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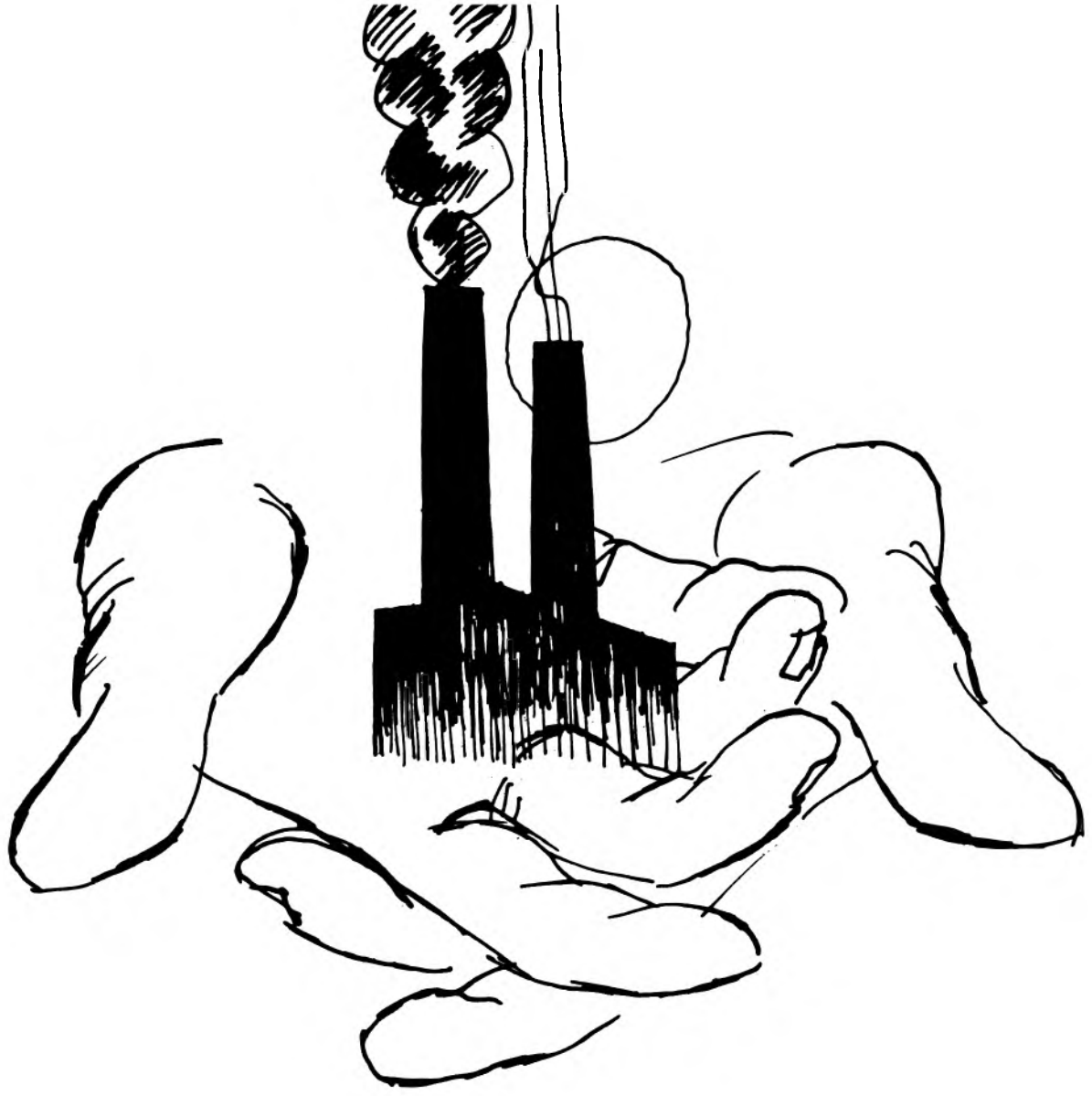

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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 15

JULY 27, 1973

5β,12α-Cholajervane and Related Compounds[1]

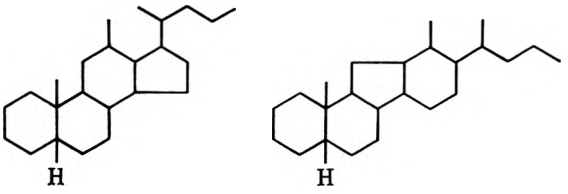
RICHARD C. EBERSOLE AND FREDERIC C. CHANG*

Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tennessee 38103

Received March 9, 1973

The three major cholajervenes obtained in the reactions, solvolysis of 5β-cholan-12α-ol mesylate, solvolysis of the 12-epimeric mesylate, and alkaline decomposition of 5β-cholan-12-one tosylhydrazone, were shown to be Δ^{12}, $\Delta^{12(18)}$, and $\Delta^{13(17)}$ isomers with α-H configurations at C-17, C-12 and C-17, and C-12, respectively. The three olefins were converted to a single hydrocarbon, 5β,12α-cholajervane, by hydrogenation and by dehydrogenation to a single compound which was demonstrated to have an aromatic D ring by spectral documentation. Diols and ketones corresponding to the three olefins were prepared and characterized. Mass spectral data of the hydrocarbons are presented.

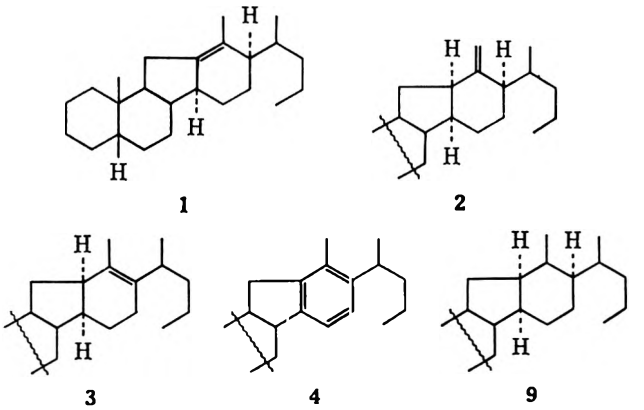
In preliminary communications[2] we presented evidence that an earlier speculation[3] that a rearrangement product of 12α-cholanol mesylate[4] (5) has the 12-methyl-18-norcholane structure (I) was incorrect; instead it has the cholajervane structure[5] (II).



I II

The original surmise of the 12-methyl-18-nor structure was based on analogy with the findings of Hirschmann and colleagues[6a] that rockogenin 12(β)-mesylate (20a) under solvolytic conditions rearranges into a *C*-nor-*D*-homo steroid, the ring expansion–contraction resulting from favorable conformational juxtaposition of the migrating and leaving bonds. Under similar solvolytic conditions a steroidal 12α-mesylate (5), with the angular methyl group at C-13 in an analogous trans-antiparallel relationship with the mesyloxy function, on rearrangement would be expected to undergo a favored Meerwein–Wagner shift to yield a compound of structure I.

When it was found that the two major rearranged products, 1 and 3, formed when the 12α-mesylate 5



1 2 3 4 9

is refluxed in collidine, are also formed both in a similar reaction of the epimeric 12β-mesylate 6, and in the alkaline decomposition of 12-cholanone tosylhydrazone[7] (8), the speculation favoring structure I for the products became dubious.[8] Confirmation of the *C*-nor-*D*-homo structure II for 1 and 3, as well

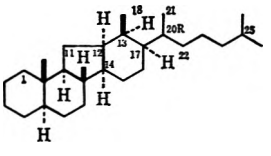
(1) Excerpted in part from the Ph.D. dissertation of R. C. E., University of Tennessee Medical Units, 1973.

(2) (a) F. C. Chang and R. C. Ebersole, *Tetrahedron Lett.*, 1985 (1968); (b) *ibid.*, 3521 (1968).

(3) F. C. Chang, *ibid.*, 2057 (1963).

(4) F. C. Chang, *J. Pharm. Sci.*, **53**, 1014 (1964). Improved syntheses of several 12-substituted 5β-cholane derivatives are reported in a companion to the present paper, R. C. Ebersole and F. C. Chang, *J. Org. Chem.*, **38**, 2713 (1973). All cholane and cholajervane compounds mentioned in this paper are of the 5β series; the designation 5β will be omitted in referring to these compounds.

(5) The name cholajervane was proposed[2b] to join the trivial names already in common use, jervane and etiojervane, with configuration and numbering as illustrated for jervane.



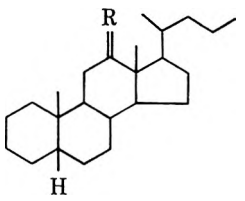
The name pregnajervane has been adopted to represent the C_{21} analog of the same series: W. F. Johns, *J. Org. Chem.*, **35**, 3524 (1970).

(6) (a) R. Hirschmann, C. S. Snoddy, C. E. Hiskey, and N. L. Wendler, *J. Amer. Chem. Soc.*, **76**, 4013 (1954); (b) J. Elks, G. H. Phillips, D. A. H. Taylor, and L. J. Wyman, *J. Chem. Soc.*, 1739 (1954).

(7) F. C. Chang, *J. Org. Chem.*, **30**, 2053 (1965).

(8) In all previously recorded rearrangements involving 12β-sulfonates and 12-tosylhydrazones, only rearranged products of the II type have been obtained.[6,11,12,26]

as for 2 which is obtained as an additional product in the reaction of 6, follows from the characterization of an aromatic derivative 4 obtained by dehydrogenation of each of the three olefinic compounds.[2b]



5, R = H,α-OMs
6, R = H,β-OMs
7, R = H,H (Δ^{11})
8, R = NNHTs
28, R = O
29, R = H,α-OH
30, R = H,β-OH
31, R = H,α-OAc
32, R = H,β-OAc

This paper presents details of the experiments, and describes further characterization of the compounds and the formation of a common hydrocarbon, 5β,12α-cholajervane (9), from its three progenitor olefins.

The Cholajervenes.—Assignment of the double bond location in each of the three isomers 1, 2, and 3 was made on the basis of a known diagnostic method[9] supported by spectral evidence. The configurations of the olefins 1 and 2 were tentative, being based only on analogy with the corresponding compounds found in similar reactions in other steroidal series.[8] However, no $\Delta^{13(17)}$ analog was known,[10] although in the pregnajervane series such an isomer had been deduced[11] from ir and nmr evidence obtained from a mixture of seco ketones derived from an olefinic mixture.

Evidence is now available which essentially establishes the α-H configuration of all three olefins at centers 12 and 17 (when H is present). The evidence is mainly based on stereochemical considerations involved in the isomerism of 1 to 3 and of 2 to 1 and 3, and in the hydrogenation of each of the three olefins by known methods to a common cholajervane.

It is reasonable to assume that the original configuration at C-17 is unchanged in the formation of olefin 1, although rearrangement mechanisms are conceivable whereby inversion has taken place at that center. The arguments regarding configuration of the other compounds are initially based on assuming the α-H configuration at C-17 of 1, but as will be evident in the sequel, independent compelling evidence supports that assignment. Each of the hydrogen atoms under discussion in the three olefins is allylic, and the isomerizations involved are 1,3-hydrogen shifts.

12α-Cholajervane.—Previous studies on steroids and other types of compounds having tetrasubstituted or hindered double bonds show that, under catalytic hydrogenation conditions, an allylic shift of hydrogen can take place. The catalyst is considered to approach from the less hindered side of the molecule, and both the hydrogen abstracted and the hydrogen inserted are on the same side as the catalyst.[12]

In this connection, 2 must be considerably hindered, as it does not undergo hydrogenation in PtO_2 even in acetic acid, but instead isomerizes to 1 and 3. Thus, assuming the 17α-H configuration of 1, the ready isomerization of 2 to 3 indicates that the catalyst approaches from the α side of the molecule, and isomerization to 1 would be expected also to involve the α side.

Hydrogenation of all three olefins to a single hydrocarbon, each in no less than 70% yield, lends support to the configurations assigned to 1, 2, and 3. Catalytic hydrogenations carried out on both Δ^{12}- and $\Delta^{13(17)}$-*C*-nor-*D*-homo analogs are known to add predominantly from the α side in cis fashion, as documented by substantial evidence,[13] indicating that the α side of the molecule is more open for the approach of the catalyst. Accordingly, hydrogenation of 1 would be expected to give the 12α*H*,13α*H* and 3 the 13α*H*,17α*H* derivative. Diimide reduction has been shown to add cis from the less hindered side,[14] so that such a reduction of 2 would yield a 13α*H* product.

Considering the stereochemical selectivity of the hydrogenations as well as of the isomerization reactions, in order for the three isomers to yield predominantly the same hydrocarbon, the latter must have all α-H configurations at positions 12, 13, and 17. Thus the original tentative assignment for 1, 2, and 3 are correct,[15] in agreement with previous assignments for compounds analogous to 1 and 2 in other *C*-nor-*D*-homo series obtained by similar hydrogenations.[13]

The Cholajervanediols 10, 11, and 12.—The hydroxyl groups in the three osmylation products are assigned α configurations on the basis of cis hydroxylation from the unhindered side, in analogy to the hydrogenation assignments (see above). Nmr and ir data do not contribute significantly to configurational characterization of the tertiary hydroxyl groups, as previously indicated.[16,17]

Two additional diols, 14 and 15, were isolated in minor yields from the diol mixtures obtained from the reactions of mesylate 5 and tosylhydrazone 6; they were not found in the diol mixture from the reaction of the 12β-mesylate 6. They are crystalline, isomeric with the other cholajervane diols, but

(9) J. Castells and G. D. Meakins, *Chem. Ind. (London)*, 248 (1956); J. Castells, G. D. Meakins, and R. Swindells, *J. Chem. Soc.*, 2917 (1964).

(10) The original[6a] assignment of $\Delta^{13(17)}$ to the endocyclic olefin of the spirostane series was shown to be erroneous. It is actually the Δ^{12} isomer. J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron Lett.*, 119 (1965).

(11) J. M. Coxon, M. P. Hartshorn, D. N. Kirk, and M. A. Wilson, *Tetrahedron*, **25**, 3107 (1969).

(12) J. B. Bream, D. C. Eaton, and H. B. Henbest, *J. Chem. Soc.*, 1974 (1957).

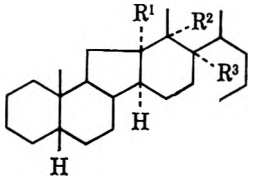
(13) (a) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964); (b) H. Mitsuhashi and N. Kawahara, *Tetrahedron*, **21**, 1215 (1965); (c) T. Masamune, N. Sato, K. Kobayashi, I. Yamazaki, and Y. Tori, *ibid.*, **23**, 1591 (1967); (d) H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Lett.*, 2671 (1969); (e) J. W. Huffman, D. M. Alabran, and A. E. Ruggles, *J. Org. Chem.*, **33**, 1060 (1968); (f) T. Masamune, S. Murai, K. Orito, H. Ono, S. Numata, and H. Suginome, *Tetrahedron*, **25**, 4853 (1969).

(14) E. J. Corey, D. J. Pasto, and W. L. Mock, *J. Amer. Chem. Soc.*, **83** 2957 (1961).

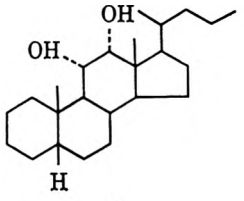
(15) Of the other seven cholajervane structures stereoisomeric at 12, 13, and 17, only the all β-H isomer would not require unusual regiospecific addition mechanisms for its formation, but then such a compound would be possible only if all the reactions are ones which proceed from the β side. Otherwise, for example, suppose 1 to be 17β-H. Expected cis addition from the α side to the Δ^{12} bond would give the 12α,13α,17β product, olefin 2 would have to be a 12α,17β isomer, 3 would be a 12α isomer; and, in order for 2 to be converted to the same hydrocarbon as was formed from 1, addition to the $\Delta^{13(17)}$ bond would have to proceed in a trans regiospecific manner.

(16) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, **21**, 2489 (1965).

(17) D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).



	R^1	R^2	R^3
10	OH	OH	H
11	H	OH	H (C-18 OH)
12	H	OH	OH



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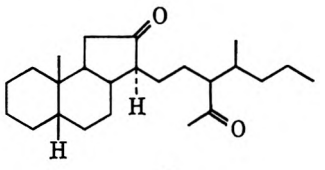

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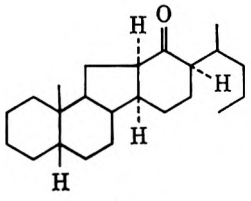

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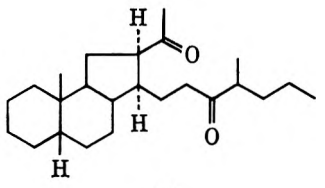


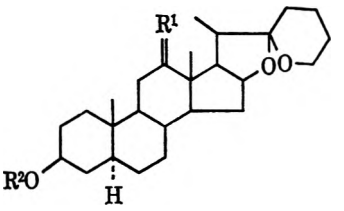
18

their structures have not been completely clarified. They are probably the αα or ββ diols from a single olefin, as on oxidation they gave the same ketone.

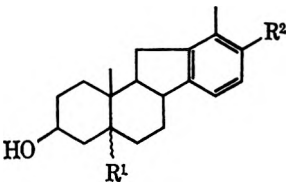
The D Ring Aromatic 4.—Conversion of all three olefins into a single hydrocarbon supplements the initial evidence of the same skeletal system provided by the successful aromatization of the three into **4**, but is more convincing because the hydrogenations conducted under mild conditions in each instance gave high yields of **9**, whereas the dehydrogenations required more vigorous conditions and afforded lesser yields.

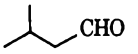
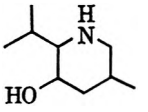
However, the cholajervane structure of these compounds requires separate documentation, which is available in the form of much spectral evidence. The nmr spectrum of **4** has in the aromatic region a two-proton (ortho) quartet which is virtually identical in chemical shift and splitting pattern with the corresponding signal exhibited in the nmr spectrum of **22**.[18] Both have their C-21 methyls (benzylic) as sharp doublets (J = 7 Hz) coupled with the C-20 protons which are quartets (J = 7 Hz) slightly obscured by overlapping signals, and the two have similar chemical shifts for the C-18 aromatic methyl protons (τ 7.84 for **4**, 7.78 for **22**). The C-19 methyl signal of **4** is at τ 8.97, which compares favorably with the value of τ 8.93 used for the C-19 methyl protons in the A/B-cis reference structure **23** in a nmr summary of 35 related aromatic D ring compounds.[19] Furthermore, uv spectra of **4** and veratramine[20] (**24**) are identical in shape and maxima of absorption.

Mass spectral analysis affords additional support for the structure of **4**. Its fragmentation pattern

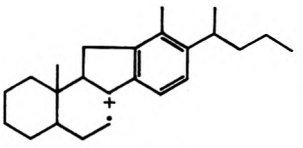


	R^1 (R^2 = Me succinyl[6a] or acetyl[11])
19	H, α-OTs
20a	H, β-OMs
20b	H, β-OTs
21	NNHTs

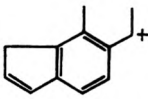


	R^1	R^2
22	α H	
23	β H	H
24	Δ^5	

resembles that of dihydroveratramine[21] in having in the higher mass range only one major ion, which is formed by fission of the side chain at the bond β to the ring. The second most intense fragment is a m/e 157 ion b which by plausible steps can be derived from a molecular ion a.



(M^+)a



b, m/e 157

Mass Spectra.—Prominent ions observed in the mass spectra of **4** and the other cholajervane derivatives prepared in this work are summarized in Table I. The

Table I

Prominent Ions in Mass Spectra of Cholajervanes

Ion	m/e (peak intensities, % of base peak) 1	2	3	9	4
M^+	328 (10)	328 (29)	328 (28)	330 (11)	324 (42)
M − 15		313 (22)	313 (8)		
M − 43 + 1		286 (75)			
M − 43[a]			285 (18)		281 (100)
M − 71 + 1[b]	258 (23)	258 (100)		258 (43)	
M − 71[c]	257 (100)	257 (92)	257 (13)	259 (100)	253 (9)
M − 85[d]		243 (67)			
	163 (9)	162 (67)		163 (23)	
	161 (10)	161 (63)	161 (26)		157 (12)[g]
149 ion[f]	149 (19)	149 (65)	149 (11)	149 (30)	
		148 (63)	133 (100)[g]	135 (15)	

[a] M − C_3H_7 (rupture of side chain at branch). [b] M − side chain + hydrogen rearrangement. [c] M − side chain. [d] M − side chain − CH_3. [e,f] See discussions in text. [g] May be artifact.

(18) R. W. Franck, G. P. Rizzi, and W. S. Johnson, *Steroids*, **4**, 463 (1964). We are indebted to Professor Johnson for a reference spectrum of compound **22**.

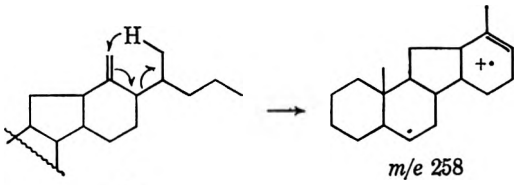
(19) T. Masamune, I. Yamazaki, K. Orito, and M. Takasugi, *Tetrahedron*, **27**, 3387 (1971).

(20) We thank Dr. Murle W. Klohs of Riker Laboratories for samples of veratramine and related compounds.

(21) H. Budzikiewicz, *Tetrahedron*, **20**, 2267 (1964).

most telling evidence supporting the six-membered D-ring structure in olefins **1**, **2**, **3**, and **9** is in the absence in their spectra of an ion corresponding to M − side chain − 42, which is a characteristic[22] frgament found in steroidal hydrocarbons substituted at C-17.

The fragmentation of the cholajervanes reflects the presence of a six-membered D ring, as it is known that alkyl cyclohexanes, unlike alkyl cyclopentanes, retain the cyclic structure in the fragmentation process.[23] The base peaks of **1** and **9** are *m/e* 257 and 259, respectively, both M − 71 ions, while the most intense peaks in the spectrum of **2**, of nearly equal intensity, are *m/e* 257 (M − 71) and 258 (M − 71 + 1). The net loss of side chain in **1** and **9** is consistent with the favored retention of the cyclic structure, the allylic 17,20 bond in **1** being favored for cleavage, and the same bond in **9** being favored in an alkyl cyclohexyl fragmentation. The two intense ions from **2** probably result from (1) an allylic cleavage to give *m/e* 257, and (2) fragmentation with a favorable, familiar hydrogen rearrangement, as depicted, to give the *m/e* 258 ion.



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The spectrum of **3** shows a quite different fragmentation pattern; in the higher mass range the most intense ion is at *m/e* 285 (M − 43); cleavage at 17,20 would be a higher energy process than at the 20,22 allylic bond. However the M − side chain ion *m/e* 257 is present in the spectrum, and could represent an isomerization of **3** to **1** or to **2**, although this rearrangement under chemical rearranging conditions proceeds in the reverse direction.

The presence of a significant *m/e* 149 and virtual absence of a *m/e* 151 ion in each of the spectra of **1**, **2**, **3**, and **9** (all 5β-cholajervanes) is of interest in connection with a recent publication[24] describing the feasibility of distinguishing between C-5 epimeric steroidal hydrocarbons substituted at C-17. 5α compounds showed a dominant *m/e* 149 ion while 5β epimers have two significant peaks, at *m/e* 149 and 151. Since deuterium-labeling studies[24] on the 17-substituted steroid hydrocarbons confirm the importance of rupture of the 13–17 bond in forming a molecular ion and consequent derivation of the *m/e* 151 ion, the absence of the latter ion in the cholajervane fragmentation can be explained on the basis that initial formation of such a molecular ion does not take place, because a 13,17 bond cleavage would mean disruption of the six-membered cyclic structure.

These and earlier studies by the same group of investigators[24] show that the formation of the *m/e* 149 ion, found ubiquitously in steroidal hydrocarbon spectra, is a complex process and results from several different fragmentation mechanisms. We must assume that the ion of the same *m/e* value derived from the cholajervanes also has a complicated genesis.

In Table I are listed lower *m/e* fragments which in reference to the known complexity of the *m/e* 149 ion probably are also of complex origin. They are included in the table mainly because the finding of the same (or differing only in one or two units) *m/e* fragments among the five compounds may be suggestive of related fragmentation processes.

Mechanism of Rearrangements.—The 12β-(equatorial) mesylate **6** reacts at a rate about 1300 times faster than the epimeric mesylate, as established by determination of the half-lives in solvolysis of the two compounds. Since solvolysis reaction rates of simple cyclic epimeric sulfonates (*e.g.*, *cis*- and *trans*-4-*tert*-butylcyclohexyl tosylates) are known to differ[25] only by a factor of a few units, with the axial epimer undergoing the faster reaction, the much faster reaction of the equatorial mesylate **6** must mean that solvolyses of **5** and **6** proceed by quite different mechanisms.

A recent study[11] of the two *C*-nor-*D*-homo steroid yielding reactions,[6,11,13,26] solvolysis of 12β-sulfonates and Bamford–Stevens decomposition[27] of 12-tosylhydrazones, has been published in which an attempt is made to explain the considerable variation in products and their yields in previously published work, on the basis of changes in mechanism caused by variation of solvent type and reaction temperature. Most of the study was carried out on the two hecogenin derivatives, rockogenin (12β) tosylate (**20b**) and hecogenin tosylhydrazone (**21**).

Our work on analogous reactions involving the 12β-mesylate **6** and the tosylhydrazone **8** were each conducted under a single set of reaction conditions, and the results independently would not be expected to shed much light on detailed mechanisms. However, since the conclusions from the paper cited rest on a consideration of products and yields, a comparison of our results with those reported in their study obtained under comparable conditions is in order.

The solvolysis of **5** in collidine under reflux should be comparable to the reaction of **20b** in pyridine under reflux, the main difference being in the temperature at reflux (171° *vs.* 115°). The difference in temperature could explain the lower proportion of the exo ($\Delta^{13(18)}$) olefin found in the reaction of **5**, but the total absence of the $\Delta^{13(17)}$ isomer among the products of their pyridine reaction, in contrast with the substantial yield in the reaction of **5**, is conspicuous. The consistent failure to find the $\Delta^{13(17)}$ isomer among the

(22) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, p 338; H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964, p 94; L. Tökes, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968); G. von Unruh and G. Spiteller, *Tetrahedron*, **26**, 3329 (1970).

(23) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 63.

(24) L. Tökes and B. A. Amoe, *J. Org. Chem.*, **37**, 4421 (1972).

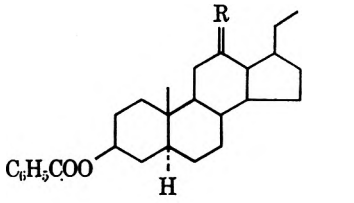
(25) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 96.

(26) H. Mitsuhashi and Y. Shimizu, *Tetrahedron*, **19**, 1027 (1963).

(27) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952); W. Kirmse, B. G. von Bulow, and H. Schepp, *Justus Liebigs Ann. Chem.*, **691**, 41 (1966); R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967); G. Kaufman, F. Cook, H. Schechter, J. Bayliss, and L. Friedman, *ibid.*, **89**, 5736 (1967); K. Geibel, *Chem. Ber.*, **103**, 1637 (1970); A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **94**, 7081 (1972). (The last paper contains an extensive summary of references to the Bamford–Stevens reaction.)

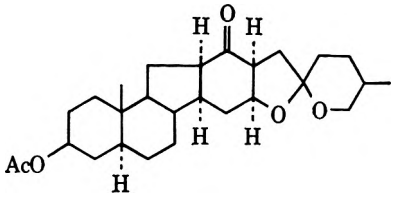
products in all the reported rearrangement reactions of **20a**, **20b**, and **21** was attributed to the possible inductive effect of the 16-oxygen function.[11] This explanation receives some support from the fact that **5** without a substituent at C-16 does yield a $\Delta^{13(17)}$ olefin, and the only other indication that another such isomer is formed is from the indirect evidence derived from the rearrangement reaction involving the 12β-pregnanol tosylate derivative **25** mentioned above in discussing the $\Delta^{13(17)}$ olefin **3**. However, it should be pointed out that both the compounds **5** and **25** are unfettered by a fused E ring.

The most glaring discrepancies are found when the results of our experiments with the 12-substituted cholanes **6** and **8** are compared with those obtained with the two corresponding pregnane derivatives **25** and **26**. The latter results are not listed in Table I,



25 R = H, β-OTs

26 R = NNHTs



27

but are discussed in the final sections of the paper.[11] The cholanol and pregnanol derivatives compared are identical in the B, C, and D rings, with the C-17 hydrocarbon side chain three carbons longer in the former, and a difference[28] in the A/B ring junction. It was reported that the reactions 12β-tosylate **25** in potassium *tert*-butoxide and **25** in pyridine, and the tosylhydrazone **26** decomposition, all failed to produce either the Δ^{11} unrearranged olefin[29] or the exocyclic $\Delta^{13(18)}$-pregnajervene. The absence of the Δ^{11} compound in 12β solvolysis, and of the $\Delta^{13(18)}$ olefin in the decomposition, is consistent with our findings, but is contrary to the results for the $\Delta^{13(18)}$ olefin in our analogous former reaction, and for the Δ^{11} olefin in the latter.

No other studies of rearrangement reactions of 12α-sulfonates have been reported in the literature, although oils of undetermined structure formed as side products in early investigations[31] designed to prepare Δ^{11} compounds were obviously products of rearrangement. The work described here carried out under a single set of experimental conditions also does not warrant more than some tentative speculations on the course of the reaction. Solvolysis of the axial **5** in collidine is slow,[29] even much slower than such a reaction of an uncomplicated cyclic equatorial sulfonate, and probably undergoes preliminary formation of a carbonium ion, or ion pair, involving the sulfonyloxy group. Stabilization of the carbonium ion follows either by direct elimination to give the Δ^{11} cholene, or by rearrangement and subsequent eliminations of the rearranged ion to give the more stable olefins **1** and **3**, rather than the exocyclic **2**.

A clear explanation of why the angular methyl group at C-13 in a conformationally favorable trans-diaxial juxtaposition relative to the 12α-mesyloxy group does not rearrange is lacking, but steric factors appear to be important.[32]

There is ample evidence that reactions of 12α-sulfonates are sensitive to steric factors. In elimination on alumina,[33] the rate of reaction is dependent on whether there is an α substituent at C-17, whether the A/B ring junction is cis or trans fused, and on the bulk of the sulfonate group. A number of other reactions of 12-substituted steroids whose behavior is regarded as "anomalous" are unsatisfactorily explained probably because, among the various factors controlling the reactions, the very important steric factor is so difficult to assess. Some of these are the much discussed erratic reduction of 12 ketones,[34] the esterification of 12α[35] and 12β[36] alcohols, the Grignard reaction on 12 ketones,[37] and the inversion of migration order in tlc of certain 12-hydroxy derivatives.[38] The rearrangement of **5** appears to be another of the

(28) Two other differences are (1) the cholanol sulfonate **6** is a mesylate while the pregnanol sulfonate **25** is a tosylate, and (2) both **6** and the tosylhydrazone **8** are unsubstituted at C-3 while **25** and the tosylhydrazone **26** have 3β-acetoxy substituents. These differences in structure would affect the reactions, but should do so only minimally. The longer side chain of **6** and **8** is still alkyl and its effect should be largely of a steric nature, and, while it has been shown[33] that the conformation of the A/B rings and the size of an 12α-substituted sulfonate group are factors, they should not be decisive factors. Apart from the relative bulk of the mesyloxy and tosyloxy groups there are also electronic differences between the two, but in the instances where direct comparisons can be made between reactions of the tosylates[11] and mesylates[6] of the spirostan series, the results as reported are similar.

(29) In the initial publication on the *C*-nor-*D*-homo rearrangements[6a] the 12α-mesylate **19** was reported to yield after 15 hr at reflux in potassium *tert*-butoxide in *tert*-butyl alcohol largely unchanged starting material. The yield of olefin was about 10%, which was of the Δ^{11} compound; no rearranged product was found. In our earlier work on the preparation of unsaturated steroids, compound **5** was recovered essentially unchanged when refluxed under the same conditions, but in potassium *tert*-butoxide in DMSO at room temperature gave 11-cholene (65%), 12α-cholanol (29%), and no rearranged olefinic material.[30]

(30) F. C. Chang, *Steroids*, **4**, 55 (1964).

(31) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **29**, 654 (1946).

(32) Failure of the methyl group to rearrange to C-12 is especially interesting, as analogous migrations of that group to C-17 are well known (N. L. Wendler in "Molecular Rearrangements," part II, P. de Mayo, Ed., Wiley, New York, N. Y., 1964, p 1020) even though the leaving 17α substituent is pseudoaxial.

(33) G. Just and C. R. Engel, *J. Org. Chem.*, **23**, 12 (1958); C. R. Engel and S. F. Papadopoulos, *ibid.*, **26**, 2868 (1961).

(34) J. W. Huffman, D. M. Alabran, and T. W. Bethea, *J. Org. Chem.*, **29**, 2963 (1964); M. Alauddin and M. Martin-Smith, *ibid.*, **28**, 886 (1963); J. W. Huffman and J. T. Charles, *J. Amer. Chem. Soc.*, **90**, 6486 (1968); W. S. Murphy and D. F. Sullivan, *Tetrahedron Lett.*, 3707 (1971).

(35) R. T. Blickenstaff, K. Atkinson, D. Breaux, E. Foster, Y. Kim, and G. C. Wolf, *J. Org. Chem.*, **36**, 1271 (1971).

(36) M. E. Wall, F. I. Carroll, and G. S. Abernathy, Jr., *ibid.*, **29**, 604 (1964).

(37) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron Lett.*, 4469 (1965).

(38) 12α-Cholanol (**29**) migrates faster on silica gel plates than either its mesylate **5** or acetate **31**, contrary to the usual order (unpublished observations from this laboratory).

reactions which will remain "anomalous" until the steric factors are better known.[39]

In summary, a retrospective review of pertinent known work must lead one to the conclusion that, at the present stage of knowledge, a sufficient understanding of the three reactions which are available for the preparation of *C*-nor-*D*-homo steroids by rearrangement of 12-substituted steroids, to make possible a valid prediction of the products, is still not at hand. While the effect of solvent and reaction temperature is important, it seems clear that the course of the reactions is controlled as much by the structure and geometry of the reacting molecule, and precise knowledge concerning the steric factor is also needed.

The Ketones 16, 17, and 18.—The ketones derived from olefins **1**, **2**, and **3** *via* the respective diols were all crystalline products, and spectral data support the olefin structure assignments.

Ketone 16, having carbonyl groups corresponding to a five-ring ketone and a methyl ketone, by ORD determination shows a weak positive Cotton effect (a + 42), the direction of which agrees with an analysis of ORD aspects of hexahydroindanones.[40] The amplitude is smaller than might be expected, as the atoms C-8 and C-9 and the A ring are all in positive octants according to the octant rule; only the C-19 methyl group is in a negative octant. Perhaps the long β substituent at C-14 in a favorable conformation extends sufficiently into the negative front octant to influence the net Cotton effect.

Ketone 17 has carbonyl absorption characteristic of a cyclohexanone, and in its ORD spectrum exhibits a strong positive Cotton effect (a + 148) which is in disagreement with the value (a − 29) reported[41] for the spirostan ketone **27** which is analogous to **17**. It is not likely that lead tetraacetate oxidation of diol **17** has caused inversion at C-12 or C-17 when periodic acid or sodium periodate oxidation of the corresponding spirostanediol to **27** does not.[41] Inspection of a Dreiding model of **17** offers a possible explanation: with ring D in a distorted chair conformation,[13c,e] the A ring (A/B cis) is very prominently in the upper positive front octant, and the β substituent at C-17 could be partly in the lower positive front octant.

Ketone 18 by ir has carbonyl absorptions corresponding to a methyl ketone and an aliphatic (or C_6 ring) carbonyl group. As expected its ORD spectrum showed very small rotation over the entire uv range.

Experimental Section

General.—Melting points were determined on an electrical micro hot stage and are uncorrected. Combustion analyses were performed by Weiler and Strauss, Oxford, England, and Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained using either a Perkin-Elmer Infracord Model 137, or Model 257 grating spectrophotometer. Optical rotation measurements were obtained with a Carl Zeiss photoelectric precision polarimeter using $CHCl_3$ as solvent. Ultraviolet spectra were measured in ethanol on a Perkin-Elmer Model 202 spectrophotometer. Gas–liquid chromatography was carried out on Hewlett-Packard Models 5750 or 402, or Varian Aerograph Model 700, chromatographs. Optical rotatory dispersion spectra were recorded on a Cary 60 spectropolarimeter at room temperature. Mass spectra were obtained either with a Jeolco Model JMS-01S, or with a Varian Model M66, or MS902, instrument. Either a Varian A-60A or HA-100 spectrometer was used for determination of nmr spectra. Tetramethylsilane was used as internal reference and chemical shifts are given on the τ scale.

Analytical thin layer chromatography and preparative thin layer chromatography (ptlc) were performed on glass plates layered (0.25 mm for tlc, 1.0 mm for ptlc) with silica gel G (Merck, Darmstadt). The plates used for ptlc were in addition impregnated with Ultraphor (Badische Anilin und Soda-Fabrik). Certain analytical tlc was done on layers containing silver nitrate (Stlc) prepared from silica gel in 7.5% silver nitrate–aqueous methanol solution, according to Gupta and Dev.[42] Analytical spots were visualized by spraying with ethanol–sulfuric acid–vanillin.[43] For cases where multiple development of plates was used, the abbreviation A,2× indicates that the plate was developed twice in solvent A (see below). Generally preparative plates required no spraying before being viewed under long wavelength (366 mμ) uv light. However, ptlc plates impregnated with silver nitrate required a preliminary spraying with 2′,7′-dichlorofluorescein[44] (0.1% in methanol) before viewing with uv radiation.

For column chromatography, either Florisil (60–100 mesh, Floridin Co.) or neutral aluminum oxide (activity grade I, Woelm Alumina) was used. Adsorbents treated with $AgNO_3$ (15%) were prepared as for tlc plates but were heated for 3 hr at 200° before use.

Solvents used for chromatographic development and elution are designated and abbreviated as follows: petroleum ether (bp 63–70°) (A), chloroform (B), ethyl acetate (C), ethyl ether (D), acetic acid (E), and acetone (F). A mixture of 50% Skelly B, 49% ethyl acetate, and 1% acetic acid is abbreviated ACE 50,49.

Solvolysis of 12α-Cholanol Mesylate (5).—A solution of **5** (10.0 g) in redistilled collidine (170 ml), after being heated at reflux for 4 hr, was stirred into a slush of ice–5% HCl and extracted with ether. The ethereal layer was washed successively with dilute acid, sodium bicarbonate solution, and water, dried with calcium sulfate, and evaporated to a dark oil. The oil (7.6 g), dissolved in petroleum ether and decolorized by passage over neutral alumina, was crystallized from THF–methanol to yield 11-cholene[45] (**7**) as colorless, elongated plates (1.4 g, 18%): mp 80.0–80.5°; $[\alpha]D$ +36.6°; ir (KBr) 13.84 μ; nmr τ 9.28 (s, 3, C-18 or C-19 Me), 9.12 (s, 3, C-18 or C-19 Me), 4.58 [d of d, 1, $J_{11,12}$ = 10, $J_{9,11(or12)}$ = 2.5 Hz, C-11 (or C-12 H)], 3.87 [d of d, 1, $J_{11,12}$ = 10, $J_{9,12(or11)}$ = 2.5 Hz, C-12 (or C-11 H)].

The mother liquor was chromatographed on a $AgNO_3$–alumina column (900 g) and eluted with petroleum ether (monitored by Stlc). The early fractions produced an oil (1.52 g) which in acetone yielded 0.92 g (12%) of Δ^{12}-cholajervene[2a] (**1**) as colorless plates: mp 55.8–56.4°; $[\alpha]D$ +2.5° (*c* 4.43); ir (KBr) 6.92 and 7.24 μ; nmr (100 MHz) τ 9.12 (s, 3, C-19 Me), 8.44 (s, 3, C-18 Me), 9.07 (d, 3, *J* = 7 Hz, C-21 Me).

Anal. Calcd for $C_{24}H_{40}$ (328.3130): C, 87.73;) H, 12.27. Found: C, 87.79; H, 12.26; M^+, 328.3116.

Continued elution provided another oily substance (0.40 g). Rechromatography of this material afforded $\Delta^{13(17)}$-12α-cholajervene[2b] (**3**) which, although shown to be homogeneous by Stlc and nmr, resisted attempts at crystallization: $[\alpha]D$ −76.2° (*c* 2.99); nmr (100 MHz) τ 8.37 (s, 3, C-18 Me), 9.15 (s, 3, C-19 Me), 7.43[46] (q, 1, 20-H), 9.08 (d, 3, *J* = 7 Hz, C-21 Me). By

(39) An *ex post facto* speculation regarding the failure of the C-18 methyl group to shift, reflecting mainly observations from X-ray studies of the detailed geometry of steroid skeletons [H. J. Geise, C. Altona, and C. Romers, *Tetrahedron*, **23**, 439 (1967); C. Altona, H. J. Geise, and C. Romers, *ibid.*, **24**, 13 (1968)] is the following. The methyl group in a cholane molecule is distorted away sufficiently from coplanarity with the leaving 12α-mesyloxy substituent to render migration of the strained 13,14 bond a more favorable (lower energy) process than the shift of the 18-methyl group. By the same reasoning, one might conclude that, in the instances where the methyl group does undergo facile shift to C-17, the distortion must be in the direction of greater coplanarity of the C-18 methyl and the 17α substituent, as compared with the departure from coplanarity when the 17α group is pseudoaxial.

(40) W. Klyne, *Tetrahedron*, **13**, 29 (1961).

(41) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Aust. J. Chem.*, **18**, 759 (1965).

(42) A. S. Gupta and S. Dev, *J. Chromatogr.*, **12**, 189 (1963).

(43) J. S. Matthews, *Biochim. Biophys. Acta*, **69**, 163 (1963).

(44) C. B. Barrett, M. Dallas, and F. B. Padley, *J. Amer. Chem. Soc.*, **40**, 580 (1963).

(45) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **81**, 2835 (1959).

(46) D. Chapman and P. D. Magnus, "Introduction to Practical High Resolution Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1966, p 89.

double irradiation it was shown that the τ 7.43 and 9.08 signals are coupled.

Anal. Calcd for $C_{24}H_{40}$ (328.313): C, 87.73; H, 12.27. Found: C, 88.20; H, 12.20; M^+, 328.313.

Subsequent fractions from the column yielded 1.05 g of compound 7 (total yield of isolated product, 32%), in addition to several unresolved products (presumably olefins) in minor yield.

Solvolysis of 12β-Cholanol Mesylate[2a,4] (6).—A solution of 6 (5.33 g) was treated with collidine as with 5 for 1 hr, although the reaction was complete before 1 hr, as monitored by tlc. The product processed similarly was a residual oil (4.87 g) which was chromatographed on $AgNO_3$–alumina. The early fractions (1.19 g) dissolved in acetone gave 0.74 g (15%) of crystals found to be identical with 1, according to tlc, glc, melting point, mixture melting point, ir, and nmr comparisons.

Intermediate fractions yielded a colorless oil (0.89 g, 24%) shown to be identical with 3 according to tlc, glc, ir, and nmr comparisons.

Material from later fractions when crystallized from acetone–benzene solution yielded 1.01 g (27%) of $\Delta^{13(18)}$-12α-cholajervene[2b] (2) as dense prisms: mp 36.0–37.2°; $[\alpha]D$ +57.1° (*c* 3.23); ir (CS_2) 11.23 μ (methylenic double bond); nmr τ 9.10 (s, 3, C-19 Me), 9.10 (d, 3, J = 6 Hz, C-21 Me), 5.17, 5.30 (two perturbed 1-H singlets, >C=CH_2).

Anal. Calcd for $C_{24}H_{40}$ (328.313): C, 87.73; H, 12.27. Found: C, 87.80; H, 12.23; M^+, 328.309.

Other minor unresolved products were detected by glc and tlc.

Alkaline Decomposition of 12-Oxocholane *p*-Toluenesulfonylhydrazone[7] (8).—A mixture consisting of the tosylhydrazone 8 (0.20 g) added to a solution of Na metal (0.18 g) in ethylene glycol (8.0 ml) was maintained at a temperature of 150–170° in a nitrogen atmosphere for 1 hr, at which time evolution of gas had ceased. After being cooled the reaction mixture was poured into ice water and extracted with ether. The etheral extract was washed with water, dried with Na_2SO_4, and evaporated to yield a crude product which after passage over a Florisil column was a colorless oil (0.072 g). By tlc and glc analysis the oil was observed to consist of many more components than the products of the 12α- and 12β-mesylate solvolyses, but with olefins 1, 3, and 7 predominating. Isolation of the olefins was not attempted; estimation of the yields was done by glc quantitation and with confirmation of products by Stlc, as described in the next section.

