a U-tube manometer, and a removable 50-ml erlenmeyer flask fitted with an additional side-arm. The burets were also connected to an external leveling bulb. One arm of the manometer was open to the atmosphere.

The hydrocarbons used in the hydrogenations were commercially available and were used without further purification, with the exception of tetralin, which was fractionally distilled. The purity of the hydrocarbons was established.

The deuterium gas (99.65 atom %) used in the deuterations was obtained from Bio-Rad Laboratories, Richmond, Calif.

The deuterium per mole values determined by nmr were calculated from the relative intensities of the nmr signals of the hydrocarbon compared to those of naphthalene, an internal standard.

All numerical values reported in data tables have been averaged.

Acetic acid-d_1 was prepared by refluxing a mixture of 2.6 mol

(14) R. L. Burwell, Jr., and K. Schrage, *Discuss. Faraday Soc.*, **41**, 215 (1966).

(15) A. S. Hussey, R. H. Baker, and G. W. Keulks, *J. Catal.*, **10**, 258 (1968).

(16) K. Schrage and R. L. Burwell, Jr., *J. Amer. Chem. Soc.*, **88**, 4549 (1966).

(17) A. W. Weitkamp, *Advan. Catal.*, **18**, 2 (1968).

(18) F. Hartog, J. H. Tebben, and C. A. M. Weterings, *Proc. Int. Congr. Catal., 3rd*, **2**, 1210 (1965).

(19) (a) J. F. Sauvage, R. H. Baker, and A. S. Hussey, *J. Amer. Chem. Soc.*, **82**, 6090 (1960); (b) *ibid.*, **83**, 3874 (1961); (c) G. V. Smith and R. L. Burwell, Jr., *ibid.*, **84**, 925 (1962).

(20) R. L. Burwell, Jr., B. K. C. Shim, and H. C. Rowlin, *ibid.*, **79**, 5142 (1957).

(21) W. S. Trahanovsky and M. P. Doyle, *J. Org. Chem.*, **32**, 146 (1967).

of deuterium oxide and 1.5 mol of acetic anhydride for 2 hr. After the mixture was allowed to cool, 0.3 mol of boron triacetate, which was prepared by the method of Cook, *et al.*,[22] was added to it. The mixture was distilled to give a 104% yield of a colorless liquid, bp 114–115.8°. The nmr spectrum indicated the presence of 1.3% light acetic acid.

Hydrogenation Procedure.—To a flask which possessed a side arm containing a stopcock was added a magnetic stirring bar, 3 ml of acetic acid, and 20 mg of platinum oxide (Sargent). The flask was connected to the hydrogenation apparatus, the system was flushed with hydrogen and filled with hydrogen at atmospheric pressure, and the catalyst was prereduced by vigorous stirring. The stirring was stopped, *ca.* 1 mmol of the benzene derivative and 2 ml of acetic acid were added to the flask through the side-arm, and the stirring was resumed. Peri-

(22) H. G. Cook, J. D. Ilett, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 3125 (1950).

odically, the pressure of the hydrogen was adjusted to atmospheric pressure. When the hydrogenation was completed, the solution was decanted from the catalyst, 10 ml of ethyl ether and 10 ml of water were added to the solution, and the water layer was drawn off. The ethereal layer was treated with two 10-ml portions of saturated sodium chloride solution and two 10-ml portions of saturated sodium hydrogen carbonate solution and dried (MgSO$_4$). The ether was partially removed by distillation and the residue was purified by glpc.

One deuteration of methyl benzoate was carried out in the same fashion except that 20 mg of 5% rhodium on alumina (Matheson Coleman and Bell) was used as the catalyst.

Notes

Dineoalkyl Ethers. A General Synthesis of the Symmetrical Ethers

V. W. GASH

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A method for the synthesis of dineoalkyl ethers has never been reported, although this type of structure should be of potential interest because of the ether functionality combined with the stability characteristics imparted by the neighboring neoalkyl groups. The di- and polypentaerythritols (obtained indirectly by the Tollens reaction of acetaldehyde with formaldehyde) are the only reported examples of this structure type excepting the parent compound itself, dineopentyl ether, which was recently prepared[1] by hydrogenolysis of neopentyl alcohol. The direct synthesis of several new members of this structure type, particularly those with tetrahydroxyl functionality as well as alicyclic β substitution, is reported.

Consideration of trimethylolethane as a starting material suggested the use of a suitable blocking group to mask two of the hydroxyl groups allowing its reaction as a monool. This was achieved by its conversion to 2,2,5-trimethyl-5-*m*-dioxanemethanol (2) in high

(1) H. Pines and P. Steingaszner, *J. Catal.*, 10, 60 (1968).

Alkaline condensation of tosylate (3) with 2 gave the desired 5,5'-(oxydimethylene)bis(2,2,5-trimethyl-*m*-dioxane) (4) in conversions ranging up to 64% depending upon solvent, base, and reaction time. Although a precipitate of tosylate salt can usually be detected early as an opalescence, the formation of this dineoalkyl ether (4) requires a minimum of 48 hr to obtain good yields of product. The mesylate 5 was also prepared and used in the alkaline condensation but offered no advantages over the tosylate. Mild acid hydrolysis of 4 gave the desired 2,2'-(oxydimethylene)bis(2-methyl-1,3-propanediol) (6) quantitatively (eq 1). Mass
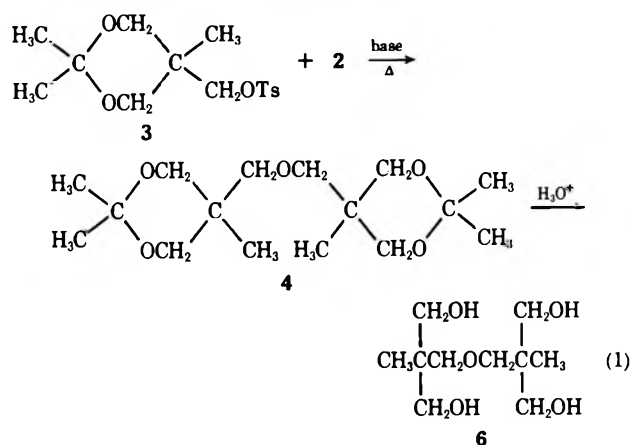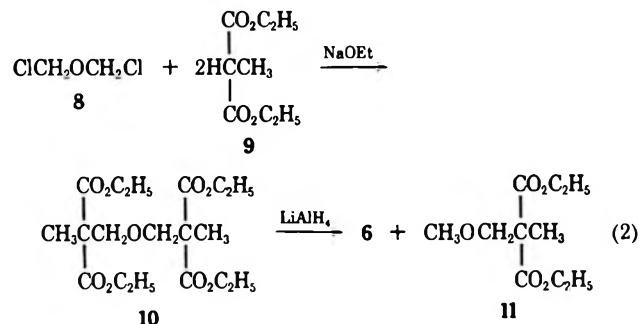

spectrographic examination of 4 showed no molecular ion species but a major peak at 287 corresponding to initial loss of a methyl group. The failure to observe a molecular ion is apparently characteristic of a 2-methyl-1,3-dioxanyl-type structure. This was confirmed by the synthesis[2] of 2,2,5,5-tetramethyl-1,3-dioxane (7). The mass spectrum of this structurally related compound showed no molecular ion but a major peak at 129 from loss of a methyl group.

Although the above analytical data on both the intermediate (4) and product (6) dineoalkyl ethers were not

yield which should be stable to basic or neutral conditions but easily cleaved by acid to regenerate the methylol groups.

(2) C. S. Rondestvedt, Jr., *J. Org. Chem.*, 26, 2247 (1961).

ambiguous, the known facile rearrangement of neoalkyl groups required an unequivocal synthesis of **6** to establish directly its dineoalkyl ether structure. This was achieved by buildup of both neoalkyl groups around a preformed ether linkage as shown in eq 2.
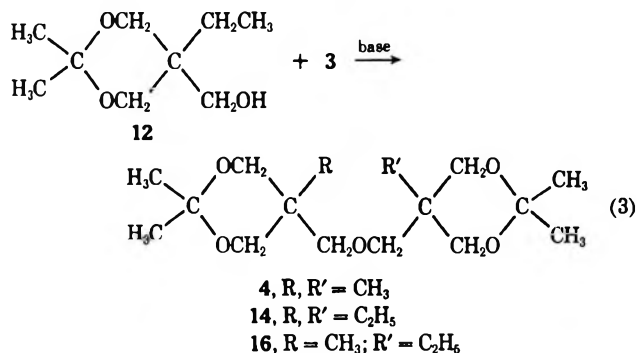
$$
\begin{array}{c}
\quad\quad\quad \text{CO}_2\text{C}_2\text{H}_5 \\
\quad\quad\quad | \\
\text{ClCH}_2\text{OCH}_2\text{Cl} + 2\text{HCCH}_3 \xrightarrow{\text{NaOEt}} \\
\quad\quad\quad | \\
\mathbf{8} \quad\quad\quad \text{CO}_2\text{C}_2\text{H}_5 \\
\quad\quad\quad \mathbf{9}
\end{array}
$$

$$
\begin{array}{c}
\text{CO}_2\text{C}_2\text{H}_5 \quad \text{CO}_2\text{C}_2\text{H}_5 \quad\quad\quad\quad \text{CO}_2\text{C}_2\text{H}_5 \\
| \quad\quad\quad | \quad\quad\quad\quad\quad\quad | \\
\text{CH}_3\text{CCH}_2\text{OCH}_2\text{CCH}_3 \xrightarrow{\text{LiAlH}_4} \mathbf{6} + \text{CH}_3\text{OCH}_2\text{CCH}_3 \quad (2) \\
| \quad\quad\quad | \quad\quad\quad\quad\quad\quad | \\
\text{CO}_2\text{C}_2\text{H}_5 \quad \text{CO}_2\text{C}_2\text{H}_5 \quad\quad\quad\quad \text{CO}_2\text{C}_2\text{H}_5 \\
\quad\quad\quad \mathbf{10} \quad\quad\quad\quad\quad\quad\quad\quad \mathbf{11}
\end{array}
$$

The by-product formation of **11** was traced to the presence of chloromethyl methyl ether in the bischloromethyl ether **8** prepared by modification of a published method.[3] Multiple fractionations of the labile ether **8** failed to remove the impurity as monitored by glc. Purification of **10** was achieved at the ester stage followed by a difficult hydride reduction to yield the dineoalkyl ether **6**. This product was identical in all respects with the dineoalkyl ether prepared by the tosylate displacement. Confirmation of this structure indicates that nucleophilic substitution of a neopentyl tosylate (or mesylate) can occur without rearrangement *even* if the attacking nucleophile is, itself, a neoalkyl structure. The absence of rearrangement products in the displacement reaction also indicates that high yields of the dineoalkyl ethers are possible in spite of the low reaction rates.

The success of the tosylate displacement reaction in the synthesis of pure dineoalkyl ethers without the formation of rearrangement products stimulated the synthesis of additional dineoalkyl ethers by the tosylate displacement reaction. Trimethylolpropane was converted to 2,2-dimethyl-5-ethyl-5-*m*-dioxanemethanol (**12**). Condensation of **12** with the tosylate **13** gave 5,5'-(oxydimethylene)bis(2,2-dimethyl-5-ethyl-*m*-dioxane) (**14**). Mild acid hydrolysis yielded the desired 2,2'-(oxydimethylene)bis(2-ethyl-1,3-propanediol) (**15**). These displacement reactions were monitored by gas chromatography and the evident lower rate of reaction of **12** with **13** must be due solely to the greater effective size of the ethyl group over the methyl group, this effect being magnified in this system of neoalkyl groups.

An unexpected result was found in the synthesis of 5-ethyl-5'-methyl-5,5'-(oxydimethylene)bis(2,2-dimethyl-*m*-dioxane (**16**) from base condensation of the tosylate **3** with the monool **12**. In addition to the expected ether (**16**), there were also obtained significant amounts of ethers **4** and **14** (eq 3). The reaction was monitored by gas chromatography proving the formation of **4** and **14** by comparison of retention times with those of authentic samples. The elution order of **4**, **16**, and **14** was consistent with molecular weight, hence boiling point, and **16** was also in greatest amount. Further confirmation of **16** was obtained by preparative gas chromatography to obtain an analytical sample

(3) F. S. H. Head, *J. Chem. Soc.*, 2972 (1963).

$$
\text{12} + 3 \xrightarrow{\text{base}}
$$

$$
\begin{array}{c}
\mathbf{4}, \text{R, R}' = \text{CH}_3 \\
\mathbf{14}, \text{R, R}' = \text{C}_2\text{H}_5 \\
\mathbf{16}, \text{R} = \text{CH}_3; \text{R}' = \text{C}_2\text{H}_5
\end{array} \quad (3)
$$

and its hydrolysis to the crystalline 2-ethyl-2'-methyl-2,2'-(oxydimethylene)di-1,3-propanediol (**17**). The rapid scan mass spectrographic analysis of the mixture **4**, **14**, and **16** showed major peaks at 287, 301, and 315 (no parent ions) corresponding to loss of a methyl group from the respective structures.