Estimation of Total Yields.—The olefin yield values cited above for the two solvolysis reactions were yields obtained by isolation. The total yields of compounds 1, 2, 3, and 7, respectively, as estimated by glc (or glc and tlc) and summarized previously,[2b] are for solvolysis of 5, 32, 0, 15, 40; for solvolysis of 6, 35, 30, 25, 0; and for decomposition of 8, 26, 0, 8, 24. The results previously reported were based on integration of peak areas with a disk integrator and use of an internal standard (2-cholestene). A subsequent reanalysis of the peak areas with a Dupont 310 curve resolver, corrected for detector response of the individual olefins, essentially confirms the published values.

Olefins 1 and 2 were not resolved by glc on the columns used (QF-1, OV-1, STAP), but were separated on Stlc plates. For the determination of the mixture from 6, in which 1 and 2 are present, further analysis was effected by the method of visual comparison by tlc.[47]

Additional confirmation of the approximate ratios of olefins in the mixtures from the three rearrangement reactions was obtained by conversion to a mixture of diols which are readily resolvable by tlc, and subsequent spot-size estimation (see section below on diols).

Kinetic Measurements.—Half-life determinations of the solvolysis of mesylates 5 and 6 were carried out as follows. Solutions in collidine of 5 (5%) and 6 (8%) were prepared and 0.2-ml aliquots were sealed in 1-ml ampoules and placed in a constant-temperature bath at 100°. Ampoules were removed at intervals, and stored in a Dry Ice–acetone bath until an ir determination was made. Mesylate concentrations were determined directly on the collidine solutions by measurement at 10.5–11.5 μ and comparing absorption at the sharp maximum at 11.1 μ for 5[4] and 11.0 μ for 6 with collidine solutions of known concentrations (base-line method[48]).

The half-life so determined for the reaction of 5 was 12.4 days (17,856 min); for 6, 13.6 min (a factor in excess of 1300). At room temperature the spectrum of an 8% solution of 6 was unchanged over a period of 4 hr.

$\Delta^{12,14,16}$-Cholajervatriene (4). A. From Δ^{12}-Cholajervene (1).—Olefin 1 (0.138 g), xylene (4 ml), and 5% palladium on alumina catalyst[49] were heated in a sealed tube at 100°. Aliquots removed at various intervals examined by glc showed that reaction was slow, and 1 was first converted to 3 before further dehydrogenation occurred. At 48 hr the reaction was still incomplete, but it was stopped by cooling and addition of petroleum ether before filtering from the catalyst. Evaporation of solvent from the filtrate yielded an oil (0.116 g) composed of unchanged 1 (20%), 3 (20%), and 4 (60%), according to estimation by glc. The oil was chromatographed on $AgNO_3$–alumina. Uv-absorbing (267, 279 mμ) fractions (0.084 g) were combined and rechromatographed by ptlc (A,2×) to give 4 as a homogeneous oil: $[\alpha]D$ +39.8° (*c* 3.72); ir (CS_2) 12.02, 12.29, 12.40 μ (aromatic); uv max (C_2H_5OH) 267 mμ (ε 810), 270, 275; nmr (100 MHz) τ 8.97 (s, 3, C-19 Me), 8.87 (d, 3, J = 7 Hz, C-21 Me), 7.84 (s, 3, C-18 Me), 7.08 (m, 1, C-20 proton), 3.20 (q, 2, aromatic).

Anal. Calcd for $C_{24}H_{36}$ (324.2824): C, 88.82; H, 11.18. Found: C, 88.79; H, 10.86; M^+, 324.2817.

Other methods of aromatization of 1 [palladium on charcoal in cymene,[50] *o*-chloranil[51] in DMF or in bis(2-methoxyethyl) ether, bromosuccinimide–collidine[52]] were all tried on 1 and found to be less satisfactory; for 2 and 3 the palladium on charcoal–cymene method gave the best yields (see below).

B. From $\Delta^{13(17)}$-12α-Cholajervene (3).—A solution (0.051 g) of $\Delta^{13(17)}$-cholajervene (3) in cymene (1 ml) was heated (100°) in a sealed tube with 0.118 g of 10% palladium on powdered charcoal for 44 hr. Filtration and evaporation of solvent afforded an oil (0.050 g) which was chromatographed over $AgNO_3$–alumina to obtain a homogeneous oil (0.017 g) shown to be identical with 4 by nmr, glc, tlc, uv, and ir determinations.

C. From $\Delta^{13(18)}$-Cholajervene (2).—Compound 2 by treatment with palladium on charcoal–cymene as in part B was found to be converted first to 3 before aromatization when monitored by glc. Estimated by comparison of peak heights, the ratio of 3 to 4 in the reaction product after 1 hr was 6.4:1, and after 24 hr, 1.4:1. Longer heating did not change the ratio appreciably. The proportion of 1 was uncertain at the early stages of the experiment inasmuch as compounds 1 and 2 are not resolved by glc (see below); although after 24 hr, when the reaction was stopped, the peak for 1 amounted to 15% of the total product, and tlc showed that olefin 2 is not present in the mixture. Confirmation of the identity of 3 and 4 was obtained by glc cochromatography with added samples of authentic 3 and 4, and by tlc comparison.

Isomerization[6a,53] of 1 and 2. A. Formic Acid.—A solution of the exocyclic olefin 2 (0.100 g) in benzene (10 ml) was stirred with 98–100% formic acid (20 ml) at room temperature for 96 hr. Ether extraction followed by neutralization, drying, and removal of the solvent furnished an oil (0.090 g) composed of endocyclic olefins 1 (15%) and 3 (75%), according to glc analysis. The formation of olefins 1 and 3 was confirmed by tlc and subsequent isolation of diols 10 and 12 from the products of isomerization (see below, diol section).

A benzene solution of endocyclic olefin 1 was unchanged when treated similarly with formic acid. However, the reaction mixture afforded numerous olefin products when held at 60° for 113 hr under an atmosphere of nitrogen. Partial (40%) conversion to 3 was detected by chromatography (glc, tlc) and confirmed by isolation of diols from the osmylation reaction.

B. With PtO_2.—Compound 2 (0.010 g) shaken in a Parr apparatus with PtO_2 (0.070 g) in $CHCl_3$ (20 ml) was unchanged after 2 hr. Eight minutes after introduction of hydrogen 3 (30% by glc) was detected. In 2 hr, a mixture of 3 (59%) and 1 (35%) was observed (glc), which remained unaltered during further (24 hr) shaking.

C. With Other Reagents.—Olefins 1 and 2 were unchanged

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(50) W. F. Johns, and I. Laos, *J. Org. Chem.*, **30**, 4220 (1965).

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by treatment with (1) collidine at 100°, (2) collidine–CH_3SO_3H (3:1 mixture), and (3) potassium *tert*-butoxide in DMSO at room temperature, and at 100°.

5β,12α-Cholajervane (9). A. From 1.—A solution of 1 (0.14 g) in methanol (140 ml) was shaken in a Parr apparatus with 5% rhodium on alumina catalyst (10.0 g) and hydrogen (3 atm) for 3 hr. The catalyst was filtered and successively washed with MeOH and $CHCl_3$. The combined filtrates, on removal of solvent, gave an oil (0.138 g) containing 85% (glc) of 9. After chromatography over $AgNO_3$–alumina a fraction (0.116 g) crystallized from a tetrahydrofuran–acetone mixture to give 0.072 g of 9 as well-shaped prisms: mp 38.0–39.5°; $[\alpha]_D$ (cyclohexane) +62.2° (*c* 0.101); nmr (100 MHz) τ 9.11 (s, 3, C-19 Me), 9.17 (d, 3, J = 7 Hz, C-18 or C-21 Me), 9.24 (d, 3, J = 7 Hz, C-18 or C-21 Me), no resonance below 7.00; ir 3.42, 3.50 μ.

Anal. Calcd for $C_{24}H_{42}$ (330.3286): C, 87.19; H, 12.81. Found: C, 87.47; H, 12.49; M^+, 330.3292.

B. From 2.—Olefin 2 (0.137 g) in benzene (1 ml) was introduced into a solution of $CuSO_4$ (0.006 g), 85% hydrazine hydrate (10 ml), and absolute ethanol (40 ml). Hydrogenation was complete after O_2 was bubbled through the refluxing hydrazine–oxygen–copper ion system[14] for 24 hr. The reaction mixture was extracted with ether, and the organic layer was washed successively with dilute acid, base, and water, then dried and freed of solvent. According to glc, the product contained 9 as the major (75%) component. Column chromatography over $AgNO_3$–alumina yielded a fraction (0.084 g) which crystallized from a tetrahydrofuran–acetone mixture to give 0.038 g of good crystalline product, which was identical with the 9 from part A, according to melting point, mixture melting point, $[\alpha]_D$, glc, tlc, nmr, ir, and mass spectral comparisons.

Catalytic hydrogenation of 2 with tris(triphenylphosphine)-rhodium chloride[54] with PtO_2 in acetic acid, with palladium on charcoal, with rhodium on charcoal, and with Raney nickel were all attempted and found to be less satisfactory than the diimide reaction. The reactions either yielded very complex mixtures which did include 9 (by glc) or, as in PtO_2 in acetic acid, resulted largely in isomerization but little hydrogenation.

C. From 3.—Olefin 3 (0.137 g) dissolved in methanol (140 ml) was shaken in a Parr apparatus with 5% rhodium on alumina catalyst (9.00 g) and hydrogen (3 atm) for 24 hr. The catalyst was removed by filtration, and concentration of the filtrate gave 0.130 g of oil, which according to glc contained 70% of 9. After Sptlc, the oil crystallized as dense prisms (0.010 g) from a mixture of tetrahydrofuran–acetone. The crystalline material was found to be identical with 9 (melting point, mixture melting point, glc, tlc, nmr, $[\alpha]_D$, and mass spectrum).

Diols of Olefins 1, 2, and 3. A. 5β-Cholajervane-12α,13α-diol (10).[2,3]—To olefin 1 (0.100 g) dissolved in anhydrous ether (10 ml)–pyridine (0.1 ml was added at room temperature OsO_4 (0.100 g) and the mixture was allowed to stand for 4 days. After H_2S gas was bubbled (15 min) into the reaction mixture, suspended in CH_2Cl_2, the solution was filtered through Celite, washed with dilute HCl and water, and dried, and solvent removed. The resulting oil (0.094 g) contained a single diol, which in acetone afforded colorless needles of the 12α,13α-diol 10: mp 159.2–160.1°; $[\alpha]_D$ +36° (*c* 4.3); ir (KBr) 2.95, 8.47, 8.98, 9.80, 10.14, 10.14, 10.53, 10.78 μ; nmr (100 MHz) τ 9.10 (s, 3, C-19 Me), 8.80 (s, 3, C-18 Me), 7.78, 7.43 (s, 2, 2-OH), 9.02 (d, 3, J = 6.5 Hz, C-21 Me).

Anal. Calcd for $C_{24}H_{42}O_2$ (362.58): C, 79.48; H, 11.68. Found: C, 79.45; H, 11.78; M^+, 362.

B. 5β,12α-Cholajervane-13α,18-diol[2b] (11) was obtained by dihydroxylation of olefin 2 as in part A as elongated prisms when crystallized from acetone: mp 121° dec; $[\alpha]_D$ +36.8° (*c* 3.96); ir (KBr) 2.81, 2.92, 9.32, 9.47, 9.72, 9.97, 10.58 μ; nmr (CCl_4) τ 9.09 (s, 3, C-19 Me), 7.43 (s, 2, –OH), 6.46 (q, 2, J = 11 Hz, $-CH_2OH$).

Anal. Calcd for $C_{24}H_{42}O_2$ (362.58): C, 79.50; H, 11.68. Found: C, 79.31; H, 11.66; M − 18, 344.

C. 5β,12α-Cholajervane-13α,17α-diol[2b] (12) was obtained by dihydroxylation of olefin 3 as in part A as prisms from a petroleum ether–acetone mixture: mp 166.3–166.9°; $[\alpha]_D$ −3.6° (*c* 4.5); ir (KBr) 2.82, 7.23, 8.47, 9.12, 9.63, 10.20, 10.38, 10.68 μ; nmr τ 9.05 (s, 3, C-19 Me), 8.93 (d, 3, J = 6 Hz, C-21 Me), 8.78 (s, 3, C-18 Me), 7.50, 7.63 (s, 2, 2-OH).

Anal. Calcd for $C_{24}H_{42}O_2$ (362.58): C, 79.50; H, 11.68. Found: C, 79.15; H, 11.83; M^+, 362.

D. 5β-Cholane-11α,12α-diol[3] (13), isolated after osmylation of Δ^{11}-cholene (7) as in part A, was crystallized from acetone–methanol in the form of prisms: mp 118.0–119.3°; $[\alpha]_D$ +3.6° (*c* 5.00); ir (KBr) 2.92, 7.24, 9.11, 9.57, 9.79, 9.93, 10.41 μ; nmr τ 9.30, 8.93 (s, 6, 2 Me), 7.82 (s, 2, 2-OH), 6.12 (m, 2, C-11β H, C-12β H).

Anal. Calcd for $C_{24}H_{42}O_2$ (362.58): C, 79.50; H, 11.68. Found: C, 79.43; H, 11.63.

Osmylation of Olefin Mixtures.—Each of the olefin mixtures obtained in the rearrangement reactions described above was dihydroxylated with OsO_4 and processed as for olefin 1. The resulting diols were easily identified by tlc, and isolated by ptlc (developed 4×, $CHCl_3$).

From the olefin mixture of 5, as expected, diols were isolated which were found to be identical with diols 10, 12, and 13, obtained from olefins 1, 3 and 7, respectively (mixture melting point, tlc, ir).

A number of other diols were present as minor components in the mixture. Among these, two were isolated and obtained in crystalline form.

Diol 14 was obtained as fine needles from petroleum ether: mp 114.3–116.4°; $[\alpha]_D$ +5.9° (*c* 5.1); ir (KBr) 2.81, 2.86, 7.26, 8.78, 8.97, 9.61, 10.28, 10.98 μ; nmr (100 MHz) τ 9.08 (s, *ca.* 5, C-19 Me plus contribution from C-21 Me), 9.05 (d, *ca.* 3, C-21 Me), 9.02 (d, *ca.* 3, $CHCH_3$).

Anal. Calcd for $C_{24}H_{42}O_2$ (362,58): C, 79.50; H, 11.68. Found: C, 78.90; H, 11.68.

Diol 15 was obtained as prisms from petroleum ether: mp 113.5–114.0°; $[\alpha]_D$ −4.9° (*c* 4.3); ir (KBr) 2.94, 9.33, 9.88, 10.02, 10.34, 11.44 μ; nmr (100 MHz) τ 9.11 (s, 3, C-19 Me), 9.02 (d, *ca.* 3, C-12 Me), 8.93 (d, *ca.* 3, $CHCH_3$), 7.84, 7.47 (s, 2, 2-OH).

Anal. Calcd for $C_{24}H_{42}O_2$ (362.58): C, 79.50; H, 11.68. Found: C, 79.35; H, 11.96.

The olefin mixture from the reaction of mesylate 6 yielded three diols which were identical with diols 10, 11, and 12 prepared from olefins 1, 2, and 3, respectively (mixture melting point, tlc, and ir).

Other minor unidentified products, probably isomeric diols, were observed by tlc, but diols 13, 14, and 15 were absent.

The olefin mixture from tosylhydrazone 8 yielded a diol mixture, from which were isolated by ptlc the same five diols (mixture melting point, tlc, ir) as were obtained from 5, namely 10, 12, 13, 14, and 15, the first three corresponding to olefins 1, 3, and 7 respectively.

A number of other minor products were present but unidentified.

The olefin mixture from the isomerization reactions reported above were also dihydroxylated. Diols were isolated which confirmed the presence of olefins detected by glc.

Oxidation of Diols to Ketones. 12,13-Seco-5β-cholajervane-12,13-dione[2a] (16).—Diol 10 (0.10 g) dissolved in a benzene (10 ml)–glacial acetic acid (10 ml) mixture was treated with $Pb(OAc)_4$ (0.20 g) for 12 hr. Ethylene glycol and water were added to the reaction solution, which was kept for 1 hr at room temperature in the dark. After extraction with ether, washing, desiccation, and removal of solvent, an oil was obtained which in petroleum ether crystallized as plates: mp 53.9–54.8°; $[\alpha]_D$ +91.8° (*c* 4.18); ORD (*c* 0.091, cyclohexane) $[\Phi]_{318}$ +2320°, $[\Phi]_{308}$ +2180°, $[\Phi]_{272}$ −1920°; ir (CCl_4) 5.72 (C_5-ring C=O), 5.83 (aliphatic C=O), 6.88, 7.08 ($-CH_2CO-$), 7.23, 7.39 μ (CH_3CO-); nmr τ 9.33 (s, 3, C-19 Me), 7.83 (s, 3, CH_3CO-).

Anal. Calcd for $C_{24}H_{40}O_2$ (360.56): C, 79.94; H, 11.18. Found: C, 79.60; H, 10.70; M^+, 360.

18-Nor-5β,12α-cholajervan-13-one[2b] (17).—By similar lead tetraacetate oxidation of 11 and subsequent processing, an oil resulted which crystallized from petroleum ether as plates: mp 37.3–38.3°; $[\alpha]_D$ +13.4° (*c* 3.43); ORD (*c* 0.11, cyclohexane) $[\Phi]_{326}$ +6450°, $[\Phi]_{316}$ +3720°, $[\Phi]_{279}$ −8340°; ir (CS_2) 5.83 μ (C_6-ring C=O); nmr τ 9.11 (s, *ca.* 8, C-19 Me and contributions from C-21 and C-24 methyls).

Anal. Calcd for $C_{23}H_{38}O$ (330.53): C, 83.57; H, 11.59. Found: C, 83.83; H, 11.62; M^+, 330.

13,17-Seco-5β,12α-cholajervane-13,17-dione[2b] (18).—Diol 12 similarly yielded an oil which in petroleum ether crystallized

(54) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).

as plates: mp 68.0–68.6°; $[\alpha]_D$ −49.2° (c 3.66); ir ($CHCl_3$ 5.84 (C_6 ring or aliphatic C=O), 6.89 (−CH_2CO−), 7.25, 7.38 μ (CH_3CO−); nmr τ 7.83 (s, 3, CH_3CO−), 9.07 (s, 3, C-19 Me), 6.90, 7.60 (m, 1, C-20 H and C-12 H).

Anal. Calcd for $C_{24}H_{40}O_2$ (360.56): C, 79.94; H, 11.18. Found: C, 79.88; H, 10.98; M^+, 360.

Registry No.—**1**, 19534-78-2; **2**, 19594-93-5; **3**, 19594-94-6; **4**, 19654-71-8; **5**, 1251-13-4; **6**, 40429-72-9; **7**, 40429-73-0; **8**, 40429-74-1; **9**, 40429-75-2; **10**, 40429-76-3; **11**, 40429-77-4; **12**, 40429-78-5; **13**, 40429-79-6; **16**, 19654-72-9; **17**, 19594-96-8; **18**, 19594-98-0.

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Stereospecific Bromination of Methyl 3α,7α-Diacetoxy-12-oxocholanate, Catalyzed by Boron Trifluoride

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Methyl 3α,7α-diacetoxy-12-oxocholanate (1) failed to react with bromine in the presence of either hydrobromic acid or sodium acetate, but the monobromination of 1 catalyzed by BF_3 proved to be stereospecific, affording a high yield of the desired 11α-bromo ketone 2. However, the epimerization of 11β-bromo ketone 7, which was prepared by an alternative route, could only be achieved by HBr and not by BF_3. IBr, in the presence of BF_3 or HBr, was found to be very reluctant as a brominating agent for 1. Interpretation of the findings in terms of steric and stereoelectronic effects is offered. The pertinent spectroscopic data, including circular dichroism of the hitherto unknown two epimeric 11-bromo ketones, are given.

Bromination of keto steroids has been widely investigated. However, relatively few studies have been reported on 12-keto analogs.[1-3]

As part of a study we had interest in a stereoselective high-yield bromination of methyl 3α,7α-diacetoxy-12-ketocholanate (1).

Exposure of 1 to the action of bromine at 70°[1] in the presence of hydrobromic acid as a catalyst produced a complex mixture, with a low yield of bromo ketones 2 or 7. Elimination of the catalyst[2] from the bromination reaction mixture (room temperature), or the addition of sodium acetate, did not induce much improvement in the reaction. None of the methods mentioned appears to be of any practical value, as evidenced by the nmr determinations of the reaction products.

A detailed study was undertaken to clarify the nature of the reaction and the factors determining the reactivity of the α hydrogens in 1.

11-Bromo ketone 7 was prepared by an alternative method[2,4] (Scheme I).

The obtained 11β-bromo ketone 7 (yield 13%) was subjected to the action of hydrobromic acid in acetic acid solution.[3] The reaction was followed by tlc and nmr at various intervals. An almost complete conversion to the 11α-bromo epimer 2 was achieved after 48 hr.

To rationalize the above findings, namely the slow bromination of 1 and the facile epimerization of 7, very low rate enolization in the parent compound 1 and enhanced enolization in its 11β-bromo derivative 7 are suggested.

To improve the reaction HBr was substituted by BF_3, a strong Lewis acid, known to be very effective as a catalyst in bromination reactions.[5]

Using bromine, in acetic acid, as the brominating agent and BF_3 as the catalyst, the desired 11α-bromo ketone 2 was obtained in a high yield of 95–97%. Only minor amounts of the 11β-bromo epimer 7 could be detected.

IBr, an effective reagent in the bromination of steroid aldehydes,[6] proved completely inactive in the presence of BF_3 or HBr. The combination, IBr and BF_3, effected a conversion of 1 to the corresponding acid (see Experimental Section).

Regarding epimerization of 11β-bromo ketone 7, BF_3, in contrast to HBr, proved ineffective, even after long periods of time.

It appears that the action of BF_3 and HBr as catalysts is of an entirely different nature in effecting bromination and epimerization of 1 and 7, respectively.

The configurations of the hitherto unknown epimers 2 and 7 were assigned by spectroscopic data. The nmr, ir, and uv data, given in the Experimental Section, are in full agreement with those reported on the 7-deoxy analogs. The circular dichroism curves of the two epimeric 11-bromo ketones and the mass spectra are given in Figure 1 and Table I, respectively.

Discussion

The preferential loss of an axial proton in the enolization of conformationally rigid cyclohexanones and the predominance of axial α-bromo ketone in kinetically

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(2) T. F. Gallagher and W. P. Long, *J. Biol. Chem.*, **163**, 495 (1946).
(3) E. J. Corey, *J. Amer. Chem. Soc.*, **76**, 177 (1954).
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(5) K. Takeda, T. Komeno, and K. Igarashi, *Chem. Pharm. Bull.*, **4**, 343 (1956).
(6) Y. Yanuka, R. Katz, and S. Sarel, *Chem. Commun.*, 849 (1968).

SCHEME I

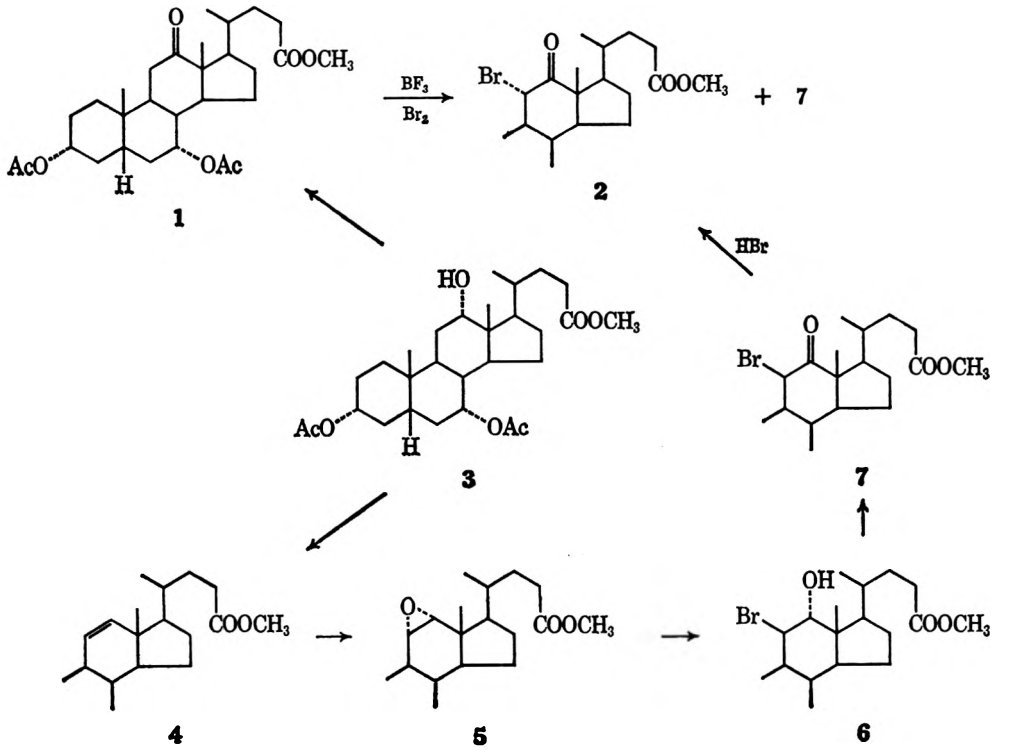


TABLE I

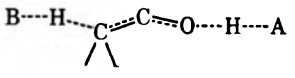
MASS SPECTRA OF COMPOUNDS 1, 2, 6, AND 7

Compd	m/e values and relative abundances (%) of characteristic ion fragments		
	M+	Base peak	
Methyl 3α,7α-Diacetoxy-12-oxocholanate (1)	504 (27)	444	384, 311, 289, 269, 251, 243, 229, 154 (32) (21) (18) (25) (23) (32) (93) (79)
Methyl 3α,7α-Diacetoxy-11α-bromo-12-oxocholanate (2)	582, 584 (0.17) (0.10)	502	550, 442, 383, 351, 275, 231 (2) (17) (90) (20) (19) (37)
Methyl 3α,7α-Diacetoxy-11β-bromo-12α-hydroxy-cholanate (6)	584, 586 (0) (0)	251	487, 444, 427, 371, 367, 351, 311, 269 (8.8) (50) (42) (64) (78) (42) (57) (50)
Methyl 3α,7α-Diacetoxy-11β-bromo-12-oxocholanate (7)	582, 584 (0) (0)	93	502, 489, 488, 429, 369, 368, (0.17) (0.34) (0.7) (28) (42) (28) 133, 131, 121, 109, 107, 95 (32) (39) (78) (51) (78) (82)

controlled bromination were rationalized by Corey[3] in terms of stereoelectronic effects.

However, this theory has been modified[7] as a result of recent studies on the bromination of steroid ketones to account also for the opposing steric hindrance factor.

The lack of bromination of 1 in contrast to the 7-deoxy analog[1,2] clearly demonstrates the great importance of even a remote bulky substituent in determining enolization rates. Thus our findings are in agreement with the demands of the "push–pull" process suggested for the reacting complex.



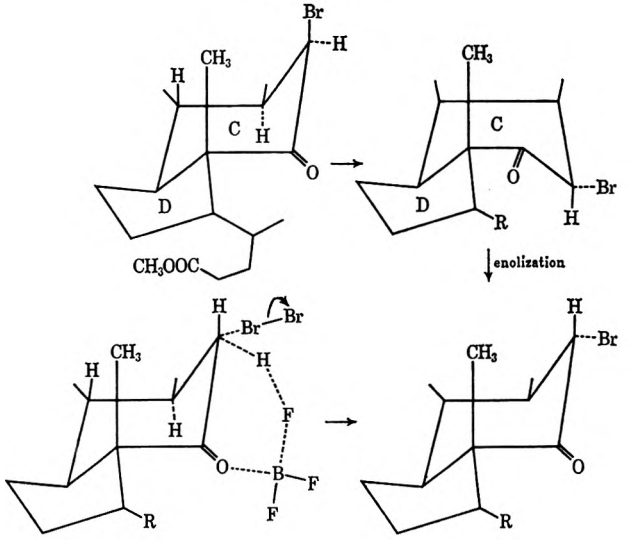
The flexibility of ring C in compound 1 is probably restrained by the bulky 7-OAc, causing the shielding effect at the 11-axial hydrogen to be more pronounced than in the 7-deoxy analog. The rigidity of ring C also prevents the equatorial hydrogen from acquiring the pseudoaxial orientation suitable for enolization. The facile epimerization of the 11β-bromo ketone 7 in the presence of HBr may be accounted for by the enhanced acidity of the equatorial hydrogen in the β-bromo compound 7. Such pronounced stereoelectronic effects imply high activation energy for the bending of ring C. The steric acceleration due to the axial bromine in 7 compensates for the energy necessary for the abstraction of what appears to be equatorial hydrogen, but in fact is pseudoaxial hydrogen in the flexible or boat conformation of ring C (Scheme II).

The fact that no epimerization could be effected by BF_3 (in contrast to HBr) under the reaction conditions, and that high stereospecificity was observed in the bromination of 1, suggest that some other factors are operative in this case.

It seems that in 1, where the steric requirements are strict, BF_3 with its small volume and polar bonds adjusts itself to the substrate in proper steric relationship. Both reacting centers are connected by the catalyst molecule (Scheme II). Thus BF_3 functions simultaneously as an acid and as a base. As a result, the suitably oriented equatorial hydrogen is abstracted and the C-11 attacked by bromine synchronously, this accounting for the high stereospecificity observed.

(7) J. Valls and E. Toromanoff, *Bull. Soc. Chim. Fr.*, 752 (1961).

SCHEME II



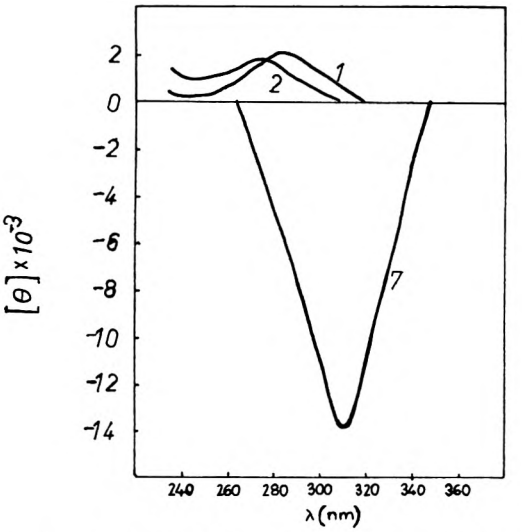


Figure 1.—Circular dichroism of compounds 1, 2, and 7.

The high activation energy required for abstraction of the axial hydrogen is the main reason for the low yield of the 11β-bromo epimer 7. At higher temperatures the percentage of 7 rises.

The behavior of IBr as a brominating agent is under further investigation in keto steroid systems.

The ir values of the 11-bromo epimers 2 and 7 (see Experimental Section) are consistent with those reported previously for the 7-deoxy analogs.[8,9] In addition, the expected bathochromic shift[10] in the uv spectrum of the 11β epimer 7 was observed.

The C-18 and C-19 methyl protons resonated at lower field in the 11β-bromo epimer 7. This is attributed to the anisotropic effect[11] of the axial bromine of 7.

In Figure 1 the curves for the two bromo ketones 2 and 7 are compared with that of the parent 12 ketone 1. The axial nature of the bromine atom in 7 is clearly evident from its strong negative Cotton effect, indicating a very high degree of asymmetry in this epimer.

The similarity of the circular dichroism absorption (positive sign) of the epimeric ketone 2 and the parent compound is characteristic of the equatorial bromine substituent. These findings are consistent with the octant rule.

The following main differences in the mass spectra of 11α-bromo (2) and 11β-bromo (7) epimers were observed. In the 11α compound spectrum the molecular ion was represented (0.17), while the M^+ of the 11β-bromo derivative did not appear. The base peak of the α isomer corresponded to the loss of a hydrogen bromide molecule: 502, M − HBr; *m/e* 442 resulted from the loss of HBr + AcOH. In the β compound the loss of either the CH_2Br or CH_3Br fragment was characteristic: 489, M − CH_2Br; 429, M − (CH_2Br + AcOH); 369, M − (CH_2Br + 2AcOH); 488, M − CH_3Br; and 368, M − (CH_3Br + 2AcOH). $CH_2{=}Br^+$ represented the base peak (*m/e* 93) and *m/e* 95 corresponded to $CH_2{=}^{81}Br$ (Table I).

(8) C. N. R. Rao, "Chemical Application of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 388.

(9) D. H. R. Barton, J. E. Page, and C. W. Shoppee, *J. Chem. Soc.*, 331 (1956).

(10) R. C. Cookson, *J. Chem. Soc.*, 282 (1954); R. C. Cookson and S. H. D. Dandegaonker, *ibid.*, 352 (1955).

(11) A. Kasal and O. Linet, *Collect. Czech. Chem. Commun.*, **34**, 3479 (1969).

Experimental Section

Ultraviolet spectra were determined with a Unicam ultraviolet spectrophotometer (Model Sp 800A). Infrared spectra were measured in potassium bromide disks using a Perkin-Elmer spectrophotometer (Model 337). Nmr spectra were recorded on a Jeol C-60-H high-resolution nmr spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on a CH5 Varian MAT mass spectrometer. CD spectra were obtained using a Cary 60 recording spectropolarimeter. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

Methyl 3α,7α-Diacetoxy-11α-bromo-12-oxocholanate (2).—To a solution of 1 (5 g) in acetic acid (50 ml) in a glass-stoppered flask, bromine (0.8 ml) and boron trifluoride etherate (5 drops) were added. After standing for 5 days at room temperature the reaction mixture was diluted with water (200 ml) and sufficient sodium bisulfite was added. The precipitate was filtered, washed with water, and dissolved in chloroform. To the concentrated solution excess diazomethane in ether was added and the reaction mixture was stirred for 2 hr, during which period solid material began to precipitate out. After an additional 1 hr the solid was filtered. Recrystallization from isopropyl alcohol gave pure 11α-bromo ketone 2 (4.7 g): mp 223–224°; $[\alpha]_D$ ($CHCl_3$) +40.7°; ir 1729 (C=O), 1250 and 1237 (CO), 753 cm^{-1} (CBr); uv (ethanol) 274 nm (ε 100); nmr (CCl_4) δ 1.02 (s, 3, 18-CH_3), 1.20 (s, 3, 19-CH_3), 1.91 (s, -$OCOCH_3$), 2.00 (s, -$OCOCH_3$), 3.57 (s, 3, 24-OCH_3), 4.80 (m, 1, HCBr); nmr ($CDCl_3$) δ 1.50 (s, 3, 18-CH_3), 1.21 (s, 3, 19-CH_3), 2.00 (s, -$OCOCH_3$), 3.63 (s, 3, 24-OCH_3), 4.97 (m, 1, HCBr).

Anal. Calcd: C, 59.1; H, 7.3; Br, 13.6. Found: C, 58.9; H, 7.3; Br, 13.4.

An additional 0.5 g of pure 11α-bromo ketone was obtained from the mother liquors. The residue (0.6 g) consisted of 2 and minor amounts of the 11β-bromo epimer 7, as was evident from nmr and tlc.

Methyl 3α,7α-Diacetoxy-11α,12α-epoxycholanate (5).—A mixture consisting of 3 (1.1 g), pyridine (25 ml), and phosphoroxy chloride (10 ml) in a glass-stoppered flask was stirred at 37° for 24 hr.[4] The reaction mixture was added slowly to a large volume of ice water; the precipitate so obtained was filtered and extracted with chloroform. The chloroform layer was washed with a saturated solution of sodium bicarbonate and water, dried over sodium sulfate, and filtered. Excess perbenzoic acid in chloroform was added, and the mixture was kept overnight at room temperature. The chloroformic solution was washed with aqueous sodium carbonate and water, dried, and evaporated at reduced pressure. The residue was recrystallized from methanol to give pure 5 (0.2 g): mp 154°; nmr ($CDCl_3$) δ 0.82 (s, 3, 18-CH_3), 1.02 (s, 3, 19-CH_3), 2.02 (s, -$OCOCH_3$), 3.06 (m, 2, 11β and 12β H), 3.65 (s, 3, 24 OCH_3).

Anal. Calcd: C, 69.0; H, 8.7. Found: C, 68.8; H, 8.6.

Methyl 3α,7α-Diacetoxy-11β-bromo-12-oxocholanate (7).—11α,12α-Epoxide 5 (400 mg) in acetone (40 ml) was subjected to the action of 48% HBr (1 ml). The crude bromohydrin 6 (400 mg) was recrystallized from methanol to give a crystalline material: mp 176°; nmr ($CDCl_3$) δ 1.00 (s, 3, 18-CH_3), 1.18 (s, 3, 19-CH_3), 1.88 and 1.91 (-$OCOCH_3$), 3.50 (s, 3, 24-OCH_3), 4.21 (m, 1, HCBr).

A 200-mg portion of the unpurified bromohydrin was oxidized (CrO_3).[2] The crude product was recrystallized from methanol to give 160 mg of 11β-bromo ketone 7: mp 190–191°; $[\alpha]_D$ ($CHCl_3$) +15.9°; ir 1738 (C=O), 1710 (C=O), 1245 (OC), 660 cm^{-1} (axial CBr); uv (ethanol) 310 nm (ε 110); nmr ($CDCl_3$) δ 1.37 (s, 18- and 19-CH_3), 2.02 (s, 3 and 7 -$OCOCH_3$), 3.66 (s, 3, 24-OCH_3), 4.42 (m, 1, HCBr); nmr (CCl_4) δ 1.37 (s, 18- and 19-CH_3), 1.90 and 1.98 ($OCOCH_3$), 3.60 (s, 3, 24-OCH_3), 4.42 (m, 1, HCBr).

Anal. Calcd: C, 59.1; H, 7.3; Br, 13.6. Found: C, 59.4; H, 7.3; Br, 13.3.

Epimerization of 11β-Bromo Ketone 7 to 11α-Bromo Ketone 2 with HBr.—To a solution of 7 (250 mg) in acetic acid (10 ml) 10% HBr in acetic acid (3 ml) was added. The reaction mixture was kept at room temperature for 2 days. Water was added and the precipitate was extracted with chloroform. The solvent was removed and diazomethane in ether was added to the residue. Recrystallization of the solid material from isopropyl alcohol afforded pure crystals identical in all respects with 11α-bromo ketone 2. The 11β-bromo epimer was detected in the mother liquor.

An Unsuccessful Attempt to Epimerize 11β-Bromo Ketone 7 with BF_3.—To a solution of 7 (200 mg) in acetic acid (10 ml) 10 drops of BF_3 etherate were added and the solution was kept at room temperature for 5 days. The isolated material was identical with 7; the 11α-bromo epimer was by no means present.

The Use of IBr as a Brominating Agent. A. With HBr as Catalyst.—To a solution of 1 (1 g) in acetic acid (30 ml), IBr (0.22 ml of bromine and 0.92 g of iodine) in acetic acid and 5 drops of 10% HBr in acetic acid were added. The reaction mixture was kept at room temperature for 7 days. The material which was isolated after the usual work-up proved to be identical with 1, mp 181°; the nmr spectrum was consistent with that previously reported;[12] for CD in ethanol, see Figure 1; for mass spectrum, see Table I.

B. With BF_3 as Catalyst.—The procedure was the same as above except that BF_3 etherate (5 drops) was used instead of HBr. The reaction mixture was kept at room temperature for 2 days and for 3 additional days at 35–40°. The only compound isolated was 3α,7α-diacetoxycholanic acid, nmr ($CDCl_3$) δ 8.75 (1, -COOH). The peak disappeared on addition of D_2O. Reaction with diazomethane gave 1. Note: the 12-keto group in 1, 2, and 7 was found to be unreactive to diazomethane.

Registry No.—1, 28535-81-1; 2, 40488-36-6; 3, 3749-87-9; 5, 40488-38-8; 6, 40488-39-9; 7, 40488-40-2; borontrifluoride etherate, 109-63-7.

(12) Jeol, "High Resolution NMR Spectra," Sadtler Research Laboratories, Inc., 1967.

Conformations of Substituted Arylureas in Solution

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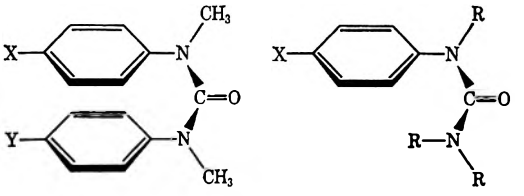
The conformation of *N,N'*-diarylureas in solution is investigated to obtain information about "stacking" interactions between aromatic rings. The only isomer which appears to exist has both aromatic rings in an anti relationship to the oxygen of the urea. Analysis of nmr and uv spectra suggests that there is a charge transfer interaction between the two rings, especially when they are substituted with electron-withdrawing and electron-donating groups.

During the past several years, a number of investigations[4] have suggested that, in aqueous solutions, parallel stacking of purine and pyrimidine bases is a major stabilizing force in oligo- and polynucleotides and in the binding of smaller aromatic compounds to nucleic acids. However, little is known about the specific factors which are responsible for this stacking. Theoretical studies have stressed the possible importance of dipole–dipole, dipole-induced dipole, London dispersion, and monopole–monopole interactions.

The crystal structure of *N,N'*-diethyl-*N,N'*-diphenylurea[5] has been shown to contain two phenyl rings aligned parallel to each other with their faces partially overlapping as shown in Figure 1. The preference for the conformation with the two bulky phenyl groups anti to the oxygen but in a "stacked" position near one another suggests that the same forces may be at work here.

In order to determine the conformation of diphenylureas in solution and to study the nature of the forces leading to the stacking of aromatic rings, we have studied the nuclear magnetic resonance and ultraviolet spectra of several substituted diphenylureas along with appropriate model compounds.

In order to establish the relative positions of the two phenyl rings, the proton magnetic resonance spectra of the *N,N'*-diaryl-*N,N'*-dimethylureas (I) were compared to those of the corresponding *N*-aryl-*N,N',N'*-trialkylureas (II). The results are shown in Table I.



Ia, X = Y = H
b, X = Y = = OCH_3
c, X = Y = NO_2
d, X = NO_2; Y = OCH_3

IIa, X = H; R = CH_3
b, X = OCH_3; R = CH_2CH_3
c, X = NO_2; R = CH_2CH_3

As may be seen, the aromatic protons of the diphenyl- (Ia) and dianisylureas (Ib) are uniformly shifted upfield in the presence of an aryl ring on the opposing nitrogen. This result suggests that the two rings are located near each other and are oriented so that the protons of each lie above the aromatic ring of the other so that a ring current induced upfield shift results.

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(2) Postdoctoral Fellow at the Polytechnic Institute of Brooklyn, 1970–1971.

(3) Postdoctoral Fellow at the University of California, San Diego, 1972–present.

(4) C. E. Bugg, J. M. Thomas, M. Sundaralingam, and S. T. Rao, *Biopolymers*, **10**, 175 (1971), and references cited therein.

(5) P. Ganis, G. Avitabile, E. Benedetti, C. Pedone, and M. Goodman, *Proc. Nat. Acad. Sci.*, **67**, 426 (1970).

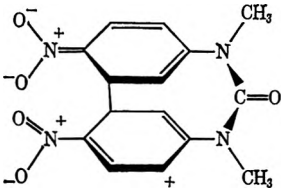
TABLE I

CHEMICAL SHIFTS[a] OF AROMATIC PROTONS IN *N*-ARYL-*N'*-METHYLUREAS AND *N,N'*-DIARYLUREAS

	N-Aryl-*N,N',N'*-trialkylurea (II)		*N,N'*-Diaryl-*N,N'*-dimethylurea (I)	
Substituent	Proton ortho to substituent	Proton meta to substituent	Proton ortho to substituent	Proton meta to substituent
H	7.09	7.32	6.79	7.02
			Δδ −0.30	Δδ −0.30
NO_2	8.11	6.93	8.02	7.07
			Δδ −0.09	Δδ +0.14
OCH_3	6.82	6.95	6.56	6.65
			Δδ −0.26	Δδ −0.30

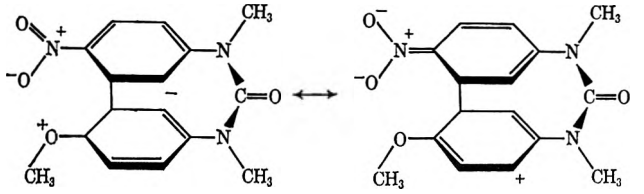
[a] In parts per million.

In contrast, the dinitrophenylurea Ic shows a smaller upfield shift for the proton ortho to the nitro group and a downfield shift for the meta protons. This result may be explained by interring electron withdrawal, which can be represented by resonance structures of the form



The importance of resonance of this type for the dianisylurea Ib is diminished by the fact that the two rings are already electron rich because of the acetamido-like substitution.

The nmr spectrum of the mixed urea clearly indicates a charge transfer effect in the interaction of the two aromatic rings. As may be seen in Table II, the protons of the nitrophenyl ring are shifted downfield and those of the anisyl ring are shifted upfield. This may be represented as resonance structures.



The lack of substantial solvent effect upon the chemical shifts is indicative of the relatively small contributions of the charge transfer to the ground state. The crucial mixed urea, Id, was studied over the concentrations 4.5–0.09%, a factor of 50, and showed no significant variation in any chemical shift. This experiment effectively rules out the possibility that the chemical shift effects result from aggregates such as dimers or trimers.

In order to establish whether the chemical shifts reported in Tables I and II represent the spectra of single conformers or the time-averaged spectrum of several conformers, the temperature dependence of the spectra were studied. Over the temperature range −30 to 55°, neither a change in coupling constants nor chemical shifts were observed in the spectra of Ia, Ib, Ic, or Id. These results indicate that either there is very strong preponderance of the syn isomer or that the equilibrium is temperature independent, which we consider to be very unlikely since the anti conformer would be very much less restricted than the syn conformer. Furthermore, at the lower temperatures, the spectra show no indications of splitting into bands for the two isomers, *i.e.*, there is no broadening of the signals.

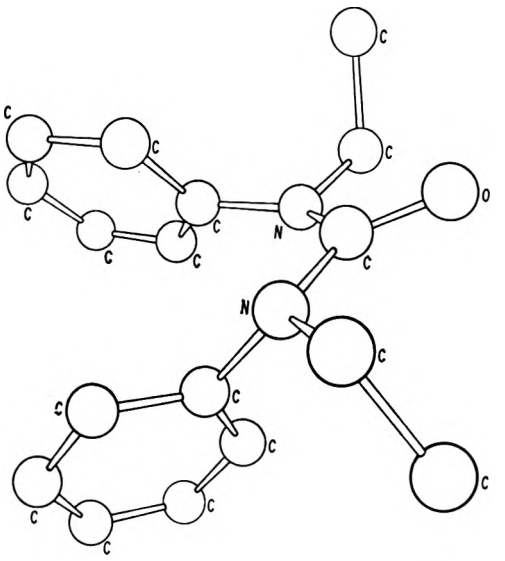


Figure 1.—Conformation of *N,N'*-diphenyl-*N,N'*-diethylurea emphasizing the relation of the two aromatic rings in space.

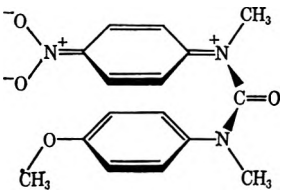
TABLE II

CHEMICAL SHIFTS[a] OF AROMATIC PROTONS OF *N*-ANISYL-*N'*-(*p*-NITROPHENYL)-*N,N'*-DIMETHYLUREA

Compd	Protons ortho to NO_2	Protons meta to NO_2	Protons ortho to OCH_3	Protons meta to OCH_3	Solvent
Ic	8.02	7.07			
Ib			6.56	6.65	$DCCl_3$
Id	7.95	6.94	6.61	6.77	
	Δδ −0.07	−0.13	+0.05	+0.12	
Ic	8.07	7.34			
Ib			6.59	6.68	O ‖ CD_3CCD_3
Id	8.02	7.16	6.72	7.00	
	Δδ −0.05	−0.18	+0.13	+0.32	
Ic	7.91	7.11			
Ib			6.57	6.68	CD_3CN
Id	7.93	7.00	6.66	6.89	
	Δδ −0.02	−0.11	+0.09	+0.21	
Ic	7.97	7.25			
Ib			6.64	6.73	O ↑ CD_3SCD_3
Id	7.97	7.09	6.73	7.00	
	Δδ 0.00	−0.16	+0.09	+0.27	

[a] In parts per million.

In order further to study the interaction of the two aromatic rings, we compared the ultraviolet spectra of the dinitrophenylurea Ib and the nitrophenyl-anisylurea Ic. The bands studied were in the region of 325–365 nm, and can be attributed to an intraring charge transfer of the nitrophenyl, the excited state of which can be represented as



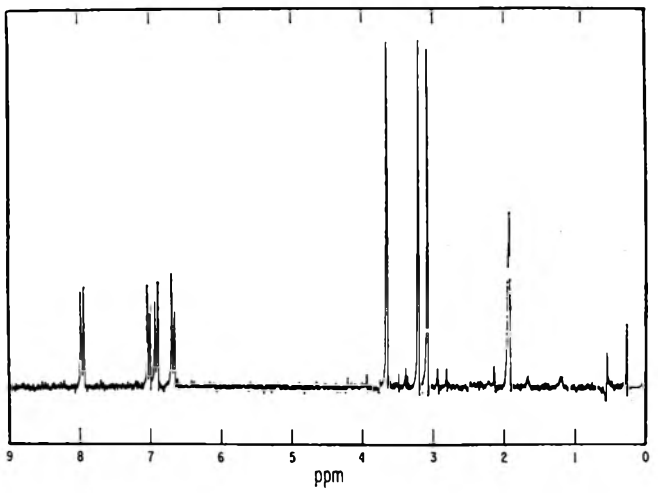
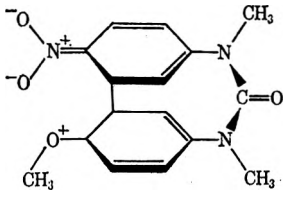


Figure 2.—Nuclear magnetic spectrum at 220 MHz in parts per million for *N,N'*-dimethyl-*N*-*p*-nitrophenyl-*N'*-*p*-methoxyphenylurea in CD_3CN at 25°.

The spectra of the dianisylurea Ia are uninterpretable since λ_{max} lies under the solvent cutoff.

The results of these studies in different solvents are shown in Table III. The longer wavelength of the mixed urea can be attributed to stabilization of the excited state by participation of resonance structures of the form



Since the mixed urea has greater dispersal of charge in the excited state owing to this resonance participation, its λ_{max} is less affected by increased solvent polarity.

TABLE III
ULTRAVIOLET SPECTRA OF DIARYLUREAS AT 25°

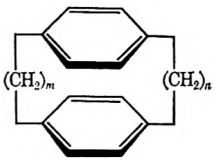
	N,N'-Di(*p*-nitrophenyl)-*N,N'*-dimethylurea (Ic)		*N*-(*p*-nitrophenyl)-*N'*-(*p*-anisyl)-*N,N'* dimethylurea (Id)	
Solvent	λ_{max}, nm	ϵ	λ_{max}, nm	ϵ
Chloroform	325	17,864	347	10,683
Acetone	337	17,600	355	12,740
Acetonitrile	333	17,364	354	12,011
DMSO	350	17,490	365	12,824

The temperature dependence of the ultraviolet spectra was also studied and the results are shown in Table IV. As stated earlier, lowering the temperature favors the more restricted forms of the molecule in which interaction between the rings is increased. Both spectra show increases in extinction coefficients with lowered temperature (1379 for the mixed urea and 676 for the dinitrourea when normalized for the presence of two chromophores). These changes depend upon the mixing of the charge transfer and ground states of the chromophores, and since this mixing is more affected by the anisyl ring than the nitro ring, the increased overlap resulting from closer contact is more evident in the mixed urea Id than the di(nitrophenyl) urea Ic.[6]

TABLE IV
TEMPERATURE DEPENDENCE OF THE UV SPECTRA OF DIARYLUREAS IN ACETONITRILE

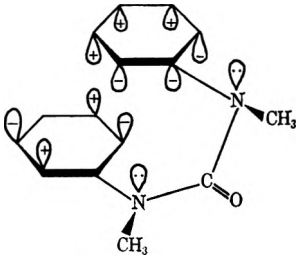
	N,N'-Di(*p*-nitrophenyl)-*N,N'*-dimethylurea (Ic)		*N*-(*p*-Nitrophenyl)-*N'*-(*p*-anisyl)-*N,N'* dimethylurea (Id)	
Temp, °C	λ_{max}, nm	$\epsilon/2$	λ_{max}, nm	ϵ
2	335	9137	355	12,632
25	333	8682	354	12,011
35	330	8619	353	11,932
50	328	8462	350	11,263

The study of compounds such as paracyclophanes[7] has shown that their spectral properties depend upon



the size of the macrocyclic system. It has been found that the λ_{max} increases with decrease in the distance between benzene rings. This effect is attributed to overlap of the two benzene rings. The nearly parallel changes in λ_{max} with temperature of the two ureas suggests that energy effects in both the ground and excited states are important and contribute to this value.

None of the data obtained by us offers evidence about the hybridization of the urea nitrogen atoms or the location of the rings other than that on the average they are close and in parallel positions. The similarities between the X-ray crystallographic structure and solution conformation are striking and lead us to expect the hybridization of the nitrogens and relative positions of the rings also to be similar. Theory suggests that the conformation in which the two aromatic rings are face to face in a mirror image relationship should not be favored. In the staggered relationship



shown in the X-ray structure, the overlap of HOMO of one ring with LUMO of the other is enhanced. These orbitals would be orthogonal in the mirror image form and the charge-transfer interactions forbidden.

Experimental Section

Nuclear magnetic resonance spectra (Figure 2) were measured on a Varian 220 spectrometer on ~5% solutions using tetramethylsilane as the internal standard. Ultraviolet spectra (Figure 3) at 25° were recorded on a Cary 14 spectrometer. Measurements at other temperatures were carried out using a Cary 17 spectrophotometer with the temperature maintained to ±0.1°. All solvents employed for spectral measurements were of spectro quality.

N,N-Dimethyl-*N',N'*-diphenylurea (Ia).—The compounds *N,N'*-diphenylurea (1.0 g, 4.71 mmol), silver oxide (4.0 g, 7.25 mmol), methyl iodide (4 ml, 64.22 mmol), and *N,N*-dimethyl-

(6) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, p 276.

(7) D. J. Cram and H. Steinberg, *J. Amer. Chem. Soc.*, **73**, 5691 (1951).

formamide (25 ml) were stirred at room temperature in a pressure bottle for 24 hr.

After filtering and washing with a few milliliters of *N,N*-dimethylformamide, chloroform (80 ml) was added to the filtrate. After filtration, the filtrate was washed three times with an aqueous solution of 5% potassium cyanide and six times with water and dried on anhydrous magnesium sulfate. Chloroform and *N,N*-dimethylformamide were evaporated; crystalline *N,N'*-dimethyl-*N,N'*-diphenylurea was obtained in 70% yield. The melting point after recrystallization from chloroform was 122° (lit. mp 122°).

***N,N'*-Di(*p*-nitrophenyl)urea (A).**—Two routes were followed for the preparation of A; the first one gave the best yields. The melting points recorded for A show some discrepancies, perhaps owing to the different crystalline forms in which it crystallizes from pyridine and *N,N*-dimethylformamide.[8] Elementary analysis was recorded on a sample crystallized from *N,N*-dimethylformamide.

A.—The compounds *p*-nitroaniline and urea, in the ratio 2:1, were allowed to react in acetic acid and water (1:1) at 130°. The starting amine dissolved slowly; after 18 hr a yellow solid formed, with ammonia evolution. After 24 hr, the solid was filtered and washed with water. The yield varied between 70 and 80%. A was soluble in *N,N*-dimethylformamide, dimethyl sulfoxide, and pyridine, and slightly soluble in acetone (0.5 g of A dissolved in 500 ml of acetone). Crystallization from *N,N*-dimethylformamide gave long, bright, yellow needles, that sublime above 325°.

B.—The compounds *p*-nitroaniline (2.8 g, 20.0 mmol) and *p*-nitrophenyl isocyanate (2.5 g, 15.0 mmol) in benzene (150 ml) and 3–4 drops of triethylamine were refluxed for 5 hr. The precipitated, yellow urea was filtered, dried, and dissolved in pyridine. Such a dissolution was very slow and was possible only after heating. From the first crystallization, 2.5 g (57%) of silky, thin needles were obtained, mp 323° dec.

Anal. Calcd for $C_{13}H_{10}N_4O_5$: C, 51.66; H, 3.34; N, 18.54. Found: C, 51.61; H, 3.24; N, 18.73.

***N,N'*-Dimethyl-*N,N'*-di(*p*-nitrophenyl)urea (Ic).**—The compounds *N,N'*-di(*p*-nitrophenyl)urea (1.0 g, 3.31 mmol), silver oxide (4.0 g, 17.25 mmol), methyl iodide (6 ml, 96.33 mmol), and *N,N*-dimethylformamide (20 ml) were stirred for 20 hr in a pressure bottle at 45°. After the procedure described for I, a crystalline, yellow solid was obtained, mp 145°, yield 80%. After crystallization from acetone, the melting point was 155°.

Anal. Calcd for $C_{15}H_{14}N_4O_5$: C, 54.54; H, 4.24; N, 16.97. Found: C, 54.32; H, 4.09; N, 16.79.

***N*-*p*-Nitrophenyl-*N'*-*p*-methoxyphenylurea.**—The compound *p*-nitrophenyl isocyanate (5.0 g, 30.5 mmol) was placed in a Soxhlet apparatus and extracted with carbon tetrachloride (500 ml) containing *p*-anisidine (3.7 g, 30 mmol). Reflux was maintained for about 1 hr. The precipitated urea was filtered and washed with boiling methanol, yield 7.4 g (86%). Crystallization in dimethyl sulfoxide–water, followed by crystallization in acetone–water, gave mp 229°.

Anal. Calcd for $C_{14}H_{13}N_3O_4$: C, 58.54; H, 4.53; N, 14.65; OCH_3, 10.80. Found: C, 57.95; H, 4.71; N, 14.39; OCH_3, 10.98.

***N,N'*-Dimethyl-*N*-*p*-nitrophenyl-*N'*-*p*-methoxyphenylurea (Id).**—The compounds *N*-*p*-nitrophenyl-*N'*-*p*-methoxyphenylurea (1.0 g, 3.48 mmol), silver oxide (4.0 g, 17.2 mmol), and methyl iodide (9 ml, 144 mmol) in *N,N*-dimethylformamide (25 ml) were stirred for 24 hr at room temperature in a pressure bottle. After the procedure described for I, a viscous oil was obtained, yield 60%. Crystallization in ethyl ether at −20° gave prismatic, light yellow crystals, mp 88°; nmr spectra showed all the resonances in the correct ratio.

***N,N'*-Di(*p*-methoxyphenyl)urea.**—The compounds *p*-methoxyphenyl isocyanate (1.86 g, 13.4 mmol) and *p*-anisidine (2.0 g, 16.2 mmol) in carbon tetrachloride (500 ml) were refluxed for 4–5 hr. The precipitated urea was crystallized from *N,N*-dimethylformamide. After two crystallizations, the yield was 38%, mp 242°.

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.18; H, 5.88; N, 10.45. Found: C, 65.90; H, 5.99; N, 10.30.

***N,N'*-Dimethyl-*N,N'*-di(*p*-methoxyphenyl)urea (Ib).**—The compound *N,N'*-di(*p*-methoxyphenyl)urea (1.0 g, 3.67 mmol) was methylated following the procedure described for I and II. The melting point of the crude, methylated urea was 79°. The urea is soluble in chloroform and acetone, but in these solvents, even at −20°, no crystallization occurred. The compound was crystallized from *n*-hexane, and the melting point after two crystallizations was 86°. The yield after the first crystallization was 80%. Examination of the product using nmr showed all the expected resonances in the correct ratio.

(8) S. A. Buckler, *J. Org. Chem.*, **24**, 1460 (1959).

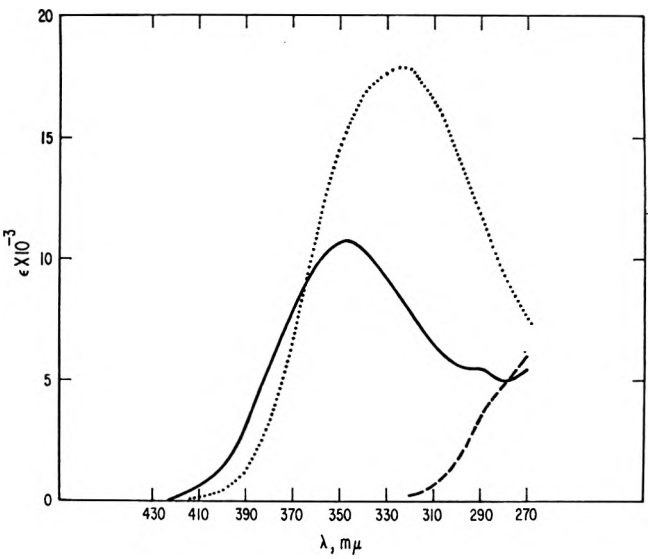


Figure 3.—Ultraviolet spectra for *N,N'*-dimethyl-*N,N'*-di(*p*-nitrophenyl)urea (dotted line), *N,N'*-dimethyl-*N*-*p*-nitrophenyl-*N'*-*p*-methoxyphenylurea (solid line), and *N,N'*-dimethyl-*N,N'*-di(*p*-methoxyphenyl)urea (dashed line), at 25° in chloroform.

***N,N*-Dimethyl-*N'*-methyl-*N'*-phenylurea (IIa).**—The compounds phenylurea (1.0 g, 7.35 mmol), silver oxide (6.0 g, 25.8 mmol), methyl iodide (7 ml, 112 mmol), and *N,N*-dimethylformamide (25 ml) were stirred at room temperature for 3 days in a pressure bottle.

After filtering, chloroform was added to the filtrate until no precipitation of silver iodide occurred. The solvent was eliminated under vacuum and the oil obtained ws purified on preparative layer chromatography plates of silica gel with a mixture of hexane–ethyl acetate (3:2).

Two main products were observed; that one with the longer R_f was recognized as IIa by nmr integration. The other one with a longer R_f was found to be *N*-*N'*-dimethyl-*N*-phenylurea, again by nmr integration.

***N,N*-Diethyl-*N'*-ethyl-*N'*-nitrophenylurea (IIc).**—The compounds *N*-ethyl-*N*-*p*-nitrophenylcarbamoyl chloride (0.5 g, 2.2 mmol), diethylamine (20 ml), and diglime (14 ml) were refluxed for 18 hr. Diethylamine hydrochloride was filtered off, and the filtrate was evaporated; the product was obtained in 87% yield. After crystallization from ethyl bromide, the melting point was 50°.

Anal. Calcd for $C_{13}H_{10}N_3O_3$: C, 58.87; H, 7.17; N, 15.84. Found: C, 58.9; H, 7.32; N, 15.63.

***N,N*-Diethyl-*N'*-ethyl-*N'*-*p*-methoxyphenylurea (IIb).**—The compounds *N*-ethyl-*N*-methoxycarbamoyl chloride (0.5 g, 2.36 mmol), diethylamine (20 ml), and diglime (15 ml) were refluxed for 18 hr. After diethylamine hydrochloride was filtered off, the filtrate was evaporated, and the residue was taken into hexane and cooled to −60° overnight. Crystals were obtained in 66% yield. Recrystallization from ethyl bromide by slow evaporation gave crystals with mp 43°.

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.20; N, 8.80; H, 11.20. Found: C, 67.01; N, 8.68; H, 10.80.

Acknowledgment.—We wish to thank the National Science Foundation for their support of this research through Grant No. GP 35810.

Registry No.—A, 587-90-6; Ia, 611-92-7; Ib, 27281-95-4; Ic, 34594-47-3; Id, 40387-31-3; IIa, 32773-27-6; IIb, 40387-32-4; IIc, 40387-33-5; *N,N'*-diphenylurea,

102-07-8; methyl iodide, 74-88-4; *p*-nitroaniline, 100-01-6; urea, 57-13-6; *p*-nitrophenyl isocyanate, 100-28-7; *N*-*p*-nitrophenyl-*N'*-*p*-methoxyphenylurea, 40387-34-6; *p*-anisidine, 104-94-9; *N*,*N'*-di(*p*-methoxyphenyl)-urea, 1227-44-7; *p*-methoxyphenyl isocyanate, 5416-93-3; phenylurea, 64-10-8; *N*-ethyl-*N*-*p*-nitrophenylcarbamoyl chloride, 34208-12-3; diethylamine, 109-89-7; *N*-ethyl-*N*-methoxycarbamoyl chloride, 40387-35-7.

Protection of Tryptophan with the Formyl Group in Peptide Synthesis[1]

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N^{α}-*tert*-Butyloxycarbonyl-N^{i}-formyltryptophan has been synthesized and used for the solid-phase synthesis of the heptapeptide Gly-Ala-Arg-Gly-Ala-(formyl)Trp-Gly which was isolated in high yield. Removal of the formyl group in 0.01 *M* ammonium bicarbonate buffer of pH 9 was accompanied by an unexpected side reaction, but this could be greatly diminished by use of 1 *M* buffer. The overall yield of the deprotected heptapeptide was substantially higher than in a parallel synthesis where tryptophan was not protected. The formyl group can also be effectively removed with little side reaction in liquid ammonia containing hydroxylamine hydrochloride.

Synthesis of tryptophan-containing peptides has been handicapped by lack of a protecting group for the indole side chain. Destruction of tryptophan in synthesis has generally been regarded to occur during the acid treatments for removal of protecting groups. Butylation of the indole moiety during this step constitutes a serious danger.[2] Use of HCl–acetic acid together with mercaptoethanol as scavenger[3] have been recommended as deprotecting agent for removal of the N^{α}-Boc group,[4] but it has been reported recently that these tactics are ineffective in solid-phase peptide synthesis and lead to a heterogeneous product.[5] On the other hand, use of HCl–formic acid as deprotecting agent gave a nearly homogeneous peptide.[5] Since reversible modification of tryptophan with the formyl group has already been described,[6] the conclusion was reached that this protection might be suitable in peptide synthesis. We wished to explore this possibility under our synthetic conditions as part of efforts to develop a complete set of side-chain protecting groups for use with N^{α}-Boc protection in solid-phase synthesis of peptides.[7] We have now synthesized the model heptapeptide Gly-Ala-Arg-Gly-Ala-Trp-Gly (I) with and without formyl protection of tryptophan and have found the protection to be well suited for peptide synthesis. Removal of the formyl group led to unexpected side reaction but conditions were established to reduce this to a minimum.

One of the most reliable means for removal of the N^{α}-Boc group in solid-phase synthesis has been 50% trifluoroacetic acid in dichloromethane.[8,9] The reagent was not recommended for tryptophan-containing peptides.[3] We decided to synthesize peptide I with use of this reagent to ascertain the extent of the problem. Boc-Glycyl resin was prepared by a modified Loffet procedure.[10,11] N^{α}-Boc protection was used along with N^{G}-tosyl protection of arginine. Removal[12] of protecting groups and the solid support in HF gave a product which proved to be heterogeneous on gel filtration on Sephadex G-10 (Figure 1a). The fast-moving side-product (Figure 1a) was purified in carboxymethylcellulose[13] and gave an ultraviolet spectrum similar to that reported for peptides containing an altered tryptophan residue.[5] Peptide I required further purification on carboxymethylcellulose and by partition chromatography[14] on Sephadex G-25 before its isolation in highly purified form[15] (yield *ca.* 23% based on starting Boc-glycyl resin.).

It has been shown that N^{i}-formyltryptophan or a suitable derivative is stable in solution under the acidic and basic conditions used for solid-phase synthesis including treatment with HF.[5] We therefore decided to attempt synthesis and isolation of the formyl derivative of I, namely Gly-Ala-Arg-Gly-Ala-(formyl)Trp-Gly (II). For this purpose N^{α}-Boc-N^{i}-formyltryptophan was required. This derivative was prepared from N^{i}-formyltryptophan[5] by the dimethyl sulfoxide procedure[16] and isolated as its crystalline dicyclohexylamine salt. Its ultraviolet spectrum was in agreement with that expected for a derivative of N^{i}-formyltryptophan. Synthesis of II was carried out by procedures entirely analogous to those used for synthesis of I, including treatment of the finished peptide resin with HF. Gel filtration of the product on Sephadex G-10 gave a single peak (Figure 1b). Further chromatography on carboxymethylcellulose in which only a single peak was detected gave peptide II in highly purified

(1) This work was supported in part by the American Cancer Society, the Allen Foundation, and the Geffen Foundation.

(2) Yu. B. Alakhov, A. A. Kiryushkin, V. M. Lipkin, and G. W. A. Milne, *J. Chem. Soc. D*, 406 (1970).

(3) G. R. Marshall in "Pharmacology of Hormonal Polypeptides and Proteins," N. Back, L. Martini, and R. Paoletti, Ed., Plenum Press, New York, N. Y., 1968, p 48.

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(11) D. Yamashiro and C. H. Li, *J. Amer. Chem. Soc.*, **95**, 1310 (1973).

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(13) E. A. Peterson and H. A. Sober, *J. Amer. Chem. Soc.*, **78**, 751 (1956).

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(15) When peptide I was synthesized with use of 1,2-ethanedithiol in the deprotecting agent the results were comparable to those indicated in Figure 1a.

(16) J. M. Stewart and J. D. Young, "Solid-Phase Peptide Synthesis," W. F. Freeman, San Francisco, Calif., 1969, p 29.

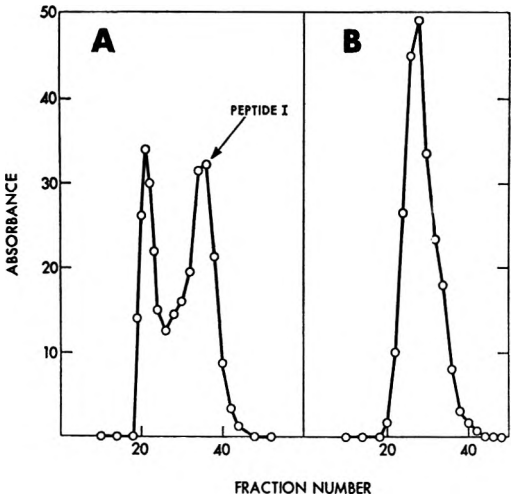

Figure 1.—Gel filtration on Sephadex G-10 in 1 *N* acetic acid: A, crude peptide I (280 nm); B, crude peptide II (300 nm). Column size, 1.37 × 42.3 cm.

form with a yield of about 88% (based on starting Boc-glycyl resin), substantially higher than in the synthesis of I. Its ultraviolet spectrum is characteristic of that of N^{i}-formyltryptophan and its derivatives.

Partition chromatography on Sephadex G-25 proved to be an effective means for the separation of peptides I and II, as shown in Figure 2. Since chromatography of II alone by this procedure gave only a single peak with no detectable trace of peptide I as contaminant, we concluded that the synthesis of II was achieved without loss of the formyl protecting group. Furthermore, the good yield and high degree of purity in which peptide II was secured show that the protected indole moiety was stable under the synthetic conditions employed.

The formyl group is removed under basic conditions and its course is conveniently followed[6] by disappearance of the strong 300 nm absorption. When peptide II was treated in 0.01 *M* NH_4HCO_3 buffer of pH 9 for 8 hr, partition chromatography of the product gave two peaks of similar size. In addition to the desired peptide I, a substantial side product was observed. Although this side product appeared on the chromatogram in the same position as peptide II, its ultraviolet spectrum was characteristic of tryptophan and it was clearly a new peptide. The amino acid composition of a toluenesulfonic acid hydrolysate[17] was identical with I. Its electrophoretic behavior was that of a substance less basic than either I or II. It gave positive reactions to Ehrlich and Sakaguchi reagents, but it was negative to ninhydrin. These results taken together indicated that the side product was identical with peptide I with the exception that the amino group was blocked. This would suggest that in the treatment of II at pH 9 the amino group can serve as nucleophile for removal of the formyl group.

Although it is evident that removal of the formyl protection might be effected without side reaction if the amino group were protected, we directed our efforts toward finding conditions for deprotection in the presence of the amino group. When peptide II was treated in 1 *M* NH_4HCO_3 buffer of pH 9 for 24 hr, partition chromatography of the product (Figure 3) showed

(17) T.-Y. Liu and Y. H. Chang, *J. Biol. Chem.*, **246**, 2842 (1971).

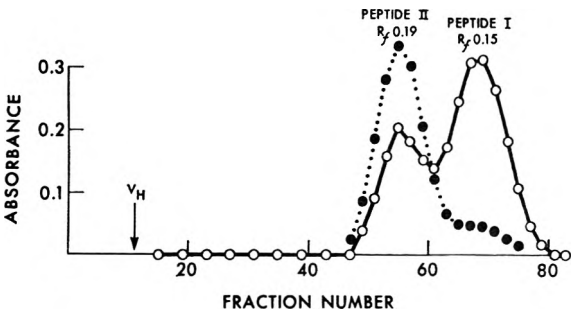

Figure 2.—Partition chromatography on Sephadex G-25 of a mixture of peptides I (1.87 mg) and II (2.00 mg) in solvent system B (see Experimental Section): 280 nm, O—O—O; 300 nm, ●···●···●; V_H = hold-up volume. Column size, 1.89 × 37 cm.

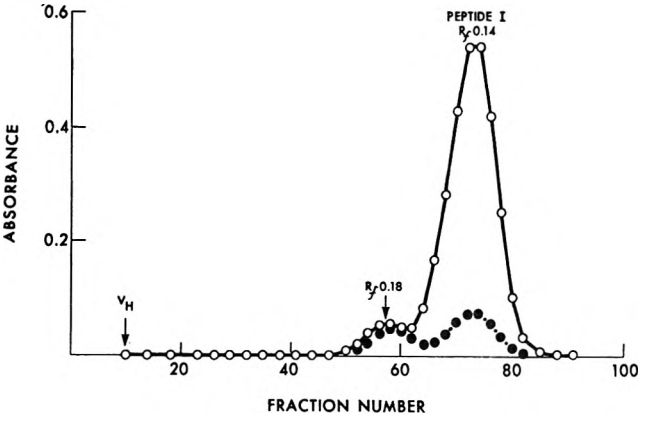

Figure 3.—Partition chromatography on Sephadex G-25 of peptide II after treatment with 1 *M* NH_4HCO_3 buffer of pH 9 for 24 hr: 280 nm, O—O—O; 300 nm, ●···●···●; V_H = hold-up volume; solvent system B. Column size, 1.89 × 37 cm.

very little side product (less than 8.5%) and the major product of deprotection was found to be identical with peptide I synthesized without protection of tryptophan. The overall yield of I through protection and deprotection of tryptophan was about 70% (based on starting Boc-glycyl resin), considerably higher than the yield where tryptophan was unprotected.

The formyl group can also be removed by treatment with liquid ammonia. However, peptide II again gave the aforementioned side product (*ca.* 19%) in addition to peptide I as the major product. When the reaction was carried out in the presence of added hydroxylamine hydrochloride the extent of side product was reduced to about 5%.

Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley. Thin layer chromatography was run on silica gel in 1-butanol–pyridine–acetic acid–water, 30:20:6:24 (BPAW). Chloromethylated styrene–divinyl benzene resin (Bio-Beads S-X-1, 200–400 mesh, 0.69 mmol/g, Bio-Rad Laboratories) served as starting material for synthesis.

Partition chromatography on Sephadex G-25 (100–200 mesh block polymerisate) was performed on a 1.89 × 37 cm column by procedures previously described.[14] Solvent systems used were 1-butanol–ethanol–0.2 *M* aqueous ammonium acetate (3:1:4, pH 7.6) (solvent system A) and the same system with pH adjusted to 6.2 with glacial acetic acid (solvent system B). Fractions of about 2.8–3.0 ml were collected and were appropriately diluted with 50% ethanol to measure absorbance at 280 or 300 nm. Isolation of peptide material was performed in

the usual manner with the exception that repeated lyophilization was required to remove ammonium acetate.

Carboxymethylcellulose chromatography was performed in a 1.23 × 44 cm column with an initial buffer of 0.01 *M* ammonium acetate of pH 5. After elution with 100 ml, a gradient with respect to pH and salt concentration was started by introducing 0.1 *M* ammonium acetate through a 500-ml mixing chamber containing starting buffer. In procedure A the 0.1 *M* buffer had pH 7.1, while in procedure B this buffer was adjusted to pH 6.3 with glacial acetic acid. Peptides were detected spectrophotometrically at either 280 or 300 nm.

N^{α}-*tert*-Butyloxycarbonyl-N^{i}-formyltryptophan Dicyclohexylamine Salt.—A mixture of N^{i}-formyltryptophan hydrochloride[5] (2.7 g, 10 mmol), diisopropylethylamine (6.0 ml, 35 mmol), and Boc-azide (15 mmol) was stirred in dimethyl sulfoxide (35 ml) overnight at room temperature. The resulting solution was diluted with cold water (175 ml) and washed with two 100-ml portions of ether. The aqueous layer was acidified with citric acid (15 g) with cooling, and the product was extracted with two 100-ml portions of ethyl acetate. The combined ethyl acetate layers were washed with three 50-ml portions of water and dried over anhydrous $MgSO_4$. Removal of drying agent and solvent gave 3.5 g of oil. Conversion to the crystalline salt was effected at 4° in anhydrous ether (30 ml) with dicyclohexylamine (2.25 ml), yield 4.1 g. For recrystallization a sample (1.03 g) was dissolved in $CHCl_3$ (4 ml) and evaporated *in vacuo* to an oil which was immediately taken up in anhydrous ether (10 ml) and stored at 4°; the product was collected and the process was repeated to give 0.78 g (60% yield), mp 121–124° dec, $[\alpha]^{24}D$ +35.5° (*c* 2, absolute ethanol).

Anal. Calcd for $C_{29}H_{43}N_3O_5$ (513.68): C, 67.81; H, 8.44; N, 8.18. Found: C, 67.57; H, 8.28; N, 8.20.

The ultraviolet absorption spectrum, taken at 270–330 nm in absolute ethanol, showed the characteristics of N^{i}-formyltryptophan and its derivatives.[5,6] The ratio of the absorbance at 300 nm to that at 280 nm was 1.59. For use in synthesis the free acid was obtained from the salt by standard procedures.

Solid-Phase Peptide Synthesis Procedures.—Boc-glycyl resin was prepared by a modification[11] of the Loffet method.[10] A sample of the resin deprotected and neutralized gave an amine content[18] of 0.40 mmol/g.

For synthesis of peptide I, Boc-glycyl resin (0.75 g, 0.30 mmol) was carried through the same schedule of operations recently described.[11] N^{α}-Boc protection was used throughout along with tosyl protection for the side chain of arginine. For the coupling of Boc-tryptophan, 5% DMF in CH_2Cl_2 was used as solvent. Yield of protected peptide I polymer was 0.97 g.

For synthesis of peptide II, Boc-glycyl resin (1.01 g, 0.40 mmol) was carried through the same aforementioned procedures with the exception that the coupling of Boc(formyl)tryptophan could be effected in CH_2Cl_2 alone. Yield of protected peptide II polymer was 1.34 g.

Peptide I.—Protected peptide I resin (505 mg) was treated with 15 ml of liquid HF for 30 min at 0° in the presence of anisole (0.5 ml). After removal of the HF the dried resin mixture was extracted with trifluoroacetic acid (10 ml) and filtered. The filtrate was evaporated *in vacuo* and after the addition of glacial acetic acid (10 ml) further evaporation gave an oily residue which was taken up in 1 *N* acetic acid (5 ml). The aqueous solution was washed with two 5-ml portions of ether, concentrated *in vacuo* to a smaller volume, and applied to a 1.37 × 42.3 cm Sephadex G-10 (40–74 μ) column. Elution with 1 *N* acetic acid and the collection of 1.53-ml fractions gave the results shown in Figure 1a. Isolation by lyophilization of the material represented by the slower moving peak (fractions 31–42) gave 63.2 mg. This material was submitted to chromatography on carboxymethylcellulose (procedure A); a large peak was detected (130 ml after buffer change) along with two minor peaks. Isolation of material represented by the large peak gave 35.5 mg. This material was resubmitted to chromatography on carboxymethylcellulose (procedure A) to give 32.1 mg. An aliquot (25.9 mg) of this material was subjected to partition chromatography on Sephadex G-25 in solvent system A to give a major peak with R_f 0.15 along with a minor peak with R_f 0.50. Isolation of material represented by the major peak gave 19.2 mg of highly purified peptide I (*ca.* 23% yield based on starting Boc-glycyl resin): tlc (BPAW) R_f 0.32; $[\alpha]^{24}D$ −59.5° (*c* 0.40, 0.5 *N* acetic acid).

Paper electrophoresis in pyridine acetate buffer (pH 3.7, 400 V, 4 hr) showed a single spot (ninhydrin and Ehrlich reagents) with R_f 0.56 relative to lysine. The ultraviolet spectrum, taken at 240–320 nm in 0.5 *N* acetic acid, showed the characteristics of a tryptophan spectrum. Amino acid analyses of a toluenesulfonic acid hydrolysate[17] and a leucine amino peptidase digest (pH 8, 24 hr, 37°) gave $Trp_{1.1}Arg_{0.9}Gly_{3.2}Ala_{2.0}$ for both.

Material represented by the faster moving peak in Figure 1a (fractions 19–25: isolated material, 29.1 mg) was submitted to chromatography on carboxymethylcellulose (procedure A). After elution with 300 ml of the 0.1 *M* buffer the gradient was increased by use of 0.2 *M* ammonium acetate. The major peak appeared 120 ml after this buffer change. The isolated peptide (17.1 mg) gave an ultraviolet spectrum, taken at 240–320 nm in 0.5 *N* acetic acid, with absorbance maximum at 284 nm, a minimum at 255 nm, and similar in appearance to that previously reported for peptides containing an altered tryptophan residue.[5]

Peptide II.—Protected peptide II resin (503 mg) was treated with HF and worked up in the same manner as just described for peptide I. Gel filtration of the product on Sephadex G-10 in the same manner gave a peak (fraction 26) with an apparent shoulder. All the detectable peptide material (300 nm) was isolated and resubmitted to gel filtration (Figure 1b) to give 111.3 mg (fractions 22–36). An aliquot (60.1 mg) of this material was subjected to chromatography on carboxymethylcellulose (procedure B) to give only one peak (135 ml after the buffer change) and isolation of material represented by this peak gave 49.7 mg of highly purified peptide II (*ca.* 88% yield based on starting Boc-glycyl resin): tlc (BPAW) R_f 0.32; $[\alpha]^{24}D$ −50.5° (*c* 0.46, 0.5 *N* acetic acid).

Paper electrophoresis in pyridine acetate buffer (pH 3.7, 400 V, 4 hr) showed a single spot (ninhydrin positive and Ehrlich negative) with R_f 0.52 relative to lysine. Partition chromatography of a sample (2.05 mg) on Sephadex G-25 in solvent system B gave one peak with R_f 0.19 and no detectable trace of material corresponding to the position of peptide I (R_f 0.15). The ultraviolet spectrum of II, taken at 270–330 nm in 0.5 *N* acetic acid, showed the characteristics of N^{i}-formyltryptophan and its derivatives. The ratio of the absorbance at 300 nm to that at 280 nm was 1.57. Amino acid analysis of a toluenesulfonic acid hydrolysate gave $Trp_{0.9}Arg_{1.0}Gly_{3.2}Ala_{2.2}$; removal of the formyl group under strong acidic aqueous conditions is known (see ref 6).

Conversion of Peptide II to Peptide I. Deprotection of Tryptophan.—A sample (31.4 mg) of peptide II from the Sephadex G-10 gel filtration step was dissolved in 9.0 ml of 1 *M* NH_4HCO_3 buffer of pH 9.1 and allowed to stand at 24° for 24 hr. The material was lyophilized three times to remove volatile salts and subjected to partition chromatography on Sephadex G-25 in solvent system B as shown in Figure 3. The side product with R_f 0.18, which appeared to be contaminated with a small amount of unreacted starting peptide II, represented about 8.5% of the total detectable material in the chromatogram. The R_f value of 0.14 for the large peak is in close agreement with the known position of peptide I (see Figure 2) and isolation of material corresponding to this peak (fractions 65–80) gave 19.9 mg of I (*ca.* 70% yield based on starting Boc-glycyl resin). This material was identical with that from the preparation of I described above on thin layer chromatography, paper electrophoresis, ultraviolet spectral analysis, and optical rotation. Amino acid analysis of a leucine amino peptidase digest gave $Trp_{1.0}Arg_{0.9}Gly_{3.1}Ala_{1.9}$.

Treatment of II on Dilute Buffer.—A sample (8.75 mg) of peptide II was treated in 10 ml of 0.01 *M* NH_4HCO_3 buffer of pH 9 until the absorbance at 300 nm had declined to 15% of its starting value (8 hr). The solution was lyophilized and subjected to partition chromatography on Sephadex G-25 in solvent system A. Two well-separated peaks of similar size were observed at 280 nm with R_f values of 0.19 and 0.15, the latter corresponding to peptide I. Isolation of material corresponding to these peaks gave 3.3 mg for each.

The side product, which had R_f 0.19, exhibited the typical ultraviolet spectrum of tryptophan and gave positive responses to both Ehrlich and Sakaguchi reagents but negative to ninhydrin. Paper electrophoresis run under the same conditions as previously mentioned gave a major spot (Ehrlich) with R_f 0.2 relative to lysine and travelling slower than either I or II. Thin layer chromatography gave a major spot with R_f 0.42 (Ehrlich) and travelling slightly faster than either I or II. Amino acid analysis of a toluenesulfonic acid hydrolysate gave $Trp_{0.9}Arg_{0.9}Gly_{3.0}Ala_{2.0}$.

(18) B. F. Gisin, *Anal. Chim. Acta*, **58**, 248 (1972).

Treatment of II in Liquid Ammonia.—A sample (3.3 mg) of II was stirred in *ca.* 20 ml of liquid ammonia for 2 hr at −60°, after which time the solution was allowed to evaporate to dryness at the boiling point. Residual ammonia was removed *in vacuo* and the product was subjected to partition chromatography on Sephadex G-25 in solvent system B. Two peaks were detected at 280 and 300 nm with R_f values of 0.19 and 0.15, the latter being the major peak and corresponding to peptide I. The smaller peak with R_f 0.19 was apparently the same aforementioned side product and represented about 19% of the total detectable material on the chromatogram.

In a second run a sample (1.9 mg) of II was treated in the same manner with the exception that hydroxylamine hydrochloride (16.7 mg) was present. Partition chromatography in the same manner gave a major peak with R_f 0.15 corresponding to peptide I and a very small peak with R_f 0.19 corresponding to side product. The latter represented about 5% of the total detectable material in the two peaks.

Registry No.—N^{α}-*tert*-Butyloxycarbonyl-N^{i}-formyltryptophan dicyclohexylamine salt, 40463-72-7; N^{i}-formyltryptophan hydrochloride, 38023-86-8; peptide I, 40463-74-9; peptide II, 40463-75-0.

Acknowledgment.—We thank Mr. Kenway Hoey and Mr. W. F. Hain for their skilled technical assistance.

In Vitro Decomposition of S-Methylmethioninesulfonium Salts

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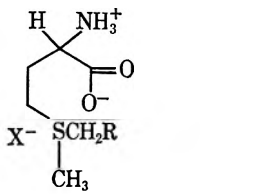
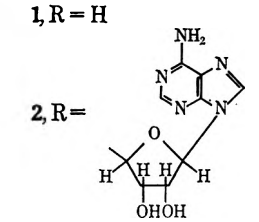
The *in vitro* decomposition of S-methylmethioninesulfonium salts (SMM) was studied in neutral, basic, and acidic aqueous solutions. The previously reported formation of dimethyl sulfide and homoserine (*via* its lactone) was verified. A new mode of self-destruction of SMM was discovered, *i.e.*, a nucleophilic attack by the dimethyl sulfide on one of the methyl groups of SMM with formation of trimethylsulfonium salt and methionine. The intermolecular demethylation of SMM was favored over the intramolecular decomposition to homoserine lactone with increasing acidity of the medium. Sodium thiosulfate effectively demethylates SMM in aqueous solution.