The formation of **4** and **14** must result from a significant equilibration of the tosylate and alkoxide ions where R and R' are neoalkyl groups. Sulfur-oxygen

$$
\text{R}'\text{-O} + \text{ROS(O}_2\text{)}\!\!-\!\!\langle\text{aryl}\rangle\!\!-\!\!\text{CH}_3 \rightleftharpoons
$$

$$
\left[\text{R-O-S}\!\!\begin{array}{c}\text{O}\;\;^-\text{O}\\ \\ \text{OR}'\end{array}\!\!-\!\!\langle\text{aryl}\rangle\!\!-\!\!\text{CH}_3 \right] \rightleftharpoons
$$

$$
\text{R}^-\text{O} + \text{R}'\text{OS(O}_2\text{)}\!\!-\!\!\langle\text{aryl}\rangle\!\!-\!\!\text{CH}_3
$$
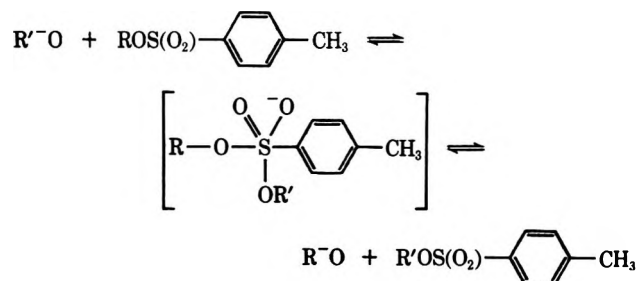
bond cleavage brought about by nucleophilic attack has been reported[4-6] in aryl sulfonates and sulfur attack by an aromatic Grignard reagent on an alkyl sulfonate ester was reported[7] to yield a sulfone. This appears to be a case of alkoxide attack with elimination of another alkoxide ion. An alternate explanation for the formation of **4** and **14** involving nucleophilic displacement of alkoxide ion on the ether resulting in an equilibration mixture was ruled out by experimental evidence. Table I below describes the several intermediates and products obtained during this investigation.

Other possible routes to these dineoalkyl ethers (**6**, **15**, and **17**) were investigated with little success. The Tollens condensation of propionaldehyde with formaldehyde failed to yield any of the tetrol **6**, although analysis of the acetylated product confirmed the presence of trimethylolethane triacetate. These data would appear to preclude bis(hydroxymethyl) ether as a mechanistic pathway to explain ether formation[8] in the Tollens reaction.

Other attempts to affect etherification of these neoalkyl systems using acid-base reactions as well as dehydrating conditions on the monool **2** failed to produce more than a trace, if any, of the desired dineoalkyl ether. Hydrogenolysis of dipentaerythritol ether (a 1,3-glycol) over copper chromite catalyst yielded a
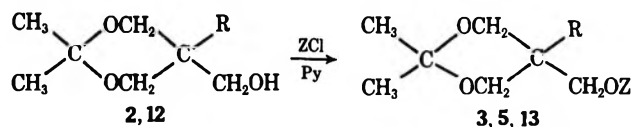
(4) C. A. Bunton and Y. F. Frei, *ibid.*, 1872 (1951).

(5) C. A. Bunton and V. A. Welch, *ibid.*, 3240 (1956).

(6) J. F. Bunnett and J. Y. Bassett, Jr., Abstracts of the 131st National Meeting of the American Chemical Society, Miami, Fla., April 1957, p 28, 29-O.
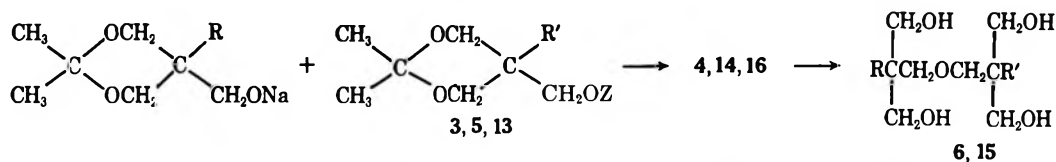
(7) J. Ferns and A. Lapworth, *J. Chem. Soc.*, 101, 273 (1912).

(8) E. Berlow, R. H. Barth, and J. E. Snow, "The Pentaerythritols," Reinhold, New York, N. Y., 1958, pp 5, 6.

<div align="center">TABLE I</div>
<div align="center">INTERMEDIATES</div>

Compd	R	Z	Formula	% yield	Bp (mm), (mp), °C	n^{25}D	Calcd, % C	H	S	Found, % C	H	S
2	CH_3		$C_8H_{16}O_3$	94	58–63 (0.15)	1.4517	59.97	10.07		59.68	9.98	
3	CH_3	Tosyl	$C_{16}H_{22}SO_6$	95	(67–69)		57.30	7.05	10.20	57.49	7.08	10.18
5	CH_3	Mesyl	$C_9H_{18}SO_6$	86	125 (0.2)	1.4578	45.36	7.61	13.46	45.33	7.79	13.32
12	C_2H_5		$C_9H_{18}O_3$		80–90 (0.2)	1.4561	62.04	10.41		62.11	10.96	
13	C_2H_5	Tosyl	$C_{16}H_{24}O_6S$	93	(68–71)		58.51	7.37	9.76	58.42	7.18	9.72

<div align="center">FINAL PRODUCTS</div>

Compd	R	R'	Formula	% yield	Bp (mm), (mp), °C	n^{25}D	Calcd, % C	H	Found, % C	H	Ir, cm^{-1}
4	CH_3	CH_3	$C_{16}H_{30}O_5$	64	97–102 (0.15), (47–50)	1.4500	63.54	10.00	63.70	9.92	...
6	CH_3	CH_3	$C_{10}H_{22}O_5$	96	(127–130)		54.03	9.98	53.99	9.92	3350–3250 (OH) 1120 (ether) 1018 (–CH₂OH)
14	C_2H_5	C_2H_5	$C_{18}H_{34}O_6$	55	110–116 (0.2), (34–38)	1.4544	65.42	10.37	65.26	10.31	
15	C_2H_5	C_2H_5	$C_{12}H_{26}O_6$	>90	(102–105)		57.57	10.47	57.37	10.45	3300 (OH) 1125 (ether) 1070–1020 (CH₂OH)
16	CH_3	C_2H_5	$C_{17}H_{32}O_5$	a	102–115 (0.15)	1.4513	64.52	10.19	64.52	10.32	

^{a} No yield estimate possible because of presence of 4 and 14 in product.

trace of **6**, determined by gas chromatography of the acetylated product, while reaction of trimethylolethane with thionyl chloride gave a stable, crystalline trisulfite **18**. The tosylate (or mesylate) displacement reaction discussed in this paper is, therefore, the only available general method for synthesis of dineoalkyl ethers. Although long reaction times are required to obtain good yields, rearrangement of the neoalkyl groups is not a problem and the bis(dioxanyl) ethers are useful intermediates since the acetonide blocking groups can be removed *in situ* for subsequent esterification or other reactions. The esters identified in Table II were prepared in this manner and showed significantly improved low temperature properties over the analogous esters of dipentaerythritol.

Dineopentyl ether (**25**)[9] and bis(1-methylcyclohexylmethyl) ether (**26**) were prepared similarly by reaction of the appropriate tosylate with alkoxide ion, usually

25

26
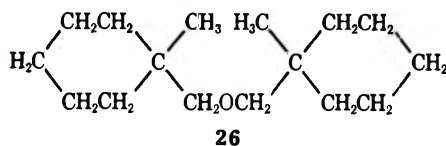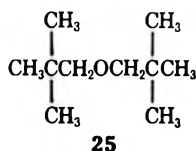
(9) The first reported synthesis of dineopentyl ether itself appeared during this work and we are indebted to Professor Pines who supplied us with a sample of the ether. The two preparations were found to have identical structures.

in refluxing toluene. Formation of **25** occurred at the slowest rate relative to that of all of the ethers reported in this paper. Since the steric effect of ethyl *vs.* methyl at the carbon atom β to the oxygen changed the rate of etherification as noted above, it must be concluded that the cyclopentamethylene and cyclo-2,4-dioxapentamethylene groups offer less hindrance to nucleophilic attack on the tosylate group than do two methyl groups similarly situated.

This chemistry represents a generally useful method for the synthesis of dineoalkyl ethers and the reaction rates, although slow for the parent compounds, can be increased by selective substitution in the alcohol moiety and probably by electron-withdrawing groups on the aromatic moiety of the sulfonyl group. Neopentyl group rearrangements were not observed in this system and, although there is evidence of significant equilibration of alkoxide with tosylate, this reaction has an effect on final product composition only when the neoalkyl groups are different. The nucleophilic attack of a nonneoalkoxide ion on a neoalkyl tosylate system (or *vice versa*) would be expected to result in a major yield of a nonneoalkyl ether and the dineoalkyl ether.

Experimental Section

All proton nmr spectra were measured with a Varian A-60 instrument using TMS reference. The mass spectrographic data were obtained at 68 eV with a CEC 21-130 mass spectrometer modified for rapid scanning. All melting points were uncorrected and all temperatures are centigrade unless otherwise noted. All vapor phase chromatographic analysis were performed isothermally on an F & M Model 500 instrument with a chart speed of 0.5 in./min. Elemental analysis and other analytical data reported in Tables I and II are not repeated in

TABLE II
TETRAESTERS OF DINEOALKYL ETHERS
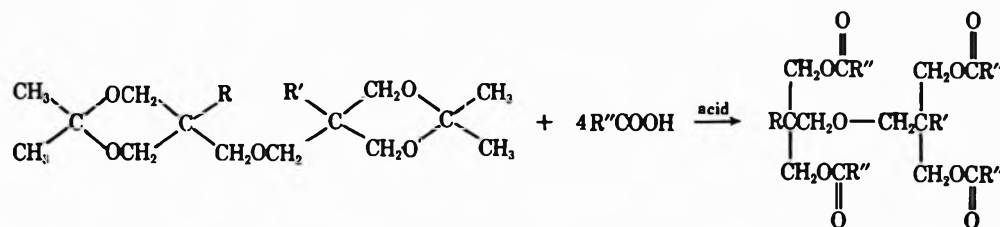
Compd	R	R′	R″	Empirical formula	Bp.[a] °F (760 mm)	Density (°F[a])	Theory,% C	Theory,% H	Found,% C	Found,% H
19	CH_3	CH_3	CH_3	$C_{19}H_{20}O_9$	663	1.1122 (77)	55.37	7.75	54.96	7.27
20	CH_3	CH_3	C_2H_7	$C_{26}H_{46}O_9$	745	1.0285 (77)	62.12	9.23	62.06	9.56
21	CH_3	CH_3	C_4H_9	$C_{30}H_{54}O_9$	716	1.0127 (68)	64.48	9.74	64.77	9.58
22	C_2H_5	C_2H_5	CH_3	$C_{20}H_{34}O_9$	701	1.0845 (100)	57.40	8.19	57.18	8.26
23	C_2H_5	C_2H_5	C_2H_7	$C_{28}H_{50}O_9$	738	1.0145 (100)	63.37	9.50	63.30	9.46
24	C_2H_5	C_2H_5	C_4H_9	$C_{32}H_{58}O_9$	802	1.0069 (68)	65.50	9.96	65.48	9.78

[a] Obtained from isoteniscope determinations of thermal stability.

this section. The Monsanto Physical Science Center cooperated in providing a part of this analytical data.

Tetraethyl(oxydimethylene)bis(methylmalonate) (10).—To a solution of sodium ethoxide, prepared under dry nitrogen from 52.4 g (2.28 g-atoms) of sodium and 900 ml of absolute ethanol, was added 394.6 g (2.27 mol) of diethyl methylmalonate and the stirred solution was refluxed for 1 hr. The bis(chloromethyl) ether (131.1 g, 1.14 mol) in 50 ml of ethanol was added dropwise to the sodiomalonate solution maintained at 40–45°, and the mixture was refluxed for 3 hr. Normal work-up and fractionation afforded 67.4 g (18.3% yield) of diethyl methoxymethylmethylmalonate (11), bp 85–95° (0.1 mm), $n^{25}D$ 1.4238, and 167 g (50.6% yield) of desired ester (10) as a colorless oil, bp 145–158° (0.1 mm), $n^{25}D$ 1.4338 (yields based on consumed malonate).

Anal. Calcd for $C_{10}H_{18}O_5$ (11): C, 55.03; H, 8.31. Found: C, 54.84; H, 8.30.

Anal. Calcd for $C_{19}H_{30}O_9$ (10): C, 55.37; H, 7.75. Found: C, 55.29; H, 7.62.

2,2′-(Oxydimethylene)bis(2-methyl-1,3-propanediol) (6).—Lithium aluminum hydride (100 g) was added to 1900 ml of cooled (0°) dry ether. A solution of 167 g (0.428 mol) of the tetraester 10 in 1 l. of dry ether was added with stirring over a 4-hr period. The mixture was refluxed for 4 hr, ethyl acetate (116 g, 1.32 mol) was added dropwise, and then a 10% excess was added. After hydrolysis of the complex at 15° with water and filtration, the ether was distilled leaving 47.2 g of the crude tetrol 6. A sample was recrystallized from water as shiny, colorless crystals, mp 128–130°.

Anal. Calcd for $C_{10}H_{22}O_5$: C, 54.03; H, 9.98. Found: C, 53.67; H, 10.10.

2,2,5-Trimethyl-5-m-dioxanemethanol (2).—A mixture consisting of 30 g (0.25 mol) of 1,1,1-trimethylolethane, 36.7 ml (0.5 mol) of acetone, 0.5 g of p-toluenesulfonic acid, and 160 ml of benzene was stirred and refluxed until 5.25 ml of water had separated (10.5 hr) in a Dean-Stark trap. The solution was distilled to obtain 37.5 g (93.6%) of colorless liquid: bp 58–63° (0.15–0.2 mm); $n^{25}D$ 1.4517; ir (neat) 3410 cm^{-1} (OH); nmr (neat) δ 3.65 (s, CH_2OH), 3.5 (s, CH_2OH), 3.5 (m, CH_2), 1.37 (s, 2-CH_3), 1.3 (s, 2-CH_3), and 0.77 ppm (s, 5-CH_3). Rapid elimination of the hydroxyl proton resonance when shaken with deuterium oxide indicated only a weak or negligible intramolecular hydrogen bonding.

2,2,5-Trimethyl-5-m-dioxanemethanol Tosylate (3).—A solution of 19 g (0.1 mol) of p-toluenesulfonyl chloride in 25 ml of pyridine was added to a solution of 16 g (0.1 mol) of 2 in 50 ml of pyridine. A slight exothermic reaction was noted and subsequent precipitation of a crystalline solid. The mixture was heated on a steam bath for 30 min, then poured into ice water, and filtered yielding 30 g (95.4%) of the tosylate as nearly colorless crystals. A sample, recrystallized from aqueous methanol, gave pure white crystals, mp 67.5–69°.