The S-methylmethioninesulfonium salts (SMM, **1**), the analogs of "active methionine" or S-adenosylmethioninesulfonium salts[1,2] (SAM, **2**), are of considerable interest biologically and medicinally. SMM is enzymatically synthesized from SAM and methionine in jack bean roots,[3] and can in turn be utilized as substrate by several methyl transferases.[4,5] SMM is widely distributed in nature and has been reported as a constituent of milk,[6] potatoes,[7] sweet corn,[8] soybean,[9] asparagus,[10] and cabbage.[11] Several reports have implicated SMM (vitamin U) in the prevention of ulcers of shay in rats,[12] of ulcers and of certain hepatic disorders in humans,[13] and of dietary hypercholesterolemia in rabbits.[14]



1, R = H



2, R =

In vitro syntheses of various SMM salts have been described,[15-17] and the pK values of the chloride have been measured.[18] McRorie, *et al.*,[11] reported the formation of homoserine (**5**, Scheme I) and of its lactone **3** (as hydroiodides) when an aqueous solution of SMM iodide was heated for 12 hr in an autoclave at unspecified temperatures. Challenger and Hayward[10] studied the decomposition of SMM in hot aqueous alkaline solution and reported the formation of dimethyl sulfide, homoserine, and methionine sulfoxide, which they regarded as the result of an oxidation of methionine. These authors[10] assumed that SMM decomposed by two paths: (1) formation of dimethyl sulfide and homoserine; (2) formation of methanol and methionine. Subsequently, Witkop and his coworkers[19] provided evidence for the initial formation of homoserine lactone (**3**) in the decomposition of SMM.

This paper describes an investigation of the behavior of SMM salts in aqueous solutions at neutral, basic, and acidic pH's, as a necessary first step in the elucidation of the much more complex behavior of SAM.

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(2) (a) H. R. Mahler and E. H. Cordes, "Biological Chemistry," 2nd ed, Harper and Row, New York, N. Y., 1971, pp 724, 806, 834; (b) p 366.

(3) R. C. Greene and N. B. Davis, *Biochim. Biophys. Acta*, **43**, 360 (1960).

(4) J. E. Turner and S. K. Shapiro, *Biochim. Biophys. Acta*, **51**, 585 (1961).

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(14) (a) K. Nakamura and H. Ariyama, Tohoku *J. Agr. Res.*, **11**, 273 (1960); *Chem. Abstr.*, **55**, 7676d (1961); (b) *J. Agr. Res.*, **12**, 49 (1961); *Chem. Abstr.*, **55**, 27657d (1961); (c) *J. Arg. Res.*, **12**, 383 (1961); *Chem. Abstr.*, **57**, 5271b (1962).

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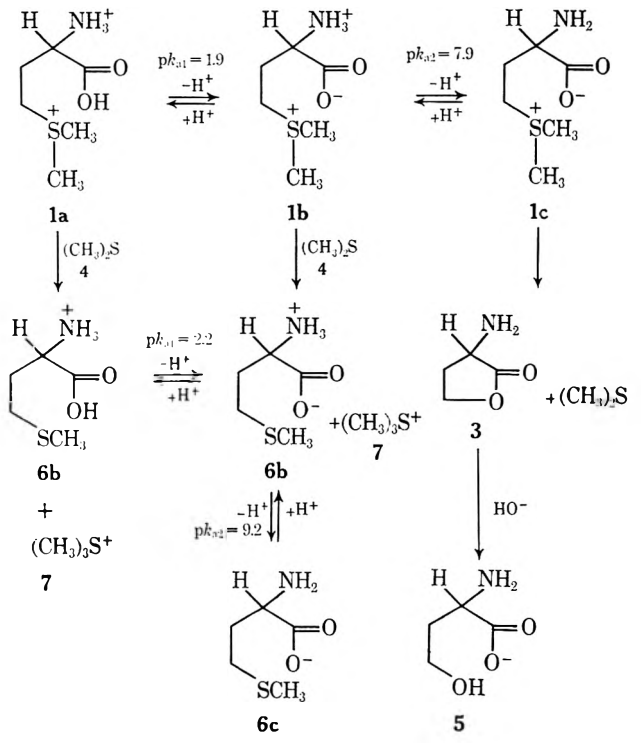
(18) W. A. Klee and S. H. Mudd, *Biochemistry*, **6**, 989 (1967).

(19) W. B. Lawson, E. Gross, C. M. Foltz, and B. Witkop, *J. Amer. Chem. Soc.*, **84**, 1715 (1962).

SCHEME I



Experimental Section

Starting Materials.—The DL amino acids were obtained from Mann Research. Trimethylsulfonium iodide (7, Scheme I) was made by the procedure of Pocker and Parker.[20] *S*-Methyl-DL-methioninesulfonium nitrate (1 nitrate) was made by addition of silver nitrate (3 mmol) to a solution of SMM chloride (1 chloride) (3 mmol) in 50 ml of water; the filtrate was evaporated to dryness under vacuum.

Experimental Conditions.—Tables I and II describe the experimental conditions and results. ^{1}H nmr spectra of authentic samples of the pertinent compounds were examined in D_2O and in H_2O solutions at 60 MHz. The chemical shifts of the CH_3 groups are listed in Table III. The composition of the various mixtures was determined by combined tlc and ^{1}H nmr analyses.

Reaction of Methionine (6) with Dimethyl Sulfide (4). A. With Added HCl.—DL-Methionine (0.075 g) and 6 *N* HCl were mixed in an nmr sample tube to a volume of 1 ml (0.05 *M* solution). An excess of $(CH_3)_2S$ was introduced, and the tube was sealed and heated to 90°. The ^{1}H nmr spectra were examined at ambient temperature after various time intervals. The first evidence for the appearance of $(CH_3)_3S^+$ (7) was obtained after 5 days.

B. With Added H_3PO_4.—The above procedure was repeated using 6 *N* H_3PO_4 instead of HCl. The spectrum of $(CH_3)_3S^+$ (7) was first noticeable after 10 days.

Reaction of Methionine (6) with Sodium Thiosulfate (10).—D_2O was added to a mixture of methionine (0.075 g, 0.05 mmol) and sodium thiosulfate (0.124 g, 0.5 mmol) to a volume of 1 ml in an nmr sample tube. The sealed tube was heated to 90° and the ^{1}H nmr spectra were determined at ambient temperature. The Bunte salt, $CH_3SSO_3^-$ (11), was first detectable only after 10 days.

Results and Discussion

The results of this investigation can be discussed with reference to Scheme I. In neutral and in basic aqueous solutions, the main pathway for the decomposition of SMM leads to homoserine (5) and dimethyl sulfide (4) *via* homoserine lactone (3), as had been previously reported.[10,11,17,19] The rate of decomposition of SMM increases markedly with increasing pH (*cf.* Table I). The lactone 3 is formed[19] by an intramolecular neigh-

(20) Y. Pocker and A. J. Parker, *J. Org. Chem.*, **31**, 1526 (1966).

TABLE I

HALF-LIVES ($t_{1/2}$) FOR THE DISAPPEARANCE OF *S*-METHYLMETHIONINESULFONIUM CHLORIDE (SMM Cl) IN 1 *M* AQUEOUS SOLUTIONS AT 90°

Reaction conditions	$t_{1/2}$
SMM Cl at pH 7[a]	50 min
SMM Cl at pH 11[a]	17 min
SMM Cl at pH 1[a]	25 hr
SMM Cl + dimethyl sulfide + HCl[b]	5 hr
SMM Cl + dimethyl sulfide[c] + methanol + HCl	100 min
SMM nitrate + dimethyl[d] sulfide + H_3PO_4	5 hr
SMM Cl + sodium thiosulfate[e]	20 min

[a] One millimole (0.200 g) of SMM Cl was diluted to a volume of 1 ml with 0.1 *M* NaOH, 1 *M* NaOH, and 1 *M* HCl, respectively, to give solutions with approximate pH's of 7, 11, and 1 in nmr sample tubes. The sealed tubes were heated to 90° and the ^{1}H nmr spectra were determined at 25° at various times. In the experiments at pH 11, the reaction was quenched by immersion of the tube in a Dry Ice–acetone bath prior to examination of the ^{1}H nmr. At the end of the reactions, the contents of the tubes were analyzed by tlc as indicated in Table II. [b] One millimole of SMM Cl was dissolved in 6 *N* aqueous HCl to a volume of 1 ml in a nmr sample tube. An excess of $(CH_3)_2S$ was introduced, and the sealed tube was heated to 90°. The ^{1}H nmr were examined at 25° at various times. [c] A mixture of 0.5 mmol of SMM Cl, 2.5 mmol of $(CH_3)_2S$, and 86 μl (1 mmol) of 38% aqueous HCl was diluted to a volume of 1 ml with methanol in an nmr sample tube. The sealed tube was kept at 90°, and the nmr spectra were determined at 25°. [d] As in *b* above except that SMM Cl was replaced by the nitrate salt and the HCl was replaced by 6 *N* H_3PO_4. [e] D_2O or water was added to a mixture of SMM Cl (0.200 g, 1 mmol) and sodium thiosulfate (0.248 g, 1 mmol) to a volume of 1 ml. The pH of this solution was 4.9. The sealed tube was heated to 90° and the ^{1}H nmr spectra were examined at 25° at various times.

TABLE II

THIN LAYER CHROMATOGRAPHY[a] OF THE PRODUCTS INVOLVED IN THE *in Vitro* DECOMPOSITION OF *S*-METHYLMETHIONINESULFONIUM CHLORIDE (1 Cl) IN AQUEOUS SOLUTIONS

		R_f values	
No.	Compd	Developing solution 1[b]	Developing solution 2[c]
1 Cl	*S*-Methyl-DL-methionine-sulfonium chloride	0.47	0.07
5	DL-Homoserine	0.61	0.50
6	DL-Methionine	0.80	0.70
8	DL-Homocysteine	0.67	0.70
9	DL-Homocystine	0.49	0.12
	Mixture from reaction at pH 7[d]	0.47, 0.61, 0.80	0.07, 0.49, 0.68
	Mixture from reaction at pH 11[e]	0.47, 0.62, 0.80	0.08, 0.50, 0.70
	Mixture from reaction at pH 1[f]	0.48, 0.63, 0.82, 0.68	0.07, 0.51, 0.70, 0.12

[a] The tlc plates were Eastman 6065 cellulose. The spots were developed with ninhydrin. [b] Developing solution 1: $CHCl_3$–CH_3OH–17% NH_4OH, 2:1:1 v/v. [c] Developing solution 2: *n*-C_4H_9OH–$(CH_3)_2CO$–$(C_2H_5)_3N$–H_2O, 10:10:2:5 v/v. [d] After 6.5 hr at 90°. Concentration of SMM = 0.11 *M*. (Initial SMM concentration = 1.0 *M*.) Major product was homoserine; minor product was methionine. [e] After 1.5 hr at 90°. Concentration of SMM = 0.045 *M*. (Initial SMM concentration = 1.0 *M*.) Major product was homoserine; minor product was methionine. [f] After 65 hr at 90°. Concentration of SMM = 0.26 *M*. (Initial SMM concentration = 1.0 *M*.) Major product was methionine; minor products were homoserine, homocysteine, and homocystine.

Table III
Chemical Shifts of CH_3 Groups[a]

Compd	λ, ppm
SMM Cl (1 Cl)	6.94
$(CH_3)_2S$ (4)	7.88
$(CH_3)_3S^+$ (7)	7.04
Methionine (6)	7.84
$^-OSO_2SCH_3$ (11)	7.35

[a] In parts per million from DSS = 10 (τ values), D_2O as solvent.

boring group participation[21a] of the carboxylate function (the nucleophile), and it is reasonable to expect higher nucleophilicity in the unprotonated form of SMM (**1c**) than in the zwitterion form (**1b**) owing to the respective charge distributions. For this reason, and taking into consideration the data on pK_a's of SMM, it seems probable that most or all of the lactone **3** arises from unprotonated SMM (**1c**) at all pH's above *ca.* 6. [In Scheme I, the acid–base equilibria for homoserine (**5**) and its lactone **3** have been omitted.]

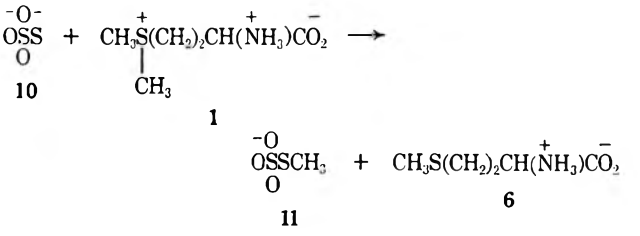
A second pathway for the disappearance of SMM can be detected in the neutral and in the basic solutions, namely, a nucleophilic attack by dimethyl sulfide (**4**) on the methyl group of SMM (**1**). This pathway, which represents the demethylation of SMM, leads to methionine (**6**, *cf.* Tables II and III) and trimethylsulfonium salt (**7**, *cf.* Table III). The overall rate of disappearance of SMM decreases significantly with decreasing pH (*cf.* Table I). This is due to a decrease in the rate of formation of lactone **3** and dimethyl sulfide (**4**) in acidic media, which is reasonable since under those conditions the less reactive zwitterion form of SMM (**1b**) is the source of the lactone (**3** in protonated form). (The amount of lactone formed from diprotonated SMM, **1a**, is probably negligible.) The specific reaction rate for the demethylation of SMM by dimethyl sulfide must be relatively large, because dimethyl sulfide has very little solubility in water, and yet the sulfide is quite effective in demethylating SMM (*cf.* Table I). (Note also the significant effect of methanol, whose role is mainly to increase the solubility of dimethyl sulfide in water.)

The formation of trimethylsulfonium salts (**7**) in the decomposition of SMM constitutes a novel observation; it accounts for the previously observed[10,17] formation of methionine in this decomposition. We failed to detect the formation of any methanol[10] at any pH from 1 to 11. Likewise, we found no methonine sulfoxide[10] in any of our experiments.

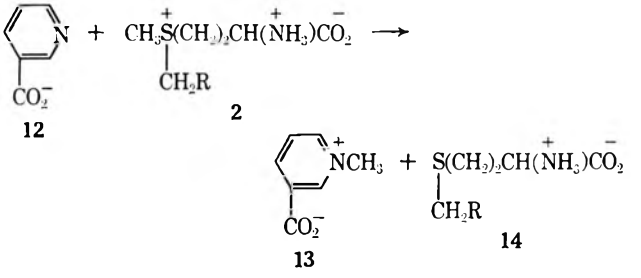
Demethylation by dimethyl sulfide plays an important role in the decomposition of SMM at pH's below 7. In this reaction, methionine (**6**) is the leaving group of a substitution by sulfur on carbon. It is reasonable to expect that the diprotonated form of methionine (**6a**) should be a better leaving group than the zwitterion **6b** or the unprotonated form **6c**, from their respective charge distributions. At the lowest pH's studied, most of the methionine (**6**) probably comes from diprotonated SMM (**1a**), while at higher pH's increasing amounts presumably arise also from the zwitterion **1b**. These considerations should be relevant to further analysis of the mechanisms of enzymatic methyl transfers from SMM (**1**) and from SAM (**2**).

To demonstrate that the demethylation of SMM chloride (**1** Cl) occurred by a nucleophilic attack of sulfur rather than chloride ion (which could give methyl chloride and thence trimethylsulfonium chloride), we determined the rate of demethylation of SMM nitrate (**1** NO_3) by dimethyl sulfide using H_3PO_4 as the acid, since both nitrate and phosphate are poor nucleophiles. The rate of disappearance of SMM was about the same as in the SMM chloride experiment (*cf.* Table I).

Thiosulfate (**10**) is a powerful nucleophile,[21b] and indeed it proved to be a most efficient demethylating agent for SMM (**1**), the products being methionine (**6**)



and the methyl Bunte[21c,22] salt, **11**. The facile *in vitro* demethylations of SMM (**1**) by sulfur nucleophiles, which compete favorably with the intramolecular decomposition to homoserine lactone (**3**) and dimethyl sulfide (**4**), find their counterpart in the enzymatic demethylation of SAM (**2**) by nitrogen nucleophiles as in the biosynthesis of trigonelline[2b] (**13**), where the by-product is *S*-adenosylhomocysteine (**14**).



CH_2R = 5′-adenosyl

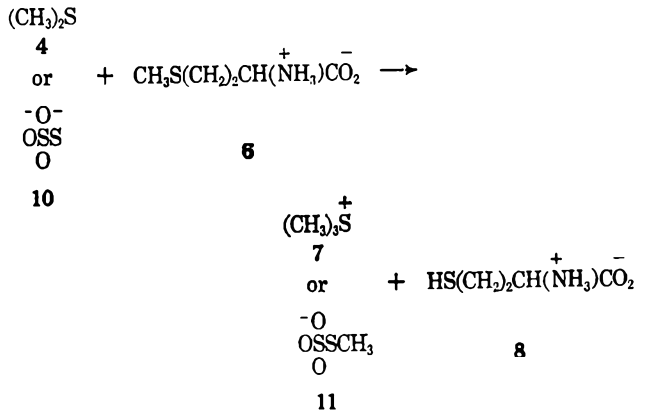
The corresponding intramolecular decomposition of SAM (**2**) would have given homoserine lactone (**3**) and *S*-methyl-5′-thioadenosine, CH_3SCH_2R (CH_2R = 5′-adenosyl). The enzyme function could be partly directed to discouraging this intramolecular decomposition and to favoring the intermolecular demethylation, both of which could be simultaneously achieved by the protonation of SAM (**2**), since the higher the state of protonation of the amino acid, the lower the nucleophilicity of the carboxyl function (lactone formation) and the higher the methylating power of the sulfonium group (*i.e.*, the better the leaving group, **14** or protonated **14**) as discussed above.

As shown in Table II, homocysteine (**8**) and its oxidation product homocystine (**9**) were observed as very minor by-products of the decomposition of SMM (**1**) in acidic solutions. Independent experiments showed that the formation of homocysteine (**8**) and trimethylsulfonium salt (**7**) from the reaction of methionine (**6**) with dimethyl sulfide (**4**) is extremely slow (see Experimental Section). Probably this reaction is susceptible

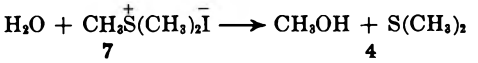
(21) (a) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 263; (b) p 328; (c) p 330.

(22) J. Kice, *J. Org. Chem.*, **28**, 957 (1963).

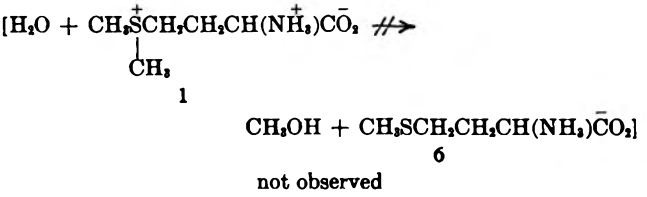
to acid catalysis in the form of protonation of the sulfur of methionine, since HCl seems to be more effective than H_3PO_4 at comparable normalities. As expected, thiosulfate **10** also caused the slow demethylation of methionine (**6**).



In conclusion, the formation of the lactone **3** as an intermediate in the hydrolytic decomposition of SMM (**1**) into homoserine (**5**) and dimethyl sulfide (**4**) is in accord with the observation that the rate of disappearance of SMM in water at neutral pH is significantly faster than solvolysis of trimethylsulfonium iodide[20] (**7**) under comparable conditions.



A neighboring group participation by the carboxylate anion would explain why the nucleophilic substitution at the methylene group of SMM (**1**) is faster than the substitution at the methyl group of the trimethylsulfonium cation (**7**). Moreover, the intermediacy of the lactone **3** also accounts for the nonoccurrence of the hydrolytic pathway for SMM that leads to methanol and methionine.



As the nucleophile becomes more effective, *i.e.*, when dimethyl sulfide is involved, the occurrence of the intermolecular nucleophilic substitution at the methyl group, with formation of trimethylsulfonium salt and methionine, becomes competitive with the intramolecular substitution at the methylene group.

Registry No.—**1** chloride, 3493-12-7; **1** nitrate, 33515-34-3; **4**, 75-18-3; **5**, 1927-25-9; **6**, 59-51-8; **7**, 676-84-6; **8**, 454-29-5; **9**, 870-93-9; **10**, 7772-98-7; **11**, 40463-71-6.

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Functionalization of Bis(phenylsulfonyl)methane

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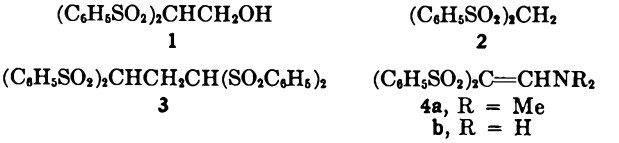
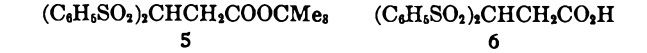
Received February 15, 1973

A convenient method is described for the single-carbon functionalization of bis(phenylsulfonyl)methane *via* thiomethylation with *N*-(benzoylthiomethyl)piperidine hydrochloride (**9**). The thiomethyl derivative **10** was easily converted to olefin **12** and thence to the disulfone alcohol **1**. In studying a similar approach to the tosyl analog of **12** some discrepancies with earlier structural assignments were noted and clarified.

As a possible precursor of reagents suitable for the development of new amino-protecting groups,[1] a disulfone alcohol such as **1** was of considerable interest. A readily available, logical precursor of **1** is **2** and



therefore a general study of the one-carbon functionalization of **2** was undertaken. Of the various techniques studied, only one proved suitable for the conversion to **1**. The most direct route, aldol condensation of **2** with formaldehyde,[1a] gave only the bis adduct **3**, which was also obtained as the sole product by alkylation of metallic salts of **2** with chloromethyl ether or *N*-chloromethylphthalimide or by application of the Mannich reaction to **2**.[2] Alkylations of the anion of **2** by means of *tert*-butyl α-bromoacetate or bromoacetic acid readily gave **5** and **6**, respectively. However, neither



of these compounds lent itself readily to conversion to **1** because of the presence of the extra carbon atom. Single-carbon functionalization of **2** was achieved *via*

(1) Urethane derivatives of the corresponding monosulfone (i) have

been recommended as amino-protecting groups removable by base-catalyzed β elimination [A. T. Kader and C. J. M. Stirling, *J. Chem. Soc.*, 258 (1964)]. Use of the disulfone alcohol was expected to lead to much greater base sensitivity. For other examples of protective groups based on β-elimination processes, see (a) L. A. Carpino and G. Y. Han, *J. Amer. Chem. Soc.*, **92**, 5748 (1970); *J. Org. Chem.*, **37**, 3404 (1972); (b) T. Wieland, G. J. Schmitt, and P. Pfaender, *Justus Liebigs Ann. Chem.*, **694**, 38 (1966); (c) E. Wünsch and R. Spangenberg, *Chem. Ber.*, **104**, 2427 (1971).

(1a) NOTE ADDED IN PROOF (MAY 7, 1973).—After the submission of this work a paper appeared [H. Stetter and B. Riberi, *Monatsh. Chem.*, **103**, 1262 (1972)] which reported that the aldol condensation between **2** and formaldehyde gave 1,1-bis(phenylsulfonyl)ethene (**12**). However, the properties reported for **12** did not correspond to those we observed for this compound. Professor Stetter has kindly informed us that the compound obtained by his group is actually the isomeric 1,2-bis(phenylsulfonyl) analog.

(2) Lack of success with Mannich condensations involving **2** has previously been reported. See W. L. Nobles and B. B. Thompson, *J. Pharm. Sci.*, **54**, 576 (1965).

reaction with *O,N,N*-trimethylformimidium methylsulfate or formamidine acetate to give **4a** or **4b**, but reduction of either of these compounds with sodium borohydride gave not the expected Mannich base but instead the overreduction product **7**, which was

$(C_6H_5SO_2)_2CHCH_3$ (**7**) $(C_6H_5SO_2)_2CHCOOC_2H_5$ (**8**)

also obtained by reduction of ester **8** by means of lithium aluminum hydride.

In view of these disappointing results it is especially gratifying that Smissman's recently described thiomethylation process[3] proved successful with 2 and provided not only an indirect approach to the Mannich bases[2] such as **11**, but also, *via* the route shown in Chart I,[4] a convenient route to alcohol **1**. The structure of the 1,1-disulfonyl olefin **12** was established by spectral techniques and an alternate synthesis which involved peracid oxidation of the corresponding sulfide **14** (Ar = C_6H_5).[5] For synthetic purposes this latter technique was used more successfully in the synthesis of the tosyl analog **15**, as outlined in Chart II. During this investigation a discrepancy was noted between our results and those of Fromm.[6] Upon oxidation of **13** by means of hydrogen peroxide in acetic acid Fromm obtained a compound, mp 222–223°, described as 1,1,2-tritosylethane (**17**). Since early in the present work[7] we presumed that treatment of **17** with alkali might lead to the tosyl analog of **1**, we attempted to obtain this compound by Fromm's method. When alkaline treatment failed to yield an alcohol we were led to question structure **17** and found that, in our hands at any rate, even though we tried to reproduce Fromm's conditions as closely as possible, oxidation of **13** gave **16**,[8a] mp 229–230°, rather than **17**, reported mp 222–223°. The structure of **16** was established by spectral examination and its alternate synthesis from the corresponding cis isomer by base-catalyzed isomerization.[8b] The availability of **15** suggested a possible alternate route to **17** and, in a search for further clarification of Fromm's results, **15** was treated with 1 equiv of sodium *p*-toluenesulfinate in dioxane–water solution. However, this reaction gave only the methylene bissulfone **18**. Other bases, such as sodium hydroxide, sodium acetate, sodium benzenesulfinate, sodium cyanate, or triethylamine, effected the same conversion. Presumably this reaction proceeds by a reverse aldol process followed by addition of the displaced methylene bissulfone anion to the unreacted disulfonylethylene.

Authentic 1,1,2-tritosylethane (**17**), mp 155–157°, could be made, however, by prior addition of *p*-thiocresol to **15** to give sulfide **19** followed by oxidation by means of *m*-chloroperbenzoic acid. Structure **17** was established by elemental analysis and spectral data (see Experimental Section). The fact that the melting point of **17** is far different from that reported by Fromm suggests that Fromm also probably isolated **16** from the oxidation of **13**. It is instructive to note in this connection that **22**, an isomer of **19** which is obtainable by addition of *p*-thiocresol to *cis*-1,2-ditosylethane (**21**), upon attempted oxidation with *m*-chloroperbenzoic acid, gives only **16**. Stepwise oxidation of **13** might well yield **22** as a first-formed product. Strangely enough, Fromm reports the synthesis of a

CHART I

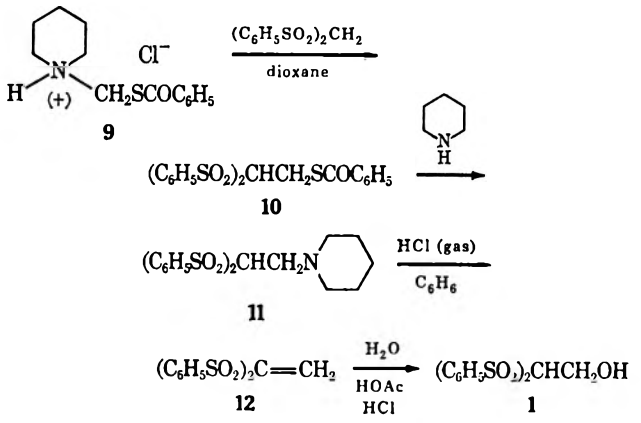
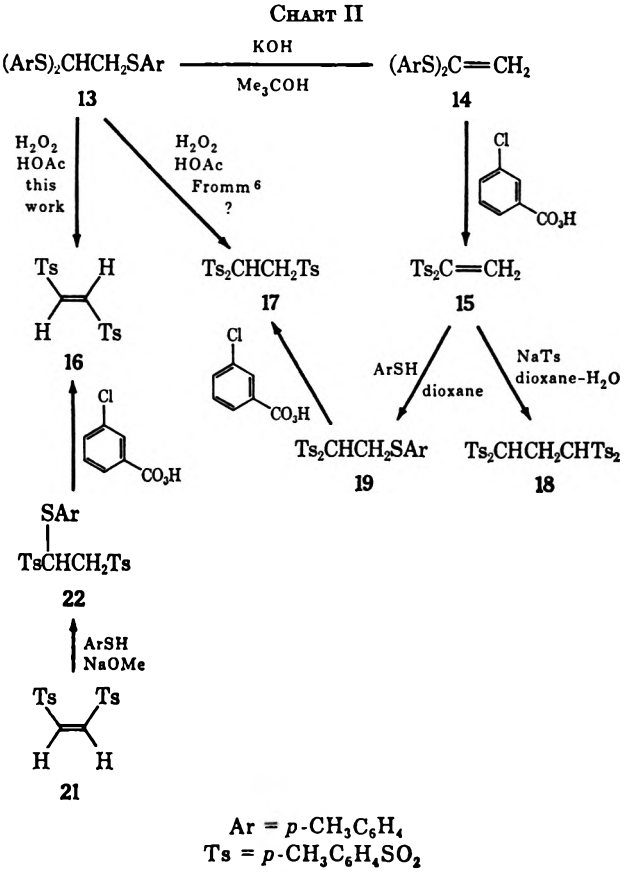


CHART II



Ar = *p*-$CH_3C_6H_4$
Ts = *p*-$CH_3C_6H_4SO_2$

(3) E. E. Smissman, J. R. J. Sorenson, W. A. Albrecht, and M. W. Creese, *J. Org. Chem.*, **35**, 1357 (1970).

(4) The conversion of **10** to **11** represents the deblocking of a protected thio ester by means of the β-elimination process which inspired this work. As yet we have been unable to study the possible utility of **1** as a protectant for carboxylic acids (*via* the simple esters) or amines (*via* the urethanes) because of the relative lack of reactivity of alcohol **1** (possibly because of the strong inductive effect of the two sulfone groups) toward acid chlorides, anhydrides, or isocyanates under conditions which avoid conversion to the corresponding olefin **12**. If a base such as triethylamine is present during these attempted acylations, bissulfone **3** is formed rather than **12**. By a similar effect, whereas it is possible to recrystallize **11** from benzene without difficulty, recrystallization from ethanol leads to the formation of **3**.

(5) Obtained by the method of T. Otsu, K. Tsuda, T. Fukumizu, and H. Inoue, *Nippon Kagaku Zasshi*, **89**, 892 (1968), except that the precursor **12** (Ar = C_6H_5) was prepared by a method analogous to that of Fromm and Siebert.[6]

(6) E. Fromm and E. Siebert, *Ber.*, **55**, 1014 (1922).

(7) On the basis of our current knowledge of the chemistry of these compounds we now realize that the reaction could not have taken place in this sense. Indeed it was shown that treatment of **12** with sodium hydroxide gave **3**, presumably *via* the reverse aldol reaction described for the homolog **16**.

(8) (a) W. E. Truce and R. J. McManimie, *J. Amer. Chem. Soc.*, **76**, 5745 (1954); (b) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, **33**, 985 (1968).

compound of structure 22 by permanganate oxidation of 13. However the melting point (119–120°) reported by Fromm differs somewhat from that which we obtained (127.5–129.5°) for this compound, and we made no attempt to compare these two substances directly.

Experimental Section[9]

S-[2,2-Bis(phenylsufonyl)ethyl] Thiobenzoate (10).—A mixture of 39 g of 9[4] and 44.8 g of bis(phenylsulfonyl)methane[10] in 500 ml of dioxane was refluxed for about 17 hr. Dilution to 3 l. with H_2O gave an oil which on seeding and cooling in an ice bath gave after 6–8 hr 50.5 g (77%) of cream-colored solid, mp 108–115°. A portion was recrystallized from ligroin (bp 60–70°)–benzene (3:1) to give a white, crystalline powder: mp 118–120°; ir (Nujol) 6.00 (C=O), 7.52, 8.72 μ (SO_2); nmr ($CDCl_3$) δ 3.82 (d, J = 6.5 Hz, 2, $CHCH_2$), 4.73 (t, 1, J = 6.5 Hz, $CHCH_2$), 7.7 (m, 15, phenyl).

Anal. Calcd for $C_{21}H_{18}S_3O_5$: C, 56.48; H, 4.06; S, 21.54. Found: C, 56.54; H, 4.05; S, 21.50.

1-[2,2-Bis(phenylsulfonyl)ethyl]piperidine (11).—In small portions 12.9 g of 10 was added over 2 min to 60 ml of piperidine. The resulting mixture was stirred magnetically for 20 min, diluted to 500 ml with H_2O, stirred 20 min longer, and filtered to give 10 g (89%) of the adduct as a white solid, mp 129–132°. Recrystallization from benzene gave an analytical sample: mp 128–130°; ir (Nujol) 7.57, 7.65, 8.69, 8.75 μ (SO_2); nmr ($CDCl_3$) δ 1.23 [m, 6, $(CH_2)_3$], 2.15 (m, 4, CH_2N), 3.07 (d, 2, $CHCH_2$), 4.6 (t, 1, $CHCH_2$), 7.75 (m, 10, phenyl).

Anal. Calcd for $C_{19}H_{23}NO_4S_2$: C, 57.99; H, 5.89. Found: C, 58.33; H, 5.72.

1,1-Bis(phenylsulfonyl)ethene (12).—A suspension of 35.8 g of crude 11, mp 129–132°, in 600 ml of benzene was treated with a stream of dry HCl gas for 15 min, which caused complete solution of the solid. The solution was refluxed with stirring for 3 hr, cooled to room temperature, and filtered to remove piperidine hydrochloride, and the filtrate was evaporated *in vacuo* to a volume of 75–100 ml. Addition of an equal volume of ligroin caused separation of an oil which soon solidified. Benzene was then added with heating until most of the solid dissolved, and the solution was filtered and allowed to stand overnight at room temperature. There was obtained 18.9 g (67.5%) of the disulfone, mp 120–125.5°. Recrystallization from ligroin–benzene (1:5) gave 15.5 g (55.5%): mp 126–127°; ir (Nujol) 7.55, 8.69 μ (SO_2); nmr ($CDCl_3$) δ 7.19 (s, 2, $=CH_2$), 7.5, 7.85 (m, 10, phenyl).

Anal. Calcd for $C_{14}H_{12}S_2O_4$: C, 54.53; H, 3.92; S, 20.79. Found: C, 54.49; H, 3.86; S, 20.85.

2,2-Bis(phenylsulfonyl)ethenol (1). A. From 1,1-Bis(phenylsulfonyl)ethene.—A mixture of 0.25 g of 12, 3 ml of H_2O, 0.25 ml of concentrated HCl, and 2 ml of dioxane was stirred at room temperature for 1 hr and diluted to 50 ml with H_2O. The mixture was stirred for 5–10 min until the tacky material became granular and filtered to give 0.13 g (49%) of the crude alcohol, mp 115–123.5°. Recrystallization from benzene gave 0.067 g (25%), of the alcohol, mp 121–122°.

B. From 1-[2,2-Bis(phenylsulfonyl)ethyl]piperidine.—A solution of 10 g of 11 in 100 ml of acetic acid and 50 ml of concentrated HCl was heated just below the boiling point on a hot plate for 5 min. The solution was diluted to 1 l. and stirred for 60 sec to coagulate some tacky material, and the mixture was filtered rapidly through a Büchner funnel. The filtrate was allowed to stand in a refrigerator for 24 hr and filtered to remove 2.5 g (30%) of flaky white crystals, mp 120–123°. An analytical sample was obtained by recrystallization from benzene: mp 121–123°; ir (Nujol) 2.86 (OH), 7.5, 8.62 μ (SO_2); nmr ($CDCl_3$) δ 3.1 (broad s, 1, OH), 4.29 (d, 2, $CHCH_2$), 4.69 (t, 1, $CHCH_2$), 7.6, 7.9 (m, 10, phenyl).

Anal. Calcd for $C_{14}H_{14}O_5S_2$: C, 51.52; H, 4.32; S, 19.65. Found: C, 51.59; H, 4.25; S, 19.60.

1,1-Bis(*p*-toluenesulfonyl)ethene (15).—To a solution of 2 g of 1,1-bis(*p*-tolylthio)ethene[11] in 60 ml of CH_2Cl_2 was added over a period of 6–7 min with stirring at room temperature 6 g of *m*-chloroperbenzoic acid (85%). After stirring for 15 hr the pasty mixture was shaken in a separatory funnel with three 75-ml portions of sodium bicarbonate solution, each containing 4 g of $NaHCO_3$. The dried ($MgSO_4$) solution was allowed to evaporate and the residue was recrystallized from ligroin–benzene (1:2) to give 1.53 g (62%) of the crude sulfone, mp 136–142°. Another recrystallization gave 1.25 g (50.6%), mp 140–143.5°. The analytical sample had mp 141.5–143.5°; ir (Nujol) 7.49, 8.61 μ (SO_2); nmr ($CDCl_3$) δ 2.44 (s, 6, CH_3), 7.17 (s, 2, $=CH_2$), 7.6 (q, 8, aryl).

Anal. Calcd for $C_{16}H_{16}S_2O_4$: C, 57.12; H, 4.79; S, 19.06. Found: C, 57.00; H, 4.70; S, 19.00.

Ethyl Bis(phenylsulfonyl)acetate (8).—A mixture of 31.4 g of ethyl *S*-phenylthioglycolate,[12] 28.6 g of *N*-bromosuccinimide, 160 ml of dry CCl_4, and a pinch of benzoyl peroxide was refluxed with stirring for 2 hr while irradiating with a Hanau sun lamp (Sole d'alta montagna 99, type 1005). The mixture was cooled to room temperature and filtered, and the CCl_4 was removed at reduced pressure. The residual oil was dissolved in 180 ml of CH_3OH and 36.4 g of sodium benzenesulfinate was added. After refluxing for 2.5 hr the solution was diluted with H_2O to 500 ml and extracted with three 25-ml portions of CH_2Cl_2. The extracts were washed with H_2O and dried ($MgSO_4$), and the solvent was removed to give an oil which was dissolved in 110 ml of acetic acid. After the addition of 45.5 ml of 30% H_2O_2 the mixture was stirred at room temperature for 20 hr, diluted to 500 ml with H_2O, filtered, dried in air, and recrystallized from 80 ml of benzene to give 12.5 g (21.2%) of the disulfone as white crystals, mp 141.5–143.5° (lit.[13] mp 140–142°).

1,1-Bis(phenylsulfonyl)ethane (7).—Reduction of ethyl bis(phenylsulfonyl)acetate (8) in ether by means of lithium aluminum hydride gave in 40% yield the disulfone: mp 98–99.5° (from benzene); ir (Nujol) 7.58, 8.65 μ (SO_2); nmr ($CDCl_3$) δ 1.72 (d, 3, CH_3), 4.55 (q, 1, $CHCH_3$), 7.7 (m, 10, phenyl).

Anal. Calcd for $C_{14}H_{14}O_4S_2$: C, 54.17; H, 4.54; S, 20.65. Found: C, 54.10; H, 4.61; S, 20.64.

1,1-Bis(phenylsulfonyl)-2-dimethylaminoethene (4a).—To a solution of 14.8 g of bis(phenylsulfonyl)methane[10] in 50 ml of dry DMF there was added 4.7 g of sodium methoxide (Matheson) followed by dropwise addition of 17.5 g of the adduct of dimethylformamide and dimethyl sulfate.[14] After stirring at room temperature for 7 hr the mixture was diluted to 500 ml with H_2O, and the solid was filtered, dried in air, and recrystallized from MeOH–$MeNO_2$ (5:1) to give 7.2 g (41%) of the enamine as yellow crystals, mp 198–199°. The analytical sample had mp 198–198.5°; ir (Nujol) 6.17 (C=C), 7.59, 8.79 μ (SO_2); nmr ($CDCl_3$) δ 3.06 (s, 6, CH_3), 7.4, 7.9 (m, 11, phenyl and =CH).

Anal. Calcd for $C_{16}H_{17}NO_4S_2$: C, 54.68; H, 4.88; N, 3.99. Found: C, 54.76; H, 4.91; N, 3.85.

1,1-Bis(phenylsulfonyl)-2-aminoethene (4b).—To a solution of 7.4 g of bis(phenylsulfonyl)methane (2) in 25 ml of dry DMF there was added 1.35 g of NaOMe (Matheson) followed by 2.5 g of formamidine acetate. The mixture, protected from moisture, was stirred at room temperature for 24 hr. Dilution with H_2O to 250 ml, filtration, and recrystallization from C_2H_5OH–$MeNO_2$ (1:4) gave 5 g (62%) of the disulfone as yellow crystals, mp 227–229°. The analytical sample had mp 228–229°; ir (Nujol) 2.90, 2.99 (NH_2), 6.12 (C=C), 7.56, 7.65, 7.8, 8.62, 8.77 μ (SO_2).

Anal. Calcd for $C_{14}H_{13}NO_4S_2$: C, 52.00; H, 4.05; N, 4.33. Found: C, 52.04; H, 4.18; N, 4.08.

tert-Butyl 3,3-Bis(phenylsulfonyl)propanoate (5).—To a solution of 1.5 g of bis(phenylsulfonyl)methane in 10 ml of dry DMF there was added 0.27 g of NaOMe followed by 0.98 g of *tert*-butyl α-bromoacetate. The mixture was stirred at room temperature for 8 hr, diluted carefully to the cloud point with water, seeded, and set aside for several hours. Filtration, washing with C_2H_5OH, and recrystallization from C_2H_5OH–$MeNO_2$ (8:1) gave 1.3 g (79%) of the ester as white crystals, mp 144.5–148°. Further recrystallization from the same solvent gave an analytical sample: mp 146–147°; ir (Nujol) 5.80 (C=O), 7.54, 8.61 μ (SO_2);

(9) Melting and boiling points are uncorrected. Infrared spectra were obtained on Perkin-Elmer 237B and 337 instruments and nmr spectra on Varian A-60, A-56/60, and Perkin-Elmer R-12 units. Elemental analyses were carried out by Charles Meade and associates, University of Massachusetts Microanalytical Laboratory.

(10) E. P. Kohler and M. Tishler, *J. Amer. Chem. Soc.*, **57**, 217 (1935).

(11) W. E. Truce and R. J. Steltenkamp, *J. Org. Chem.*, **27**, 2816 (1962).

(12) R. Pummerer, *Ber.*, **43**, 1401 (1910).

(13) R. Breslow and E. Mohacsi, *J. Amer. Chem. Soc.*, **83**, 4100 (1961).

(14) H. Bredereck, F. Effenberger, and G. Simchen, *Chem. Ber.*, **96**, 1350 (1963).

nmr ($CDCl_3$) δ 1.45 (s, 9, CH_3), 3.10 (d, 2, CH_2), 5.20 (t, 1, CH), 7.5–8 (m, 10, phenyl).

Anal. Calcd for $C_{19}H_{22}O_6S_2$: C, 55.59; H, 5.40; S, 15.62. Found: C, 55.44; H, 5.08; S, 15.80.

3,3-Bis(phenylsulfonyl)propanoic Acid (6).—To a solution of 2.86 g of KOH in 250 ml of CH_3OH there was added 7.15 g of bromoacetic acid, and after complete solution had occurred 17.1 g of the potassium salt of bis(phenylsulfonyl)methane was added and the mixture was stirred magnetically and refluxed for 20 hr and diluted to 1.7 l. with water. After 2 hr, unreacted disulfone was removed by filtration and the filtrate was acidified with concentrated HCl (Congo Red). After 24 hr at room temperature filtration gave 5.93 g (29.5%) of white solid, which after recrystallization from benzene containing a few drops of nitromethane gave 5.1 g (25.4%) of crusty white crystals, mp 159–162°. Recrystallization from the same solvent gave an analytical sample: mp 161–161.7°; ir (Nujol) 2.78, 2.83 (OH), 5.82 (C=O), 7.6, 7.66, 8.7, 8.8 μ (SO_2); nmr ($CDCl_3$) δ 3.25 (d, 2, CH_2), 5.18 (t, 1, CH), 6.75 (s, 1, OH, erased by D_2O), 7.5–8 (m, 10, phenyl). The same compound could be obtained by treatment of the *tert*-butyl ester with hydrochloric acid in acetic acid.

Anal. Calcd for $C_{15}H_{14}O_6S_2$: C, 50.83; H, 3.98; S, 18.09. Found: C, 50.81; H, 3.91; S, 17.80.

1,2-Bis(*p*-toluenesulfonyl)-1-*p*-toluenethioethane (22).—A mixture of 3.36 g of *cis*-1,2-ditosylethene (21), 2.48 g of *p*-toluenethiol, and 0.1 g of NaOMe (Matheson) in 25 ml of MeOH was stirred at room temperature for 24 hr. The mixture was filtered and the residual solid was washed with MeOH to give 2 g of white powder, mp 95–118°. Several recrystallizations of this crude material, which appeared to be a mixture of the desired compound and *cis*-$TsCH{=}CHSC_6H_4CH_3$-*p*, gave 0.51 g (11%) of the sulfide: mp 127.5–129.8°; ir (Nujol) 7.6, 8.78 μ (SO_2); nmr ($CDCl_3$) δ 2.3 (s, 3, CH_3), 2.41 (s, 6, CH_3), 3.7 (distorted dq, 2, CH_2), 4.55 (dd, 1, CH), 3.4 (m, 12, aryl); uv (95% C_2H_5OH) λ_{max} 228 nm (ε 34,100), 258 (6800), 275 (3890).

Anal. Calcd for $C_{23}H_{24}O_4S_3$: C, 59.97; H, 5.25; S, 20.88. Found: C, 60.05; H, 5.55; S, 20.70.

Attempted oxidation of 22 by means of *m*-chloroperbenzoic acid by the method described for 19 gave only *trans*-1,2-bis(*p*-toluenesulfonyl)ethene, mp 229–230°, identified by comparison with an authentic sample.[8] The same compound was obtained by oxidation of 13 with *m*-chloroperbenzoic acid or according to the method of Fromm.[6]

1,1-Bis(*p*-toluenesulfonyl)-2-*p*-toluenethioethane (19).—A mixture of 3.36 g of 15 and 1.24 g of *p*-toluenethiol was dissolved in 24 ml of warm dioxane and the solution was allowed to stand at room temperature for 24 hr. Upon dilution with 250 ml of H_2O an oil separated which solidified after several days standing or more readily on seeding. Filtration and recrystallization from methanol gave 3.56 g (77.5%) of the sulfide as white crystals, mp 106–108°. The analytical sample had mp 107–109° (MeOH); ir (Nujol) 7.49, 8.55 μ (SO_2); nmr ($CDCl_3$) δ 2.39 (s, 3, CH_3), 2.54 (s, 6, CH_3), 3.69 (d, 2, CH_2, J = 6.5 Hz), 4.66 (t, 1, CH, J = 6.5 Hz), 7.33 (s, 4, ArS–), 7.8 (q, 8, $ArSO_2$); uv (95% C_2H_5OH) λ_{max} 232 nm (ε 33,600), 264 (6150), 275 (4030).

Anal. Calcd for $C_{23}H_{24}O_4S_3$: C, 59.97; H, 5.25; S, 20.88. Found: C, 60.26; H, 5.52; S, 20.59.

1,1,2-Tris(*p*-toluenesulfonyl)ethane (17).—A solution of 3.56 g of 19 in 35 ml of CH_2Cl_2 was cooled in an ice bath and with stirring there was added over about 15 min 3.5 g of *m*-chloroperbenzoic acid. The mixture was stirred in the ice bath for 2 hr and at room temperature for 24 hr and then washed in a separatory funnel with two 75-ml portions of 1 *M* $NaHCO_3$ solution. Evaporation of the dried ($MgSO_4$) solution left a tacky white solid which was recrystallized from MeOH to give 0.55 g (14.5%) of the crude sulfone as white needles, mp 145–155°. Several recrystallizations from ethanol, from which an ethanol solvate was obtained, followed by $MeNO_2$–MeOH (1:10) and finally MeOH, gave an analytical sample: mp 155.5–157.5°; ir (Nujol) 7.43, 8.62 μ (SO_2); nmr ($CDCl_3$) δ 2.45 (s, 9, CH_3) 4.0 (d, 2, CH_2, J = 4.5 Hz), 5.09 (t, 1, CH, J = 4.5 Hz), 7.5 (q, 12, aryl); uv (95% C_2H_5OH) λ_{max} 264 nm (ε 2960), 275 (2195).

Anal. Calcd for $C_{23}H_{24}O_6S_3$: C, 56.08; H, 4.91; S, 19.53. Found: C, 55.82; H, 4.75; S, 19.77.

1,1,3,3-Tetrakis(*p*-toluenesulfonyl)propane (18).—A mixture of 1.01 g of 15 and 0.54 g of sodium *p*-toluenesulfinate in 15 ml of dioxane and 1.5 ml of H_2O was stirred at room temperature for 18 hr, 100 ml of H_2O was added, and the solid was filtered, dried in air, and recrystallized from C_2H_5OH–$MeNO_2$ (1:1) to give 0.75 g (76%) of white crystals: mp 225.5–227.5°; ir (Nujol) 8.62, 8.72 μ (SO_2); nmr ($CDCl_3$) δ 2.55 (s, 12, CH_3), 3.0 (t, 2, $CHCH_2CH$), 5.87 (t, 2, $CHCH_2$), 8.0 (q, 16, aryl); uv (95% C_2H_5OH–CH_2Cl_2, 65:35 v/v) λ_{max} 267 nm (ε 3930), 275 (3170); mass spectrum (80 eV) M^+ m/e 660.

Anal. Calcd for $C_{31}H_{32}O_8S_4$: C, 56.34; H, 4.88; S, 19.41. Found: C, 56.10; H, 4.72; S, 19.25.

Registry No.—1, 39837-25-7; 2, 3406-02-8; 2 potassium salt, 19472-81-2; 4a, 39837-27-9; 4b, 39082-61-6; 5, 39837-29-1; 6, 39837-30-4; 7, 33419-26-;0 8, 39837-32-6; 9, 886-07-7; 10, 39837-34-8; 11, 39837-35-9; 12, 39082-53-6; 14, 39837-37-1; 15, 39837-38-2; 17, 39837-39-3; 18, 39837-40-6; 19, 39837-41-7; 21, 15645-75-7; 22, 39837-43-9; piperidine, 110-89-4; *m*-chloroperbenzoic acid, 937-14-4; ethyl *S*-phenylthioglycolate, 7605-25-6; *N*-bromosuccinimide, 128-08-5; formamidine acetate, 3473-63-0; *tert*-butyl α-bromoacetate, 5292-43-3; bromoacetic acid, 79-08-3; *p*-toluenethiol, 106-45-6; sodium *p*-toluenesulfinate, 824-79-3.

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A Stable Glycinonitrile Radical. Evidence Suggesting Generation of Aminocyanocarbenes from Aminomalononitriles in Basic Media

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In basic media both dimethylaminomalononitrile (4) and *tert*-octylaminomalononitrile (1) decompose with generation of hydrogen cyanide. In the case of 4, α elimination is indicated, implying formation of dimethylaminocyanocarbene (6). Evidence is presented which suggests that in the decomposition of 1 analogous α elimination occurs to give *tert*-octylaminocyanocarbene (3). A solution of 1 in triethylamine shows a strong 16-line esr signal which is assigned to the stable *N*-*tert*-octylglycinonitrile radical (7). It is proposed that the carbene 3 abstracts a hydrogen from 1 to give 7 and the *N*-*tert*-octylaminomalononitrile radical (8). Three products are identified corresponding to dimerization of 7, disproportionation of 8, and combination of 7 and 8. There is no evidence for dimerization of the aminocyanocarbene 3 or for its addition to olefins. However, 3 may add to 1 and to *tert*-octylaminocyanoketene-*N*-*tert*-octylimine (24) to give the corresponding aminoiminopropenes. In aqueous base 4 gives dimethylamine. Hydrolysis of the carbene 6 appears to be the indicated mechanism. In the same medium 1 gives *tert*-octylamine, possibly owing to the analogous hydrolysis of *tert*-octylaminocyanocarbene (3). A novel synthesis of 1 is described.

In an earlier article,[1] the reaction of 2,4,4-trimethylpentene-2 with hydrogen cyanide and hydrogen fluoride was shown to give *tert*-octylaminomalononitrile (1), *tert*-octylaminocyanoketene-*N*-*tert*-octylimine (23), and other products. Also, it was suggested that *tert*-octylaminocyanocarbene (3) is generated when 1 is decomposed in basic media. The following report presents further evidence pointing to carbene 3 as an intermediate.

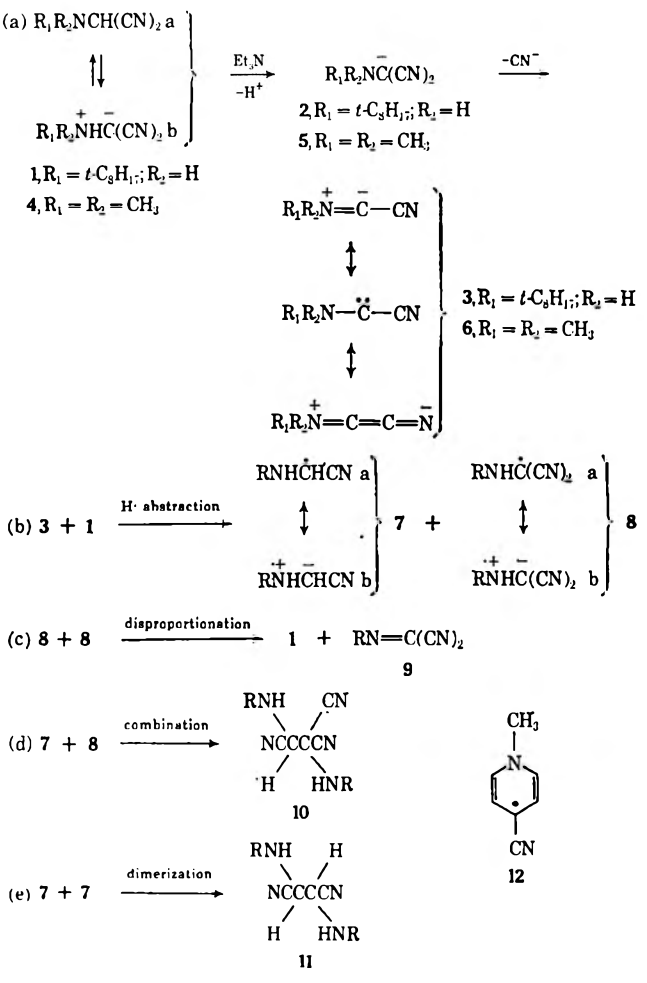
Results and Discussion

Evidence for a Radical Intermediate.—An oxygen-free solution of 1 in triethylamine decomposes smoothly at room temperature. Glpc shows that after 4 hr all 1 has disappeared. During the decomposition, the solution generates a strong 16-line esr signal, which persists for several hours (Figure 1). Computer simulation supports assignment of the observed spectrum to the *N*-*tert*-octylglycinonitrile radical 7[2] (Scheme I). The high stability of this radical is not unexpected since the vinylogous 4-cyano-*N*-methylpyridyl radical (12) is reportedly stable for a week.[3]

Another radical with a closely related α-aminonitrile structure is the di-*tert*-octylaminomaleonitrile radical whose stability was reported earlier.[1] The stability of the radical 7 is probably due to resonance involving a charge-separated canonical form 7b (Scheme I).

No conventional explanation seems to account for the formation of the glycinonitrile radical 7 from 1 under such mild conditions. It is, therefore, proposed that initially α elimination of hydrogen cyanide occurs to give the aminocyanocarbene 3 (discussed in detail below). Once formed, 3 abstracts a hydrogen atom from unreacted 1 (reaction b, Scheme I) to give 7. In this process, the *tert*-octylaminomalononitrile radical 8 should be the second product. This radical may be responsible for a very broad unstructured doublet that underlies the signal for radical 7. The broadness and apparent lack of hyperfine structure can be ascribed to a very short relaxation time, which may result from two possible exchange processes. These are electron exchange between the radical 8 and the aminomalononitrile anion 2 and possibly also hydrogen exchange be-

SCHEME I

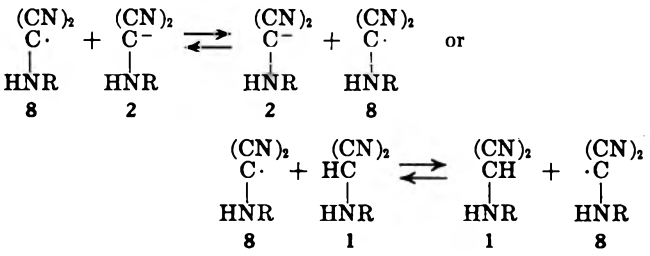


(1) L. deVries, *J. Org. Chem.*, **36**, 3442 (1971).

(2) Dr. J. Q. Adams has closely matched the observed hyperfine structure (Figure 1A) through computer simulation. The odd electron is assumed to interact with two nitrogen atoms and two hydrogen atoms as in radical 7. Hyperfine splitting constants and line width giving the best agreement (Figure 1c) follow: N_1, 2.77 G; N_2, 3.32 G; H_1, 12.84 G; H_2, 22.81 G; line width 1.38 G. An even closer approach to the experimental spectrum results when a simple doublet is superimposed. The doublet spectrum (hyperfine splitting constant 17.54 G; line width, 9.23 G) is shown in Figure 1D and the composite spectrum (1D + 1C) in Figure 1b. It is probable that the doublet actually contains additional fine structure which is broadened owing to exchange processes discussed below. As an alternate possibility, we considered interaction of the odd electron with one hydrogen atom and three nitrogen atoms (two of which are equivalent) as in radical 8 (Scheme I). A satisfactory match could, however, not be obtained.

(3) M. Itoh and S. Nagakura, *Tetrahedron Lett.*, **No. 8**, 417 (1965).

tween the radical **8** and the aminomalononitrile **1**, *e.g.*



The stability of the radical **8** could be comparable to or even greater than that of the radical **7**. The doublet shape of the spectral envelope suggests that in **8** the largest hyperfine splitting constant is associated with the hydrogen atom.

Hydrogen abstraction by the aminocyanocarbene **3** is plausible if the structure of this carbene is similar to the structure recently proposed for unsubstituted aminocyanocarbene by Loew and Chang.[4] These authors postulate a bent singlet ground state resembling a spin-paired biradical in which slightly more than one electron is localized on the "methylene" carbon and somewhat less than one electron is delocalized throughout the π system. This results in a carbon atom which is more accurately described as trivalent and with greater kinship to a radical than a methylene carbon. According to Wagner and Hammond,[5] hydrogen abstraction by such a singlet biradical is no less probable than by a triplet, providing that the singlet has a sufficiently long lifetime.

It is, therefore, unnecessary to invoke for carbene **3** a triplet state which, moreover, is expected to be of higher energy than the singlet ground state.[4]

In a valence bond description **3** is represented by a resonance hybrid with a major contribution from an ylide form (Scheme I). Similar resonance-stabilized structures have been proposed for various so-called "nucleophilic" carbenes,[6] but the aminocyanocarbene structure is unique because the carbene carbon carries an electron-supplying amino group as well as an electron-withdrawing nitrile group. This substitution pattern should be conducive to maximum stabilization of carbenes.[7] One may, therefore, expect aminocyanocarbenes to exhibit an enhanced stability relative to carbenes with only amino or cyano substituents.

In the absence of data about carbene stabilities, such a postulate cannot be supported by calculation, nor has it been demonstrated experimentally. However, some stable compounds, such as carbon monoxide, the isonitriles, and fulminic acid derivatives, represent extremes of stabilization of divalent carbon by charge-separated forms. An important factor in the unusual stability of these compounds is that a highly electronegative sp orbital is available to accommodate the negative charge on carbon.

The carbene **3** has not been reported, but Moser,

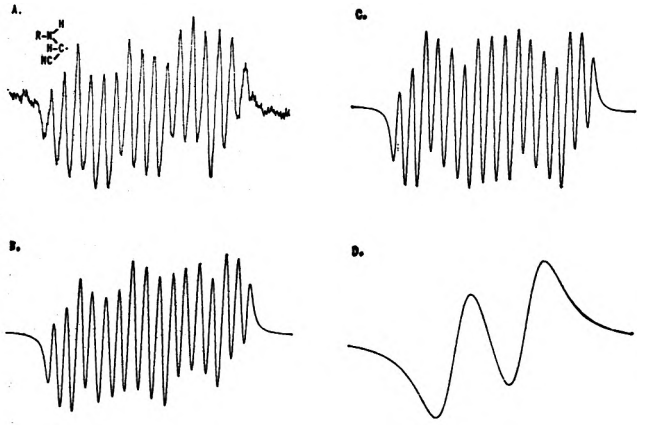
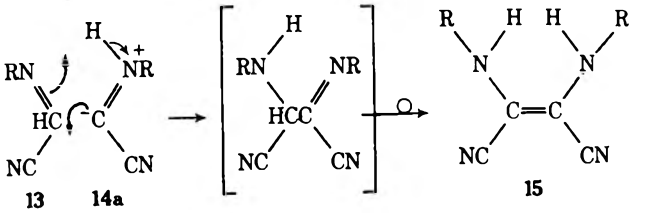


Figure 1.—Esr spectrum of **7** and computer simulation (width of spectra = 70 G): (A) experimental spectrum; (B) best computer match composite spectrum; (C) computed fine structure for **7** alone; (D) background doublet (amplitude magnified ~40×).

et al.,[8] have claimed the generation of unsubstituted aminocyanocarbene by photolysis of aminodiazoacetonitrile in a 2-methyltetrahydrofuran glass at −196°. They postulate a singlet ground state similar to the one described above.

Three recent calculations compare the stabilities of aminocyanocarbene and the tautomeric iminoacetonitrile (NH=CHCN). Serre and Schneider[9] suggest that aminocyanocarbene should be the more stable isomer, but recently Loew and Chang[4] and later yet Jameson and Yang[10] have reached the opposite conclusion. Respectively, these authors arrive at energy differences of 76 and 56 kcal in favor of the iminoacetonitrile. The greater stability of the iminoacetonitrile tautomer is supported by recent work of Ferris, *et al.*,[11] who find alkyliminoacetonitriles to be relatively stable compounds which show no evidence of carbene character. On the other hand, iminoacetonitriles have recently been reported to dimerize upon heating to give the diaminomaleonitriles **15**.[12a] This suggests that the aminocyanocarbene may be present in a small equilibrium concentration and that dimer formation may result from attack of the carbene **14** (shown in the ylide form **14a**) on the iminoacetonitrile,[13] *i.e.*



(4) G. H. Loew and S. Chang, *Tetrahedron*, **27**, 2989 (1971); G. H. Loew, *J. Theor. Biol.*, **33**, 121 (1971).

(5) P. J. Wagner and G. S. Hammond, *J. Amer. Chem. Soc.*, **87**, 4009 (1965), especially footnote 12.

(6) (a) H. Quast and S. Hünig, *Chem. Ber.*, **99**, 2017 (1966); D. M. Lemal, R. A. Lovald, and K. J. Kawano, *J. Amer. Chem. Soc.*, **86**, 2518 (1964); (b) H. W. Wanzlick and F. Esser, *Angew. Chem.*, **76**, 614 (1964); **74**, 129 (1962); H. W. Wanzlick and H. Arens, *Chem. Ber.*, **97**, 2447 (1964).

(7) (a) W. Wilberg, *Angew. Chem.*, **80**, 809 (1968); (b) J. Hine, "Divalent Carbon," Ronald Press, New York, N. Y., 1964, p 168ff.

(8) R. E. Moser, J. M. Fritsch, T. M. Fritsch, T. L. Westman, R. M. Kliss, and C. N. Matthews, *J. Amer. Chem. Soc.*, **89**, 5673 (1967).

(9) J. Serre and F. Schneider, *J. Chim. Phys.*, **60**, 1655 (1964).

(10) C. J. Jameson and W. Yang, *J. Theor. Biol.*, **35**, 247 (1972).

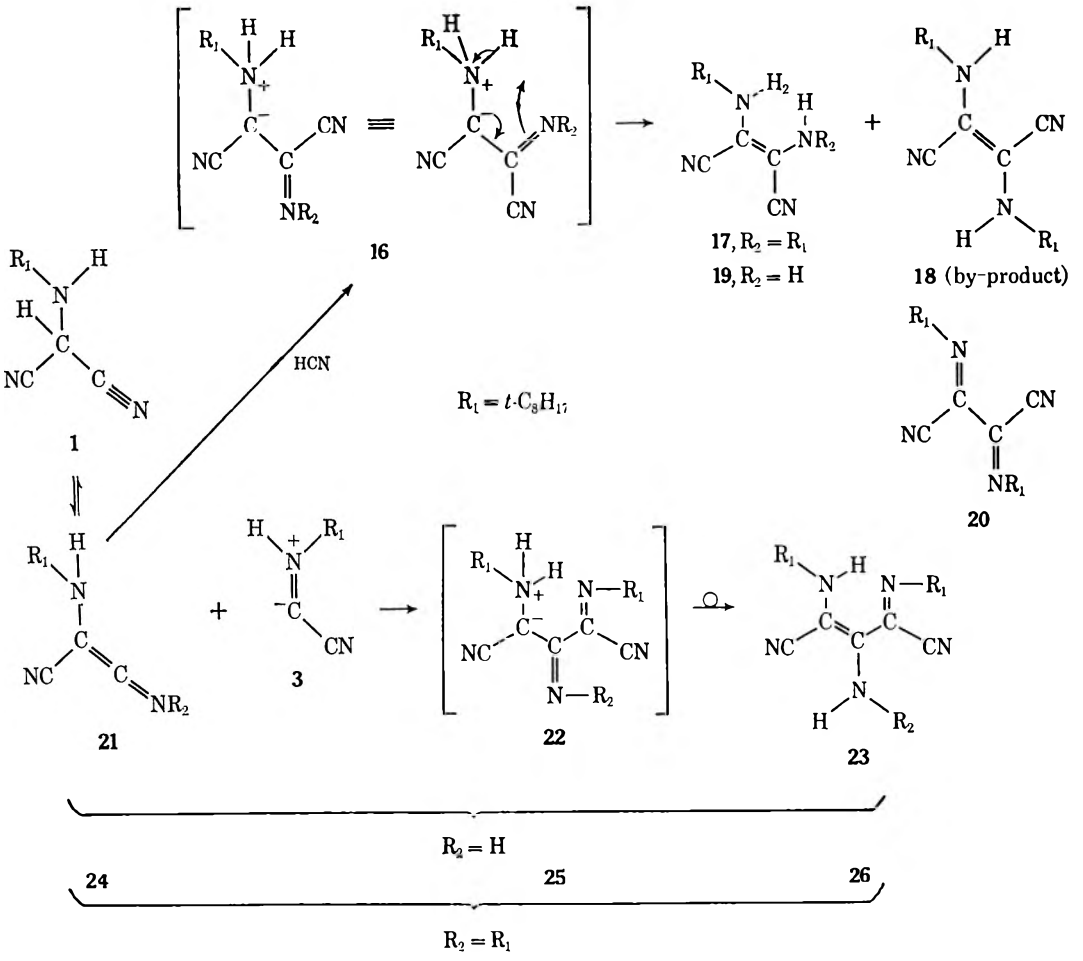
(11) J. P. Ferris, D. B. Donner, and W. Lotz, *J. Amer. Chem. Soc.*, **94**, 6968 (1972).

(12) (a) H. Dabek, R. Selvarajan, and J. H. Boyer, *Chem. Commun.*, 244 (1972); (b) J. H. Boyer and H. Dabek *ibid.*, 1204 (1970).

(13) Direct dimerization of the aminocyanocarbene **14** is unlikely, since the carbene carbon is expected to carry a partial negative charge owing to a major contribution of the ylide structure **14a** to the resonance hybrid representing **14**. Therefore, Coulombic repulsion in the transition state is likely to result in a prohibitively high energy barrier to dimerization, although such a process is expected to be highly exothermic. Additionally, dimerization is unlikely because the concentration of **14** is probably very low. Balli[14] finds accordingly that nucleophilic carbenes alone do not produce dimers.

(14) H. Balli, *Angew. Chem., Int. Ed. Engl.*, **3**, 809 (1964).

SCHEME II



Evidence for α Elimination in Triethylamine Solution.—The hydrogen cyanide generated in the decomposition of **1** in triethylamine solution was identified by the glpc coinjection technique. Its formation was confirmed by the isolation of a crystalline product, shown by elemental analysis and spectral properties to be 1-*tert*-octylamino-2-aminomaleonitrile (**19**), the addition product of **1** and hydrogen cyanide[15] (Scheme II).

The generation of hydrogen cyanide is only then indicative of formation of the aminocyanocarbene **3** when α elimination can be demonstrated. Direct proof is complicated in the case of **1** because β elimination and a number of bimolecular mechanisms are alternative possibilities (Scheme III). Instead, indirect evidence pointing to α elimination and formation of the carbene comes from the investigation of three related compounds.

The first is dimethylaminomalononitrile[16] (**4**, Scheme I), which in triethylamine solution also generates hydrogen cyanide, though at a lower rate than **1**. This was demonstrated by glpc, by high resolution mass spectroscopy, and also chemically. When **4** was treated with triethylamine in the presence of the aminocyanoketenimine **24**, the only identified product was bis-*tert*-octylaminomaleonitrile (**17**), which is the known[1] product of addition of hydrogen cyanide to **24**. (See Scheme II.)

In the case of **4**, two reactions are ruled out which are alternatives to α elimination in the case of **1**. These are β elimination of hydrogen cyanide and concerted elimination of cyanide ion owing to attack of the aminomalononitrile anion on the ketenimine tautomer (reactions a and d, Scheme III).

There appear to remain only two alternatives to α elimination. Both of these are bimolecular mechanisms.

(1) Nucleophilic displacement of cyanide ion from **4** by the aminomalononitrile anion **5** could occur (reaction b, Scheme III). This mechanism appears unlikely because the nucleophile, the substrate, and the product are all sterically crowded; moreover, the nitrile group is a very poor leaving group. There appears to be no precedent for its nucleophilic displacement in an SN2 reaction unless it is assisted by a complexing metal.[18]

(2) Attack on the aminomalononitrile **4** by its ylide tautomer **4b** (reaction c, Scheme III) could occur. Such a cyclic mechanism implies independence on the medium and fails to explain why **4** is stable in nonbasic

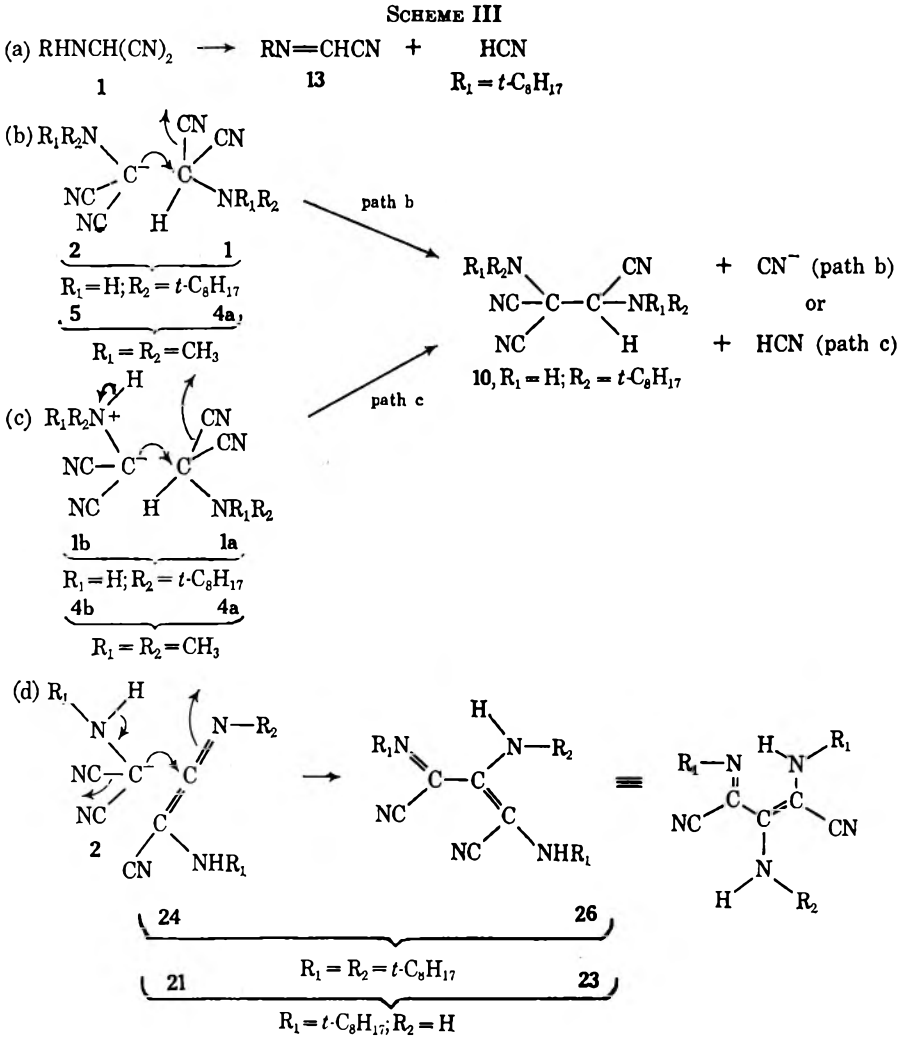
(15) The reaction of **1** with hydrogen cyanide is analogous to the reported additions of hydrogen cyanide to dimethylaminomalononitrile to give 1-dimethylamino-2-aminomaleonitrile[16] and to aminomalononitrile to give diaminomaleonitrile.[17] These reactions can be explained by assuming that the aminomalononitrile reacts in the tautomeric aminocyanoketenimine form **21** (Scheme II).

(16) Z. Arnold, *Collect. Czech. Chem. Commun.*, **26**, 1113 (1961); see also H. Gold and O. Bayer, *Chem. Ber.*, **94**, 2594 (1961).

(17) J. P. Ferris and L. E. Orgel, *J. Amer. Chem. Soc.*, **88**, 3829 (1966).

(18) Y. Yoshimura, Y. Ohgo, and T. Sato, *Bull. Chem. Soc. Jap.*, **38**, 1809 (1965); M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954, Chapter 10.

SCHEME III



solvents but decomposes in triethylamine or aqueous base (see below.)

Assuming that the two alternate mechanisms can thus be discounted, it appears that hydrogen cyanide evolution from **4** must occur by α elimination, resulting in the initial formation of the corresponding aminocyanocarbene **6** (Scheme I).

The second model compound was *N-tert*-octylamino-*tert*-octylmalononitrile[19] (**37**). This compound was indefinitely stable in triethylamine, even at reflux. In this case, α elimination of hydrogen cyanide is impossible, but β elimination does not appear to occur.

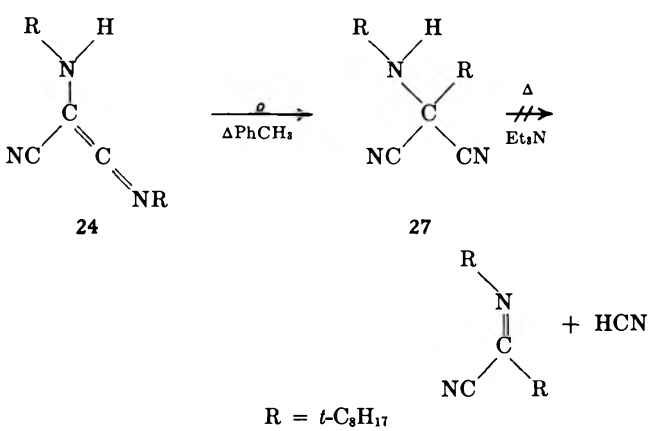
The third model compound was malononitrile. This compound is unstable in triethylamine solution; however, glpc showed that hydrogen cyanide is not produced.[20]

This thermolysis will be discussed in a separate article.

For all three compounds the initial proton-abstraction process is readily apparent: malononitrile is a known carbon acid, and nmr spectra show rapid deuterium exchange of the protons on both nitrogen and carbon for **1** and of the proton on carbon for **4** (see Experimental Section).

For the feasibility of the next step, the elimination of a cyanide ion from the resulting malononitrile anion, an amino substituent appears to be essential. Stabilization of the incipient aminocyanocarbene by an ylide form, as proposed above for **3**, allows the developing positive charge to be accommodated at the amino nitrogen while electron density increases at the neighboring "carbene" carbon. The resulting repulsion

(19) Compound **27** is the main product in the thermal rearrangement of *tert*-octylaminocyanoketen-*N-tert*-octylimine (**34**).



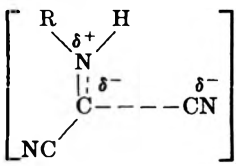
This thermolysis will be discussed in a separate article.

(20) A small amount of hydrogen cyanide is generated when oxygen is not rigorously excluded. This is to be expected, since hydrogen cyanide forms when cyanoalkyl radicals react with oxygen.[21] The mechanism is probably analogous to that proposed by Russell[22] for the generation of nitrous acid in the autoxidation of 2-nitropropane.

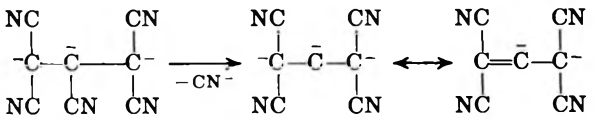
(21) M. Talât-Erben and N. Önol, *Can. J. Chem.*, **38**, 1154 (1960).

(22) G. A. Russell, *J. Amer. Chem. Soc.*, **76**, 1595 (1954).

could effectively promote departure of the cyanide ion, *i.e.*,

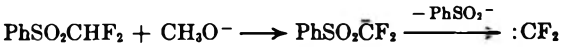


α elimination of a cyanide ion from an anion to give a carbene has been reported by Riegel, *et al.*,[23] *i.e.*,



In this case, stabilization is probably due to a decreased accumulation of negative charge and to resonance of the carbene form with two olefinic anion forms.

Formation of a carbene from an anion by α elimination of a group capable of stabilizing the negative charge has a well-established precedent: in the generation of difluorocarbene from difluoromethylphenyl sulfone,[24] α elimination of the benzenesulfinate ion occurs, *e.g.*,



Difluoromethylene resembles **3** in two respects: it has a singlet ground state and it is unusually stable,[25] owing in part to contribution of such forms as $^{+}F{=}\bar{C}F$.

In summary, the evidence points to the conclusion that in triethylamine solution aminomalononitriles generate hydrogen cyanide by α but not by β elimination. The implied formation of the aminocyanocarbene **3** is consistent with the earlier, independent evidence for such an intermediate based on the observed generation of the radical **7** (see above).

Products.—Further evidence pointing to the formation of **3** and the radicals **7** and **8** comes from identification of a number of additional products in the decomposition of **1** in triethylamine. Three of these can be explained as combination or disproportionation products of the radicals **7** and **8** (reactions c, d, and e in Scheme I). Many such combination and disproportionation reactions of cyanoalkyl radicals have been reported.[26]

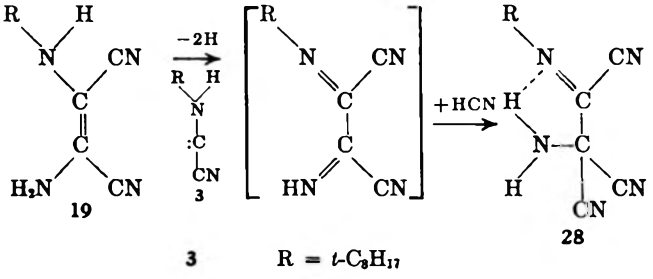
Disproportionation of the radical **8** according to reaction c may account for the formation of *tert*-octyliminomalononitrile (**9**), which is a decomposition product when **1** is treated with triethylamine. This was demonstrated by glpc using authentic **9**[27] and also by coupled gas chromatography–mass spectroscopy.

A small amount of the diaminotricyanoethane (**10**) was isolated. The formation of **10** can be explained by combination of the radicals **7** and **8** (reaction d). This is equivalent to insertion of the carbene **3** in the C–H bond of the aminomalononitrile **1**.

It is, however, also possible that the radicals **7** and **8** are not involved in the formation of **10**. The carbene **3** may initially rearrange to the more stable *tert*-octyliminoacetonitrile (**13**, R = t-C_8H_{17}), to which **1** may add to give **10**.[29]

Mass spectra of the crude reaction product of **1** and triethylamine provide strong evidence for the presence of the diaminosuccinonitrile **11**,[30] which is the dimerization product of radical **7** (reaction e, Scheme I).

One additional product was isolated and identified as 1-*tert*-octylimino-2-*tert*-octylamino-1,2,2-tricyanoethane (**28**). It is assumed that the aminocyanocarbene **3** is responsible for the hydrogen abstraction which is implied in this structure. The following mechanism is tentatively suggested.



3 R = t-C_8H_{17}

It is significant that no evidence was found for either 1,2-di-*tert*-octylaminotetracyanoethane or *tert*-octylglycinonitrile ($RNHCH_2CN$).[32] The absence of the former compound may indicate that the radical **8** does not dimerize. This could reflect an important

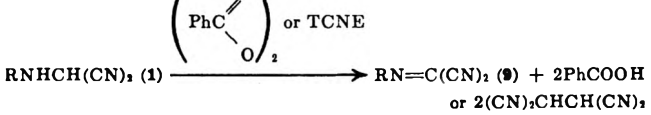
(23) P. H. Riegel, I. Bernal, W. H. Reinsmith, and G. K. Fraenkel, *J. Amer. Chem. Soc.*, **85**, 683 (1963).

(24) J. H. Hine and J. J. Porter, *J. Amer. Chem. Soc.*, **82**, 6178 (1960).

(25) J. P. Simons, *J. Chem. Soc.*, 5406 (1965); *Nature (London)*, **192**, 943 (1961); J. H. Hine, "Divalent Carbon," Ronald Press, New York, N. Y., 1964, pp 40, 41, and 45.

(26) C. G. Overberger and A. Lebovits, *J. Amer. Chem. Soc.*, **76**, 2722 (1954); A. F. Bichel and W. A. Waters, *Rec. Trav. Chim. Pays-Bas*, **69**, 1490 (1950); G. S. Hammond, J. N. Sen, and C. E. Boozer, *J. Amer. Chem. Soc.*, **77**, 3244 (1955); C. G. Overberger and M. B. Berenbaum, *ibid.*, **73**, 4883 (1951); **74**, 3293 (1952).

(27) Compound **9** is prepared in high yield by dehydrogenation of **1** with tetracyanoethylene or benzoyl peroxide (TCNE), *e.g.*,



The analogous dehydrogenation of the diaminomaleonitrile **17** (Scheme II) by benzoyl peroxide was described in an earlier article.[1] The use of tetracyanoethylene in dehydrogenation has been reported.[28]

(28) D. T. Logone and G. L. Smith, *Tetrahedron Lett.*, 205 (1962).

(29) Authentic **10** was isolated as a product in the thermolyses of **1** and of the aminocyanoketenimine **26** (to be published). Boyer and Dabek[12b] and very recently Ferris, *et al.*,[11] have reported that reaction of *tert*-butyliminoacetonitrile (**13**, R = t-C_4H_9) with hydrogen cyanide gives 1,2-di-*tert*-butylamino-1,2,2-tricyanoethane, the *tert*-butyl analog of **10**. Ferris proposed that **13** adds hydrogen cyanide to give *tert*-butylaminomalononitrile, which adds to **13** to give the diaminotricyanoethane. The present author has observed the analogous addition of hydrogen cyanide to *tert*-octyliminoacetonitrile (**13**, R = t-C_8H_{17}) in an aprotic medium containing methanesulfonic acid. Under these conditions, the salt of *tert*-octylaminomalononitrile (**1**) precipitates. This reaction has been developed into a novel high-yield synthesis of **1** (see Experimental Section).

(30) In an attempt to obtain unambiguous proof for the presence of **11**, its preparation was tried by various reduction methods, *i.e.*, catalytic hydrogenation of the diaminomaleonitrile **17** and of di-*tert*-octyliminosuccinonitrile[1] (**20**, Scheme II), as well as reduction of **20** with lithium aluminum hydride, sodium borohydride, or dimethylaminoborane, which is a specific reagent for the reduction of imines.[31] In each case, only **17** was formed, which could not be reduced further by any method tried.

(31) J. H. Billman and J. W. McDowell, *J. Org. Chem.*, **26**, 1437 (1961).

(32) An authentic sample of *tert*-octylglycinonitrile was prepared according to the method of Luskin, *et al.*[33]

(33) L. S. Luskin, M. L. Gulver, G. E. Gantert, W. E. Craig, and R. S. Cook, *J. Amer. Chem. Soc.*, **78**, 4042 (1956).

contribution of the charge-separated structure **8b** (Scheme I). High charge density at the central carbon atom would give rise to Coulombic repulsion and consequently a high activation energy in dimerization. The absence of *tert*-octylglycinonitrile indicates that hydrogen abstraction by the glycinonitrile radical **7** does not occur. This is consistent with its high stability and with the relatively low nucleophilicity expected for this radical.

The evidence suggests that the aminocyanocarbene **3** is not a direct precursor for any of the products of the decomposition of **1** in triethylamine that have been described thus far. Rather, it suggests that their immediate precursors are the radicals **7** and **8**, whose formation is proposed to involve **3** as an intermediate (see above).

From the decomposition mixture, one additional compound was isolated which could be derived directly from the carbene **3**. Elemental analysis and spectral data show this to be 1-*tert*-octylamino-2-amino-3-*tert*-octylimino-1,3-dicyanopropene-1 (**23**, Scheme II) which formally is the product of addition of **3** to **1** (as the tautomeric aminocyanoketenimine **21**).

Possibly **21** traps the carbene **3** to give an ylide intermediate **22** which, after a prototropic rearrangement, gives the enaminoimine **23**. Such a mechanism appears consistent with the general pattern proposed for the addition reactions of the analogous *tert*-octylaminocyanoketen-*N*-*tert*-octylimine (**24**), specifically, the addition of hydrogen cyanide.[1] In that reaction, protonation of the *tert*-octylamino group of **24** and attack of cyanide ion at the imino carbon atom is proposed to give an ylide intermediate **16**. A prototropic rearrangement of **16** then gives di-*tert*-octylaminomaleonitrile as the final product (**17**, Scheme II).

Additional support for involvement of the aminocyanoketenimine tautomer **21** in the formation of **23** comes from the observation that reaction of the authentic aminocyanoketenimine **24** with **1** in basic media (the conditions for the proposed generation of aminocyanocarbene **3**) gives an enaminoimine **26** (see below) which is a homolog of **23**.

A mixture of **1** and the aminocyanoketenimine **24** in mole ratio 1:2 was treated with either triethylamine or aqueous potassium hydroxide at room temperature. Under both sets of conditions, an orange-red reaction product was obtained, mainly consisting of approximately equimolar amounts of two major components. These were separable through their different solubilities in hexane. The less soluble compound was colorless and was proved to be di-*tert*-octylaminomaleonitrile (**17**). The more soluble product **26** was orange-red. Elemental analysis and spectral data indicate that this compound is 1,2-di-*tert*-octylamino-3-*tert*-octylimino-1,3-dicyanopropene-1.[34] This is formally the product of addition of **3** to aminocyanoketenimine **24**. It is proposed that the mechanism is analogous to that postulated for the formation of **23** from **1** in the absence of **24**.

There is no direct evidence to exclude alternative routes for the formation of the enaminoimines **23** and **26**. One such mechanism involving addition of the aminomalononitrile anion **2** and concerted elimination of cyanide ion is shown in Scheme III (reaction d). However, these alternatives fail to account for the formation of the radicals **7** and **8** and the decomposition products which evidently are derived from them. Economy of mechanism, therefore, favors the aminocyanocarbene route.

The aminoiminopropene **26** was also obtained directly from the reaction of 2,4,4-trimethylpentene-2 with hydrogen cyanide and hydrogen fluoride when the crude product was treated with triethylamine or with concentrated potassium hydroxide for a prolonged period of time. Under these conditions, the amino cyanoketenimine **24**, which is the main reaction product, slowly decomposes. This is evident from the disappearance of the characteristic ketenimine band at 2025 cm^{-1}. The initial products apparently are 2,4,4-trimethylpentene-1 (demonstrated by glpc) and *tert*-octylaminomalononitrile (**1**). Formation of **26** can then occur as outlined above. The hydrogen cyanide which is the second product in the decomposition of **1** adds to **24** to give the diaminomaleonitrile **17** accompanied by a small amount of the tautomeric diaminofumaronitrile **18**[35] (Scheme II). According to glpc, both compounds are absent in the product of decomposition of **1** in triethylamine. This suggests that dimerization of the aminocyanocarbene **3** to give **17** or **18** does not occur.

The above interpretation is supported by the isolation of the enaminoimine **26** as a minor product in the decomposition of pure **24** in refluxing triethylamine. The main product was **17**, and the formation of 2,4,4-trimethylpentene-1 was demonstrated by glpc.

Evidence for α Elimination in Aqueous Base.—In the decomposition reactions of aminomalononitriles which have been discussed so far, triethylamine was the medium. Aminocyanocarbenes may also be formed in aqueous base. The aminomalononitriles **1** and **4** dissolve in aqueous potassium hydroxide to give initially colorless solutions. In these solutions the aminomalononitriles must occur as the corresponding anions **2** or **5**[38] since immediate neutralization followed by solvent extraction allows their recovery in high yields.