The 2,2,5-trimethyl-5-m-dioxanemethanol mesylate (5), 2,2-dimethyl-5-ethyl-5-m-dioxanemethanol (12), and tosylate 13

of the latter compound reported in Table I were similarly prepared.

5,5′-(Oxydimethylene)bis(2,2,2-trimethyl-m-dioxane) (4).—To a dry solution of 44.9 g (0.280 mol) of 2 in 200 ml of toluene was added 5.9 g (0.255 g-atom) of sodium. The stirred system was slowly heated to reflux over a 1-hr period and finally refluxed for 3 hr to obtain a homogeneous solution of alkoxide. A dry solution of 80.2 g (0.255 mol) of the tosylate 3 in 110 ml of toluene was added to the above alkoxide solution at 35° and the stirred mixture was brought to reflux in 35 min. The solution was clear at reflux. An initial opalescence followed in 4 min. The reaction progress was monitored by periodic withdrawal of 1-ml samples. After washing three times with 3 ml of water, a 1-μl sample was analyzed by gas chromatography using a 6-ft 12% silicone grease on 45/50 Chromosorb P column operated at 200° and 85-ml/min helium flow. The progressive increase in product 4 was observed at 5-min elution time. After 64 hr, the cooled mixture was poured into water and the isolated organic layer was washed to neutrality. Fractionation gave 49.2 g (63.8%) of product as a colorless oil: bp 97–102° (0.15 mm); $n^{25}D$ 1.4500; nmr (neat) δ 3.78 (d, 4, ring CH_2), 3.51 (d, 4, ring CH_2), 3.43 (s, 4, ether CH_2), 1.41 (s, 12, CH_3), and 0.90 ppm (s, 6, CH_3). The product ether, which can be crystallized to a solid (mp 47–50°), has a thermal stability (T_D) of 520°F (isoteniscope measurement) and a kinematic viscosity of 28.4 cSt at 100°F and 3.39 cSt at 210°F. The use of the mesylate 5 rather than the tosylate appeared to offer no advantage in this reaction.

Hydrolysis of 4 to 2,2′-(Oxydimethylene)bis(2-methyl-1,3-propanediol) (6).—A 2-g sample of the acetonide ether 4 was dissolved in 20 ml of 50% ethanol, 10 drops of concentrated HCl was added, and the solution was brought to reflux for 5 min. The solution was evaporated leaving 1.429 g (96%) of colorless crystalline product 6. The analytical sample was recrystallized from hot water as shiny crystals, mp 127–130°, and caused no melting point depression upon admixture with the tetrol obtained by the hydride reduction. Ir analysis showed a broad OH absorption at 3350–3250, ether absorption at 1120, and a primary COH absorption at 1018 cm^{-1}.

5,5′-Diethyl-5,5′-(oxydimethylene)bis(2,2-dimethyl-m-dioxane) (14).—This ether was prepared in the same manner as the homologous ether above. The steric effect of the ethyl group was noted in the longer reaction time required for alkoxide preparation (about twice that of the methyl compound) and in the subsequent slower condensation with the tosylate. After 70 hr, a 55% yield of the ether 14 was obtained, bp 110–116° (0.2 mm), as a colorless oil which later was crystallized. The product has a thermal stability (T_D) of 516°F, and a kinematic viscosity of 38.1 cSt at 100°F and 3.76 at 210°F.

2,2′-(Oxydimethylene)bis(2-ethyl-1,3-propanediol) (15).—This product was obtained by acid hydrolysis of the above ether (14) as colorless crystals from water, mp 102–105°. Ir analysis showed absorptions at 3300 (hydroxyl), 1125 (ether), and a band at 1070–1020 cm^{-1} characteristic of primary alcohol.

5-Ethyl-5'-methyl-5,5'-(oxydimethylene)bis(2,2-dimethyl)-*m*-dioxane) (16).—A stirred solution of 17 g (0.1 mol) of 12 in 75 ml of dry toluene was refluxed with 1.6 g (0.07 g-atom) of sodium until it was completely reacted. Then 22 g (0.07 mol) of dry 3 was added. After 1-hr reflux, a precipitate (sodium tosylate) was apparent. After 80-hr reflux there was no further change in the glc spectrum as monitored by a 6-ft 30% silicone grease on 45/55 Chromosorb P column at 200° and 85-ml/min helium flow. This spectrum showed the two symmetrical ethers 4 and 14 at 6.4- and 12-min retention times, respectively, and the major unsymmetrical product 16 at 8.8-min retention. The product was twice fractionated to obtain the colorless oil, bp 102–115° (0.15 mm). Acid hydrolysis of 16 gave the crystalline 2-ethyl-2'-methyl-2,2'-(oxydimethylene)di-1,3-propanediol (17) which was converted to the tetrabutyrate 27 by butyric anhydride. The tetrabutyrate showed a retention time of 15.5 min on the 6-ft silicone grease column at 275°, 85-ml/min flow.

Reaction of Trimethylolethane with Thionyl Chloride.—To a stirred mixture of 24 g (0.2 mol) of trimethylolethane in 150 ml benzene at 50° was added dropwise 29 ml (0.4 mol) of thionyl chloride. The homogeneous solution was refluxed 2 hr, then the solvent was removed, and the residue was poured into ice water, yielding 15 g of water-insoluble product. Recrystallization from aqueous isopropyl alcohol yielded shiny crystals of the trisulfite 18, mp 101–103°.

Anal. Calcd for $C_{10}H_{10}O_9S_3$: C, 31.74; H, 4.79; S, 25.42. Found: C, 31.30; H, 4.75; S, 25.04.

Dineopentyl Ether 25.—A stirred mixture of 22 g (0.25 mol) of neopentyl alcohol and 5.8 g (0.25 g-atom) of sodium in 150 ml of toluene was refluxed until homogeneous; then a solution of 55.3 g (0.23 mol) of neopentyl tosylate in 70 ml of toluene was added. After a reflux period of 1 week, 84% of the tosylate had reacted as determined by glc analysis on the 6-ft silicone grease column which showed the formation of dineopentyl ether (3.7-min retention, 75°, 85-ml/min flow) and disappearance of the tosylate (4.5-min retention time, 200°, 85-ml/min flow). The pure dineopentyl ether was obtained by preparative gas chromatography as a colorless liquid: n^{25}D 1.3931; nmr (toluene) δ 0.94 (s, 9, CH₃) and 2.94 ppm (s, 2, CH₂); mass spectrum (70 eV) *m/e* (ion) 158 (molecular ion), 101 (neopentyloxymethyl), 71 (neopentyl ion).

Anal. Calcd for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 76.26; H, 13.77.

Bis(1-methylcyclohexylmethyl) Ether (26).—This dineoalkyl ether was obtained similarly as a colorless oil: bp 81° (0.25 mm); n^{25}D 1.4690; T_D 552°F; $d^{0°}$F 0.9381; viscosity, cSt (°F), 5114, (−40), 283 (0), 10.65 (100), 2.49 (210).

Anal. Calcd for $C_{16}H_{30}O$: C, 80.60; H, 12.68. Found: C, 80.50; H, 12.34.

Registry No.—2, 3663-46-5; **3,** 34541-77-0; **4,** 34578-24-0; **5,** 21139-47-9; **6,** 34541-79-2; **10,** 5898-79-3; **11,** 21398-92-5; **12,** 20761-68-6; **13,** 34541-83-8; **14,** 34541-84-9; **15,** 23235-61-2; **16,** 34541-86-1; **18,** 11098-52-5; **19,** 34541-87-2; **20,** 34541-88-3; **21,** 34541-89-4; **22,** 34578-25-1; **23,** 34541-90-7; **24,** 34541-91-8; **25,** 28509-24-2; **26,** 34541-92-9.

Preparation of Some Methylenecycloalkenes *via* a Novel 1,4 Hofmann Elimination Reaction[1]

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In the course of photochemical studies of conjugated dienes in this laboratory, the preparation of significant

(1) Abstracted in part from the Ph.D. Dissertation of M. R. S., The University of Texas at Austin, Austin, Texas, 1971.

quantities of several s-trans dienes of general structure A was required. Historically, two routes that have

A
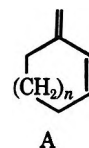
been used are acetate pyrolysis[2] and the Wittig reaction,[3] but in our hands these reactions have given variable results (both in quantity and quality); hence it was deemed desirable to explore another method.

Since one of the better methods for the preparation of olefinic compounds is the Hofmann elimination, attention was turned to the availability of suitable amines. One possibility that immediately came to mind was a novel 1,4 Hofmann elimination sequence using a β,γ-unsaturated amine such as N,N-dimethyl-N-cyclohexenylmethylamine (2), which in turn is readily available from cyclohexene-1-carboxylic acid (1) *via*
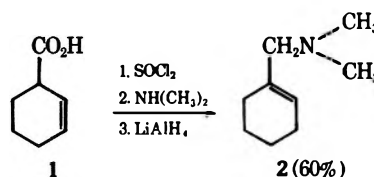
the sequence outlined below. Acid 1, in turn, is readily prepared from the corresponding ketone, cyclohexanone (3), by cyanohydrin formation, followed by dehydra-

tion and hydrolysis. Some double-bond migration was observed, but, as both isomers should give the same product when converted to their respective amines and subjected to the Hofmann degradation sequence, the presence of minor amounts of the Δ^2 isomer did not present a synthetic problem.
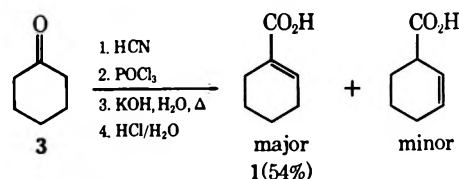
Reaction of 2 with iodomethane in hexane solution gave the quaternary ammonium salt, which was treated with freshly precipitated, alkaline-free silver oxide to give the quaternary ammonium hydroxide, which on pyrolysis yielded methylenecyclohexene (5). Methy-

lenecycloheptene (6), methylenecyclooctene (7), and 3,5-dimethylmethylenecyclohexene (8) were also prepared by this method. Their yields[4] (from the respec-
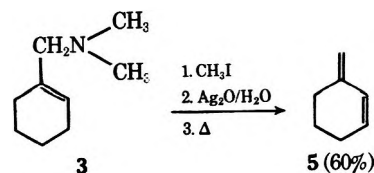
(2) C. H. Depuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960); W. G. Dauben, C. D. Poulter, and C. Suter, *J. Amer. Chem. Soc.*, **92**, 7043 (1970).

(3) W. G. Dauben and J. S. Ritscher, *ibid.*, **92**, 2925 (1970).

(4) Analysis of the dienes for isomeric purity was accomplished using a Perkin-Elmer Model F-11 capillary chromatograph with a 50 ft × 0.01 in. column packed with *m*-bis(*m*-phenoxy)benzene plus Apiezon L (8:2). Purity in all cases was >95%.

tive amine), boiling points, uv absorption maximums, and refractive indices are shown in Table I.

TABLE I

Diene	% yield	Bp, °C (mm)	Uv (pentane), nm (ϵ)	n^{25}D
5^a	60.0	109–111°	232 (15,500)	1.4896
6	40.0	140–143°	233 (25,500)	1.4986
7	86.5	87–89° (57)	228 (19,700)	1.5079
			234 (21,000)	
8	57.0	92–96° (150)	234 (22,500)	1.4852

^{a} W. J. Bailey and J. C. Goossens, *J. Amer. Chem. Soc.*, **78**, 2804 (1955). I. N. Nazarov and N. V. Kuznetsov, *Dokl. Akad. Nauk SSSR*, **111**, 358 (1956); *Chem. Abstr.*, **51**, 9504d (1957).

Experimental Section

Boiling points are uncorrected. Refractive indices were obtained on a Bausch and Lomb Abbe refractometer. Uv, ir, and nmr spectra were determined on Cary 14, Beckman IR-5, and Varian A-60 instruments, respectively. Satisfactory elemental analyses were obtained on all new compounds.

Cyclohexene-1-carboxylic acid,[5] cycloheptene-1-carboxylic acid,[5] and cyclooctene-1-carboxylic acid[6] were prepared by previously published methods. The following method is the general method used to prepare all of the dienes.

1-Cyano-3,5-dimethylcyclohexene.—A mixture of 3,5-dimethylcyclohexanone (114.0 g, 0.91 mol) and hydrogen cyanide[7] (54.0 g, 2.0 mol) in 200 ml of 95% ethanol with 2 drops of 50% aqueous potassium hydroxide was allowed to stand for 18 hr in a tightly closed flask. The solution was then made acidic with saturated aqueous oxalic acid solution. After the ethanol was removed under reduced pressure, ~300 ml of benzene was added and the solution was filtered. The filtrate was dried over sodium sulfate and filtered again and the cyanohydrin was dehydrated by the slow addition of phosphorus oxychloride (154 g, 1 mol) in benzene–pyridine (250 ml of each) and then refluxed for 1 hr. The dark solution was poured over crushed ice; the organic phase was separated and washed five times with 500-ml portions of 10% hydrochloric acid. The benzene solution was dried over sodium sulfate and filtered and benzene was removed at reduced pressure. The residue was distilled [bp 97–103° (16 mm)] and redistilled [bp 69–75° (2 mm)] to yield 62.2 g of 1-cyano-3,5-dimethylcyclohexene, ir 2222 cm^{-1} (α,β-unsaturated nitrile).

Δ^1- and Δ^2-3,5-Dimethylcyclohexene-1-carboxylic Acid.—A mixture of 1-cyano-3,5-dimethylcyclohexene (30 g, 0.22 mol) and potassium hydroxide (60 g) in 500 ml of water was stirred under reflux for 72 hr. The solution was cooled in an ice bath and the solution was made acidic with concentrated hydrochloric acid, with the temperature being kept below 10°. The solution was extracted five times with 200-ml portions of ether, the combined ether extracts were dried over sodium sulfate and filtered, the solvent was removed, and the residue was distilled [bp 83–97° (0.1 mm)] to yield 34.8 g (98%) 3,5-dimethylcyclohexene-1-carboxylic acid. The nmr spectrum indicated a mixture of α,β- and β,γ-unsaturated acids (70:30) by the presence of absorptions at δ 6.87 and 5.45.

N,N-Dimethyl-N-(3,5-dimethylcyclohexenyl)methylamine.—The acid mixture (96.7 g, 0.64 mol) from the previous preparation was treated with thionyl chloride (84 g, 0.70 mol) in refluxing benzene (~300 ml). The acid chloride was cooled and added dropwise to 200 ml of anhydrous dimethylamine and stirred overnight. The solution was filtered and benzene was then removed under reduced pressure. The crude amide was dissolved in 500 ml of anhydrous ether and added dropwise to a stirring slurry of lithium aluminum hydride (19.0 g, 0.50 mol) in 1 l. of anhydrous ether. The mixture was refluxed for 72 hr and then the reaction was quenched by the careful addition of water (18.0 g, 1.0 mol). Sodium sulfate (50 g) was added and the mixture was filtered. The precipitate was washed twice with 100-ml portions of ether. The ethereal solution was concen-

trated and distilled giving 66.5 g (63%) of the amine, bp 62–64° (4 mm), n^{25}D 1.4603.

1-Methylene-3,5-dimethylcyclohex-2-ene.—The amine (57.7 g, 0.35 mol) from the previous preparation was dissolved in 500 ml of hexane and to this was added iodomethane (100 g, 0.70 mol) over a 2-hr period. The solution was then stirred overnight. Enough water was added to dissolve the salt, the aqueous solution was added to freshly prepared silver oxide (from 0.4 mol of silver nitrate), and the mixture was stirred for 4 hr at 60°. The dark solution was then filtered through a fine sintered-glass funnel. The filtrate was distilled, first at atmospheric pressure and then at reduced pressure (~40 mm), while the oil-bath temperature was allowed to rise to 180°, all distillate being collected in a receiver immersed in a Dry Ice-2-propanol bath. The distillate was thawed and extracted four times with 200-ml portions of pentane. The combined pentane washings were dried and filtered and the solvent was distilled. The residue was subjected to distillation [bp 92–96° (150 mm)] to yield 24.5 g (57%) of the diene: n^{25}D 1.4852; uv max (pentane) 234 nm (ϵ 22,500); ir (neat) 890 cm^{-1} (=CH$_2$); nmr (CCl$_4$) δ 5.86 (s, 1 H, =C<^{H}), 4.59 (s, 2 H, =CH$_2$).
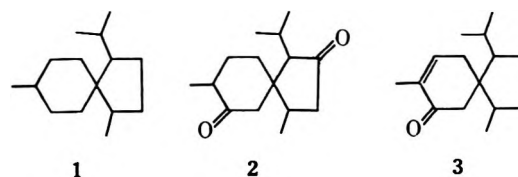

Synthesis of the Spiro[4.5]decane System. An Approach to the Acorane Sesquiterpene Group

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The acorane group of bicyclic sesquiterpenes, characterized by the carbon skeleton 1, is typified by the

1   **2**   **3**

acorones, stereoisomeric diketones represented by structure 2,[1] and the two acorenones, stereoisomers of 3.[2]

(5) O. H. Wheeler and I. Leiner, *J. Amer. Chem. Soc.*, **78**, 64 (1956).

(6) E. A. Braude, W. F. Forbs, B. F. Gofton, R. P. Houghton, and E. S. Waight, *J. Chem. Soc.*, **171**, 4711 (1957).

(7) K. Ziegler, "Organic Syntheses, Coll. Vol. I, Wiley, London, 1941, p 314. It is strongly recommended for the worker to smoke while preparing this reagent.

(1) F. Šorm and V. Herout, *Collect. Czech. Chem. Commun.*, **13**, 177 (1948); **14**, 723 (1949); V. Sykora, V. Herout, J. Pliva, and F. Šorm, *Chem. Ind. (London)*, 1231 (1956); *Collect. Czech. Chem. Commun.*, **23**, 1072 (1958); V. Sykora, V. Herout, A. Reiser, and F. Šorm, *ibid.*, **24**, 1306 (1959); J. Vrkoč, V. Herout, and F. Šorm, *ibid.*, **27**, 2709 (1962).

(2) J. Vrkoc, V. Herout, and F. Šorm, *ibid.*, **26**, 1021, 3183 (1961); R. J. McClure, K. S. Schorno, J. A. Bertrand, and L. H. Zalkow, *Chem. Commun.*, 1135 (1968).
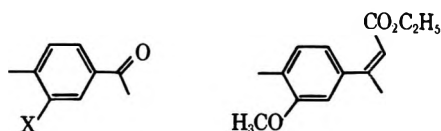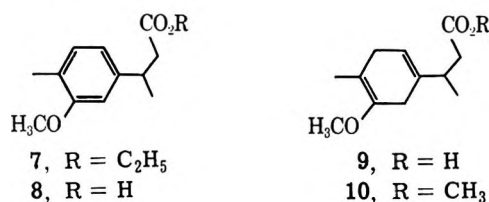
We have investigated a synthetic approach to the acorones along the following lines. After we had become deeply involved in the project, we discovered that an almost identical route had already been outlined, culminating in a synthesis of acorone, though not substantiated by published details.[3]

We began with *p*-methylacetophenone (4) which was


4, X = H
5, X = OCH₃

6

7, R = C₂H₅
8, R = H

9, R = H
10, R = CH₃

converted by successive nitration, reduction, diazotization, acid treatment,[4] and methylation[5] into a 3-methoxy-4-methylacetophenone (5). A Reformatsky reaction between 5 and ethyl bromoacetate[5] gave, after dehydration, the unsaturated ester 6,[5] as a mixture of cis and trans modifications, hydrogenation of which yielded saturated ester 7. The corresponding acid 8 was reduced with lithium and *tert*-butyl alcohol in liquid ammonia–tetrahydrofuran, under carefully defined conditions, to the dihydro acid 9, which was quickly esterified with diazomethane to 10, and then hydrolyzed with acid to the conjugated enone 11. The ethylene
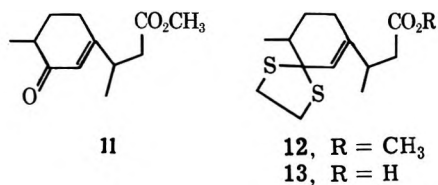
11

12, R = CH₃
13, R = H
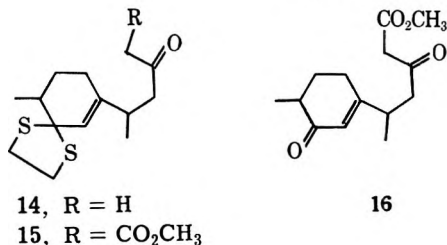
14, R = H
15, R = CO₂CH₃

16

dithioketal 12 of the latter on hydrolysis afforded the corresponding acid 13, which with methyllithium was converted into ketone 14.[6] Reaction of 14 with dimethyl carbonate and sodium hydride[7] furnished the β-keto ester 15, hydrolyzed by mercuric chloride–

mercuric oxide in aqueous methanol[8] to the diketo ester 16. The latter underwent smooth cyclization by internal Michael addition to the spiro diketo ester 17
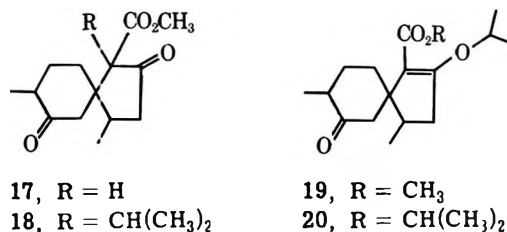
17, R = H
18, R = CH(CH₃)₂

19, R = CH₃
20, R = CH(CH₃)₂

on treatment with sodium methoxide. Since 17 was almost entirely crystalline, it seems likely that one of the several possible stereoisomers corresponding to this structure predominated.

The penultimate step in the sequence was isopropylation of 17 to 18, hydrolysis and decarboxylation of which would yield acorone 2. Unfortunately, despite claims to the contrary,[3] all efforts to C-isopropylate 17 were unsuccessful. Treatment of 17 with methanolic sodium methoxide and isopropyl iodide yielded almost entirely the enol ether 19, while the thallous salt[9] of 17, when heated with the same halide, afforded a complex mixture of products including the same enol ether, accompanied by isopropyl esters, possible retro-Michael reaction products, and unchanged starting material. Presumably steric factors, opposing the setting up of three contiguous groups on the same side of the cyclopentane ring,[10] are responsible for the failure of the alkylation.

Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer, and mass spectra on a Du Pont 21-490 mass spectrometer.

Ethyl 3-(3′-Methoxy-*p*-tolyl)butanoate (7).—3-Hydroxy-4-methylacetophenone was synthesized according to a published sequence,[4] and methylated[5] to give 5: bp 74–75° (0.25 mm); nmr (CHCl₃) δ 2.16 (s, 3), 2.47 (s, 3), 3.80 (s, 3), 7.24 (AB q, 2, *J* = 8.5 Hz), 7.38 (d, 1, *J* = 2 Hz). The unsaturated ester 6 was obtained, as a mixture of cis and trans forms, *via* a Reformatsky reaction[5] between ketone 5 and ethyl bromoacetate, followed by dehydration with iodine.[5] It had bp 120–121° (0.15 mm) [lit.[5] bp 132–138° (0.6 mm)]; ir (film) 1710, 1640 cm⁻¹. The ester 8 (58.25 g, 0.25 mol), methanol (200 ml), and 5% palladized carbon were mixed and shaken in hydrogen at 45 psi and room temperature until uptake of gas ceased. The catalyst was removed by filtration and the filtrate was freed of solvent. The residual saturated ester 7 distilled at 102–103° (0.2 mm) (52 g, 88%): ir (film) 1735 cm⁻¹; nmr (CDCl₃) δ 1.15 (t, 3, *J* = 7.0 Hz), 1.28 (d, 3, *J* = 8.0 Hz), 2.20 (s, 3), 2.55 (d, 2, *J* = 8.0 Hz), 3.20 (m, 1), 3.80 (s, 3), 4.05 (q, 2, *J* = 7.0 Hz), 6.90 (m, 3). *Anal.* Calcd for C₁₄H₂₀O₃: C, 71.16; H, 8.53. Found: C, 70.93; H, 8.53.

3-(3′-Methoxy-*p*-tolyl)butanoic Acid (8).—The foregoing ester (118 g, 0.5 mol) and 3 *N* aqueous sodium hydroxide (1 l.) were refluxed for 3 hr. The cooled, homogeneous solution was rendered acidic with 6 *N* hydrochloric acid and extracted twice with ether. Concentration of the combined, dried extracts afforded the acid 8: bp 124–125° (0.04 mm) (103 g, 99%); ir (film) 3100–3500, 1715 cm⁻¹; nmr (CDCl₃) δ 1.20 (d, 3, *J* = 7.0 Hz), 2.15 (s, 3), 2.50 (d, broad, 2, *J* = 7.0 Hz), 3.20 (m, 1), 3.80 (s, 3), 6.90 (AB q, 3), 11.50 (s, broad, 1). *Anal.* Calcd for C₁₂H₁₆O₃:

(3) W. Parker, R. Ramage, and R. A. Raphael, quoted as a personal communication by J. M. Mellor and S. Munavalli, *Quart. Rev., Chem. Soc.,* **18**, 270 (1964), footnote 87 on p 293.

(4) O. L. Brady and J. N. E. Day, *J. Chem. Soc.,* 114 (1934); G. T. Morgan and A. E. J. Pettet, *ibid.,* 418 (1934), R. E. Lutz, *et al., J. Org. Chem.,* **12**, 617 (1947).

(5) L. Ruzicka and L. Sternbach, *Helv. Chim. Acta,* **23**, 355 (1940).

(6) *Cf.* C. Tegner, *Acta Chem. Scand.,* **6**, 782 (1952); M. J. Jorgenson, *Org. React.,* **18**, 1 (1970).

(7) *Cf.* A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Syn.,* **47**, 20 (1967).

(8) *Cf.* D. Seebach, N. R. Jones and E. J. Corey, *J. Org. Chem.,* **33**, 300 (1968).

(9) E. C. Taylor, G. C. Hawks, and A. McKillop, *J. Amer. Chem. Soc.,* **90**, 2421 (1968); E. C. Taylor and A. McKillop, *Accounts Chem. Res.,* **3**, 338 (1970).

(10) *Cf.* T. G. Crandall and R. G. Lawton, *J. Amer. Chem. Soc.,* **91**, 2127 (1969).

C, 69.21; H, 7.74, neut equiv, 208.3. Found: C, 69.47; H, 7.94 neut equiv, 208.4.

Methyl 3-(4'-Methyl-3'-oxo-1'-cyclohexenyl)butanoate (11).[11] —The preceding acid (29.2 g, 0.14 mol) in purified tetrahydrofuran (600 ml) and dry *tert*-butyl alcohol (600 ml) was added gradually to distilled, stirred liquid ammonia (1500 ml). With continued stirring, lithium metal (16.7 g, 2.4 mol) was added in small pieces during 45 min. The deep blue solution was stirred for 5 hr, then quenched with methanol (150 ml) and stirred overnight during evaporation of the ammonia. Water was added and the organic solvents were removed *in vacuo*. The residue was diluted with water to 2 l., then cooled in ice, acidified with cold 4 *N* hydrochloric acid, and quickly extracted thrice with ether. The combined extracts were dried, cooled in ice, and mixed with an excess of ethereal diazomethane. The ether solution was washed with aqueous sodium bicarbonate and water, dried, and concentrated. The residue was stirred with 2.5 *N* hydrochloric acid (500 ml) for 3 hr, and organic material was isolated with ether. The extract was dried and concentrated, and the residual keto ester 11 distilled: bp 110° (0.25 mm) 22.4 g, 76%); λ_{max} (EtOH) 234 nm (ϵ 11,000); ir (film) 1735, 1720 (weak), 1665, 1635 cm^{-1}; nmr (CDCl$_3$) δ 0.90–1.30 (dd, 6), 3.60 (s, 3), 5.80 (s, 1). *Anal.* Calcd for C$_{12}$H$_{18}$O$_3$: C, 68.54; H, 8.63. Found: C, 68.44; H, 8.60.