A solution of **4** in aqueous potassium hydroxide

(34) The nmr spectrum of **26** shows the presence of two magnetically equivalent *tert*-octyl groups. This suggests that **26** occurs in a single configuration in which the terminal amino and imino groups are bridged by an intramolecular hydrogen bond through which very fast proton exchange occurs. The nmr spectrum of **23** is consistent with an equilibrium mixture of two conformational isomers A and B in approximately equimolar proportions. The two *tert*-octyl groups are equivalent in A and nonequivalent in B. The equivalence in A is ascribed to the occurrence of very fast proton exchange as postulated for **26**. The nonequivalence in B implies the absence of such exchange. The structures of **26** and **23** are the subject of a forthcoming article.

(35) Compound **18** is apparently in thermodynamic equilibrium with the diaminomaleonitrile **17**. Small amounts of **18** are formed when **17** is treated with bases (KOH or Et_3N) for a prolonged period and also when **17** is prepared by catalytic hydrogenation of di-*tert*-octyliminosuccinonitrile[1] (**20**, Scheme II) or by addition of hydrogen cyanide to the aminocyanoketenimine **24** (Scheme II). The diaminofumaronitrile structure of **18** is proven by its acid-catalyzed conversion to **17** at room temperature (see Experimental Section). This is similar to the acid-catalyzed cis–trans isomerization of enamino esters[36] and of unsubstituted diaminofumaronitrile.[37] The structure of **18** is confirmed by elemental analysis and spectral data. The ir activity of the C=C stretching band at 1575 cm^{-1} seems unexpected for a symmetrical structure, but the analogous band was also observed for unsubstituted diaminofumaronitrile.[37]

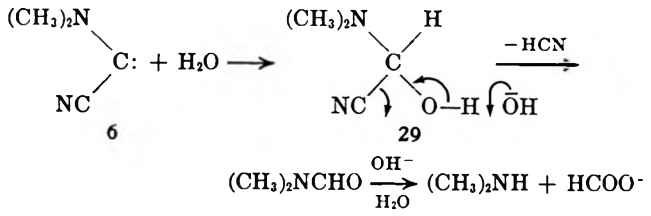
(36) K. Herbig, R. Huisgen, and H. Huber, *Chem. Ber.*, **99**, 2546 (1966).

(37) Y. Yamada, N. Nagashima, Y. Iwashita, A. Nakamura, and T. Kumashiro, *Tetrahedron Lett.*, **43**, 4529 (1968).

(38) Ferris and Orgel[39] showed similarly that bromomalononitrile dissolves in aqueous potassium hydroxide as the anion.

(39) J. P. Ferris and L. E. Orgel, *J. Org. Chem.*, **30**, 2365 (1965).

evolves dimethylamine essentially at once as shown by its characteristic odor, by glpc, and by mass spectra. A possible explanation is that the dimethylamine originates from hydrolysis of the carbene **6**. Pre-



cedents for such a reaction are the reported methanolyses of the related resonance-stabilized carbenes, cyanophenylcarbene[40] and diphenylcarbene,[41] to give the corresponding ethers.

Analogously, dimethylaminocyanocarbinol (**29**) is expected to be the initial hydrolysis product of dimethylaminocyanocarbene. In the basic medium **29** can eliminate hydrogen cyanide to give dimethylformamide, whose further hydrolysis gives dimethylamine.

Conceivably, ionization of **4** to give the cyanoimmonium cyanide $[(CH_3)_2N{=}CHCN]^+(CN)^-$, followed by hydrolysis, could account for the formation of **29** and finally dimethylamine. This mechanism does not involve the aminocyanocarbene **6**. It is, however, unlikely for the following reasons. Firstly, ionization of **4** and subsequent hydrolysis should proceed about as well in neutral as in basic aqueous solution, but **4** is found to be insoluble in neutral water and to be stable in its presence.

Furthermore, ionization of cyanide ion in aminomalononitriles is inductively opposed by the second nitrile group and should be far slower than in diaminoacetonitriles, where a highly stabilized amidinium counterion can be formed. Aminoacetonitriles are expected to be intermediate in this respect. Of these three classes of compounds only the diaminoacetonitriles show some evidence of ionization. Dipiperidinoacetonitrile[42] is a distillable compound which partially ionizes in the highly polar solvent phenol but is un-ionized in aprotic solvents.

Aminoacetonitriles split off a nitrile group only when treated with a Grignard reagent which aids the elimination through complexation.[18] In aqueous base the nitrile group hydrolyzes instead,[43a] demonstrating the lack of ionization even in this highly ionizing medium. *tert*-Octylglycinonitrile gives *tert*-octylglycine in high yield.[43b]

The hydrolysis of **1** is markedly analogous to the above-described hydrolysis of **4**. From an initially homogeneous solution of **1** in aqueous potassium hydroxide, a second phase separates upon standing. The major part of this phase is pentane soluble and is identified by ir and glpc as *tert*-octylamine of higher than 80% purity. The major component of the pentane-insoluble part is the diaminomaleonitrile **19** (Scheme II), which was identified by glpc. Since **19** results from the addition of hydrogen cyanide to **1**, this is proof of the generation of hydrogen cyanide.

In the hydrolysis of **1** in strong aqueous base, initial loss of hydrogen cyanide could, conceivably, occur by β elimination. Further hydrolysis of the resulting *tert*-octyliminonitrile (**13**, R = t-C_8H_{17}) could account for the observed formation of *tert*-octylamine. There is no specific evidence to disprove this route, which does not require the aminocyanocarbene **3** as an intermediate. However, the analogy with the case of **4**, where similar alternatives do not exist, suggests that the carbene mechanism is operative in the case of **1** as well.

Evidence is available that the radicals **7** and **8** and probably the aminocyanocarbene **3** are also intermediates in the thermolyses of the aminocyanoketenimine **24** and of the aminomalononitrile **1**.

Additionally, it has been found that a modification of the published[16] reaction conditions for the formation of dimethylaminomalononitrile yields a bisdimethylaminodicyanoethylene as the main product. Dimethylaminocyanocarbene is a possible intermediate.

These reactions will be discussed in forthcoming publications.

Experimental Section

Equipment and Technique.—The following instruments were used: a Perkin-Elmer 621 double-beam grating ir spectrometer, a Laser-Raman Carey 81 spectrometer, and a Varian HA-100 nmr spectrometer.

In analyzing the composition of mixtures, frequent use is made of the glpc coinjection technique. This technique identifies a mixture component through the increased intensity of a specific peak when a new mixture containing an added authentic compound is injected. In all glpc work the support was 5% silicone SE-30 (General Electric Co.) on Chromosorb W (Johns-Manville). In each case injection was followed by a 4-min period at 40°. After this the temperature was raised to 250° using a 15°/min program.

Materials.—*tert*-Octylaminocyanoketen-*N*-*tert*-octylimine (**24**) was prepared as described previously.[1]

Using a novel method, *N*-*tert*-octylaminomalononitrile (**1**) was prepared in high overall yield from *N*-*tert*-octylglycinonitrile *via N*-*tert*-octyliminoacetonitrile (**13**, R = t-C_8H_{17}).

N-*tert*-Octylglycinonitrile was prepared in high yield from *tert*-octylamine and glycolonitrile (available from J. T. Baker) according to Luskin, *et al.*[33]

tert-Butyl hypochlorite, used in the preparation of **13**, is available from K & K Laboratories, Inc.

N-*tert*-Octyliminoacetonitrile (**13**) from *N*-*tert*-Octylglycinonitrile[44]—A 13.6-g (0.162 mol) quantity of finely ground sodium bicarbonate was suspended in a solution of 131 g (0.778 mol) of *N*-*tert*-octylglycinonitrile in 1400 ml of ether. The stirred solution was cooled to 10° in an ice bath, and under exclusion of light 106.4 g (0.98 mol) of *tert*-butyl hypochlorite was added over a 25 min period. Stirring at 10° was continued for 1 hr. The inorganic salts were removed by filtration. Under continued exclusion of light 200 g (1.97 mol) of triethylamine was added. Precipitation of triethylammonium chloride started at once. After 19 hr at room temperature, the solids were removed by filtration and triturated with 300 ml of ether. The extracts were combined with the filtrate, and the ether was removed *in vacuo*. Distillation of the residue gave 103.4 g (0.621 mol, 80%) of *tert*-octyliminoacetonitrile (**13**), bp 61–63° (0.2 mm), $n^{20}D$ 1.4519.

Anal. Calcd for $C_{10}H_{18}N_2$: C, 72.22; H, 10.93; N, 16.85. Found: C, 72.13; H, 10.90; N, 16.78.

Ir (CCl_4) 2220 (w, C≡N), 1618 cm^{-1} (m, C=N).

Methanesulfonic Acid Salt of *tert*-Octylaminomalononitrile

(40) P. C. Petrellis, H. Dietrich, E. Meyer, and G. W. Griffin, *J. Amer. Chem. Soc.*, **89**, 1967 (1967).

(41) W. Kirmse, L. Horner, and H. Hoffmann, *Justus Liebigs Ann. Chem.*, **666**, 9 (1963).

(42) M. Seefelder, *Chem. Ber.*, **99**, 2678 (1966).

(43) (a) H. Zahn and H. Wilhelm, *Justus Liebigs Abn. Chem.*, **579**, 1 (1953); (b) J. S. Strong, U. S. Patent 2,787,640 (April 2, 1957); *Chem. Abstr.*, **51**, 13909a (1957).

(44) This is an adaptation of the method of Boyer and Dabek;[12b] see also Ferris, Donner, and Lodge.[11]

(1 CH_3SO_3H) from 13, HCN, and CH_3SO_3H.—The above product (103.4 g) was dissolved in 1000 ml of ether. The solution was stirred and cooled to 0° in an ice bath, and 70 g (2.59 mol) of hydrogen cyanide was introduced by distillation using an ice-cooled condenser. After completion of the addition, 63 g (0.652 mol) of methanesulfonic acid was added from an addition funnel over a 5-min period. A precipitate started to form at once. Stirring at 0° was continued for 45 min. The solution was allowed to warm to room temperature, and the precipitate was collected by filtration. (Caution: excess HCN present.)

After washing with 200 ml of ether, the product was dried *in vacuo* at room temperature for 30 min and then stored in the refrigerator, yield 136.6 g (76%) of colorless 1 CH_3SO_3H.

The combined filtrate and washings were concentrated *in vacuo* at room temperature and allowed to stand for 17 hr. Filtration yielded an orange-colored precipitate which was largely decolorized upon trituration with 60 ml of acetonitrile. The washed precipitate was dried *in vacuo* at room temperature to give an additional 27.8 g of slightly impure (faintly orange colored) 1 CH_3SO_3H.

tert-Octylaminomalonitrile (1) from the Methanesulfonic Acid Salt.—Treatment of 1 CH_3SO_3H with potassium bicarbonate solution as described in ref 1 gave 1, mp 35.0–35.5°, which was spectrally identical with 1 prepared according to that reference. Statisfactory elemental analyses were obtained for both 1 and its methanesulfonic acid salt.

The *tert*-Octylglycinonitrile Radical (7) from Decomposition of *tert*-Octylmalononitrile (1) in Triethylamine.—To a vacuum line system were attached an esr tube containing 0.1 g of 1 (freshly recrystallized from pentane) and a tube containing 2 ml of triply distilled triethylamine. The triethylamine was frozen in liquid nitrogen, the system was evacuated, and the triethylamine was degassed by repeated (three) freezing–pumping cycles. The epr tube was then cooled to −76° and the triethylamine was transferred into it by distillation. The cold epr tube was closed and detached from the vacuum system. When it reached room temperature, it was inserted into the esr spectrometer. As soon as 1 dissolved in the triethylamine, the solution became reddish orange and the spectrum of 7 emerged.

Products from Decomposition of *tert*-Octylaminomalononitrile (1) in Triethylamine.—Under strict exclusion of oxygen, 12.2 g of 1 (twice recrystallized from pentane) was dissolved in 50 ml of freshly distilled triethylamine. The solution was stirred at room temperature for 3 hr in a nitrogen atmosphere. The triethylamine and the volatile products were removed by distillation *in vacuo* (distillate A). The residue was extracted with 250 ml of refluxing pentane to give an insoluble precipitate (B) and a pentane extract (C).

Isolation of 1-*tert*-Octylimino-2-amino-1,2,2-tricyanoethane (28).—The pentane insoluble fraction B (see above) was dissolved in 250 ml of refluxing ether. After treatment with 5 g of Norit the filtered ether solution was concentrated to a 25 ml volume. Crystallization started and was completed in the refrigerator. After one additional crystallization from ether, 0.35 g of 28 was obtained, mp 138.5–139.5°.

Anal. Calcd for $C_{13}H_{19}N_5$: C, 63.63; H, 7.82; N, 28.56. Found: C, 63.86; H, 7.96; N, 28.67. Mass spectrum (70 eV) *m/e* parent 245; ir ($CHCl_3$) 3472 (m), 3380 (ms), 3325 (m), 3220 (m), 3170 (sh) (all NH stretch, bonded and free), 2270 (sh, vw), 2220 (vs) (C≡N); 1625 (s, C=N), 1552 cm^{-1} (ms, NH_2 def); nmr ($CDCl_3$) δ 0.88 [9 H, $C(CH_3)_3$], 1.90 [6 H, $C(CH_3)_2$], 2.01 (2 H, CH_2), 3.77 ppm (2 H, NH_2).

Isolation of 1-*tert*-Octylamino-2-aminomaleonitrile (19).—The ether mother liquors of 28 were freed of solvent *in vacuo*. The residue was dissolved in 25 ml of benzene. The solution was treated with Norit, filtered, concentrated to a 3-ml volume *in vacuo*, and finally diluted with 3 ml of hexane.

After 3 hr at −10°, the crystalline precipitate was collected by filtration and recrystallized from benzene–hexane, yield 0.076 g of 19, identified by mixture melting point determination and by identity of ir spectra, using an authentic sample of 19 (see below).

Isolation of 1-*tert*-Octylamino-2-amino-3-*tert*-octylimino-1,3-dicyanopropene-1 (23).—The pentane extract C, obtained from decomposition of 1 in triethylamine, was treated with Norit, filtered, and then concentrated to a 50-ml volume. After 12 hr at −10°, a crystalline precipitate was obtained. One recrystallization from hot hexane gave after 3 hr at −10° 4.07 g of 23 as yellow needles, mp 79.0–79.5°.

Anal. Calcd for $C_{21}H_{37}N_5$: C, 70.12; H, 10.40; N, 19.48. Found: C, 70.43; H, 10.61; N, 19.44.

Mass spectrum (70 eV) *m/e* parent 359; uv max (isooctane) 400.0, 234.0 nm (log ε 3.747, 3.922); ir (KBr pellet) 3466 (m), 3438 (s), 3292 (m), (NH), 2182 (sh), 2175 (s, C≡N), 1598 (vs), 1537 cm^{-1} (s), (C=CC=N); ir (CCl_4) 3476 (m), 3360 (m) (NH), 2212 (m), 2192 (m), 2183 (sh) (C≡N), 1598 (sh), 1580 (s), 1522 cm^{-1} (s) (C=CC=N); Raman (cryst) 2221 (mw), 2176 (s) (C≡N), 1592 (vs), 1537 cm^{-1} (s) (C=CC=N); nmr (CCl_4) δ 1.017 [2 $C(CH_3)_3$, A + $C(CH_3)_3$ B],[45] 1.100 [$C(CH_3)_3$ B], total 18 H, 1.386 [$C(CH_3)_2$ B], 1.474 [2 $C(CH_3)_2$ A], 1.586 [($C(CH_3)_2$ B], total 12 H, 1.693 (CH_2 B), 1.860 (2 CH_2 A), 1.920 (CH_2 B), total 4 H, 3.636, 4.800, 7.650 ppm (NH_2 A + B and NH A + B), total 3 H.

Isolation of 1,2-Di-*tert*-octylamino-1,2,2-tricyanoethane (10).—The pentane and hexane mother liquors of 23 were combined and concentrated to a 30-ml volume *in vacuo*. The solution was cooled to −10° and crystallization was initiated by seeding with authentic 10.[29] After 12 hr at −10°, the precipitate was collected by filtration. Recrystallization from hexane yielded 0.224 g of 10 identified by ir spectrum and mixture melting point determination, using a sample of authentic 10.[29]

Identification of *tert*-Octyliminomalononitrile (9).—The mother liquors of 10 were chromatographed through a silica column. In the oily residue, recovered from the pentane–ether (95:5) eluate, 9 was identified as a major component by mass spectrum, ir spectrum, and the glpc coinjection technique using authentic 9 (see below).

Preparation of *tert*-Octylamino-*tert*-octylmalononitrile (27) by Thermal Rearrangement of *tert*-Octylaminocyanoketen-*N*-*tert*-octylimine (24).—An 11.4-g (0.037 mol) quantity of 24 was dissolved in 75 ml of toluene, and the solution was heated at reflux in a nitrogen atmosphere for 14 hr. The toluene and the volatile reaction products were collected by distillation *in vacuo*. The residue was diluted with 20 ml of pentane, chilled to −10°, and filtered to give 6.5 g of a crystalline product. With the exception of a small residue, this product could be redissolved in cold pentane. After three recrystallizations from this solvent at −10° (including a treatment with Norit), 4.1 g of pure 27 was recovered, mp 67.0–67.5°.

Anal. Calcd for $C_{19}H_{35}N_3$: C, 74.69; H, 11.54; N, 13.75. Found: C, 74.61; H, 11.63; N, 13.84.

Ir (CCl_4) 3405, 3360 (w) (NH), 2235 cm^{-1} (vw) (C≡N);[46] nmr (CCl_4) δ 0.97, 1.01 [18 H, 2 $C(CH_3)_3$], 1.26, 1.41 [each 6 H, $C(CH_3)_2$], 1.46, 1.54 ppm (each 2 H, CH_2); mass spectrum (70 eV) *m/e* parent 305; mol wt, 303 (Thermonam).

Stability of 27 in Triethylamine.—A solution of 0.5 g of 27 in 10 ml of triethylamine was heated at reflux under a nitrogen blanket for 12 hr. The slightly yellow solution was freed of triethylamine *in vacuo*. The crystalline residue was recrystallized from hot hexane. Cooling to −10° gave 0.461 g of unchanged 27, identified by ir spectrum and mixture melting point determination.

Glpc Analysis of the Reaction Product of 1 and Triethylamine.—Glpc analysis (coinjection technique) of the crude reaction product of 1 and triethylamine showed that hydrogen cyanide is developed copiously within the first minutes of the reaction. It also showed the presence of *tert*-octyliminomalononitrile (9) and the absence of di-*tert*-octylaminomaleonitrile (17),[1] di-*tert*-octylaminofumaronitrile (18), and N-*tert*-octylglycinonitrile.[33] The preparation of 17 was reported earlier,[1] and the preparation of 18 and 9 is described below.

Mass Spectral Analysis of the Reaction Product of 1 and Triethylamine. Evidence for the Formation of 1,2-Di-*tert*-octylaminosuccinonitrile (11).—An aliquot of the mother liquors from the crystallization of 23 was freed of solvent *in vacuo*. The mass spectrum of the residue showed the presence of a parent compound of mass 334. This is consistent with $C_{20}H_{38}N_4$ (11); attempts to synthesize 11 are described below.

Analysis of the crude reaction product of 1 and triethylamine by combined gas chromatography–mass spectrometry was consistent with the glpc results. It showed the presence of a fraction (mass 191) with a mass spectrum identical with that of *tert*-octyliminomalononitrile (9) (see below); compounds of higher mass were not observed owing to decomposition in the instrument.

1-*tert*-Octylamino-2-aminomaleonitrile (19).—A 0.7-g quantity of 1 was dissolved in 3 ml of benzene. A 5-ml quantity of a

(45) A and B refer to the two conformational isomers of 23.

(46) Extremely weak C≡N bands are the rule in aminomalononitriles.[1]

concentrated aqueous solution of sodium cyanide was added, and the mixture was stirred under nitrogen at room temperature for 24 hr. The organic layer, in which a crystalline precipitate had formed, was diluted with 10 ml of pentane, separated from the aqueous layer, and filtered to give 0.4 g of crude 19. After two recrystallizations from benzene, the melting point was 136–137°.

Anal. Calcd for $C_{12}H_{20}N_4$: C, 65.45; H, 9.09; N, 25.46. Found: C, 65.37; H, 9.34; N, 25.47.

Ir ($CHCl_3$) 3475 (w), 3350 (s), 3315 (sh) (all NH), 2210 (sh), 2180 (s) (C≡N), 1610 (s), 1590 cm^{-1} sh (C=C); nmr ($CDCl_3$) δ 1.04 [9 H, $C(CH_3)_3$], 1.40 [6 H, $C(CH_3)_2$], 1.70 (2 H, CH_2), 3.26 (1 H, NH), 3.60 ppm (2 H, NH_2); mass spectrum (70 eV) *m/e* parent 220; mol wt, 221 (Thermonam).

Compound 19 was also formed from 1 and hydrogen cyanide in triethylamine solution. This was demonstrated by glpc.

Preparation of *tert*-Octyliminomalononitrile (9). A. From 1 and Tetracyanoethylene.—A 1.13-g (0.006 mol) quantity of 1 and 0.75 g (0.006 mol) of tetracyanoethylene were dissolved in 20 ml of tetrahydrofuran. The solution was left at room temperature overnight and then filtered. The solvent was evaporated from the filtrate *in vacuo*, and the residue was extracted with pentane. After Norit treatment, the pentane was removed *in vacuo*. This left 0.73 g (65%) of 9 as a colorless oil: bp (determined by differential thermal analysis) 237–238° (760 mm), 100° (7 mm); $n^{20}D$ 1.4569.

Anal. Calcd for $C_{11}H_{17}N_3$: C, 69.02; H, 8.97; N, 22.00. Found: C, 68.93; H, 8.79; N, 21.88.

Ir (CCl_4) 2210 (m) (C≡N), 1595 cm^{-1} (m) (C=N); nmr ($CDCl_3$) δ 1.01 [9 H, $C(CH_3)_3$], 1.54 [6 H, $C(CH_3)_2$], 1.66 ppm (2 H, CH_2); mass spectrum (70 eV) *m/e* 191 (parent, weak), 176 (parent − CH_3), 150 (176 − CN), 120 (parent − C_5H_{11}, strong).

B. From 1 and Benzoyl Peroxide.—A 1.0-g (0.005 mol) quantity of 1 and 1.21 g (0.005 mol) of benzoyl peroxide were dissolved in 15 ml of benzene. The solution was allowed to stand at room temperature for 24 hr. The benzene solvent was then removed *in vacuo*. The residue was extracted with pentane. The pentane-insoluble part was pure benzoic acid identified by ir spectrum and mixture melting point determination using an authentic sample. The pentane extract was washed with a concentrated solution of sodium bicarbonate to remove any dissolved benzoic acid. The washed pentane extract was treated with Norit, and the pentane solvent was removed *in vacuo* to leave a colorless oil (0.74 g, 77%), which was identified as essentially pure 9 by identity of ir spectrum and by glpc (coinjection technique).

Di-*tert*-octylaminofumaronitrile (18). A. From Di-*tert*-octylaminomaleonitrile (17) and Triethylamine.—A solution of 10 g of 17 in 50 ml of triethylamine was stirred magnetically and kept at reflux overnight. The triethylamine was removed *in vacuo*. The solid residue, consisting mainly of 17, was extracted with 25 ml of pentane. The pentane extract was kept at −15° overnight and gave upon filtration a precipitate which consisted of pure 17 according to ir spectrum and mixture melting point determination. The pentane mother liquors were chromatographed through a silica column. From the pentane–1% ether eluate a crystalline residue was obtained which was recrystallized three times from pentane at −30°, yield 0.32 g of 18 as colorless crystals, mp 55.5–56.5°.

Anal. Calcd for $C_{20}H_{36}N_4$: C, 72.24; H, 10.91; N, 16.85. Found: C, 72.28; H, 11.13; N, 16.98.

Uv max (isooctane or MeOH) 340 nm (log ε 4.05); ir (CCl_4) 3380 (m, NH), 2195 (m) with shoulders at 2160 and 2210 (C≡N), 1575 cm^{-1} (m, C=C); nmr ($CDCl_3$) δ 1.05 [18 H, 2 $C(CH_3)_3$], 1.37 [12 H, 2 $C(CH_3)_2$], 3.50 ppm (2 H, 2 NH), disappears upon deuteration; mass spectrum (70 eV) *m/e* parent 332.

B. From *tert*-Octylaminocyanoketen-*N*-*tert*-octylimine[1] (24) and Hydrogen Cyanide.—A 10-g quantity of 24 was dissolved in 20 ml of triethylamine, and 3 g of hydrogen cyanide was introduced by distillation. After 2 hr, all volatiles were removed by sparging with nitrogen. The residue, consisting mainly of 17, was extracted with 25 ml of pentane. From this pentane extract 0.43 g of 18 was obtained by the procedure described above for the preparation of 18 from 17 and triethylamine. Compound 18 was identified by ir spectrum and mixture melting point determination.

C. From Catalytic Hydrogenation of Di-*tert*-octyliminosuccinonitrile[1] (20).—A 2-g quantity of 20 in ethyl acetate solution was hydrogenated using 75 mg of a 5% palladium on carbon catalyst. When 1 equiv of hydrogen had been absorbed, the hydrogen uptake virtually stopped. After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, a crystalline residue remained which, according to the ir spectrum, consisted mainly of 17. This residue was extracted with 25 ml of pentane. The pentane extract was treated by the procedure described above to give 0.075 g of 18, identified by ir spectrum and mixture melting point determination.

Rearrangement of 18 to Give 17.—A 0.20-g quantity of 18 was dissolved in 10 ml of ether. A 0.050-g quantity of methanesulfonic acid dissolved in 5 ml of ether was added. After standing at room temperature for 2 hr, the solution was extracted with aqueous sodium bicarbonate to remove the methanesulfonic acid. The ether layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to leave a crystalline residue which was recrystallized from hexane, yield 0.180 g of 17, identified by ir spectrum and mixture melting point determination.

Attempts to Prepare 1,2-Di-*tert*-octylaminosuccinonitrile (11). A. By Catalytic Hydrogenation of 20.—Catalytic hydrogenation of 20 (5% Pd/C) gave a product which was 17, containing some 18, according to ir spectrum, mixture melting point determination, and glpc analysis.

B. By Catalytic Hydrogenation of 17.—Hydrogenation of 17 using a 5% palladium on carbon catalyst was unsuccessful since even at reflux of the ethyl acetate solvent no hydrogen was taken up. With a 5% rhodium on alumina catalyst, hydrogen was absorbed at room temperature, but the product was dark colored, and chromatography through a silica column did not yield an identifiable pure compound.

C. By Lithium Aluminum Hydride Reduction of 20.—Lithium aluminum hydride reduction of 1 g of 20 in ether by the usual procedure gave a product that was pentane soluble except for a small amount of 17, identified by ir spectrum. Chromatography through a silica column did not yield a pure, identifiable product.

D. By Dimethylamine Borane Reduction of 20.—A 2-g quantity of 20 was treated with 1.59 g of dimethylamine borane in glacial acetic acid according to the method of Billman and McDowell.[31] The product appeared to consist exclusively of a mixture of 17 and unreacted 20; no other compound could be isolated.

E. By Sodium Borohydride in Dimethylformamide (DMF).—Treatment of 20 with a twofold molar excess of sodium borohydride in DMF followed by decomposition with water gave a product from which only 17 could be isolated. Chromatography of the mother liquors through a silica column yielded some additional 17 (pentane–5% ether eluent) and some starting material (pentane–2% ether eluent) but no other identifiable compound.

Malononitrile and Triethylamine.—Under strict exclusion of oxygen, a 1-g quantity of malononitrile was dissolved in 20 ml of freshly distilled triethylamine at room temperature. After 30 min, the solution had become dark colored. Glpc (coinjection technique using authentic hydrogen cyanide) demonstrated the absence of hydrogen cyanide. When oxygen was not excluded, hydrogen cyanide was shown to be present in small amount.

***tert*-Octylamine and 19 from 1 and Potassium Hydroxide.**—A 1-g quantity of the methanesulfonic acid salt of 1 was dissolved in 10 ml of 25% aqueous potassium hydroxide to give a clear, colorless solution. After 24 hr of stirring at room temperature in a nitrogen atmosphere, a second, orange-colored layer had formed. This layer dissolved in added benzene and was separated from the aqueous layer. The benzene solvent was removed *in vacuo*, and the residue was extracted with pentane. Evaporation of the pentane from this extract left 0.43 g of an oil. The ir spectrum of this oil was essentially identical with that of authentic *tert*-octylamine. Glpc (coinjection technique) showed the oil to be *tert*-octylamine of >80% purity.

The pentane-insoluble part of the residue was recrystallized (after Norit treatment) from a 50:50 mixture of benzene and hexane to give 0.067 g of 19, identified by ir spectrum and mixture melting point determination.

1,2-Di-*tert*-octylamino-3-*tert*-octylimino-1,3-dicyanopropene-1 (26). A. From Reaction of 24 and 1 in Triethylamine.—A solution of 2.75 g (0.009 mol) of 24 and 0.87 g (0.0045 mol) of 1 in a mixture of 3 ml of triethylamine and 10 ml of benzene was allowed to stand at room temperature for 48 hr. The benzene and triethylamine were then removed *in vacuo*. The deep orange residue was dissolved in 40 ml of pentane, chilled to −15°, and filtered to give a crystalline precipitate and an orange filtrate.

The precipitate was recrystallized from hot hexane to give 1.06 g of colorless crystals, identified as **17** by mixture melting point determination and identity of ir spectra.

The filtrate was concentrated *in vacuo* to a volume of 5 ml and chilled. Filtration of this solution after 12 hr at −15° gave orange-colored crystals. After one additional crystallization from pentane, 0.67 g of pure **26** was obtained, mp 93.4–94.3°. Chromatography of the mother liquors through an alumina column yielded an additional 0.55 g of **26** from the pentane eluate.

Anal. Calcd for $C_{29}H_{53}N_5$: C, 73.70; H, 11.33; N, 14.95. Found: C, 73.48; H, 11.22; N, 14.97.

Ir (CCl_4) 3385, 3335, 3180 (vw) (NH), 2220 (w), 2180 (vvw) (C≡N), 1575, 1530 cm^{-1} (s) (N=CC=C); nmr ($CDCl_3$) δ 0.97 [18 H, 2 $C(CH_3)_3$], 1.06 [9 H, $C(CH_3)_3$], 1.10 [6 H, $C(CH_3)_2$], 1.42 [12 H, 2 $C(CH_3)_2$], 1.54 (2 H, CH_2), 1.79 (4 H, 2 CH_2), 2.68 and 9.88 ppm (2 H, NH, disappear on deuteration); mass spectrum (70 eV) *m/e* parent 471; mol wt, 474 (Thermonam).

B. From Reaction of 1 and 24 in Aqueous KOH.—To 5 ml of 25% aqueous KOH were added 0.8 g of **1** and 2.5 g of **24**, and the mixture was stirred under a nitrogen blanket at room temperature for 12 hr. The organic layer in which crystals had formed was diluted with pentane, separated from the aqueous layer, chilled to −15°, and filtered to give a crystalline precipitate and a deeply orange-colored filtrate. The precipitate was twice recrystallized from hot hexane to give 0.45 g of colorless crystals identified as **17** by mixture melting point determination and identity of ir spectra.

The orange-colored filtrate was concentrated *in vacuo* to a volume of 5 ml and chilled. After 12 hr at −15°, the solution was filtered to give 0.35 g of orange-yellow crystals identified as **26** by mixture melting point determination and identity of ir spectra. Chromatography of the mother liquors through a silica column yielded an additional 0.25 g of **26** eluted with pentane containing 2% ether.

C. Directly from Reaction of 2,4,4-Trimethylpentene-2 (TMP) with HF and HCN. Isolation of Di-*tert*-octylaminofumaronitrile (18).—A polyethylene reactor with a polyethylene condenser and magnetic stirrer was charged with 150 g (1.34 mol) of TMP (freshly distilled and dried over CaH_2) and 250 ml of dichloromethane (dried over CaH_2). At 0° 155 ml (108.6 g, 4.01 mol) of HCN was distilled in, followed by 81 ml (80.15 g, 4.04 mol) of HF. The reaction mixture was stirred at room temperature for 2 hr. The solvent and unreacted HCN and HF were removed by sparging with nitrogen. The residue was diluted with 350 ml of fresh dichloromethane, and stirring at room temperature was continued overnight. The reaction mixture was then poured into a stirred slurry of 300 g of KOH, 300 g of water, and 600 g of crushed ice. Upon reaching room temperature, the mixture was filtered through a sintered glass funnel. A 12.8 g quantity of 4-cyano-5-*tert*-octylaminoimidazole[1] was collected, identified by its ir spectrum and mixture melting point with authentic compound.

The filtrate (organic as well as aqueous layers) was stirred under a nitrogen blanket at room temperature. After 96 hr, the ir spectrum proved the absence of **24** (initially a major component) through disappearance of the characteristic ketenimine band at 2025 cm^{-1}. The organic layer was separated, the dichloromethane was removed *in vacuo*, and the residue was diluted with 200 ml of pentane.

After cooling at −20° overnight, the solution was filtered to yield 38.5 g of crude **17**, identified by ir spectrum and mixture melting point.[1]

The mother liquor was chromatographed through a silica column (solvent-free substrate to SiO_2 ratio 1:30). The initial pentane eluate contained an unidentified oil. Later pentane fractions, which were bright orange, yielded 7.42 g (after two recrystallizations from pentane at −20°) of **26**, identified through ir spectrum and mixture melting point.

From the subsequent pentane–ether (98:2) eluate, 3.2 g of an impure crystalline product was obtained. Rechromatography of this product through a silica column yielded from the pentane eluate 0.47 g of **26**. The residue from the subsequent pentane–ether (99:1) eluate was recrystallized three times from pentane at −30° (using decolorizing carbon the first time), yield 1.96 g of colorless crystals, mp 55.5–56.5°. This compound was identified as **18** by its ir spectrum and by mixture melting point determination.

D. From 24 and Triethylamine.—An 11.0-g quantity of **24** in 200 ml of triethylamine was kept at reflux in a nitrogen atmosphere for 32 hr. The triethylamine was removed *in vacuo*, and the residue was dissolved in 160 ml of pentane. Filtration after 14 hr at −10° yielded 2.4 g of a crystalline precipitate which was identified as **17** by ir spectrum and mixture melting point determination. After concentration, the mother liquors were chromatographed through a silica column (500 g of SiO_2). From the pentane–2% ether eluate an orange-yellow residue was obtained. After one recrystallization from 3 ml of pentane at −30°, 0.62 g of orange-yellow crystals were recovered which were identified as **26** by ir spectrum and mixture melting point determination.

Preparation of Dimethylaminomalononitrile (4).—This compound was prepared according to Arnold,[16] nmr ($CDCl_3$) δ 2.47 [6 H, $N(CH_3)_2$], 4.76 ppm (1 H, CH), disappears upon deuteration.

Hydrogen Cyanide from Dimethylaminomalononitrile (4) and Triethylamine.—A 500-mg quantity of **4** was dissolved in 3 ml of triethylamine at room temperature in a nitrogen atmosphere. After the solution had stood for 20 min, the presence of hydrogen cyanide was demonstrated by the glpc coinjection method. The amount continued to increase over a 4-hr period.

The generation of hydrogen cyanide was also confirmed by high-resolution mass spectrometry. A solution of **4** in triethylamine, blanketed with nitrogen, was allowed to stand in the probe for 30 min at room temperature. The solution was then frozen in liquid nitrogen and a mass spectrum was obtained of the vapors. The presence of hydrogen cyanide was proven by a peak at mass 27.01097 (calcd 27.01090).

17 from 4, 24, and Triethylamine.—A mixture consisting of 10 ml of benzene, 6.1 g (0.02 mol) of **24**, 1.1 g (0.0067 mol) of **4**, and 10 ml of triethylamine was kept at room temperature in a nitrogen atmosphere for 36 hr. The benzene and triethylamine were then removed, and the residue was dissolved in 35 ml of pentane. After 12 hr in the refrigerator, a precipitate had formed which was collected and recrystallized from hot hexane. A 0.95-g yield of colorless crystals was obtained, shown to be **17** through identity of ir spectra and by mixture melting point determination. From the mother liquors, an additional 0.63 g of **17** was recovered. The reaction product which had not crystallized was chromatographed through a silica column, but no pure identifiable compound was isolated.

Dimethylamine from 4 and Aqueous Potassium Hydroxide.—A 1-g quantity of **4**, dissolved in 5 ml of benzene, and 10 ml of 25% aqueous potassium hydroxide was stirred at room temperature in a nitrogen atmosphere. An aliquot drawn after 5-min reaction time evolved basic vapors with a strong amine odor. Glpc analysis (coinjection technique) of a sample of the benzene layer, drawn after 2-hr reaction time, showed dimethylamine to be the main product in that layer.

The generation of dimethylamine was also confirmed by mass spectroscopy. A solution of **4** in aqueous potassium hydroxide was allowed to stand in the probe for 30 min at room temperature. The solution was then frozen in liquid nitrogen and a mass spectrum was obtained of the vapors. A large peak at mass 44 ($M^+ - H$) and a smaller peak at mass 45 (M^+) proved the presence of dimethylamine.

Registry No.—**1**, 40127-60-4; **1** CH_3SO_3H, 40127-61-5; **4**, 19555-13-6; **7**, 40110-57-4; **9**, 40127-63-7; **11**, 40127-64-8; **13**, 40317-81-5; **17**, 30768-59-3; **18**, 40132-89-6; **19**, 40132-90-9; **20**, 30768-62-8; **23**, 40127-66-0; **24**, 30768-56-0; **26**, 40127-68-2; **27**, 40127-69-3; **28**, 40127-70-6; HCN, 74-90-8; CH_3SO_3H, 75-75-2; *N-tert*-octylglycinonitrile, 40127-71-7; tetracyanoethylene, 670-54-2; benzoyl peroxide, 94-36-0.

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The Reaction of Phenyl Isocyanate with N-Methyl-2-pyrrolidinone

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The reaction of 1-methyl-2-pyrrolidinone with phenyl isocyanate at 140 and 210° was studied. Besides 1-methyl-2-phenyliminopyrrolidine (2), a pyrroline carbanilide (7) and pyrroloquinolines (10, 11) and pyrrolopyrimidines (12, 13) are formed. The reaction mechanism is discussed and earlier reported findings on this reaction are corrected.

Aryl isocyanates react at elevated temperature with a variety of compounds containing carbonyl groups to give imines and carbon dioxide. The method is used for the preparation of azomethines, ketimines, amidines, and guanidines from the corresponding aromatic aldehydes, benzophenones, and N-persubstituted amides and ureas.[1-5] In some cases, other products are obtained owing to successive interaction of the formed imines with excess isocyanate. Good examples are the extensively studied reactions of *N,N*-dimethylformamide[6-8] and *N,N*-dimethylacetamide[9] with aryl isocyanates.

In connection with thermostability studies of *N*-methyl-2-pyrrolidinone (NMP, 1)–isocyanate mixtures, we found that phenyl isocyanate reacts with 1 at temperatures above 100°. Generation of carbon dioxide was observed when an equimolar mixture of the two components was kept at 140° for 16 hr. During the reaction the isocyanate was consumed completely (as shown by the disappearance of the NCO band at 2270 cm^{-1} in the ir) while about 65% of 1 remained unchanged.

N-Methyl-2-phenyliminopyrrolidine (2), expected to be the main product, can be isolated after removal of unreacted 1 from the semisolid reaction mixture by distillation in only 18% yield (based on converted 1). From the residue seven solid compounds were isolated by repeated fractional crystallization from different solvent combinations (see Table I and Scheme I). Carbanilide, triphenyl isocyanurate, the pyrroline-3-carboxanilide 7 and the hexahydropyrrolopyrimidine 12 are the major products, whereas the pyrroloquinolines 10 and 11 and the hexahydropyrrolopyrimidine 13 together account for only 1–2%.

Structure assignments of the new compounds are based on elemental analysis, nmr, ir, and in some cases mass spectroscopy (see Experimental Section); the known compounds (carbanilide, triphenyl isocyanurate, and 2) were compared with authentic samples. The yields given vary somewhat with work-up methods but are correct in the order of magnitude.

The product ratio can be changed drastically by increasing the reaction temperature. For example, a 1:1 mixture of 1 and phenyl isocyanate kept for 4 hr at 210° yielded 41% of 2, only 7% of the pyrrolopyrimidine 12, and 16% of the pyrroloquinoline 11 (58% of 1 is recovered unchanged). The yield of the pyrroloquinoline 10 remained under 2% and 7, 13, and triphenyl isocyanurate could not be detected among the reaction products.

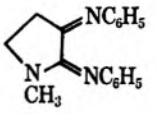
TABLE I

YIELDS[a] OF PRODUCTS OBTAINED IN REACTIONS OF *N*-METHYL-2-PYRROLIDINONE WITH PHENYL ISOCYANATE AT 140 AND 210°

Compd	Yield, % 140°	Yield, % 210°
1-Methyl-2-phenyliminopyrrolidine (2)	18	41
1-Methyl-2-phenylamino-2-pyrrolino-3-carboxanilide (7)	18	
1-Methyl-4-hydroxy-1,2-dihydro-3*H*-pyrrolo-[2,3-*b*]quinoline (10)	0.4	1.8
1-Methyl-4-anilino-1,2-dihydro-3*H*-pyrrolo-[2,3-*b*]quinoline (11)	0.8	16
7-Methyl-1,3-diphenyl-2,4-dioxohexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidine (12)	31	7
7-Methyl-1,3-diphenyl-4-phenylimino-2-oxohexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidine (13)	<0.2	

[a] Yields based on consumed 1.

These results are in contrast to a recent report in which a mixture of NMP and phenyl isocyanate (molar ratio 1:1) was kept for 4 hr at 235°[10] and carbanilide and 1-methyl-2,3-diphenyliminopyrrolidone (14), mp



14

227–228°, were claimed to be the reaction products. For 14, the structure of 9 is also discussed as a possibility but discarded, since the ir spectrum of the product did not show absorption bands characteristic of the >C=C=N– group. The given C, H, and N values of the elemental analysis do agree better with a molecular formula of $C_{18}H_{17}N_3$ (9 or 11) rather than $C_{17}H_{17}N_3$ (14). Despite a difference in melting points for 14 (227–228°) and 11 (238°), a comparison of the ir (which also differ slightly, possibly owing to deviations in the spectrophotometers used) and nmr spectra (14 taken in CF_3COOH, 11 in CD_3COOD) suggests the identity of the compounds. The two triplets for the four protons of the neighboring CH_2 groups show that positions 4 and 5 on the pyrrolidine ring are not involved in the product formation.