Ethylene Dithioketal 12.—The above keto ester (22.8 g, 0.11 mol), 1,2-ethanedithiol (10.8 g, 0.115 mol), and methanol (200 ml) were stirred and cooled in ice during the dropwise addition of boron trifluoride etherate (17 ml). After 16 hr of stirring, excess ice–water was added and the product was isolated with ether. Evaporation of the dried extract gave the desired dithioketal 12: bp 135° (0.1 mm) (24.7 g, 80%); ir (film) 1735 cm^{-1}; nmr (CDCl$_3$) δ 1.05 (d, 3, *J* = 7.0 Hz), 1.20 (d, 3, *J* = 6.5 Hz), 3.30 (m, 4), 3.80 (s, 3), 5.75 (s, broad, 1). *Anal.* Calcd for C$_{14}$H$_{22}$O$_2$S$_2$: C, 58.70; H, 7.75; S, 22.46. Found: C, 58.73; H, 7.77; S, 22.35.

4-(3',3'-Ethylenedithio-4'-methyl-1'-cyclohexenyl)-2-pentanone (14).—The dithioketal 12 (38.9 g, 0.136 mol) was refluxed with 2.5 *N* aqueous sodium hydroxide (500 ml) for 2 hr, then cooled, acidified with 6 *N* hydrochloric acid, and extracted with ether. The dried extract, containing the crude acid 13, was stirred and cooled in ice during the gradual addition, under nitrogen, of ethereal methyllithium[6] (133 ml of 2 *N*), during 1 hr. After a further 2 hr of stirring the product was poured into ice–water and the organic phase was separated. The aqueous layer was extracted twice with ether and the combined extracts were washed with water, dried, and concentrated. The residual methyl ketone 14 distilled at 125° (0.01 mm) (30.7 g, 85%): ir (film) 1710, 1360 cm^{-1}; nmr (CDCl$_3$) δ 1.00 (d, 3, *J* = 6.0 Hz), 1.15 (d, 3, *J* = 6.0 Hz), 2.15 (s, 3), 3.30 (m, 4), 5.70 (s, broad, 1). *Anal.* Calcd for C$_{14}$H$_{22}$OS$_2$: C, 62.66; H, 8.20; S, 23.68. Found: C, 62.20; H, 8.23; S, 23.67.

1-Carbomethoxy-4-(3',3'-ethylenedithio-4'-methyl-1'-cyclohexenyl)-2-pentanone (15).[7]—Sodium hydride (11.0 g of a 50% dispersion in mineral oil, 0.23 mol) was washed thrice with petroleum ether (bp 30–60°) by decantation, then mixed with dry benzene (500 ml), dimethyl carbonate (20.5 g, 0.23 mol), and the foregoing methyl ketone (30.7 g, 0.23 mol). The whole was refluxed under nitrogen for 72 hr, then cooled, acidified cautiously with glacial acetic acid, and treated with ice–water. The organic layer was separated and the aqueous layer was extracted twice with ether. The combined extracts were shaken with aqueous sodium bicarbonate and water, dried, and concentrated. The remaining β-keto ester 15 distilled at 170–180° (bath, 0.01 mm) (35.4 g, 94%). It gave a wine-red color with ferric chloride, was soluble in cold, aqueous alkali, and formed a copper complex with cupric acetate: ir (film) 1730, 1706, 1639, 1621 cm^{-1}; nmr (CDCl$_3$) δ 1.00 (d, 3, *J* = 6.0 Hz), 1.17 (d, 3, *J* = 6.0 Hz), 3.30 (m, 4), 3.80 (s, 3), 5.60 (s, broad, 1). *Anal.* Calcd for C$_{16}$H$_{24}$O$_3$S$_2$: C, 58.52; H, 7.37; S, 19.53. Found: C, 58.63; H, 7.41; S, 19.32.

1-Carbomethoxy-4-(4'-methyl-3'-oxo-1'-cyclohexenyl)-2-pentanone (16).—The dithioketal above (10.5 g, 0.032 mol) was refluxed with methanol (300 ml), water (24 ml), mercuric oxide (5.4 g, 0.025 mol), and mercuric chloride (183 g,. 0.0675 mol) for 4 hr.[8] Inorganic material was removed by filtration, the filtrate was diluted with water, and the product was isolated with ether. The ether extract was washed with aqueous ammonium chloride

(11) *Cf.* H. L. Dryden, G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

and water, dried, and concentrated. The residual β-keto ester 16 distilled at 160–165° (bath, 0.04 mm) (6.2 g, 77%). It showed the usual properties of an enolic compound, forming a bluish-gray copper complex with cupric acetate: ir (film) 1748, 1712, 1669, 1629 cm^{-1}; nmr (CDCl$_3$) δ 1.10 (two d, 4), 3.50 (s, 2), 3.70 (s, 3), 5.75 (s, broad, 1). *Anal.* Calcd for C$_{14}$H$_{20}$O$_4$: C, 66.64; H, 7.99. Found: C, 66.84; H, 8.25.

4,7-Dimethyl-1-methoxycarbonylspiro[4,5]decane-2,6-dione (17).—Sodium metal (0.455 g, 0.0198 mol) was dissolved in dry methanol (200 ml) and the preceding β-keto ester 16 (5.0 g, 0.0198 mol) was added, the solution being stirred under nitrogen at room temperature for 1 hr. After acidification with glacial acetic acid the solvent was removed *in vacuo*. Ice–water was added and the product was isolated with ether. The extract was concentrated to small bulk and shaken with an excess of aqueous cupric acetate for 2 hr. The light green copper complex was collected, washed with water, and dried; it crystallized from benzene in light green prisms, mp 213–214° dec. *Anal.* Calcd for C$_{28}$H$_{38}$O$_8$Cu: C, 59.42; H, 6.72. Found: C, 59.28; H, 6.81. The copper complex (5.0 g), suspended in ether, was shaken vigorously with cold 2 *N* sulfuric acid for 45 min. The clear layers were separated and the organic phase was washed with water, dried, and concentrated. The remaining spiro keto ester 17 distilled at 150–155° (bath, 0.05 mm) (2.75 g). It crystallized almost entirely on keeping and separated from methanol in prisms: mp 113°; ir (film) 1764, 1715 cm^{-1}, with broad OH and C=O bands characteristic of enolic form; nmr (CDCl$_3$) δ 1.05 (two d overlapping, 6), 3.75 (m, 3, keto–enol mixture). *Anal.* Calcd for C$_{14}$H$_{20}$O$_4$: C, 66.64; H, 7.99; mol wt, 252.3. Found: C, 66.78; H, 8.02; mol wt, 252 (mass spectrum).

Registry No.—7, 34638-68-1; 8, 34638-69-2; 11, 34638-70-5; 12, 34638-71-6; 14, 34638-72-7; 15, 34638-73-8; 16, 34638-74-9; 16 copper complex, 34630-94-9; 17, 34638-75-0.
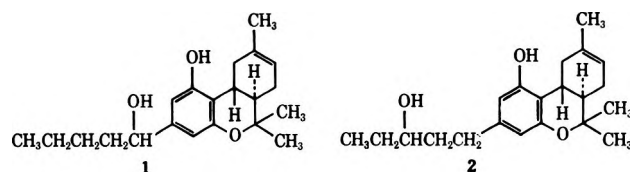

The Synthesis of Two Metabolites of (−)-Δ^8-Tetrahydrocannabinol

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Recent studies from these laboratories have resulted in the isolation[1] of two *in vitro* dog liver metabolites of (−)-Δ^8-tetrahydrocannabinol. By inspection of their mass and nmr spectra and comparison of their nmr spectra with those of suitable monocyclic model compounds, structures 1 and 2 were established for these metabolites. The microgram quantities of these materials isolated from the metabolic mixtures were too small to allow determination of the configuration of the introduced hydroxyl groups. We now report the

unequivocal syntheses of these two metabolites as diasteromeric mixtures at the carbinol carbons.

We envisioned the synthesis of 1 as proceeding *via* an acid-catalyzed condensation of the known[2] resorcinol

(1) D. E. Maynard, O. Gurny, R. G. Pitcher, and R. W. Kierstead, *Experientia*, **27**, 1154 (1971).
(2) R. Huls and A. Hubert, *Bull. Soc. Chim. Belg.*, **65**, 596 (1956).

derivative **3** with a suitable terpene derivative, such as (−)-verbenol[3] or (+)-*trans-p*-mentha-2,8-dien-1-ol (**5**).[4] Since the latter compound was more readily available to us we attempted the condensation of **3** and **5**. However, **3** was recovered unchanged after the complete disappearance of **5** due to the reduced reactivity of the aromatic ring in **3**. The side chains of more reactive analogs of **3**, such as the corresponding alcohol, acetate, or benzoate, were too unstable under the condensation reaction conditions. The carbonyl group of **3** was therefore converted into the ethylene acetal. Upon attempted condensation with **5**, the ethylene acetal group was cleaved and **3** was recovered from the reaction mixture.

However, **3** was converted[5] readily to the dithioethylene acetal **4**, which on condensation with **5** gave a 50% yield of the desired **6**. Removal of the protecting
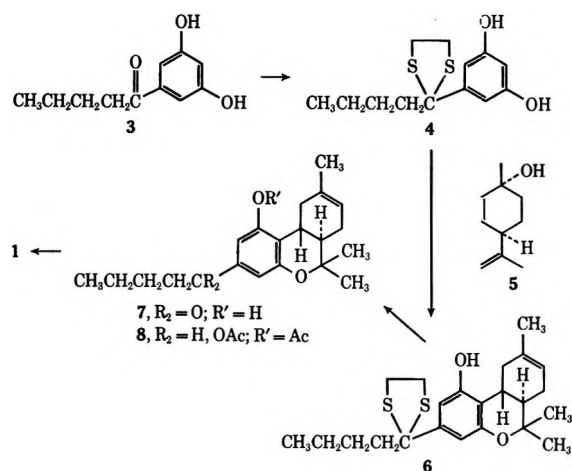
group of **6** was accomplished in three ways: shaking an aqueous suspension of **6** and mercuric acetate,[6] treating **6** with mercuric chloride[7] and cadmium carbonate in aqueous acetone, or, preferably, allowing **6** to react with mercuric oxide[8] and boron trifluoride etherate. Sodium borohydride reduction of **7** then gave **1**. Synthetic **1** (a 1:1 mixture of the two diastereomers at C-1′) was clearly identical by mass spectral criteria with **1** isolated[1] from the metabolic mixture. Acetylation of **1** gave the diacetate **8**, which was shown to be identical with the diacetate prepared[1] from the metabolically derived **1** by comparison of the nmr[9] and mass spectra and by identical mobility in several tlc and glpc systems.[1,10]

A similar approach was used for the synthesis of **2**. Condensation of the known[11] aldehyde **9** with methyl ethyl ketone in the presence of sodium hydroxide in

methanol[12] gave a respectable yield of the linear product **10**. Attempted simultaneous hydrogenation and hydrogenolysis of **10** to give **11** by shaking under a hydrogen atmosphere either an ethyl acetate solution of **10** with platinum dioxide[13] or an ethanol solution of **10** with a 10% palladium on carbon catalyst was not promising. Heating a solution of **10** with cyclohexene and a palladium on carbon catalyst[14] gave, after 3 hr, predominantly the dibenzyl ether of **11**. After 8 hr
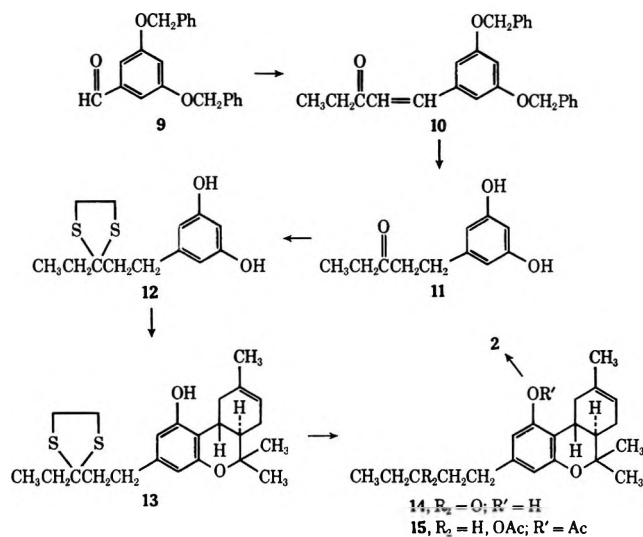
the monobenzyl ether of **11** predominated, and after 2.5 days of heating the major product was the desired **11**.[15] An attempted acid-catalyzed condensation of **11** with **5** failed and nonpolar products lacking a carbonyl group predominated. Analogs of **11** containing hydroxyl, ester, or ketal groups were also unsatisfactory. However, the dithioethyleneacetal **12** was readily prepared and converted into **13**.

Cleavage of the protecting group of **13** was not nearly as facile as with **6**. Treatment of **13** with an aqueous suspension of mercuric acetate[6] or oxidation of **13** with 1-chlorobenzotriazole followed by base cleavage[16] gave a number of products from which useful amounts of **14** could not be isolated. Cleavage of the dithioethylene acetal of **13** was accomplished with mercuric oxide[8] and boron trifluoride etherate, or, better, with mercuric chloride[7] and cadmium carbonate. Reduction of **14** with sodium borohydride then gave **2** as a mixture of diastereomers at the carbinol carbon. Synthetic **2** was clearly identical with the sample of **2** isolated from the metabolic mixture by mass spectral criteria. Acetylation of **2** gave the diacetate **15**, identical with the diacetate of the metabolically derived **2** by nmr[9] and mass spectral, tlc, and glpc[10] criteria.

(3) R. Mechoulam, P. Braun, and Y. Gaoni, *J. Amer. Chem. Soc.*, **89**, 4552 (1967).

(4) T. Petrzilka and C. Sikemeier, *Helv. Chim. Acta*, **50**, 1416 (1967); T. Petrzilka, W. Haefliger, and C. Sikemeier, *ibid.*, **52**, 1102 (1969).

(5) L. F. Fieser, *J. Amer. Chem. Soc.*, **76**, 1945 (1954).

(6) G. P. Pollini, A. Barco, M. Anastasia, and G. Traverso, *Farmaco, Ed. Sci.*, **23**, 405 (1968).

(7) N. Pappas and H. R. Nace, *J. Amer. Chem. Soc.*, **81**, 4556 (1959).

(8) E. Vedejs and P. L. Fuchs, *J. Org. Chem.*, **36**, 366 (1971).

(9) We thank Mr. R. Pitcher for this comparison.

(10) We thank Mrs. O. Gurny for these comparisons.

(11) K. Wismayr, O. Schmid, and G. Zoelss, German Patent 1,233,410 (1967).

(12) M. G. J. Beets and H. van Essen, *Recl. Trav. Chim. Pays-Bas*, **77**, 1138 (1958).

(13) N. A. Burditt, M. C. Whiting, and L. M. Venanzi, *J. Chem. Soc. C*, 2273 (1967).

(14) We thank Mr. S. Teitel for suggesting these conditions.

(15) Earlier attempts to prepare **11** by cleavage of the *dimethyl* ether of **11** were unsuccessful. From a wide range of reaction conditions the major products were less polar than the starting material and lacked a carbonyl group. Cyclization to an indene had most probably taken place.

(16) P. R. Heaton, J. M. Midgley, and W. B. Whalley, *Chem. Commun.*, 750 (1971).

<center>Experimental Section[17]</center>

Butyl 3,5-Dihydroxyphenyl Ketone Dithioethylene Acetal (4).—To 3.60 g (17.1 mmol) of butyl 3,5-dihydroxyphenyl ketone (3) was added 4.00 ml of 1,2-ethanedithiol followed by 4.00 ml of boron trifluoride etherate. The reaction mixture was swirled until it became homogeneous, allowed to stand at ambient temperature for 10 min, and then washed onto a 100-g column of silica gel with dichloromethane. Dichloromethane and 2% ether in dichloromethane eluted odorous materials, and 5 and 10% ether in dichloromethane eluted 4.50 g (97%) of 4 as a colorless oil which soon crystallized, homogeneous by tlc in 10% methanol in chloroform and sufficiently pure for use in the next step.

(6aR:10aR)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-valeryl-6H-dibenzo[b,d]pyran-1-ol Dithioethylene Acetal (6).—A mixture of 1.00 g (3.7 mmol) of 4, 565 mg (4.15 mmol) of (1S:4R)-(+)-*trans*-p-mentha-2,8-dien-1-ol (5), and 110 mg of p-toluenesulfonic acid monohydrate in 40 ml of benzene was heated under reflux for 35 min, cooled, and washed onto a column of silica gel. Elution with benzene gave an oil which soon crystallized. Recrystallization from ether–hexane gave 742 mg (50%) of the analytical sample of 6 as colorless crystals: mp 130–132.5°; ir (CHCl₃) 3600, 1620, and 1570 cm⁻¹; no carbonyl absorptions; uv max (EtOH) 281 nm (ε 1620) and 287 (1640); nmr (CDCl₃) δ 6.70 and 6.56 (two d, J = 2 Hz, H-2 and H-4), 5.42 (m, H-8), 4.93 (s, OH), 3.26 (s, SCH₂CH₂S), 3.17 (m, H-10a), 1.70 (s, 9-CH₃), 1.37 and 1.10 (two s, 6,6-diCH₃), and 0.84 (t, H-5′); [α]²⁵ᴅ −225.6° (c 0.9259, CHCl₃).

Anal. Calcd for C₂₃H₃₂O₂S₂: C, 68.27; H, 7.97; S, 15.85. Found: C, 68.51; H, 8.17; S, 16.02.

(6aR:10aR)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-valeryl-6H-dibenzo[b,d]pyran-1-ol (7).—To a vigorously stirred mixture of 8.1 g of red mercuric oxide, 100 ml of tetrahydrofuran, 26.3 ml of water, and 3.9 ml of boron trifluoride etherate was added dropwise a solution of 7.8 g (19.3 mmol) of 6 in 30 ml of tetrahydrofuran. The mixture was stirred for an additional 20 min, diluted with ether, and filtered. The filtrate was washed with water, sodium bicarbonate solution, and water, dried, and concentrated to a yellow oil. This was dissolved in benzene and adsorbed onto a column of silica gel. Elution with from 20% dichloromethane in benzene to 20% ether in dichloromethane gave 6.6 g (97%) of 7 as a colorless oil, homogeneous by tlc in 15% ethyl acetate in benzene and sufficiently pure for conversion into 1. This oil soon crystallized and was recrystallized from dichloromethane–ether–hexane to give the analytical sample of 7 as colorless crystals: mp 96.5–98.5°; ir (CHCl₃) 3600, 3400 (broad), 1675, and 1575 cm⁻¹; uv max (EtOH) 277 nm (ε 10,400) and 325 (2230); nmr (CDCl₃) δ 7.27 and 6.98 (two sharp d, H-2 and H-4), 7.11 (s, OH), 5.42 (m, H-8), 3.30 (m, H-10a), 2.89 (t, H-2′), 1.68 (s, 9-CH₃), 1.38 and 1.08 (two s, 6,6-diCH₃), and 0.92 (t, H-5′); [α]²⁵ᴅ −322.6° (c 0.7019, CHCl₃).

Anal. Calcd for C₂₁H₂₈O₃: C, 76.79; H, 8.59. Found: C, 76.95; H, 8.55.

(6aR:10aR:1′RS)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-(1-hydroxypentyl)-6H-dibenzo[b,d]pyran-1-ol (1).—To a solution of 2.40 g of crude 7 in 20 ml of ethanol was added 380 mg of sodium borohydride. The resulting green mixture was stirred at room temperature for 3 hr, another 160 mg of sodium borohydride was added, and after another 1 hr the reaction was diluted with water and extracted with dichloromethane. The solution was dried and concentrated to a colorless foam. This was dissolved in benzene and adsorbed onto a column of silica gel. Elution with from 15 to 50% ether in dichloromethane gave 1.19 g (51% overall from 6) of 1 as a colorless foam, homogeneous by tlc in 15% ethyl acetate in benzene: ir (CHCl₃) 3600, 3360 (broad), 1625, and 1590 cm⁻¹; uv max (EtOH) 230 nm (infl) (ε 10,000), 277 (1520), and 284 (1620); nmr (CDCl₃) δ 7.32 and

(17) Melting points were determined in a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were recorded on a Beckman instrument, Model IR-9. Ultraviolet spectra were recorded on a Cary instrument Model 15. Nuclear magnetic resonance spectra were recorded with a Varian A-60 or Varian HA-100 instrument using tetramethylsilane as internal standard. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Low-resolution mass spectra were recorded on a Jeolco JMS-01SG instrument at 70 eV. High-resolution mass spectra were recorded on a CEC 21-110 instrument at 70 eV. Gas-liquid partition chromatography was carried out on a Hewlett-Packard 402 instrument with a flame ionization detector.

7.01 (two sharp m, 1-OH), 6.42 and 6.25 (two sharp d, H-2 and H-4), 5.40 (m, H-8), 4.41 (m, H-1′), 3.38 (br d, H-10a), ~3.1 (m, 1′-OH, exch), 1.69 (s, 9-CH₃), 1.36 and 1.05 (two s, 6,6-diCH₃), and 0.87 (t, H-5′); low-resolution mass spectrum, molecular ion m/e 330 (100%), major fragments m/e (rel intensity) 274 (60) and 247 (65); high-resolution mass spectrum, molecular ion m/e 330.2069 (C₂₁H₃₀O₃).

(6aR:10aR:1′RS)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-(1-acetoxypentyl-6H-dibenzo[b,d]pyran-1-ol) Acetate (8).—The diol 1 obtained from 404 mg (1 mmol) of 6 via 7 was acetylated with acetic anhydride and pyridine overnight at room temperature. The solution was poured into water and extracted with dichloromethane. The organic layers were dried, passed over a short column of silica gel, and concentrated to give 227 mg (55% overall from 6) of 8 as a colorless oil: ir (CHCl₃) 1765 and 1740 cm⁻¹; uv max (EtOH) 225 nm (infl) (ε 8155), 276 (1950), and 283 (2115); nmr (CDCl₃) δ 6.67 and 6.52 (two sharp m, H-2 and H-4), 5.64 (t, H-1′), 5.42 (m, H-8), 2.25 and 2.07 (two s, OAc's), 1.67 (s, 9-CH₃), 1.36 and 1.08 (two s, 6,6-diCH₃), and 0.85 (t, H-5′); compatible⁹ with the time-averaged 211 scan spectrum obtained from the metabolically derived 8; low-resolution mass spectrum, molecular ion m/e 414 (100%), major fragments m/e (rel intensity) 372 (95), 354 (50), 329 (35), 312 (35), 289 (50), and 269 (30); high-resolution mass spectrum, molecular ion m/e 414.2436 (C₂₅H₃₄O₅).

Heating a mixture of 100 mg of 8, 100 mg of sodium bicarbonate, 9 ml of methanol, and 1 ml of water under reflux caused the formation of the 1′-acetate of 1 after 15 min and the regeneration of 1 within 2 hr.

1-(3,5-Dibenzyloxyphenyl)pent-1-en-3-one (10).—A solution of 1.125 g of sodium hydroxide in 125 ml of methanol was heated under reflux with an oil bath. A solution of 105.7 g (0.33 mol) of 3,5-dibenzyloxybenzaldehyde (9) in 202 ml of 2-butanone was heated to about 70° on the steam bath and added rapidly to the sodium hydroxide solution. The reaction mixture was heated under reflux for a further 10 min, cooled in an ice bath, acidified with acetic acid, diluted with water, and extracted with dichloromethane. The extracts were dried and concentrated to a mixture of oil and crystals. The oily portion was adsorbed onto a column of silica gel. Elution with from 50% benzene in hexane to 5% dichloromethane in benzene gave fractions rich in product. These were crystallized from ether–hexane and the combined solids were recrystallized to give 39.8 g (32%) of 10 as colorless crystals, mp 92–96°. Further recrystallization gave the analytical sample: mp 95.5–96.5°; ir (CHCl₃) 1690, 1665, 1615, and 1595 cm⁻¹; Raman (4880 Å, neat) 1655, 1620, and 1595 cm⁻¹; uv max (EtOH) 230 nm (ε 19,700) and 299 (18,600); nmr (CDCl₃) δ 7.35 (s, C₆H₅), 7.48 and 6.57 (two d, J = 16 Hz, H-1 and H-2), 5.02 (s, OCH₂C₆H₅), 2.58 (q, H-4), and 1.13 (t, H-5).

Anal. Calcd for C₂₆H₂₄O₃: C, 80.62; H, 6.49. Found: C, 80.71; H, 6.49.

1-(3,5-Dihydroxyphenyl)pentan-3-one (11).—A mixture of 33.4 g (0.09 mol) of 10, 527 ml of cyclohexene, 5.06 g of a 10% palladium-on-charcoal catalyst, and 1 l. of tetrahydrofuran was heated under reflux for 2.5 days. The cooled catalyst-free solution was concentrated, dissolved in methanol, diluted with water, and extracted with dichloromethane and with ethyl acetate. The combined extracts were dried and concentrated. The residue was dissolved in dichloromethane, passed over a short column of silica gel, and concentrated. Crystallization from chloroform gave 9.3 g (53%) of 11 as colorless crystals, mp 89–93°. Further recrystallization gave the analytical sample: mp 92.5–93.5°; ir (KBr) 1710 and 1615 cm⁻¹ plus strong OH absorption; uv max (EtOH) 225 nm (infl) (ε 7800), 276 (1710), and 282 (1680); nmr (CDCl₃ containing a little CD₃OD) δ 6.19 (s, aromatic), 2.72 (s, H-1 and H-2), 2.44 (q, H-4), and 1.02 (t, H-5).

Anal. Calcd for C₁₁H₁₄O₃: C, 68.02; H, 7.27. Found: C, 68.03; H, 7.32.

1-(3,5-Dihydroxyphenyl)pentan-3-one Dithioethylene Acetal (12).—To 3.00 g (15.4 mmol) of 11 was added 3.3 ml of 1,2-ethanedithiol followed by 3.3 ml of boron trifluoride etherate. The mixture was swirled until it became homogeneous, allowed to stand at ambient temperature for 10 min, and washed onto a column of 180 g of silica gel with dichloromethane. After elution with less polar solvents, from 10 through 40% ether in dichloromethane eluted material which upon crystallization and recrystallization from methanol–water gave 3.04 g (73%) of 12 as colorless crystals: mp 83.5–85.5°; ir (KBr) 1675 (w), 1630, and 1605 cm⁻¹; uv max (EtOH) 225 nm (infl) (ε 15,000), 275

(1450), and 282 (1415); nmr (CDCl₃ plus some DMSO-d_6) δ 6.15 (s, aromatic), 3.27 (s, SCH₂CH₂S), 2.60 and 2.14 (two m, H-1 and H-2), 1.95 (q, H-4), and 1.04 (t, H-5); low-resolution mass spectrum, molecular ion m/e 270 (55%), major fragments m/e (rel intensity) 241 (45), 177 (25), 137 (30), 133 (100), 123 (40), and 44 (30); high-resolution mass spectrum, molecular ion m/e 270.0765 (C₁₃H₁₈O₂S₂).