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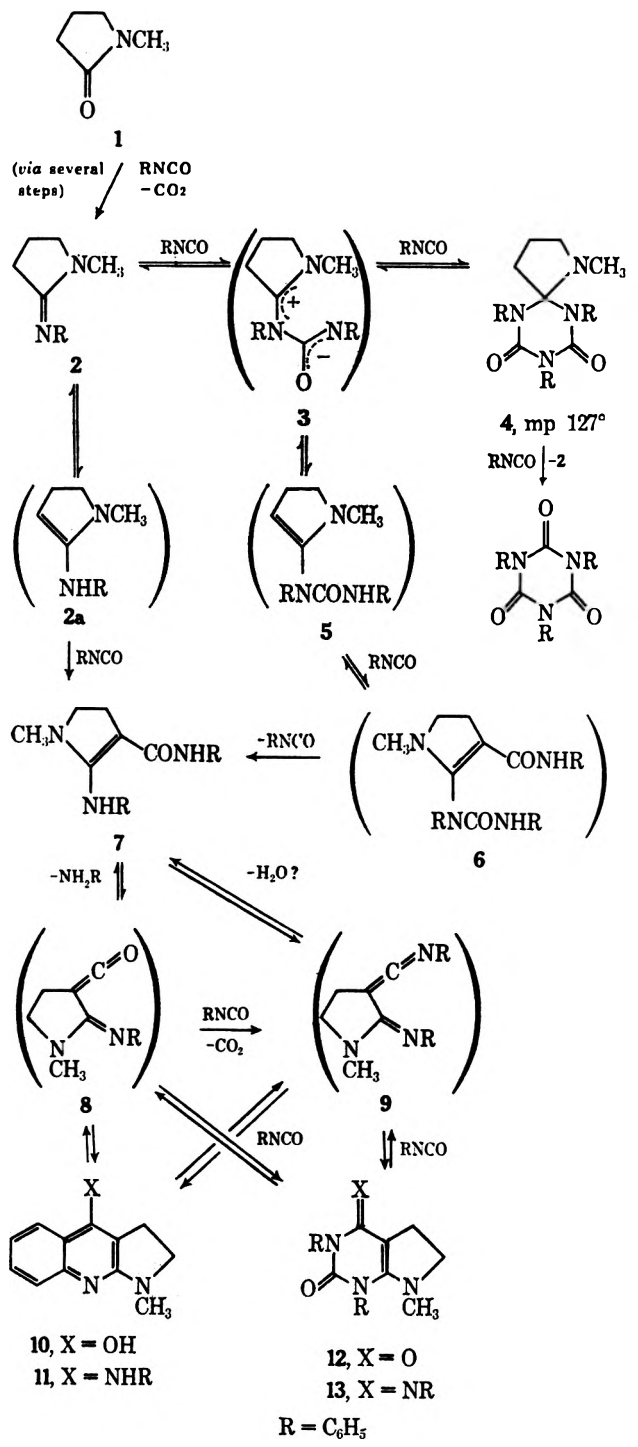
SCHEME I

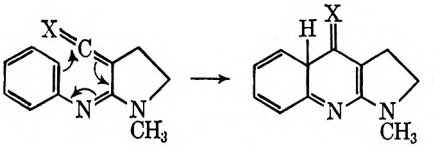


A possible pathway for the formation of all the reaction products is given in Scheme I. The conversion of the amide **1** into the amidine **2** proceeds *via* [2 + 2] cycloaddition with phenyl isocyanate followed by ring scission of the adduct to give **2** and carbon dioxide. Reactions of this type are described in detail elsewhere.[1,2] Subsequent interaction of the amidine **2** with phenyl isocyanate proceeds *via* substitution in the 3 position to give **7**. In Scheme I two possible pathways to the substituted vinylogous urea **7** are shown, which basically differ in the site of the initial isocyanate attack. In the sequence **2** → **3** → **5** → **6** → **7**, isocyanate attacks first on the exocyclic imino nitrogen, whereas in **2** → **2a** → **7** isocyanate attack is preceded by proton shift in **2** to the ketene aminal **2a**. Both reactions are known to occur with other imines and iso(thio)cyanates.[11-16]

Since **2** and phenyl isocyanate form the 2:1 cycloadduct **4** at room temperature in high yield[17] in a reaction generally known to proceed *via* a 1,4 dipole of type **3**,[18,19] it seems logical to assume an initial N attack of isocyanate also for the formation of **7**. Proton shift in **3** and C attack of phenyl isocyanate on the substituted ketene aminal **5** is followed by the loss of 1 mol of isocyanate initially bonded to the exocyclic nitrogen. The last step, **6** → **7**, is aided by a basicity decrease on the exocyclic nitrogen owing to the electron-withdrawing effect of the carboxamide group in position 3. In this reaction sequence phenyl isocyanate acts as catalyst in the proton shift in **2** *via* **3** to **5**.

No evidence for a thermal equilibrium **2** ⇄ **2a** could be obtained by independently recording the ir spectrum of a solution of **2** in *o*-dichlorobenzene in the NH stretching region (2900–3500 cm^{-1}) at various temperatures (32–165°). If any **2a** is formed at elevated temperatures, the amount is small and below the sensitivity limits of the spectrophotometer.

The trimerization of phenyl isocyanate to triphenyl isocyanurate might involve the compounds **2**, **3**, and **4**, as outlined in the reaction scheme, but a catalytic effect can also be expected from **1**, since it is known that N-substituted amides such as *N*,*N*-dimethylformamide trimerize aryl isocyanates.[20] Thermal dissociation of the vinylogous urea **7** could give either aniline and the phenylimino ketene **8**, or water and the phenylimino-*N*-phenyl ketenimine **9** (water or aniline would be constantly removed from the mixture by reacting with phenyl isocyanate to produce carbanilide, which has been isolated from the reaction mixture). Both ketene intermediates **8** and **9** can undergo cycloaddition reactions as shown in Scheme I. In the presence of excess phenyl isocyanate, intermolecular [4 + 2] addition produces the pyrimidine derivatives **12** and **13**, while intramolecular cyclization, as indicated in eq 1, gives the pyrroloquinolines **10** and **11**.



8, X = O
9, X = NC_6H_5

Reactions with a similar cyclization step were reported recently[21,22] and related intermediates are also

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discussed in the Conrad–Limpach quinoline synthesis.[23,24]

Since N,N′-disubstituted ureas are not known to lose water to give carbodiimides on heating, the direct formation of **9** from **7** is doubtful. It is more likely that **9** is formed from **8** and phenyl isocyanate in another [2 + 2] cycloaddition reaction.

Confirmation for a conversion of **8** to **9** was obtained in the thermolysis of **12**, which yielded not only the expected pyrroloquinoline **10** (32%) but also **11** (36%).

Experimental Section[25]

Reaction of 1-Methyl-2-pyrrolidinone with Phenyl Isocyanate. A. At 140°.—A mixture of 238 g (2.0 mol) of phenyl isocyanate and 198 g (2.0 mol) of **1** was kept at 140° for 16 hr. Carbon dioxide was generated during the first period of reaction, totaling 32.2 g, while the color of the mixture turned to deep yellow. After cooling to room temperature, 129.2 g of **1** (65%) was recovered by vacuum distillation, bp 40° (0.1 mm). A semisolid residue remained from which, on treatment with methanol and methanol–diethyl ether, solid fractions were obtained. The following separation procedure was typical, and reproducible with only minor deviations in amounts and composition of the fractions.

Treatment of the residue with 400 ml of methanol gave a colorless precipitate, 149 g (fraction 1), after filtering and washing with 100 ml of methanol. On concentrating the filtrate, a second portion of crystals, 51 g (fraction 2), did separate. The remaining filtrate was further concentrated and distilled at reduced pressure, giving 22.5 g of **2** (fraction 3), bp 85–90° (0.01 mm), which was identical in ir comparison with authentic material.[26]

Treatment of the distillation residue with methanol gave 7.2 g (fraction 4), which was collected by filtration and washed with methanol. The combined filtrate and methanol washings gave, on cooling to −10° for 17 hr, another crop of crystals, 5.9 g (fraction 5), after filtration and methanol washing. Addition of diethyl ether to the filtrate to beginning turbidity and scratching led to the separation of more crystals, which were collected after standing for several hours, 12.5 g (fraction 6) after washing with methanol–diethyl ether and finally diethyl ether. Another crop of crystalline material, 2.1 g (fraction 7), was obtained on concentrating the filtrate *in vacuo*. Filtrate and methanol–diethyl ether washings were again concentrated at reduced pressure, which led to the separation of 3.8 g (fraction 8) of colorless crystals.

No further solid material could be obtained from the remaining yellow-brownish resinous residue. Tlc with benzene–acetone (1:1) showed that most of the solid fractions were mixtures of two or more components.

Separation of Solid Fractions. Fraction 1.—The mixture was dissolved in 300 ml of hot *N,N*-dimethylformamide (DMF) and the resulting solution was diluted with 700 ml of diethyl ether, which caused separation of 39.0 g of **7-methyl-1,3-diphenyl-2,4-dioxo-1,2,3,4,5,6-hexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidine (12)**, mp 227–228°, colorless plates, ir (KBr) 1698, 1668 cm^{-1} (C=O), R_f 0.71.

Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.45; H, 5.37; N, 13.16. Found: C, 71.41; H, 5.36; N, 13.43.

On concentrating the DMF–diethyl ether filtrate *in vacuo* a second crop of crystals was obtained. The material, a mixture by tlc, was dissolved in 1700 ml of hot acetone and the solution deposited on cooling 36.5 g of carbanilide, mp 245°, R_f 0.9, identical in ir comparison with authentic material. On evaporation of the filtrate to dryness colorless crystals were obtained, which were recrystallized from warm DMF. Thus, 20.7 g of **1-methyl-2-phenylamino-2-pyrrolino-3-carboxanilide (7)**, mp 170–172° (from acetone), colorless needles, were isolated: ir (KBr) 3250 (NH), 1662, 1639 cm^{-1} (C=O, C=N, or C=C); R_f 0.24.

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.79; H, 6.53; N, 14.33. Found: C, 73.75; H, 6.53; N, 14.33.

From the filtrates, more material of the same compounds was isolated by repeated recrystallization from the named solvents totaling 43.9 g of carbanilide, 42.9 g of **12**, and 26.0 g of **7**.

Fraction 2.—On treating the mixture with DMF–diethyl ether and acetone as described above for fraction 1, a total of 3.7 g of carbanilide, 22.0 g of **12**, and 10.6 g of **7** could be isolated in pure form. The combined filtrates yielded on evaporation to dryness a crystal mixture containing a further component. Separation by column chromatography on silica gel (Bio-Rad Laboratories, Richmond, Calif.) with DMF as eluent gave 0.5 g of **7-methyl-1,3-diphenyl-4-phenylimino-2-oxo-1,2,3,4,5,6-hexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidine (13)**, mp 258–260° (from acetone), colorless needles, ir (KBr) 1682, 1646 cm^{-1} (C=O, C=N), R_f 0.82.

Anal. Calcd for $C_{25}H_{22}N_4O$: C, 76.12; H, 5.62; N, 14.20. Found: C, 76.34; H, 5.64; N, 14.10.

Fraction 4.—Tlc did indicate the presence of only one component, which was identified as triphenyl isocyanurate, mp 275°, R_f 0.9, identical in ir comparison with authentic material.

Fraction 5.—The separation into components was omitted, since tlc did show only the presence of carbanilide, **12**, **7**, and traces of triphenyl isocyanurate.

Fraction 6.—Recrystallization from hot DMF gave a crystal mixture, which on boiling with acetone left 0.6 g of **1-methyl-4-hydroxy-1,2-dihydro-3*H*-pyrrolo[2,3-*b*]quinoline (10)**, undissolved: mp >300° (from DMF); colorless crystals; ir (KBr) 1638, 1589 cm^{-1} (quinoline); uv λ_{max}^{EtOH} (log ϵ) 222 nm (4.47), 243 (4.34), 319 (4.17); R_f 0.43 (benzene/DMF, 7:3).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99; mol wt, 200. Found: C, 71.90; H, 6.06; N, 13.92; mol wt, 200 (from mass spectral data).

From the acetone filtrate 5.9 g of **12** and from the DMF filtrate 5.0 g of triphenyl isocyanurate were obtained.

Fraction 7 did consist of pure **7**.

Fraction 8.—Repeated recrystallizations from DMF–diethyl ether gave 1.7 g of **1-methyl-4-anilino-1,2-dihydro-3*H*-pyrrolo-[2,3-*b*]quinoline (11)**: mp 238°; colorless crystals; ir (KBr) 1640, 1600, 1595, 1574 (quinoline system), 765, 755, 698 cm^{-1} (CH out of plane vibrations for mono- and 1,2-disubstituted benzene); nmr (CD_3COOD) δ 2.40 (t, 2, CH_2, J = 8 Hz), 3.15 (s, 3, CH_3), 3.68 (t, CH_2, J = 8 Hz), 6.98–8.45 (m, 9, aromatic H), NH exchanged by CD_3COOD; uv λ_{max}^{EtOH} (log ϵ) 206 nm (4.51), 247 (4.52), 330 (4.10); R_f 0.62.

Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.51; H, 6.22; N, 15.26; mol wt, 275. Found: C, 78.79; H, 6.29; N, 15.38; mol wt, 275 (from mass spectral data).

The following total amounts of product were obtained: 22.5 g (18%) of **2**, 38.7 g (18%) of **7**, 0.6 g (0.4%) of **10**, 1.7 g (0.8%) of **11**, 70.8 g (31%) of **12**, 0.5 g (<0.2%) of **13**, 47.6 g of carbanilide, and 16.0 g of triphenyl isocyanurate.

B. At 210°.—A mixture of 99 g (1.0 mol) of **1** and 119 g (1.0 mol) of phenyl isocyanate was kept for 4 hr at 210°. During the reaction, carbon dioxide was generated and the mixture became highly viscous. For isolation and identification the procedure outlined above was followed. The unreacted **1**, 58.4 g (59%), was removed by initial vacuum distillation, bp 40° (0.1 mm), and solid fractions were obtained from the residue on treatment with methanol and methanol–diethyl ether; the amidine **2**, 29.4 g (41%), was also obtained by vacuum distillation from the residue at bp 80–90° (0.1 mm). By repeated recrystallization from solvents as outlined in A, the following amounts of products were obtained pure: 1.5 g (1.8%) of **10**, 18 g (16%) of **11**, and 9.2 g (7%) of **12**.

4′,6′-Dioxo-1-methyl-1′,3′,5′-triphenylspiro[pyrrolidine-2,2′-perhydro-*s*-triazine] (4).[18]—A mixture of 3.5 g (0.02 mol) of **2** and 4.8 g (0.04 mol) of phenyl isocyanate was kept for 17 hr at room temperature. Colorless crystals were formed during the reaction. Treatment with diethyl ether and filtration yielded 8.0 g (97%) of **4**, mp 130–132° (from chloroform–diethyl ether), ir (KBr) 1670, 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{25}H_{24}N_4O_2$: C, 72.79; H, 5.87; N, 13.58. Found: C, 72.44; H, 5.92; N, 13.46.

Thermal Decomposition of 12.—A sample of 3.0 g (<0.01 mol) of **12** was heated in an open flask to ~240° and kept at that

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(25) Infrared, uv, mass, and nmr spectra were recorded using P-E 625, Cary 14, CH-4, and Varian T-60 (TMS as internal standard) spectrophotometers, respectively. Tlc was performed on precoated silica gel plates (Quantum Ind., Fairfield, N. J.). All melting points were determined on a Fisher-Johns apparatus and are uncorrected.

(26) H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961).

temperature for 5 min. Evolution of a colorless gas was observed. The reaction mixture was diluted with 10 ml of methanol, and the yellowish, crystalline precipitate was collected and washed with ether. Thus, 1.6 g of a mixture of starting material and 11 was obtained. Recrystallization from DMF–diethyl ether yielded 0.95 g (36%) of 11, mp 237°, identical in ir comparison with material obtained above. Dilution of the methanol filtrate with diethyl ether gave 0.6 g (32%) of 10, mp >300°, identical in ir comparison with material obtained above.

Registry No.—1, 872-50-4; 2, 7544-93-6; 4, 40387-20-0; 7, 40387-21-1; 10, 40387-22-2; 11, 40387-23-3; 12, 40387-24-4; 13, 40387-25-5; phenyl isocyanate, 103-71-9.

Quinazolines. I. The Oxidation of Indole-1,2-dicarboximides and Subsequent Conversion of Their Oxidation Products to Quinazolinones

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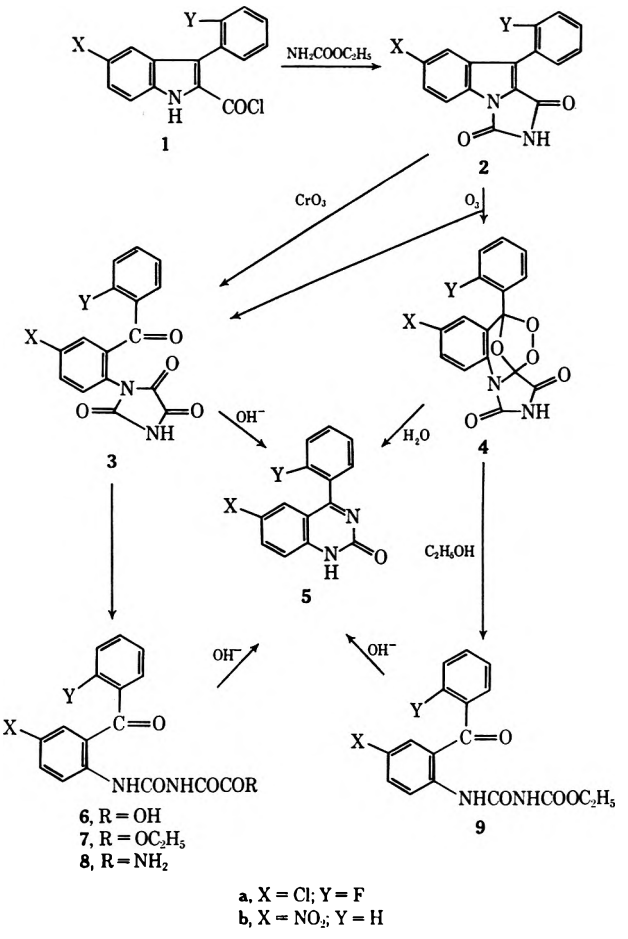
Chromic acid oxidation of indole-1,2-dicarboximides **2** led to imidazolidinetriones **3**, which on hydrolysis with base gave the corresponding dihydroquinazolinones **5**. Ozonolysis of **2**, on the other hand, resulted in the formation and isolation of crystalline ozonides **4**. On simply heating with water, the ozonides **4** were readily converted into **5** in nearly quantitative yields. The mechanism for this conversion is discussed.

In the past few years, we have reported the syntheses of 1,4-benzodiazepine ring systems by the oxidative ring cleavage of indoles bearing a substituent such as 2-aminomethyl,[1] 1-aminoethyl,[2] and 1-phthalimidoacetyl groups.[3] We have now extended our studies to another heterocyclic system, dihydroquinazolinone. Several reports have appeared in the literature on syntheses of the quinazoline ring system by rearrangement reactions of other heterocyclic structures, such as isatins,[4] quinolines,[5] and 1,4-benzodiazepines,[6] bearing an N-monosubstituted carbamoyl group at N-1. These methods, however, led only to the tetrahydroquinazolinones, rather than to the dihydro derivatives, because of the presence of a substituent on the carbamoyl nitrogen. We turned our attention to the synthesis and oxidation of indole-1,2-dicarboximides **2**. By analogy with the previously described conversion[2] of pyrazino[1,2-*a*]indol-1(2*H*)-ones into 2,3-dihydro-1*H*-1,4-benzodiazepines, compounds **2** seemed likely to produce the desired dihydroquinazolinones **5** by oxidative cleavage of the indole ring, followed by hydrolysis of the imidazolidinetriones **3** thus obtained (Scheme I).

The synthesis of **2** was achieved by condensation of indole-2-carboxylic acid chlorides[1c,d] with urethane.[7] The ir spectrum of **2** showed the expected NH absorptions and two carbonyl bands at relatively high frequencies (1790 and 1728 cm^{-1}), consistent with the hydantoin structure and in good agreement with those observed in the spectrum of *N*-phenylindole-1,2-dicarboximide.[8]

SCHEME I



6, R = OH
7, R = OC_2H_5
8, R = NH_2

a, X = Cl; Y = F
b, X = NO_2; Y = H

Chromic Acid Oxidation.—When compounds **2** were treated with chromic acid in acetic acid at 60–70°, the expected imidazolidinetriones **3** were obtained together with small amounts of **5**. While **3a** was isolated only in amorphous form, **3b** formed a crystalline etherate, which on heating *in vacuo* was converted to free, crystalline **3b**. Their ir spectra showed carbonyl bands at 1750 cm^{-1} with a shoulder near 1790 cm^{-1}, owing to imidazolidinetrione structure,[9] as well as the benzophenone C=O absorption at 1670 cm^{-1}.

(1) (a) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968); (b) S. Inaba, T. Hirohashi, and H. Yamamoto, *Chem. Pharm. Bull.*, **17**, 1263 (1969); (c) S. Inaba, K. Ishizumi, and H. Yamamoto, *ibid.*, **19**, 263 (1971); (d) S. Inaba, K. Ishizumi, K. Mori, and H. Yamamoto, *ibid.*, **19**, 722 (1971).

(2) S. Inaba, K. Ishizumi, T. Okamoto, and H. Yamamoto, *ibid.*, **20**, 1628 (1972).

(3) K. Ishizumi, K. Mori, S. Inaba, and H. Yamamoto, *ibid.*, **21**, 1027 (1973).

(4) (a) L. Capuano and M. Welter, *Chem. Ber.*, **101**, 3671 (1968); (b) L. Capuano, M. Welter, and R. Zander, *ibid.*, **103**, 2394 (1970).

(5) A. Brack, *Justus Liebigs Ann. Chem.*, **730**, 166 (1969).

(6) T. Masuda, S. Fujii, and K. Naito, Japanese Patent 15,500 (1971); *Chem. Abstr.*, **75**, 36104z (1971).

(7) The synthesis of indole-1,2-dicarboximide itself is achieved by condensing ethyl indole-2-carboxylate with the sodium derivative of urethane: J. D. Dutcher and A. Kjaer, *J. Amer. Chem. Soc.*, **73**, 4139 (1951).

(8) E. P. Papadopoulos and S. B. Bedrosian, *J. Org. Chem.*, **33**, 4551 (1968).

(9) H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.*, **30**, 2781 (1965).

Hydrolysis of **3** with base gave the desired dihydroquinazolinones **5** in high yields. The structure of **5** was confirmed by comparison with authentic samples.[10] When **3a** was heated simply with water, the intermediate carbamoyloxamic acid **6a** was isolated, thus indicating that the imidazolidinetrione ring is initially opened at the anilino nitrogen. The position of the oxalyl group in **6a** was shown by the appearance of two exchangeable singlets at δ 10.95 and 11.15 in the nmr spectrum. Further hydrolysis of **6a** with base gave **5**. Ethanolysis or aminolysis of **3** also opened the imidazolidinetrione ring at the same position to give the oxamate **7** or oxamide **8**, respectively.

Ozonolysis.—Compound **2a** did not react with ozone in carbon tetrachloride, and only sluggishly in ethanol. However, when ozonized in acetic acid, **2a** went into solution and a new solid gradually precipitated in 43% yield, to which structure **4a** was assigned. The ir spectrum of **4a** exhibited carbonyl absorptions attributable to the hydantoin structure at somewhat higher frequencies than found with **2a** (1826 and 1742 cm^{-1}). The structure of **4a** was further supported by its ability to oxidize iodide ions. The acetic acid filtrates from the ozonolysis afforded a 40% yield of **3a**.

Ozonolysis of **2b** under similar conditions gave the soluble ozonide **4b**, which could be precipitated in 76% yield by addition of water to the ozonized solution.

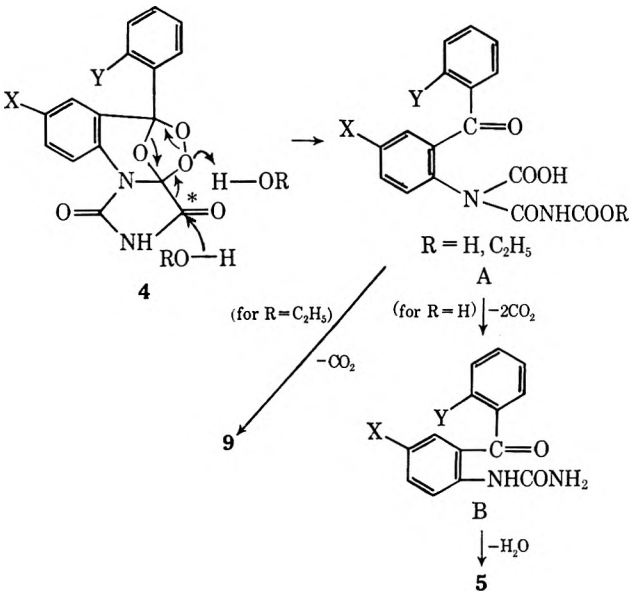
The use of acetic acid as a solvent for ozonolysis is known to be unfavorable for the formation of a stable ozonide because of its reactivity to a zwitterion intermediate.[11] However, we have shown previously[3] the formation of stable ozonides in acetic acid from some 3-phenyl-1-phthalimidoacetylindoles in which the indole 2,3 double bond is stabilized both by conjugation with the 3-phenyl group and by inhibition of the imino–ketimine tautomerism in the indole ring by an *N*-acyl group.[12] In view of the similarity of the double-bond system, therefore, the formation of **4** from acetic acid solvent was to be expected.[13]

Further conversion of ozonides **4** was best accomplished by hydrolysis, a method generally inferior to an oxidative or reductive work-up.[11] Hot water converted **4** to **5** in nearly quantitative yield with remarkable ease. A plausible mechanism is given in Scheme II in which the first step is nucleophilic attack by hydroxide at the starred carbonyl function.[15]

Subsequent loss of 2 mol of carbon dioxide followed by 1 mol of water from the allophanic acid intermediate A would give **5**. This mechanism is in good agreement with the observation that **4** was converted into ethyl allophanates **9** by the addition of ethanol.

Hydrolysis of **9** with base also gave **5** in high yields.

SCHEME II



Experimental Section

Infrared spectra were measured on a Hitachi Model EPI-G3 spectrophotometer and nmr spectra on a Varian T-60 instrument using tetramethylsilane as an internal standard. Mass spectra were taken on a Shimadzu LKB instrument with the direct sample inlet system and ionizing potential at 70 eV. All melting points were determined in open capillary tubes and are uncorrected.

5-Chloro-3-(*o*-fluorophenyl)indole-1,2-dicarboximide (2a). Method A.—A mixture of 30 g of 5-chloro-3-(*o*-fluorophenyl)-indole-2-carboxylic acid[1c] and 60 ml of thionyl chloride was heated under reflux for 2 hr. Excess of thionyl chloride was evaporated under reduced pressure. To the residual acid chloride (**1a**) was added 30 g of urethane. The mixture was heated to 170–180° for 2 hr. The resulting ethanol and excess reagent were distilled off under reduced pressure. The residue was triturated with ether and recrystallized from acetone to give 11.8 g of **2a**, mp 249–251.5°. A second crop (5.2 g, mp 248.5–251°) was obtained from the mother liquor to give a combined yield of 17.0 g (52.2%). Further recrystallizations from acetone gave yellow rods: mp 253–254°; ir (Nujol) 3130, 3025, 1790, 1728 cm^{-1}; mass spectrum *m/e* 314 (M^+), 271, 208.

Anal. Calcd for $C_{16}H_8ClFN_2O_2$: C, 61.07; H, 2.56; N, 8.90; Cl, 11.27. Found: C, 61.02; H, 2.66; N, 8.81; Cl, 11.13.

[4-Chloro-2-(*o*-fluorobenzoyl)phenyl]imidazolidinetrione (3a).—To a suspension of 2.0 g of **2a** in 30 ml of acetic acid was added a solution of 3 g of chromic anhydride in 3 ml of water. The mixture was stirred at 65° for 5 hr. Acetic acid was evaporated under reduced pressure. The residue was treated with water and extracted with ether, and the insoluble **5a** (0.05 g, 2.9%) was filtered off. The ether filtrate was dried over anhydrous sodium sulfate and evaporated. The residue was triturated with pentane and filtered to give 1.74 g (79.0%) of **3a** as an amorphous powder: ir (Nujol) 3230, 3075, 1792, 1755, 1673, 1613 cm^{-1}; nmr ($CDCl_3$) δ 6.95–7.70 (m, 7, aromatic H), 9.64 (s, 1, D_2O exchangeable, NH); mass spectrum *m/e* 346 (M^+), 275, 223, 180, 123 (*o*-FC_6H_4CO, base peak).

Anal. Calcd for $C_{16}H_8ClFN_2O_4$: C, 55.43; H, 2.33; N, 8.08; Cl, 10.23. Found: C, 54.90; H, 2.81; N, 7.98; Cl, 9.80.

(2-Benzoyl-4-nitrophenyl)imidazolidinetrione (3b).—A suspension of 5.0 g of **2b** was treated with a solution of 5 g of chromic anhydride in 5 ml of water in the same manner as above. After acetic acid was evaporated, the residue was triturated with water, and the solid, which was separated by filtration, was dried in a vacuum desiccator at room temperature. This gave 5.55 g of crude **3b**, mp 135–140°. The crude product was suspended in ether and heated under reflux. The insoluble solid was removed by filtration, and the filtrate was concentrated to a small volume and chilled in a refrigerator. The precipitate formed was collected by filtration to give 3.41 g (50.7%) of the etherate of **3b**

(10) S. Inaba, M. Yamamoto, K. Ishizumi, K. Takahashi, K. Mori, and H. Yamamoto, German Patent 1,935,404 (1970); *Chem. Abstr.*, **72**, 90494c (1970).

(11) P. S. Bailey, *Chem. Rev.*, **58**, 926 (1958).

(12) C. M. Atkinson, J. C. E. Simpson, and A. Taylor, *J. Chem. Soc.*, 165 (1954).

(13) Stable ozonides from acetic acid solvent have also been reported in 1,2-diphenylindene[14a] and 2-methyl-3-phenylindenone[14b] where the double bond is conjugated with the phenyl or carbonyl group.

(14) (a) P. S. Bailey, *Chem. Ber.*, **87**, 993 (1954); (b) R. Criegee, P. de Bruyn, and G. Lohaus, *Justus Liebigs Ann. Chem.*, **583**, 19 (1953).

(15) A similar mechanism has been proposed for "abnormal" ozonolyses of α,β-unsaturated acids, aldehydes, and ketones, assuming the formation of an ozonide: D. H. R. Barton and E. Seoane, *J. Chem. Soc.*, 4150 (1956). On the other hand, Bailey[11] has explained those ozonolyses by the zwitterion rearrangement mechanism.

as colorless prisms: mp 90–94° dec; ir (Nujol) 3550, 3300–2720, 1790, 1760, 1672, 1622, 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (t, 6, J = 7 Hz, 2 CH_3), 3.52 (q, 4, J = 7 Hz, 2 CH_2), 7.30–8.50 (m, 8, aromatic H).

Anal. Calcd for $C_{20}H_{19}N_3O_7$: C, 58.11; H, 4.63; N, 10.16. Found: C, 58.15; H, 4.52; N, 10.15.

The etherate, on heating at 70° in a vacuum oven, gave pure, ether-free **3b** as colorless prisms: mp 165–168° dec (softening at 117°); ir (Nujol) 3225, 3075, 1795, 1757, 1672, 1620, 1600 cm^{-1}.

Anal. Calcd for $C_{16}H_9N_3O_6$: C, 56.65; H, 2.67; N, 12.39. Found: C, 56.93; H, 2.55; N, 12.36.

Hydrolysis of 3a to 5a. Method B.—A mixture of 0.20 g of **3a**, 6 ml of ethanol, and 0.8 ml of 20% sodium hydroxide solution was refluxed for 45 min. After evaporation of ethanol, the residue was diluted with water and acidified with hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried to give 0.14 g (88.4%) of **5a**, mp >300°. Recrystallization from dimethylformamide afforded yellow needles, mp >300°. The material was identical with an authentic sample[10] by comparison of ir spectra.

Anal. Calcd for $C_{14}H_8ClFN_2O$: C, 61.22; H, 2.94; N, 10.20; Cl, 12.91. Found: C, 61.29; H, 2.90; N, 10.12; Cl, 12.88.

[4-Chloro-2-(*o*-fluorobenzoyl)phenyl]carbamoyloxamic Acid (6a).—A suspension of 0.50 g of **3a** in 7 ml of water was heated in a water bath for 3.5 hr. After cooling, the precipitate was collected by filtration and washed with ether to give 0.45 g (85.6%) of **6a**, mp 199.5–200° dec. Recrystallization from ethylene dichloride afforded slightly yellow needles: mp 198° dec; ir (Nujol) 3160, 1714, 1653 cm^{-1}; nmr (DMSO) δ 7.20–8.30 (m, 7, aromatic H), 10.95 (s, 1, D_2O exchangeable, NH), 11.15 (s, 1, D_2O exchangeable, NH); mass spectrum m/e 346 ($M - H_2O$), 275, 180, 123 (o-FC_6H_4CO, base peak).

Anal. Calcd for $C_{16}H_{10}ClFN_2O_5$: C, 52.69; H, 2.76, N, 7.68. Found: C, 53.04; H, 3.04; N, 7.81.

Compound **6a** was hydrolyzed with sodium hydroxide solution as described in method B to give **5a** in 96.3% yield.

Ethyl [4-Chloro-2-(*o*-fluorobenzoyl)phenyl]carbamoyloxamate (7a). Method C.—A solution of 0.20 g of **3a** in 3 ml of ethanol was heated under reflux for 6.5 hr. The reaction mixture was cooled, and the precipitate that formed was collected by filtration to give 0.04 g of **7a**, mp 192–193° dec. On heating the filtrate, a further 0.08 g of product was obtained to give a combined yield of 0.12 g (53.0%). Recrystallization from ethanol afforded colorless needles: mp 199–200° dec; ir (Nujol) 3307, 3155, 1720, 1667, 1657, 1616 cm^{-1}.

Anal. Calcd for $C_{18}H_{14}ClFN_2O_5$: C, 55.04; H, 3.59; N, 7.13; Cl, 9.03. Found: C, 55.01; H, 3.71; N, 7.15; Cl, 9.08.

[4-Chloro-2-(*o*-fluorobenzoyl)phenyl]carbamoyloxamide (8a).—A suspension of 0.20 g of **3a** in 2 ml of concentrated ammonium hydroxide was stirred at room temperature for 3 hr. Filtration and washing with water gave 0.19 g (90.6%) of **8a**, mp 207–208° dec. After recrystallization from a mixture of dimethylformamide and ethanol, slightly yellow needles were obtained: mp 212–212.5° dec; nmr (DMSO) δ 7.30–8.52 (m, 7, aromatic H), 8.28 and 8.35 (2, D_2O exchangeable, $CONH_2$), 10.40 (s, 1, D_2O exchangeable, NH), 11.53 (s, 1, D_2O exchangeable, NH).

Anal. Calcd for $C_{16}H_{11}ClFN_3O_4$: C, 52.83; H, 3.05; N, 11.55; Cl, 9.75. Found: C, 52.77; H, 3.07; N, 11.56; Cl, 9.78.

5-Chloro-3-(*o*-fluorophenyl)indole-1,2-dicarboximide Ozonide (4a).—An ozone–oxygen stream[16] was passed through a stirred suspension of 1.0 g of **2a** in 25 ml of acetic acid for 3 hr. During the course of the reaction, **2a** went into solution and then a new fine white suspension appeared. The white precipitate was collected by filtration, washed with water, and dried in a vacuum desiccator to give 0.41 g of **4a**, mp 136.5–137° dec. The filtrate was concentrated to a small volume to give an additional 0.09 g of **4a** for a combined yield of 0.50 g (43.4%): ir (Nujol) 3190, 3075, 1826, 1741, 1621 cm^{-1}; mass spectrum m/e 275, 180.

(16) Ozone was generated from oxygen using a Nippon ozone 0-10-2 ozonator.

The ozonide **4a** gave a positive active oxygen test with sodium iodide in acetic acid solution.

Anal. Calcd for $C_{16}H_8ClFN_2O_5$: C, 52.98; H, 2.22; N, 7.72; Cl, 9.77. Found: C, 52.64; H, 2.40; N, 7.62; Cl, 9.78.

The filtrate from which the second crop was filtered was evaporated to dryness under reduced pressure below 40°. The residue was dissolved in ether, washed with water, and dried over anhydrous sodium sulfate. Evaporation of the solvent and trituration with pentane gave 0.44 g (39.9%) of **3a**. The ir and nmr spectra of this compound were identical with those of the product obtained above from chromic acid oxidation of **2a**.

5-Nitro-3-phenylindole-1,2-dicarboximide Ozonide (4b).—A suspension of 5.0 g of **2b** in 125 ml of acetic acid was ozonized as above. The resulting solution was diluted with cold water. The precipitate that formed was collected by filtration, washed with water, and dried to give 4.4 g (76.1%) of **4b**: mp 100° dec; ir (Nujol) 3600, 3500, 3225, 1828, 1809, 1775, 1620, 1598 cm^{-1}. This material also gave a positive active oxygen test.

Anal. Calcd for $C_{16}H_9N_3O_7$: C, 54.09; H, 2.55; N, 11.83. Found: C, 54.29; H, 2.57; N, 11.85.

Conversion of 4a to 5a. Method D.—A suspension of 0.10 g of **4a** in 3 ml of water was heated to 70–80° for 1 hr. Cooling and filtration gave 0.07 g (92.4%) of **5a**, mp > 300°. The ir spectrum of this compound was identical with that of the sample obtained by hydrolysis of **3a**.

Ethyl 4-[4-Chloro-2-(*o*-fluorobenzoyl)phenyl]allophanate (9a). Method E.—To 2 ml of ethanol was added 0.10 g of **4a**. Evolution of carbon dioxide immediately occurred. The mixture was refluxed for 1 hr and cooled. The precipitate was collected by filtration to give 0.09 g (89.5%) of **9a**, mp 208–209° dec. Recrystallization from ethanol afforded colorless needles: mp 208–209° dec; ir (Nujol) 3130, 1740, 1715, 1665, 1618 cm^{-1}; nmr (DMSO) δ 1.24 (t, 3, J = 7 Hz, CH_3), 4.20 (q, 2, J = 7 Hz, CH_2), 7.20–8.40 (m, 7, aromatic H), 10.48 (s, 1, D_2O exchangeable, NH), 11.45 (s, 1, D_2O exchangeable, NH); mass spectrum m/e 364 (M^+), 275, 180, 123 (o-FC_6H_4CO, base peak).

Anal. Calcd for $C_{17}H_{14}ClFN_2O_4$: C, 55.98; H, 3.87; N, 7.68; Cl, 9.72. Found: C, 56.29; H, 3.85; N, 7.47; Cl, 9.64.

Compound **9a** was hydrolyzed with sodium hydroxide solution as in method B to give **5a** in 93.6% yield.

The remaining **b** compounds were prepared as described for **a** series and are given in Table I.

TABLE I

COMPOUNDS **2b**, **5b**, **7b**, AND **9b**[a]

Compd	Method	Recrystn solvent	Mp, °C	Yield, %
2b	A	Acetone	262–262.5	50.2
5b[b]	B	EtOH	>300	87.9
5b[b]	D	EtOH	>300	92.0
7b	C	EtOH	213–214	59.0
9b	E	EtOH	202–203	80.1[c]

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all new compounds listed in the table: Ed. [b] The ir spectrum of this material was identical with that of an authentic sample.[10] [c] This reaction yielded **5b** in 12.5% yield as a by-product isolated from the reaction filtrate.

Registry No.—**1a**, 32502-22-0; **1b**, 30016-54-7; **2a**, 40387-03-9; **2b**, 40387-04-0; **3a**, 40387-05-1; **3b**, 40387-06-2; **3b** etherate, 40387-07-3; **4a**, 40387-08-4; **4b**, 40387-09-5; **5a**, 40069-75-8; **5b**, 26313-36-0; **6a**, 40387-12-0; **7a**, 40387-13-1; **7b**, 40387-14-2; **8a**, 40387-15-3; **9a**, 40387-16-4; **9b**, 40387-17-5; 5-chloro-3-(*o*-fluorophenyl)indole-2-carboxylic acid, 40387-18-6; thionyl chloride, 7719-09-7.

Electrochemical and Chemical Reduction of Di-*tert*-butyldiaziridinone[1a]

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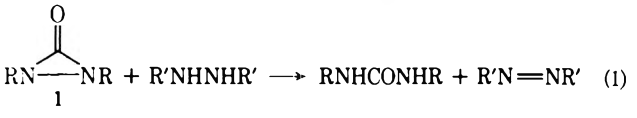
Received February 26, 1973

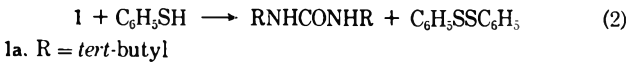
Di-*tert*-butyldiaziridinone (**1a**) was reduced both electrochemically and by *tert*-butyllithium and sodium naphthalenide. The product in all three cases was di-*tert*-butylurea, indicating that the preferred mode of reduction of **1a** under electron-transfer conditions is cleavage of the N–N single bond. Cyclic voltammetry indicated that, if the radical anion of **1a** is an intermediate, its half-life must be less than 2 msec. Mechanisms of the reductions are discussed.

The synthesis and a number of reactions of diaziridinones, **1** (R = *tert*-alkyl), have been described.[2] A property of special interest is the mild oxidizing action (ease of reduction) of **1**.[2] We summarize here information on the reduction of diaziridinones.

As described earlier, reaction of di-*tert*-butyldiaziridinone (**1a**) with sodium borohydride leads to cleavage of the C–N bond with formation of 1,2-di-*tert*-butyl-1-formylhydrazine.[2] Reaction of **1a** with substituted hydrazines[3] or mercaptans[2] effects reduction of the N–N bond (eq 1 and 2). Results of a detailed study



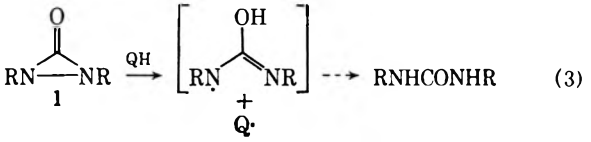
1 + R'NHNHR' → RNHCONHR + R'N=NR' (1)



1 + C_6H_5SH → RNHCONHR + $C_6H_5SSC_6H_5$ (2)

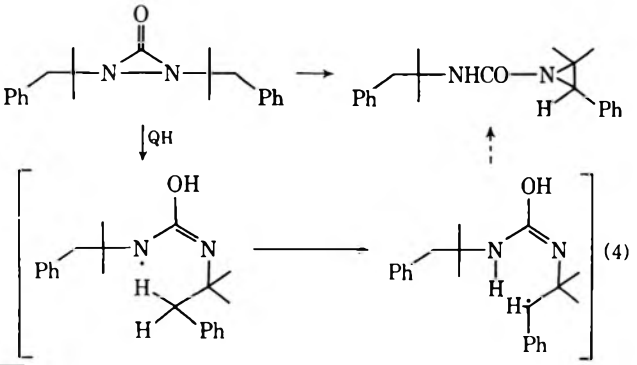
1a, R = *tert*-butyl

of the oxidation–reduction reaction of eq 1[3] led to the suggestion that the reaction proceeded by a free-radical chain reaction involving hydrogen atom transfer to the diaziridinone (eq 3). That study also led to the



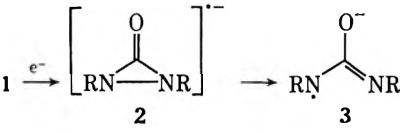
RNHCONHR (3)

discovery of a rearrangement reaction of diaziridinones to aziridinecarboxamides (eq 4), competitive with the oxidation–reduction reaction of eq 1.



(4)

Another possible mode of reduction of a diaziridinone (or possible mode of catalysis of the rearrangement reaction of eq 4) would be by electron transfer (eq 5).



(5)

In search of species such as **2** and **3**, we have examined the reduction of di-*tert*-butyldiaziridinone by electrochemical and chemical methods.

Electrochemical Reduction.—Diaziridinone **1a** exhibits a single diffusion-controlled polarographic wave at −0.76 V (relative to the cadmium amalgam reference electrode of Marple),[4] in dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) containing tetraethylammonium bromide (TEAB). The diffusion current constant, I_d,[5,6] was equal to 4.2 in DMF indicating an overall two-electron reduction process.[6] Tomes' criterion,[5] *i.e.*, $E_{1/4} - E_{3/4}$, was 140 mV, indicating an element of irreversibility to be associated with the reduction. This was confirmed by cyclic voltammetry; no anodic peak was observed upon scan reversal just beyond the cathodic peak, even at the fastest scan rate employed (200 V/sec).[7] Thus any intermediate(s) generated during reduction of the diaziridinone must be too short-lived to be observed under our conditions. The polarographic behavior of **1a** was unaffected by the addition of excess phenol, normally an efficient proton donor in DMF and DMSO.[8] Controlled-potential electrolysis of **1a** in DMF afforded di-*tert*-butylurea in high yield; integration of the current passed during electrolysis demonstrated that two electrons were consumed per molecule of starting material, in agreement with the observed polarographic diffusion current constant. The solution became dark yellow during electrolysis. When electrolysis was carried out in the

(1) (a) Financial support from the Petroleum Research Fund administered by the American Chemical Society and the National Science Foundation is gratefully acknowledged; (b) National Science Foundation trainee.

(2) F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969).

(3) F. D. Greene, W. R. Bergmark, and J. G. Pacifici, *ibid.*, **34**, 2263 (1969).

(4) L. W. Marple, *Anal. Chem.*, **39**, 844 (1967). This electrode is *ca.* −0.7 V relative to sce.