(6aR: 10aR)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol-3′-one Dithioethylene Acetal (13).—A mixture of 5.162 g (19.1 mmol) of 12, 2.83 g (20.8 mmol) of 5, and 575 mg of p-toluenesulfonic acid monohydrate in 200 ml of benzene was heated under reflux for 35 min, cooled, and washed onto a column of silica gel. Elution with benzene and dichloromethane gave 3.647 g (47%) of 13 as a colorless oil, suitable for use in subsequent steps: ir (CHCl₃) 3600, 1625, and 1580 cm⁻¹; uv max (EtOH) 235 nm (infl) (ε 12,200), 275 (1500), and 282 (1400); nmr (CDCl₃) δ 6.28 and 6.10 (two d, H-2 and H-4), 5.42 (m, H-8), 4.87 (s, OH), 3.24 (s, SCH₂CH₂S), 1.68 (s, 9-CH₃), 1.36 and 1.09 (two s, 6,6-diCH₃), and 1.07 (t, H-5′); low-resolution mass spectrum, molecular ion m/e 404 (35%), major fragments m/e (rel intensity) 311 (60), 271 (100), and 133 (80).

(6aR: 10aR: 3′RS)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-(3-hydroxypentyl)-6H-dibenzo[b,d]pyran-1-ol (2).—A heterogeneous mixture of 3.02 g (7.5 mmol) of 13, 3.00 g of mercuric chloride, and 3.00 g of cadmium carbonate in 300 ml of acetone and 15 ml of water was stirred at room temperature for 16 hr. Another 3.00 g of each inorganic salt was added, and 7 hr later a further 3.00 g of each salt was again added. The reaction was stirred for an additional 20 hr, the inorganic salts were removed by filtration through a filter aid, and the acetone was evaporated under vacuum. The residue was shaken with ether; the ether layer was washed with water, 10% potassium iodide solution, and water, dried, and concentrated. The green residue was dissolved in benzene and adsorbed onto a column of silica gel. Elution with 15-20% ether in dichloromethane gave 1.40 g of the ketone 14 as a light tan oil, almost homogeneous by tlc in 15% ethyl acetate in benzene. This oil was dissolved in 12 ml of ethanol, and 200 mg of sodium borohydride was added. The reaction was stirred for 2.5 hr, during which time an additional 125 mg of sodium borohydride was added. The reaction was diluted with water, acidified with hydrochloric acid, and extracted with dichloromethane. The extracts were washed with sodium bicarbonate solution, dried, and concentrated to 1.2 g of a yellow foam. This was chromatographed over silica gel. Twenty per cent ether in dichloromethane eluted 445 mg (17%) of 2 as a colorless foam: homogeneous by tlc in 15% ethyl acetate in benzene; ir (CHCl₃) 3605, 1625, and 1590 cm⁻¹; uv max (EtOH) 230 nm (infl) (ε 10,600), 276 (1330), and 283 (1380); nmr (CDCl₃) δ 6.35 (OH), 6.25 and 6.14 (two sharp m, H-2 and H-4), 5.42 (m, H-8), 3.55 (m, H-3′), 3.21 (br d, H-10a), 2.09 (OH), 1.65 (s, 9-CH₃), 1.35 and 1.07 (two s, 6,6-diCH₃), 0.90 (t, H-5′); low-resolution mass spectrum, molecular ion m/e 330 (25%), major fragment m/e (rel intensity) 258 (100); high-resolution mass spectrum, molecular ion m/e 330.2196 (C₂₁H₃₀O₃).

(6aR: 10aR: 3′RS)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-(3-acetoxypentyl)-6H-dibenzo[b,d]pyran-1-ol Acetate (15).—A sample of 2 was acetylated with acetic anhydride in pyridine overnight at room temperature. The solution was then poured into water and extracted with dichloromethane. The solution was dried and concentrated. The residue was dissolved in benzene and adsorbed onto a column of silica gel. Elution with 5% ether in dichloromethane gave 15 as a colorless oil, homogeneous by tlc in benzene: nmr (CDCl₃) δ 6.54 and 6.39 (two sharp m, H-2 and H-4), 5.43 (m, H-8), 4.84 (t, H-3′), 2.25 and 2.01 (two s, OAc's), 1.68 (s, 9-CH₃), 1.37 and 1.08 (two s, 6,6-diCH₃), and 0.88 (t, H-5′); compatible⁹ with the time-averaged 100 scan spectrum obtained from the metabolically derived 15; low-resolution mass spectrum, molecular ion m/e 414 (100%), major fragments m/e (rel intensity) 372 (90), 312 (35), 298 (45), 289 (40), and 258 (70); high-resolution mass spectrum, molecular ion m/e 414.2385 (C₂₅H₃₄O₅).

Registry No.—1 (1′-R isomer), 34589-81-6; 1 (1′-S isomer), 34589-82-7; 2 (3′-R isomer), 34589-83-8; 2 (3′-S isomer), 34589-84-9; 6, 34589-85-0; 7, 34589-86-1; 8 (1′-R isomer), 34589-87-2; 8 (1′-S isomer), 34589-88-3; 10, 34589-89-4; 11, 34589-90-7; 12, 34589-91-8; 13, 34635-37-5; 15 (3′-R isomer), 34589-92-9; 15 (3′-S isomer), 34589-93-0.

1- and 3-Methoxy-3-phenyloxindoles. A Rearrangement of a Methoxy Group from Nitrogen to Carbon

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In connection with other work we desired 1-methoxy-3-phenyloxindole (2a). The preparation of 2a should be analogous to that of 1-dimethylamino-3-phenyloxindole (2b). Compound 2b is prepared¹ by the reaction at −20° between α,α-diphenylchloroacetyl chloride and N,N-dimethylhydrazine (1b). When this reaction was performed using methoxyamine (1a) the product isolated (by crystallization from aqueous methanol) had melting point, ir (N–H present), and nmr (Ar-CHC:O absent) properties strongly suggesting that it was 3-methoxy-3-phenyloxindole (3a). Comparison

a series, R = OCH₃
b series, R = N(CH₃)₂
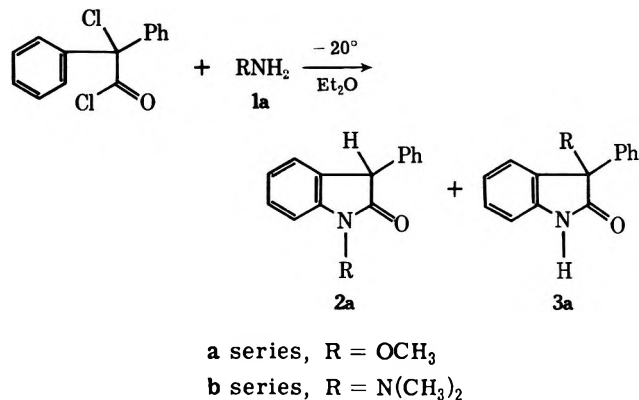
with an authentic sample² confirmed this assignment.

When the crude oily reaction product, essentially solvent-free, was allowed to stand, the desired 2a very slowly crystallized first and could be picked out. The residual oil afforded 3a. The isolated ratio of 2a to 3a was approximately 1:4. Neither 2a nor 3a could be isomerized to the other by boiling in ether, by recrystallization, or by seeding the melt. This suggests that the isomerization occurs during the initial reaction steps, in
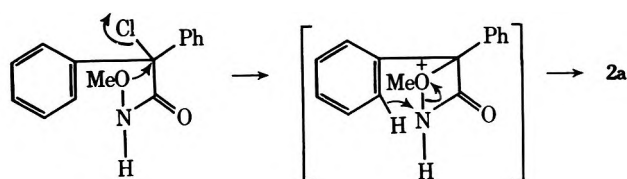
(1) R. F. Meyer, *J. Org. Chem.*, **30**, 3451 (1965).
(2) J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 4789 (1957). We thank Professor Bruce for kindly supplying a sample of 3a.

spite of the low temperature. A four-membered ring intermediate is conceivable.

The reaction using **1b** was reexamined. There was no spectral evidence for the formation of **3b**; the exclusive product was the expected **2b**.

Experimental Section

Melting points are uncorrected. Ir (KBr) spectra were recorded on a Perkin-Elmer Infracord spectrometer; nmr spectra on a Perkin-Elmer Hitachi R-20 instrument (CDCl₃ solvent, TMS standard). Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

1-Methoxy- and 3-Methoxy-3-phenyloxindoles.—In a flask equipped with a magnetic stirrer, a dropping funnel, and drying tubes were placed 7.25 g (0.0265 mol) of α,α-diphenylchloroacetyl chloride (Aldrich) and 75 ml of dry ether. The funnel was charged with a solution of 4.7 g (0.1 mol) of methoxyamine[3] in 25 ml of ether. The mixture was kept near −20° with a Dry Ice–acetone bath while the amine was added slowly with stirring. The slurry was allowed to warm to room temperature and was stirred for an additional 4 hr. Water (100 ml) was added and the layers were separated. The ether layer was washed with 2 × 50 ml of water, dried (K₂CO₃), and evaporated to leave a pale yellow oil. When left at room temperature, this deposited transparent cubes during a period of 5 weeks. These were removed manually and triturated with a 1:1 benzene–hexane mixture at room temperature. There was obtained 0.95 g (15%) of **2a**, mp 93–95°. Its ir spectrum showed no N–H stretching, while its nmr spectrum exhibited a three-proton singlet at 4.01 ppm (NOCH₃) and a one-proton singlet at 4.54 ppm (Ar₂CHC:O).

Anal. Calcd for C₁₅H₁₃NO₂: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.30; H, 5.51; N, 5.70.

The oil left after the removal of **2a** was crystallized from aqueous methanol to give 4.0 g (63%) of **3a**, mp 168–169°. Its spectra showed N–H stretching at 3200 cm⁻¹ and no proton resonance near 4.5 ppm. It was identical, by ir and nmr spectral comparisons and by mixture melting point, with an authentic sample of **3a**.[2] When the total crude reaction product was crystallized directly from aqueous methanol the less soluble **3a** was isolated first.

Except for the N–H region, the ir spectra of **2a** and **3a** differ significantly only below 1200 cm⁻¹. **2a** exhibited bands at 1065, 759, and 748 cm⁻¹ not shown by **3a**, whereas **3a** showed bands at 1118, 1095, 773, 753, and 706 cm⁻¹.

When **1b** was used, the crude reaction product showed no evidence in its ir or nmr spectra that any **3b** was present, and only **2b**[1] was isolated.

Attempted Isomerizations of 2a and 3a.—A mixture of 0.24 g of **2a**, 0.08 g of methoxyamine hydrochloride, and 20 ml of ether was refluxed with stirring for 6 hr and filtered. Evaporation of the filtrate gave a quantitative recovery of **2a**, identified by its melting point and ir spectrum. Similarly, **3a** was recovered unchanged. Further, **2a** and **3a** were recovered unchanged, even when seeded with the other, when each was recrystallized from aqueous methanol or from a melt.

In similar experiments, **2b** did not isomerize to **3b**.

Registry No.—**2a**, 34638-56-7; **3a**, 34638-57-8.

(3) T. C. Bissot, R. W. Parry, and D. H. Campbell, *J. Amer. Chem. Soc.*, **79**, 796 (1957).

Reductive Cleavage of Sulfonamides with Sodium Bis(2-methoxyethoxy)aluminum Hydride

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Received December 7, 1971

We wish to report that the new versatile reducing agent sodium bis(2-methoxyethoxy)aluminum hydride

(SMAH),[1] in contrast to lithium aluminum hydride (LiAlH₄),[2] is a useful reagent for the regeneration of primary and secondary aliphatic and aromatic amines from the corresponding sulfonamides. This reaction provides an additional approach that complements those methods reported[2,4] for carrying out this transformation. The usual procedure consists of refluxing a mixture of the sulfonamide and excess SMAH (mole ratio 1:4) in an aromatic hydrocarbon or, if desired, in an ethereal solvent such as glyme, until sulfonamide is consumed. Addition of water or alkali quenches the reaction, and the amine may be isolated by standard procedures. Typical results are recorded in Table I.[5,6]

TABLE I

CLEAVAGE OF SULFONAMIDES WITH NaAlH₂(OCH₂CH₂OCH₃)₂

Series	Sulfonamides (1)	Product (2)	Solvent	Yield,[a] %
a	N-Tosylpiperidine	Piperidine	Benzene	75[b]
b	N-Tosyldeoxyephedrine	Deoxyephedrine	Benzene	64[b]
			Glyme	77[b]
c	N-Mesyldeoxyephedrine	Deoxyephedrine	Benzene	67[b]
d	(S)-N-Tosylamphetamine	(S)-Amphetamine	Toluene	27[b]
e	cis- and trans-1,5-Bis(tosyl)-3,7-dihydroxyoctahydro-1,5-diazocine[c]	cis-3,7-Dihydroxyoctahydro-1,5-diazocine[c]	Benzene	33[d]
f	N-Tosyl-2-(N-methylaminomethyl)-2-phenyl-1,3-dioxolane	2-(N-Methylaminomethyl)-2-phenyl-1,3-dioxolane	Toluene	56[e]
g	1-Tosylaziridine	N-Tosylethylamine	Benzene	100
h	2g	Ethylamine	Toluene	57[b]
i	3-Methoxymethoxy-3-phenyl-1-tosyl-azetidine[f]	3-Methoxymethoxy-3-phenylazetidine[f]	Benzene	69[g]
j	N-Mesylaniline	Aniline	Toluene	63[h]

[a] No special effort was made to optimize yields. [b] Isolated as picrate and compared by ir, melting point (and [α]D where applicable) with an authentic sample.[5] [c] No attempt was made to purify the trans product.[5] [d] Isolated as the ditosylate. [e] Yield as distilled free amine. [f] Reference 6. [g] Isolated as the hemioxalate. [h] Isolated as hydrochloride and compared as in b.

With the exception of (S)-N-tosylamphetamine (**1e**), it can be seen from Table I that both toluenesulfonamides and methanesulfonamides are cleaved by this reagent in acceptable yield. Although reduction of tertiary sulfonamides is generally readily carried

(1) (a) V. Bazant, M. Capka, M. Cerny, V. Chvalovsky, K. Kochloefl, M. Kraus, and J. Malek, *Tetrahedron Lett.*, 3303 (1968); (b) M. Cerny and J. Malek, *ibid.*, 1739 (1969); (c) M. Cerny, J. Malek, M. Capka, and V. Chvalovsky, *Collect. Czech. Chem. Commun.*, **34**, 1025 (1969); (d) M. Capka, V. Chvalovsky, K. Kochloefl, and M. Kraus, *ibid.*, **34**, 118 (1969).

(2) S. Searles and S. Nukina, *Chem. Rev.*, **59**, 1077 (1959); cf. p 1094. Primary sulfonamides have not been cleaved with LiAlH₄. Secondary sulfonamides (generally aniline derivatives) have been cleaved by using unusually vigorous conditions for this reagent, e.g., reduction of N-ethyl-p-toluenesulfonanilide at 120° in dibutyl ether.[3]

(3) D. Klamann, *Monatsh. Chem.*, **84**, 651 (1953).

(4) (a) L. Horner and H. Neumann, *Chem. Ber.*, **98**, 3462 (1965); (b) W. D. Closson, P. Wriede, and S. Bank, *J. Amer. Chem. Soc.*, **88**, 1581 (1966); (c) S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, W. D. Closson, and P. Wriede, *ibid.*, **89**, 5311 (1967); (d) K. Okamura, T. Iwasaki, M. Matsuoka, and K. Matsumoto, *Chem. Ind. (London)*, 929 (1971).

(5) W. W. Paudler, A. G. Zeiler, and G. R. Gapski, *J. Org. Chem.*, **34**, 1001 (1969).

(6) E. H. Gold, *J. Amer. Chem. Soc.*, **93**, 2793 (1971).

out in refluxing benzene,[7] secondary sulfonamides first form salts and thus require higher boiling solvents such as toluene or xylene.

The low yield of (S)-amphetamine is due to olefin formation, probably *via* abstraction of the benzylic hydrogen by base and subsequent elimination of *p*-toluenesulfonamide. In addition to (S)-amphetamine, the only other identifiable product, characterized by glc, in approximately 15% yield, was allylbenzene. Although β-methylstyrene is the expected primary olefinic product, it was discovered that when β-methylstyrene was treated under the reaction conditions (see Experimental Section), it disappeared completely and only allylbenzene, in about 25% yield, could be identified. Similarly, allylbenzene treated under the reaction conditions was recovered in about 25% yield, and no β-methylstyrene was formed. Since only about one quarter of the olefin survives this treatment, the 15% yield of allylbenzene obtained from the sulfonamide reduction would be equivalent to *ca.* 60%. The isomerization of β-methylstyrene to allylbenzene is base catalyzed, since no isomerization of either olefin took place in refluxing toluene.

From Table I, it is clear that protected carbonyls (*i.e.*, ketals or acetals) survive the reduction. Of course, such groups as carbonyl and carboxyl would be concomitantly reduced, and this may be useful when the corresponding amino alcohol is the desired product.

Finally, it should be noted that while this represents a practical synthesis of substituted azetidines from the corresponding sulfonamide derivatives[6] (*e.g.*, 1i), aziridine sulfonamides are ring cleaved by this method (*e.g.*, 1g).

Although no attempts at isolation have been made, it is reasonable to assume that the RSO₂⁻ moiety is further reduced to the corresponding thiol.[8]

Experimental Section[9]

Reagents.—All solvents were reagent grade and dried over 3A molecular sieves. SMAH[10] was used as a 70% benzene solution. Glc analyses were performed with a Perkin-Elmer Model 800 gas chromatograph, with a 0.125 in. × 12 ft 8% castorwax column on 80–100 mesh HMDS Chromosorb W at 150° and at a 10 ml min⁻¹ flow rate. Allylbenzene and β-methylstyrene were respectively obtained from Columbia Organic Chemicals Co. and Aldrich Chemical Co. Nmr spectra were recorded on a Varian Model A-60A spectrometer.

Tosyl Amides.—All previously reported compounds (1a, 1e, 1g, 2g, and 1j) were prepared *via* the respective literature procedures from the amine and sulfonyl chloride.

N-Tosyldeoxyephedrine (1b).—Tosyl chloride (19.1 g, 0.10 mol), dissolved in 210 ml of ether, was added to a solution of 14.9 g (0.1 mol) of deoxyephedrine in 210 ml of dry pyridine at *ca.* 5°. The mixture was stirred for 15 min, warmed to 25°, stirred for 1 hr, poured into 1 l. of ice–water, and extracted with ether. The ether extract was washed with 10% H₂SO₄, followed by water and then saturated NaHCO₃, dried over Na₂SO₄, filtered, and evaporated to yield crude 1b. Recrystallization from hexane afforded 15.1 g (50%) of analytically pure 1b, mp 63–64°.

Anal. Calcd for C₁₇H₂₁NO₂S: C, 67.29; H, 6.98; N, 4.62; S, 10.57. Found: C, 67.57; H, 6.78; N, 4.33; S, 10.66.

N-Mesyldeoxyephedrine (1c) was prepared in an analogous manner to 1b, using CH₃SO₂Cl, and recrystallized from hexane, mp 49–50°.

Anal. Calcd for C₁₁H₁₇NO₂S: C, 58.11; H, 7.53; N, 6.16; S, 14.10. Found: C, 58.09; H, 7.55; N, 5.94; S, 14.29.

(S)-*N*-Tosylamphetamine (1d) was synthesized in an identical manner with 1b and was obtained as a noncrystallizable oil. It was converted into its sodium salt (2.5 M NaOH), which was recrystallized from isopropyl alcohol–ether and then regenerated with 10% HCl as an analytically pure oil,[11] which crystallized after 2 years, mp 44–46°.

Anal. Calcd for C₁₆H₁₉NO₂S: C, 66.44; H, 6.60; N, 4.84; S, 11.08. Found: C, 66.51; H, 6.75; N, 4.76; S, 11.30.

N-Tosyl-2-(*N*-methylaminomethyl)-2-phenyl-1,3-dioxolane (1f).—*N*-Tosyl-α-aminoacetophenone[12] (230 g, 0.8 mol) and 100 g (1.6 mol) of ethylene glycol were refluxed for 48 hr (Dean-Stark condenser) in 500 ml of benzene containing 1 g of *p*-toluenesulfonic acid. The benzene was removed and the ketal was obtained in 90% yield after trituration with ether (mp 132–136°). An analytical sample was recrystallized from isopropyl ether–CH₂Cl₂, mp 139–139.5°.

Anal. Calcd for C₁₇H₁₉NO₄S: C, 61.24; H, 5.74; N, 4.20; S, 9.62. Found: C, 61.48; H, 5.81; N, 4.18; S, 9.42.

A mixture of 60 g (0.18 mol) of the ketal and 12.3 g (0.21 mol) of NaOCH₃ was stirred in 350 ml of dry DMF, and 43 g (0.30 mol) of CH₃I was added. The mixture was heated on a steam bath for 1.5 hr, poured into 1 l. of ice–water, extracted with three 250-ml portions of CH₂Cl₂, washed with 150 ml of 10% NaOH followed by 150 ml of saturated NaCl solution, dried (Na₂SO₄), filtered, evaporated, and crystallized from isopropyl ether–CH₂Cl₂ to afford 53.4 g (83%) of 1f, mp 96–105°. Several recrystallizations from isopropyl ether afforded analytically pure material, mp 104.5–106.5°.

Anal. Calcd for C₁₈H₂₁NO₄S: C, 62.22; H, 6.09; N, 4.03; S, 9.23. Found: C, 62.50; H, 6.06; N, 3.85; S, 9.38.

3-Methoxymethoxy-3-phenyl-1-tosylazetidine (1i).—A solution of 60.7 g (0.2 mol) of 3-phenyl-1-tosyl-3-azetidinol[6] in 100 ml of dry DMF was slowly (*ca.* 15 min) added under nitrogen to a cooled (water bath), stirred mixture of 10.9 g (0.25 mol) of NaH (55% in mineral oil) in 250 ml of dry DMF. The mixture was stirred for 1 hr at 25°, then cooled to *ca.* 10° and 16.5 g (0.21 mol) of chloromethyl methyl ether was added dropwise, maintaining the temperature at 15–20°. Stirring was continued for 15 min, after which 50 ml of saturated aqueous NaCl was added, and the mixture was poured into 1 l. of ice-cold water. The product was filtered and washed with water and hexane, and 67.2 g (97%) of crude 1i was obtained, mp 93–96°, and recrystallized from CH₂Cl₂–isopropyl ether, mp 97–97.5°.

Anal. Calcd for C₁₈H₂₁NO₄S: C, 62.22; H, 6.09; N, 4.03; S, 9.23. Found: C, 62.51; H, 6.22; N, 3.99; S, 8.90.

General Reduction Method.—The reductive cleavage reactions were carried out in air (calcium chloride drying tube) in a manner analogous to the reduction of 1f described below. The reactions were terminated as soon as no more starting sulfonamide could be detected (tlc).

2-(*N*-Methylaminomethyl)-2-phenyl-1,3-dioxolane (2f).—A mixture of 0.59 mol of SMAH (172 g, benzene removed on rotary evaporator) and 52.4 g (0.147 mol) of 1f in 320 ml of toluene was refluxed for 22 hr. The mixture was cooled, decomposed with 200 ml of 10% NaOH, extracted with ether, washed consecutively with 10% NaOH, water, and saturated aqueous NaCl, and then extracted with 250 ml of 1.1 M aqueous oxalic acid. The acid extract was washed with ether, basified with 50% NaOH, extracted with ether (after removing the sodium oxalate by filtration through celite), dried (Na₂SO₄), and distilled to give 15.8 g (56%) of 2f: bp 73–75° (0.05 mm); nmr (CDCl₃) τ 8.63 (s, 1, NH), 7.62 (s, 3, NCH₃), 7.12 (s, 2, CH₂N), 6.12 (AA′BB′, OCH₂CH₂O), 2.64 (m, 5, C₆H₅).

Anal. Calcd for C₁₁H₁₅NO₂: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.61; H, 7.80; N, 7.29.

The hydrochloride salt of 2f was prepared by addition of 1 ml of 4 N ethereal HCl to 0.23 g of 2f in 25 ml of ether, filtration, and recrystallization from methanol–EtOAc, mp 227–228° (lit.[13]

(7) The reduction of 1f required toluene to obtain an acceptable rate, presumably for steric reasons.

(8) A powerful thiol-like odor was noted throughout the reactions and work-ups. *p*-Thiocresol has been isolated in the LiAlH₄ reduction of *N*-tosyl-*N*-ethylaniline.[3]

(9) Melting points were determined in a capillary tube, and are corrected.

(10) Obtained from the Hynes Chemical Co., Watertree, S. C.; trade name Vite reducing agent.

(11) 1d was isolated as an oil *via* a different route: P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

(12) W. Kirmse and L. Horner, *Chem. Ber.*, **89**, 1674 (1956).

(13) H. Scheffer and A. Kottler, U. S. Patent 2,830,988 (1958).

mp 155–157°),[14] mass spectrum (70 eV) m/e 193 (M·+), 149, 105.

Anal. Calcd for $C_{11}H_{16}ClNO_2$: C, 57.51; H, 7.02; N, 6.10; Cl, 15.44. Found: C, 57.74; H, 7.06; N, 6.03; Cl, 15.33.

cis-3,7-Dihydroxyoctahydro-1,5-diazocine (2e).—To 22.73 g (0.05 mol) of 1e in 300 ml of benzene, 136.5 g (0.5 mol) of SMAH was added dropwise with stirring, after which the mixture was refluxed for 20 hr. The mixture was cooled and decomposed with 300 ml of water, 200 ml of ether was added, and it was filtered through Celite. The aqueous phase was acidified with HCl and washed well with ether, after which 19 g (0.11 mol) of *p*-toluenesulfonic acid was added and the solution was evaporated to dryness. The solid residue was crystallized from 150 ml of water to yield 8.0 g (33%) of the ditosylate salt 2e, mp 279–280° dec (lit.[5] mp 279°).

3-Methoxymethoxy-3-phenylazetidine (2i).—Excess oxalic acid was added to the ether–benzene extract, obtained after decomposition of the excess SMAH, and the resulting crude hemioxalate (69%) was recrystallized from ethanol, mp 153.5–154°.

Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.95. Found: C, 54.84; H, 5.93; N, 5.02.

Addition of tosyl chloride to the hemioxalate of 2i in pyridine regenerated 1i. Hydrolysis of the hemioxalate of 2i (refluxing ethanolic HCl) afforded, after basification with NaOH, 3-phenyl-3-azetidinol, mp 157–158.5° (lit.[15] mp 160–162°).

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(14) Although there is a large discrepancy in melting points, our data are fully consistent with the assigned structure of **2f**.

(15) E. Testa and L. Fontanella, *Justus Liebigs Ann. Chem.*, **671**, 106 (1964).

Reduction of (S)-N-Tosylamphetamine (1d) with SMAH.—This reduction required 72 hr in refluxing toluene (0.0218 mol of 1d and 0.089 mol of SMAH in 50 ml of toluene). The ether–toluene extract, after decomposition of the excess SMAH, was washed with 10% NaOH and water and then extracted with 0.6 M HCl, leaving an organic solution A. The acidic fraction was basified with NaOH, extracted with ether, dried (MgSO$_4$), filtered, and evaporated to give a 27% yield of (S)-amphetamine (ir), further characterized as its picrate (mixture melting point, ir, and [α]D).

Glc analysis of solution A revealed only one component with a retention time identical with that of allylbenzene (*ca.* 0.003 mol).

Allylbenzene and β-Methylstyrene in Refluxing Toluene.—In separate experiments, 0.0015 ml of allylbenzene and of β-methylstyrene were each refluxed for 72 hr in 5 ml of toluene. Glc analysis of each experiment showed only the original olefin.

Allylbenzene and β-Methylstyrene under Conditions of the SMAH Reduction of 1d.—In separate experiments, 0.0015 mol of allylbenzene and of β-methylstyrene were each refluxed for 72 hr in 5 ml of toluene containing 0.0015 mol of *p*-toluenesulfonamide and 0.0089 mol of SMAH. The work-up procedure was identical with that used in the reduction of 1d. Glc analysis of both experiments revealed *ca.* 0.0004 mol (25%) of allylbenzene and no detectable β-methylstyrene.

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