(5) $I_d = 708nD^{1/2} = i_d/Cm^{2/3}t^{1/6}$, using an undamped recorder to measure diffusion currents: L. Meites, "Polarographic Techniques," 2nd ed, Wiley-Interscience, New York, N. Y., 1965.

(6) In DMF, values of I_d of *ca.* 4–6 correspond to a two-electron reduction process: *cf.* (a) Meites, ref 5, pp 678–711; (b) J. L. Sadler and A. J. Bard, *J. Amer. Chem. Soc.*, **90**, 1979 (1968).

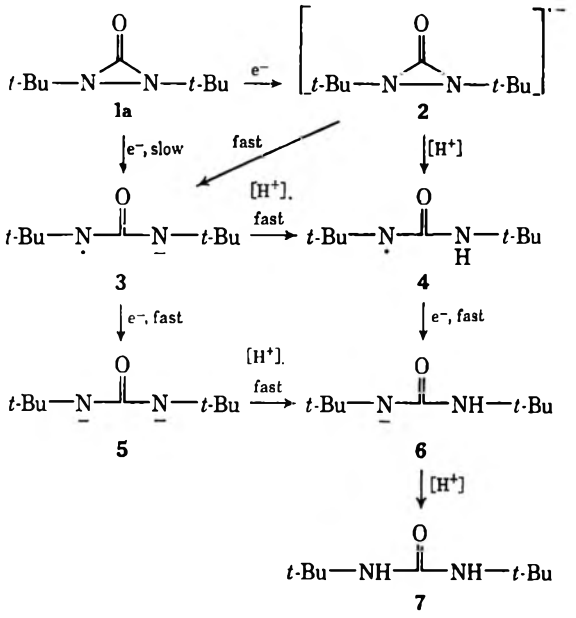
(7) The faradaic wave at $E_{p/2}$ = −0.7 V was accompanied by two other waves, a cathodic peak at −1.4 V and an anodic peak at 0.4 V. The markedly symmetrical shape of these peaks and the fact that they are relatively much smaller than the wave at −0.7 V at low scan rates or high concentrations of **1** suggest that they are due to adsorption phenomena [see R. H. Wopschall and I. Shain, *Anal. Chem.*, **39**, 1514 (1967)].

(8) J. R. Jezorek and H. B. Mark, Jr., *J. Phys. Chem.*, **74**, 1627 (1970).

presence of added phenol, the solution remained colorless; the product was still the urea.

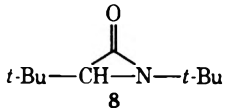
The principal result is clean reduction of the N–N bond. Several paths are possible (Scheme I).

SCHEME I



Whether the initial electron-transfer step affords a diaziridinone radical anion (2) as a discrete intermediate, or whether the ring is opened during the first electron-transfer step to afford 3 is not resolvable with the data at hand, other than to note that cyclic voltammetry data indicate that, if 2 is actually a discrete intermediate, it must be short-lived ($t_{1/2} \leq 2$ msec). The dark yellow color observed upon reduction in the absence of any added proton donor might be due to the dianion 5, but is more likely the monoanion 6, since 5 should be sufficiently basic to effect a rapid Hofmann elimination upon the tetraalkylammonium ion used as electrolyte.[9]

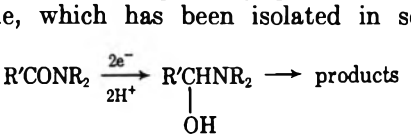
The α-lactam, 1,3-di-*tert*-butylaziridinone (8), is not reducible electrochemically even at the most negative potentials accessible in dimethyl sulfoxide (−2.6 V *vs.* sce). This indicates that relief of strain cannot alone account for the ease of reduction of 1a. The large (>1.3 V) difference in reduction potentials between 1a and 8 should derive at least in part from a greater strength of the C–N bond in 8 relative to the



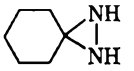
N–N bond in 1a and is suggestive that reduction of 1a does involve breaking of the N–N bond in the transition state for the initial electron transfer.

It is of interest to compare these results with the electrochemical reduction of amides and diaziridines. Reduction of 1a involves cleavage of the N–N bond rather than reduction of the carbonyl group as with amides.[10,11] Also, 1a is considerably easier to reduce than ordinary amides (DMF was the solvent for preparative scale electrolysis of 1a) or ureas.[12a]

Direct electrochemical reduction of simple aliphatic and aromatic amides occurs only at very negative potentials and in fairly strongly acidic media, where the electroactive species may actually be the protonated amide.[10] It is also possible to reduce amides indirectly, using solvated electrons generated by the electrochemical reduction of lithium ion in methylamine.[11] Both types of reduction apparently proceed *via* the carbinolamine, which has been isolated in several in-



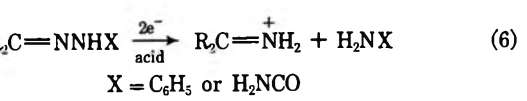
stances.[12b] Probably the most notable feature of the electrochemical reduction of 1a is the fact that it can be carried out under neutral conditions. Hydrazo compounds,[13] including diaziridines, *e.g.*, 9,[14] are inert



9

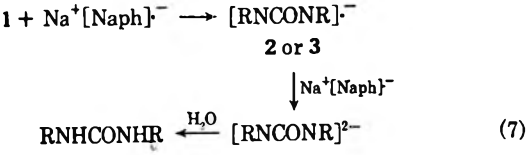
10

toward electrochemical reduction under neutral or alkaline conditions although the N–N bond can be cleaved in acid. For example, 9 could be prepared in quantitative yield by electrolytic reduction of diazirine, 10 at pH 9, while at pH 6 cyclohexanone was formed, presumably *via* reduction of 9 to the *gem*-diamine, followed by hydrolysis.[14] The pH dependence of the polarographic half-wave potentials of hydrazo compounds and diaziridines is generally ascribed to the fact that the electroactive substance is a protonated species.[13,14] The activated N–N bond of phenylhydrazones and semicarbazones is reduced in acid media (eq 6) but inert in neutral or alkaline media.[13]



(6)

Reduction by Sodium Naphthalenide.—Combination of equimolar amounts of diaziridinone 1a and of sodium naphthalenide in tetrahydrofuran led to the immediate discharge of the color of the naphthalenide radical ion and formation of a precipitate. The reaction mixture, after quenching with water, afforded the urea 7 (46%) and unchanged diaziridinone (48%). Reaction of the diaziridinone with 2 mol of sodium naphthalenide followed by quenching with water afforded the urea in high yield (eq 7). The capability



(7)

of sodium naphthalenide to serve as a single-electron transfer agent seems well established.[15] The implica-

(9) A. J. Fry and R. G. Reed, *J. Amer. Chem. Soc.*, **93**, 553 (1971).

(10) S. Swann, Jr., in "Technique of Organic Chemistry," Vol. 2, A. Weissberger, Ed., 1956, pp 502, 503.

(11) R. A. Benkeser, H. Watanabe, S. J. Mels, and M. A. Sabol, *J. Org. Chem.*, **35**, 1210 (1970).

(12) (a) W. E. Bull and R. H. Stonestreet, *J. Electroanal. Chem.*, **12**, 166 (1966); (b) G. Farnia, A. Romanin, G. Capobianco, and F. Torzo, *ibid.*, **33**, 31 (1971).

(13) C. L. Perrin, *Progr. Phys. Org. Chem.*, **3**, 165 (1965).

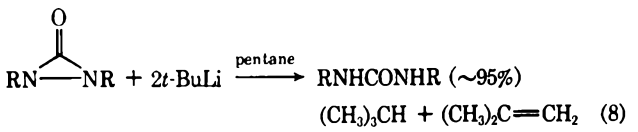
(14) H. Lund, *Collect. Czech. Chem. Commun.*, **31**, 4175 (1966).

(15) P. W. Ayers, J. F. Garst, and R. C. Lamb, *J. Amer. Chem. Soc.*, **88**, 4266 (1966); G. D. Sargent, J. N. Cron, and S. Bank, *ibid.*, **88**, 5363 (1966).

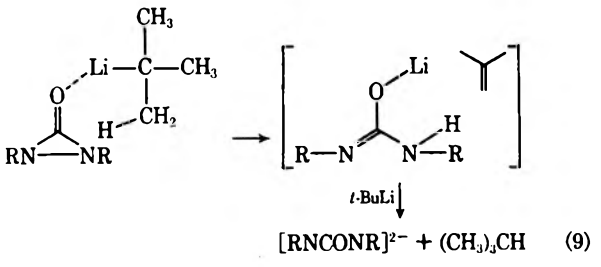
tion of the above experiment is that either the further reduction of the first-formed radical ion is faster than the initial reduction, or the radical ion disproportionates[16] to diaziridinone and the urea dianion, which precipitates as the disodium salt.

Reaction of sodium naphthalenide with bis(1,1-dimethyl-2-phenylethyl)diaziridinone (**1b**, eq 4) also shows the stoichiometry of eq 7, affording the urea in high yield. Reaction of sodium naphthalenide with an excess of diaziridinone **1b** followed by quenching with water afforded largely unchanged diaziridinone along with a small amount of the corresponding urea. Here, also, the only reaction observed is reduction of the N–N bond.[17]

Reduction by *tert*-Butyllithium.—Reaction of diaziridinones **1a** and **1b** with *tert*-butyllithium in pentane is rapid (eq 8). No products of addition to the carbonyl group (or to nitrogen) were observed. Here, also, the exclusive path, overall, is reduction of the N–N bond of the diaziridinone to the urea dianion, possibly proceeding by electron transfer from *tert*-butyllithium[18] or by a cyclic path (*e.g.*, as in eq 9).



(8)



(9)

Summary.—Hydride transfer reagents effect reduction of diaziridinones at the C–N bond; hydrogen atom transfer reagents effect reduction at the N–N bond, sometimes accompanied by a rearrangement reaction (eq 3 and 4); electron transfer by electrochemical means or by sodium naphthalenide effects clean reduction of the N–N bond.

Experimental Section

Polarography and cyclic voltammetry were carried out using a Princeton Applied Research Model 170 electrochemistry system. The working electrode for cyclic voltammetry was a mercury drop hanging from a very short (0.1 mm) platinum wire. The reference electrode for all experiments was the cadmium amalgam–cadmium chloride electrode of Marple.[4] Preparative electrolyses were carried out using a potentiostat based upon a Kepco KS-120-2.5 programmable power supply.[19] To obtain coulometric data, the voltage drop across a standard resistor in series with the cell was measured on a 1-mV strip-chart recorder equipped with Disc integrator and digital printer. The electrochemical cell has been described previously.[20]

Electrochemical Reduction of Di-*tert*-butyldiaziridinone (1).—A 5-ml sample of a 0.1 *M* solution of tetraethylammonium bromide in dimethylformamide was preelectrolyzed at −0.8 V until the current had decayed to a constant value (~1 mA). A solution of 0.200 g of **1a**[2] in 0.5 ml of dimethylformamide was then injected, and electrolysis was continued until the current had returned to the background value. Integration of the current passed in the electrolysis showed that 2.1 ± 0.2 F had been consumed per mole of **1a**. The dark yellow electrolysis solution was poured into water (whereupon the yellow color disappeared), and the resulting solution was extracted with ether. After the solution was dried over sodium sulfate, the ether was distilled to afford 1,3-di-*tert*-butylurea, 0.190 g [95%], mp (sealed capillary) 238–240° (lit.[2] mp 243–244°).

Reaction of Di-*tert*-butyldiaziridinone with *tert*-Butyllithium.—To a solution of *tert*-butyllithium (6.5 mmol) in 10.0 ml of pentane was added, all at once and under a nitrogen atmosphere, 0.522 g (3.04 mmol) of di-*tert*-butyldiaziridinone in 5.0 ml of pentane. The reaction proceeds rapidly with the evolution of gases and the formation of a white precipitate. Water (5 ml) was added, hydrolyzing the precipitate and forming a white crystalline solid, 0.511 g (2.9 mmol) (95% yield) of di-*tert*-butylurea, mp 240–241°, mmp 240–241°, identical in ir and vpc with an authentic sample. A sample of the pentane solution was removed from the flask and injected into the vpc. The chromatogram showed the presence of isobutane and isobutylene; no di-*tert*-butyl was formed.

To a second solution of *tert*-butyllithium, 3.0 mmol in 2.0 ml of pentane, was added 0.256 g (1.5 mmol) of di-*tert*-butyldiaziridinone in 2.0 ml of pentane by a hypodermic syringe in a closed system. Samples of the gases given off were analyzed by vpc at 25° on SE-30 on Chromosorb W. The gases were identified as isobutane and isobutylene, formed in equal amounts. Yields were determined in a separate experiment by manometric techniques, 0.25 mmol of diaziridinone affording 0.51 mmol of isobutane and isobutene.

The same results (95% yield of the urea) were obtained by reaction at −76°.

Reaction of Sodium Naphthalenide with Diaziridinones.—Preparation of sodium naphthalenide from sodium metal and naphthalene in THF was accomplished by standard vacuum line methods. Samples of the diaziridinone were added all at once by means of a break-seal attached to the reaction vessel. In each case the hydrolysis was carried out by the addition of water to the system by means of a second break-seal. All reactions were carried out at room temperature.

A. Reaction with Di-*tert*-butyldiaziridinone.—To a solution of sodium naphthalenide (1.0 mmol in 8.0 of THF) was added 0.171 g (1.0 mmol) of di-*tert*-butyldiaziridinone. Immediately upon addition a white precipitate was formed with the disappearance of the green color. To the mixture was added 5.0 ml of water which hydrolyzed the precipitate and produced two clear phases. The contents were removed, the two phases were separated, and the ether phase was dried over $MgSO_4$. Removal of the ether left an oily-crystalline residue from which was isolated by trituration with CCl_4 0.080 g (0.46 mmol) of di-*tert*-butylurea identified by mp 239–241°, mmp 239–241°, and comparison of infrared spectrum of authentic sample. The filtrate was condensed to a volume of 5.0 ml and analyzed by ir. Comparison to standard solutions indicated that 0.082 g (0.48 mmol) of dizairidinone was present. The spectrum showed no other carbonyl absorption.

To a second solution of sodium naphthalenide (2.0 mmol in 10.0 ml of THF) was added 0.171 g (1.0 mmol) of di-*tert*-butyldiaziridinone. The contents were treated as before, affording 0.160 g (0.93 mmol) of di-*tert*-butylurea.

B. Reaction with Bis(1,1-dimethyl-2-phenylethyl)diaziridinone.—To a solution of sodium naphthalenide (0.05 mmol in 10.0 ml of THF) was added 0.200 g (0.66 mmol) of bis(1,1-dimethyl-2-phenylethyl)diaziridinone.[3] The addition of the diaziridinone rapidly destroys the naphthalenide producing a clear homogeneous solution which was quenched by the addition of 1.0 ml of H_2O. The contents of the vial were carefully transferred to a separatory funnel and the two phases separated; the

(16) *E.g.*, see J. J. Silber and H. J. Shine, *J. Org. Chem.*, **36**, 2923 (1971), and J. Marcoux, *J. Amer. Chem. Soc.*, **93**, 537 (1971), and references cited therein.

(17) It is of interest that this reaction did not afford the rearrangement product, aziridinecarboxamide, eq 4. The use of excess diaziridinone was chosen to maximize the opportunity for a possible radical anion path for this isomerization.

(18) R. Waack and M. A. Doran, *J. Organometal. Chem.*, **2**, 92 (1965).

(19) P. Birman, "Power Supply Handbook," Kepco Inc., Flushing, N. Y., 1965, p 129.

(20) A. J. Fry, M. A. Mitnick, and R. G. Reed, *J. Org. Chem.*, **35**, 1232 (1970).

ether solution was dried over magnesium sulfate and the ether removed. A white crystalline residue remained which was diluted to 5.0 ml with CCl_4 and analyzed by ir for unreacted diaziridinone. Comparison of the infrared spectrum to a standard solution revealed that less than 4% of the diaziridinone had been destroyed; a band at 1665 cm^{-1} of very low intensity indicated the formation of the urea.

A solution of sodium naphthalenide (2.1 mmol in 10.0 ml of THF) was treated with 0.297 g (0.99 mmol) of the diaziridinone under the same conditions as before affording 0.230 g of 1,3-bis-(1,1-dimethyl-2-phenylethyl)urea, mp 180–182°, mmp 180–182°, and identical in infrared spectrum with an authentic sample.

Registry No.—**1a**, 19656-74-7; 1,3-di-*tert*-butylurea, 5336-24-3; *tert*-butyllithium, 594-19-4; sodium naphthalenide, 3481-12-7; bis(1,1-dimethyl-2-phenylethyl)-diaziridinone, 19694-14-5.

Acknowledgment.—We wish to thank C. S. Hutchins for the attempted reduction of the α-lactam, **8**.

Seven-Membered Heterocycles. V. Synthesis and Structure of Halogenated 3,4-Dihydro-1-benzothiepin-5(2*H*)-ones[1a,b]

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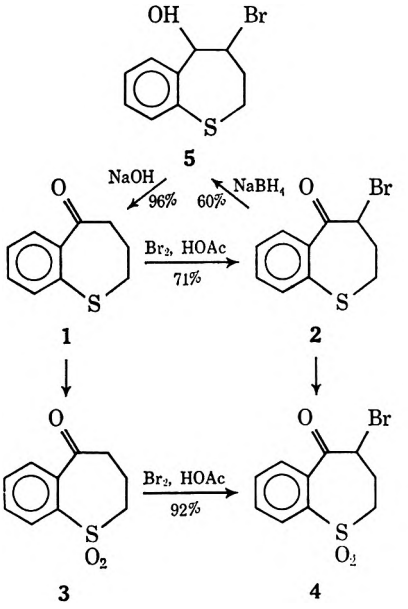
Bromination of 3,4-dihydro-1-benzothiepin-5(2*H*)-one (1) gave 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (2), which was reduced to the bromohydrin 5. Treatment of 5 with base regenerated the starting ketone 1. Chlorination of 1 with *N*-chlorosuccinimide (NCS) or sulfuryl chloride produced exclusively *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (6). *trans*-2,4-Dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (7) was available by the stereoselective ring-opening addition of HCl on 8-chlorocyclopropa[*b*][1]benzothiopyran-7-one (8). In contrast the reaction of 2 with sulfuryl chloride or NCS provided a mixture of *cis*- (11) and *trans*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (12) in which the trans isomer was highly predominant. Nucleophilic displacement reactions were used to convert 2 to 4-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (17) and 4-iodo-3,4-dihydro-1-benzothiepin-5(2*H*)-one. Sulfones of the above halo ketones were also prepared either by oxidation of the corresponding sulfides or halogenation of keto sulfones. The structural and stereochemical assignments for these compounds were made from interpretation of ir and nmr spectra. The mechanism offered for the stereoselective chlorination of 1 to give *cis*-6 entailed first C_2 chlorination followed by C_4 substitution *via* a transannular chlorination in the chlorosulfonium ion 19 intermediate. Formation of predominantly trans 12 in the sulfuryl chloride reaction with 2 is rationalized by the usual ion pair intermediate 21 proposed for α-chlorination of sulfides by sulfuryl chloride.

Halogenated 3,4-dihydro-1-benzothiepin-5(2*H*)-ones can serve as potential intermediates for introducing unsaturation into the thiepin ring and thus providing precursors for the synthesis of 1-benzothiepin derivatives. In this paper we emphasize the synthesis and structural assignments for a variety of halogenated 3,4-dihydro-1-benzothiepin-5(2*H*)-ones and in the subsequent report[2] concentrate on the reactions of these halo ketones with base.

Bromination of 3,4-dihydro-1-benzothiepin-5(2*H*)-one (1) proceeded readily to form the 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (2),[3] which was characterized as the corresponding sulfone **4** also available by direct bromination of **3**. The position of bromination was established by reduction of 2 to the bromohydrin **5**, which undergoes base-catalyzed elimination of HBr to form the starting ketone 1. An infrared study of the carbonyl frequencies for ketones 1 and 2 (see Table I) showed a band displacement of 15 cm^{-1} to higher frequency for the bromo ketone 2, thus favoring the conformation which places the bromine atom in a quasi-equatorial position[4] and puckers the C_2 and C_3 carbons out of the plane of the ring. The absence of any appreciable bathochromic shift in the uv spectra of 1 and 2 is also consistent with the quasiequatorial assignment



(1) (a) For part IV in this series see V. J. Traynelis and D. M. Borgnaes, *J. Org. Chem.*, **37**, 3824 (1972). (b) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. (c) Abstracted from a portion of the Ph.D. Dissertation submitted by J. C. S. in Dec 1971 and Y. Y. in May 1973 at West Virginia University. (d) Abstracts from a portion of the Ph.D. Dissertation submitted by R. F. L. in June 1960 and D. M. B. in Aug 1968 at the University of Notre Dame.

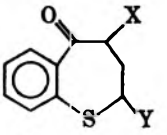
(2) V. J. Traynelis, J. C. Sih, and D. M. Borgnaes, *J. Org. Chem.*, **38**, 2629 (1973).

(3) K. Sindelar and M. Protiva, *Collect. Czech. Chem. Commun.*, **33**, 4315 (1968).

(4) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Amer. Chem. Soc.*, **74**, 2828 (1952); E. J. Corey, *ibid.*, **75**, 2301 (1953); N. L. Allinger and J. Allinger, *ibid.*, **80**, 5476 (1958).

TABLE I

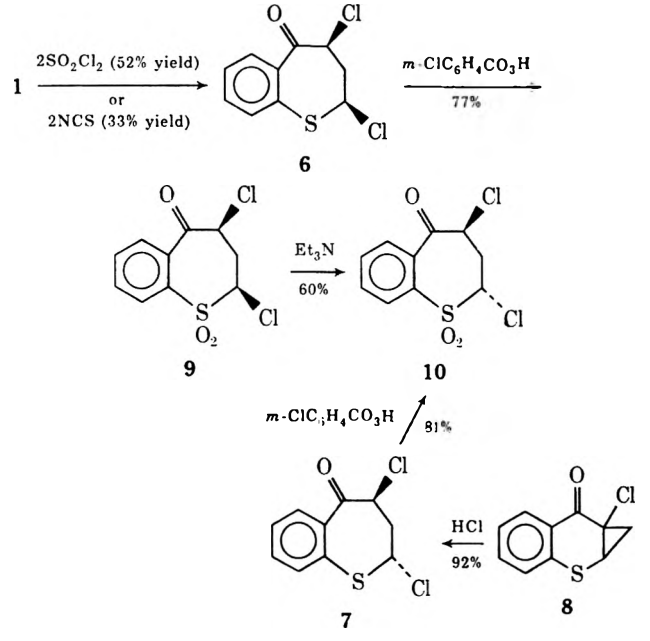
UV AND IR SPECTRAL DATA FOR KETONE 1 AND ITS HALOGENATED DERIVATIVES



Compd	95% EtOH λ_{max}, nm ($\epsilon \times 10^{-3}$)	95% EtOH Δ, nm	CCl_4 soln >C=O, cm^{-1}	CCl_4 soln Δ, cm^{-1}	$CHCl_3$ soln >C=O, cm^{-1}	$CHCl_3$ soln Δ, cm^{-1}
X = Y = H (1)	241 (18.3)		1680		1675	
X = Br; Y = H (2)	243 (17.6)	2	1695	15	1690	15
X = Cl; Y = H (15)					1690	15
cis, X = Y = Cl (6)			1710	30	1700	25
trans, X = Y = Cl (7)			1700	20	1690	15
cis, X = Br; Y = Cl (11)			1705	25	1695	20
trans, X = Br; Y = Cl (12)			1700	20	1695	20

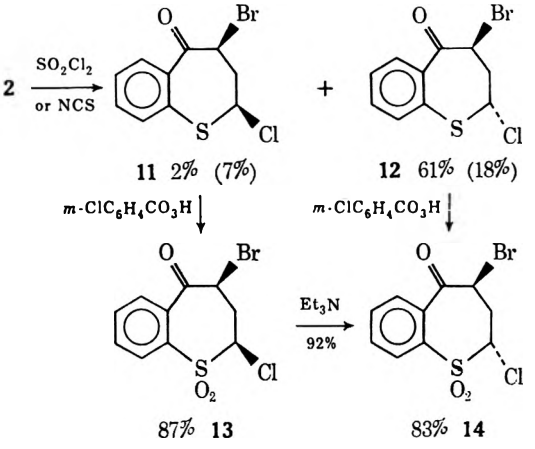
for bromine.[5] Such a geometry for **2** favors an axial approach of the borohydride ion from the side opposite the bromine. Therefore, the resulting bromohydrin most likely has the hydroxyl and bromine cis, which permits a facile trans elimination of hydrogen bromide to regenerate ketone **1**.

The reaction of simple sulfides with sulfuryl chloride[6] or *N*-chlorosuccinimide (NCS)[7] readily forms α-chloro sulfides. In addition sulfuryl chloride is known to react with ketones to give α-chloro ketones.[8] When 3,4-dihydro-1-benzothiepin-5(2*H*)-one (**1**) was allowed to react with sulfuryl chloride or NCS, the only stable crystalline product isolated was *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**6**). The yield of **6** was improved with the use of 2+ equiv of chlorinating agent and only the cis isomer was formed. A spectroscopic study of the reaction mixture failed to detect any of the trans isomer. *trans*-3,4-Dihydro-1-benzothiepin-5(2*H*)-one (**7**) was obtained by a stereoselective ring-opening addition of hydrogen chloride to 7a-chloro-



cyclopropa[*b*][1]benzothiopyran-7-one (**8**).[9] The dichloro ketones were characterized by conversion to their corresponding sulfones **9** and **10**. The cis dichloro keto sulfone **9** was readily isomerized by weak base to the more stable trans compound **10**.

A different stereochemical outcome results in the chlorination of 4-bromo-3,4-dihydro-1-benzothiepin-5-(2*H*)-one (**2**) with either sulfuryl chloride or NCS. Both *cis*- and *trans*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**11** and **12**, respectively) were isolated with the trans isomer highly predominant. Again oxidations to the corresponding sulfones **13** and **14** were readily accomplished with *m*-chloroperbenzoic



acid and the conversion of the cis halo sulfone **13** to the more stable trans isomer **14** occurred rapidly with triethylamine.

Inspection of the data in Tables I and II, particularly the nmr data, reveals marked spectral similarities between the cis dihalo ketones **6** and **11** and between the trans dihalo ketones **7** and **12**. Displacement of the carbonyl stretching frequency to higher values (see Table I) for all the dihalogenated ketones supports a quasiequatorial location for the C_4 halogen. However, the magnitude of the carbonyl band displacement appears larger than expected and may be rationalized by bending the carbonyl group out of the plane of the benzene ring. Additional support for the nonplanar relationship of the carbonyl group and the benzene ring is found in the reduced deshielding effect of the car-

(5) R. C. Cookson, *J. Chem. Soc.*, 282 (1954); E. J. Corey and H. J. Burke, *J. Amer. Chem. Soc.*, **77**, 5418 (1955); A. Hassner and N. H. Cromwell, *ibid.*, **80**, 893 (1958).

(6) F. G. Bordwell and B. M. Pitts, *ibid.*, **77**, 572 (1955); L. A. Paquette, and L. S. Wittenbrook, *ibid.*, **90**, 6790 (1968).

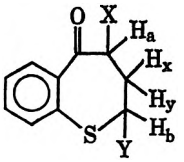
(7) D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969), and earlier papers.

(8) D. P. Wyman and P. R. Kaufman, *ibid.*, **29**, 1956 (1964).

(9) The preparation of this compound is described in ref 2.

TABLE II

NMR SPECTRAL DATA FOR 2,4-DIHALO-3,4-DIHYDRO-1-BENZOTHIEPIN-5(2*H*)-ONES



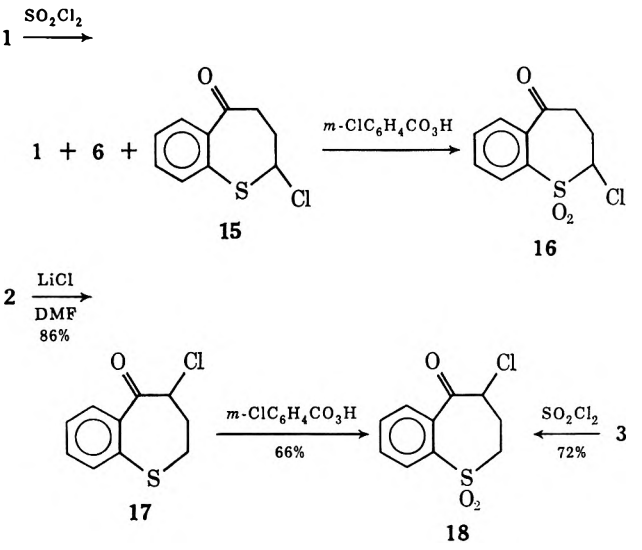
Compd	C_4 H_a[a]	J_{ax}[b]	J_{ay}[b]	C_2 H_b[a]	J_{bx}[b]	J_{by}[b]	C_3 H_x[a]	J_{xy}[b]	C_3 H_y[a]
cis, X = Y = Cl (6)	5.55 (t)	7	7	4.95 (dd)[c]	4.3	11.2	3.24 (two dd)[d]	14	2.63 (two dd)
trans, X = Y = Cl (7)	5.29 (dd)	7.5	7	5.09 (dd)	7	7	2.98 (dd)	0	2.98 (dd)
cis, X = Br; Y = Cl (11)	5.37 (dd)	6	8	4.72 (dd)	4	12	3.18 (two dd)	14	2.57 (two dd)
trans, X = Br; Y = Cl (12)	5.25 (dd)	6.5	8.5	5.02 (dd)	6.5	5.5	2.96 (dd)	0	2.92 (dd)

[a] Chemical shifts are in parts per million. [b] Coupling constants are in hertz. [c] A doublet of doublets. [d] Eight lines, two doublet of doublets.

bonyl group on the C_6 H.[10] A study of the solvent effect on the nmr resonance of the C_4 H of the dihalo ketones **6**, **11**, and **12** showed solvent shifts ($\Delta^{CHCl_3}_{C_6H_6}$ = $\delta_{CHCl_3} - \delta_{C_6H_6}$) of +1.05, +0.40, and +0.25. These values, interpreted according to Bhacca and Williams,[11] lend further support to the quasiequatorial assignment for the C_4 halogens.

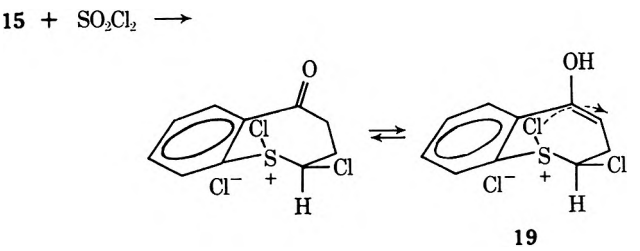
Cis and trans configurational assignments for the dihalogenated ketones were initially made on the basis of the coupling constants between the C_4 H and C_3 H's and the C_2 H and C_3 H's (see Table II). An examination of Dreiding models of the trans dihalo ketones **7** and **12** shows that the C_4 H and the C_2 H have a similar dihedral angular relationship with each of the C_3 H's and thus the coupling constants are comparable. However, with the cis dihalo ketones **6** and **11** the C_2 H has a markedly different angular relationship with each of the C_3 H's and therefore one observes considerable differences in the coupling constants between C_2 H and the C_3 H's as well as differences from the C_4 H and C_3 H's coupling constants.

The stereoselective dichlorination of **1** to give only *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**6**) in contrast to the chlorination of **2** to give predominantly *trans*-2-chloro-4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**12**) merits explanation. A study of the chlorination of **1**, where sulfuryl chloride was added in half-mole increments until a total of 2 mol was introduced, revealed that chlorination occurred at the C_2 position first and subsequent chlorination went to C_4. However, even with limited quantities of sulfuryl chloride (after the first 0.5 mol) some dichloro ketone **6** was formed. Since 2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**15**) appeared to be thermally sensitive, the reaction mixture was oxidized with *m*-chloroperbenzoic acid and **15** was converted to the stable sulfone **16**. Sulfone **16** differed in physical and spectral properties from 4-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (**18**), which was prepared as shown below. Chlorination of keto sulfone **3** should proceed into the C_4 position, since sulfones are not known to α-chlorinate with sulfuryl chloride. This



position of substitution was confirmed by the alternate synthesis of sulfone **18** from the 4-bromo ketone **2** *via* 4-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**17**).

The conversion of **1** to **6** *via* sulfuryl chloride or NCS requires C_2 substitution first followed by C_4-chlorination, with the stereochemical control exercised in the second step. If the C_4-chlorination proceeded *via* intermolecular attack by sulfuryl chloride or Cl^+ on the enol of **15**,[8] one would expect to obtain a mixture of *cis*- and *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-ones (**6** and **7**, respectively).[12] A more likely alternative for conversion of **15** to **6** involves formation of the chlorosulfonium salt **19**, which undergoes a transannular transfer of Cl^+ from sulfur to the C_4 position.[13] Such chlorosulfonium salts form rapidly



(10) R. H. Martin, N. Defay, and F. Gaerts-Evrard, *Tetrahedron*, **20**, 1505 (1964). Deshielding effects of the carbonyl group in tetralone on the C_8 H (ortho to the carbonyl) causes the C_8 H to be displaced approximately 0.7 ppm downfield from the remainder of the aromatic hydrogens. This difference between the ortho hydrogen and the other aromatic hydrogens in 2,3-benzocyclohept-2-enone is reduced to 0.4 ppm. In the bromo chloro ketones **11** and **12** the ortho hydrogen (C_8 H) is not displaced appreciably and simply merges with the absorption of the other aromatic hydrogens.

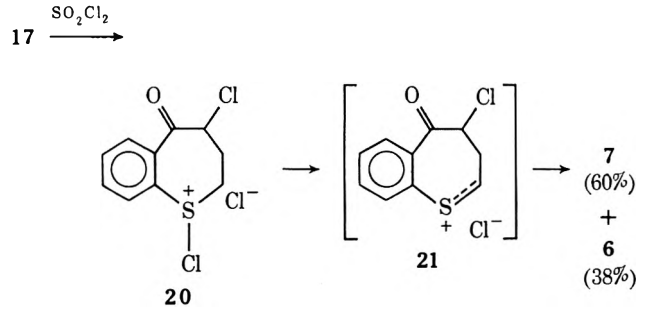
(11) D. H. Williams, and N. S. Bhacca, *Tetrahedron*, **21**, 2021 (1965); *Tetrahedron Lett.*, 3127 (1964).

(12) In equilibration experiments of **6** and **7** *via* their common enol, one finds approximately equal amounts of each ketone; see ref 2.

(13) Since the reaction of sulfides and sulfuryl chloride generates HCl, the most likely sulfonium salt intermediate involved in Cl^+ transfer is the enol form **19**.

in the reaction of sulfides with sulfuryl chloride[14] and are proposed intermediates in the α-chlorination of sulfides.[7] Chlorosulfonium ion **19** exhibits a conformation which places the SCl near the C_4 position while the C_2 chlorine occupies an equatorial-like position. Thus transannular chlorination from this conformation would lead stereoselectively to the cis isomer **6**. When chlorosulfonium salt formation is precluded as with sulfones, the reaction of **16** and sulfuryl chloride produced exclusively the more stable trans dichloro sulfone **10**.

Further support for the C_2, C_4 dichlorination sequence in the conversion of **1** to **6** is available from the reaction of 4-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**17**) with sulfuryl chloride. The products from this reaction were trans (**7**) (60%) and cis isomer (**6**) (38%) in a ratio similar to an equilibrium mixture.[12] The initial chlorosulfonium ion **20** forms the ion pair intermediate[7] **21**, which lacks stereochemical control



and leads to the product mixture **6** and **7**. The markedly different stereochemical outcome of the reaction of **17** and sulfuryl chloride excludes **17** as an intermediate in the formation of **6** from **1**.

The reaction of 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**2**) with sulfuryl chloride introduces the C_2 chlorine in a pathway analogous to reaction of **17** and sulfuryl chloride. Therefore the stereochemical outcome in the chlorination of **2** which forms predominantly the trans isomer **12** probably reflects the greater stability of trans (**12**) over cis isomer (**11**).

4-Iodo-3,4-dihydro-1-benzothiepin-5(2*H*)-one was readily available from the bromo ketone **2** and potassium iodide in acetone.

Experimental Section[15]

4-Bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (2).—A solution of bromine (16 g, 0.10 mol) in acetic acid (30 ml) was slowly added to a stirred solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one[16] (**1**) (20 g, 0.112 mol) in acetic acid (50 ml). The reaction mixture was stirred for 2 hr and poured into 400 ml of H_2O containing $NaHSO_3$ (0.5 g), and the solid which separated was filtered and crystallized from methanol to give 19.6 g (71%) of 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**2**), mp 87–89°. Recrystallization from ethanol and cyclohexane gave an analytical sample: mp 89–90° (lit.[3] mp 86.5–87°); uv max (95% C_2H_5OH) 243 nm (log ϵ 4.24), 261 (3.79), 330 (3.55); ir ($CHCl_3$) 1694 cm^{-1} (>C=O); nmr ($CDCl_3$) δ 7.84 (m, 1, C_9 H), 7.36 (m, 3, C_6, C_7, C_8 H's), 5.35 (m, 1, $-SCH_2CH_2CHBr$), 2.40–3.47 (m, 4, $-SCH_2CH_2-$).

Anal. Calcd for $C_{10}H_9BrOS$: C, 46.70; H, 3.53. Found: C, 46.84; H, 3.68.

4-Bromo-5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin (5).—A solution of 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**2**) (5.00 g, 0.019 mol) in 95% ethanol (15 ml) was added over 1 hr to a stirred slurry of sodium borohydride (0.36 g, 0.009 mol) in 60% ethanol (10 ml), and the mixture was refluxed for an additional 1 hr. After the solution was poured onto crushed ice and hydrochloric acid, the resulting solid was filtered, dried, and recrystallized from Skelly B to give 2.9 g (60%) of 4-bromo-5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin (**5**): mp 93–94°; ir (KBr) 3410 cm^{-1} (strong, broad, $^-$OH); nmr ($CDCl_3$) δ 7.27 (m, 4, aromatic H's), 5.36 (s, 1, OH), 4.61 (m, 1, $-CHBrCH-OH-$), 2.2–2.9 (m, 5, $-SCH_2CH_2CHBr$).

Anal. Calcd for $C_{10}H_{11}BrOS$: C, 46.33; H, 4.25; Br, 30.89. Found: C, 46.58; H, 4.30; Br, 30.80.

Reaction of 4-Bromo-5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin with Sodium Hydroxide.—After a mixture of 4-bromo-5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin (**5**) (580 mg, 2.30 mmol), sodium hydroxide (94 mg, 2.3 mmol), and water (20 ml) was stirred at room temperature for 80 min, the solution was neutralized with HCl and extracted with $CHCl_3$ (2 × 20 ml) and the $CHCl_3$ extract was washed with water and dried (Na_2SO_4). Removal of the solvent under vacuum gave 380 mg (96%) of 3,4-dihydro-1-benzothiepin-5(2*H*)-one (**1**) which had an infrared spectrum identical with that of an authentic sample.

4-Bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-Dioxide (4). Method A.—Bromine (16.0 g, 0.10 mol) was added over a period of 30 min to a solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide[16] (**3**) (21.0 g, 0.10 mol) in glacial acetic acid (200 ml) maintained at 60°. The reaction mixture was kept at 60° for an additional 1 hr, cooled to room temperature, and poured into 1 l. of ice water and the solid which separated was filtered and dried. Recrystallization of the solid from acetone afforded 26.8 g (92%) of 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (**4**): mp 156–157° (lit.[3] mp 143.5–144°); uv max (95% C_2H_5OH) 224 nm (log ϵ 3.59), 242 (3.56), 270 (3.29), 308 (2.64); ir ($CHCl_3$) 1702 (>C=O), 1335, 1310, 1160, 1110 cm^{-1} ($>SO_2$); nmr (CD_3COCD_3) δ 8.05 (m, 1, C_9H), 7.87–7.46 (m, 3, C_6, C_7, C_8 H's), 5.05 (dd, J = 3, 6 Hz, 1, $SO_2CH_2CH_2CHBr$), 3.90–3.58 (m, 2, $-SO_2CH_2-$), 3.40–2.45 (m, 2, $-SO_2CH_2CH_2CHBr^-$).

Anal. Calcd for $C_{10}H_9BrO_3S$: C, 41.54; H, 3.14. Found: C, 41.82; H, 3.40.

Method B.—A solution of 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**2**) (1.0 g, 3.9 mmol), glacial acetic acid (10 ml) and 30% hydrogen peroxide (3 ml) was allowed to stand overnight, poured into water (50 ml) and the precipitate filtered and dried. Recrystallization of this solid from acetone gave 0.35 g (39%) of 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide, mp 156–157°.

***cis*-2,4-Dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (6). Method A.**—After a mixture of 3,4-dihydro-1-benzothiepin-5(2*H*)-one[16] (**1**) (4.00 g, 22.5 mmol), *N*-chlorosuccinimide (6.14 g, 46.0 mmol), and CCl_4 (30 ml) was stirred at room temperature for 16 hr, the succinimide was filtered, and evaporation of the solvent under vacuum gave a pale yellow solid. Recrystallization of this solid from hexane–$CHCl_3$ afforded 1.80 g (33%) of *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**6**), as a white, crystalline solid: mp 108–109°; ir (KBr) 1695 cm^{-1} (>C=O); nmr ($CDCl_3$) δ 7.33–8.00 (m, 4, aromatic H's), 5.55 (t, $J_{C_4-C_{3x}} = J_{C_4-C_{3y}}$ = 7 Hz, 1, O=CCHCl), 4.95 (dd, $J_{C_2-C_{3x}}$ = 11.2, $J_{C_2-C_{3y}}$ = 4.3 Hz, 1, –SCHCl), 3.24 (two dd, $J_{C_{3x}-C_{3y}}$ = 14, $J_{C_{3x}-C_2}$ = 4.5, $J_{C_{3x}-C_4}$ = 7 Hz, 1, $-SCHClCH_xH_yCHCl$), 2.63 (two dd, $J_{C_{3y}-C_{3x}}$ = 14, $J_{C_{3y}-C_2}$ = 11, $J_{C_{3y}-C_4}$ = 7 Hz, 1, $-SCHClCH_xH_yCHCl$).

Anal. Calcd for $C_{10}H_8Cl_2OS$: C, 48.60; H, 3.26; Cl, 28.69. Found: C, 48.66; H, 3.32; Cl, 28.79.

Method B.—Sulfuryl chloride (10.0 ml, 124 mmol) was added dropwise over 30 min to a stirred solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one[16] (**1**) (10.0 g, 56 mmol) in CH_2Cl_2 (100 ml) at room temperature. The reaction mixture was refluxed (opening fitted with a $CaCl_2$ drying tube) for 2 hr, the solvent was removed under vacuum, and the residue was recrystallized from hexane–$CHCl_3$. The yield of *cis*-2,4-dichloro-3,4-dihydro-1-benzothie-

(14) V. J. Traynelis and Y. Yoshikawa, unpublished results. Reaction of sulfides with sulfuryl chloride occurred rapidly at low temperatures to form the chlorosulfonium chloride, which was readily converted to the corresponding sulfoxide or alkoxysulfonium salt.

(15) All melting points and boiling points are uncorrected. Elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind., or Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined on a Perkin-Elmer Model 137-B, Model 21, or a Beckman IR-8 spectrophotometer, uv spectra were measured on a Perkin-Elmer Spectracord or a Bausch and Lomb 505 spectrophotometer, and nmr spectra were obtained on a Varian Associates Model HA-60 or Model T-60 spectrometer.

(16) This ketone was prepared as previously described: V. J. Traynelis and R. F. Love, *J. Org. Chem.*, **26**, 2728 (1961).

pin-5(2*H*)-one (6), mp 108–109°, was 7.20 g (52%). The ir and nmr spectra and mixture melting point were identical with those of the sample prepared by method A. An nmr spectrum of the crude residue before crystallization showed the absence of the trans dichloro isomer.

cis-2,4-Dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-Dioxide (9).—A solution of *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (6) (1.52 g, 6.16 mmol) in $CHCl_3$ (15 ml) was added dropwise over a 15-min period to a stirred solution of *m*-chloroperbenzoic acid (2.44 g, 14.2 mmol) in $CHCl_3$ (30 ml) maintained at −10 to −15°. After the reaction mixture was allowed to warm to room temperature and remain overnight, the *m*-chlorobenzoic acid was filtered, and the filtrate was washed with Na_2CO_3 (10%) and dried (Na_2SO_4). After the solvent was removed, the white residue was recrystallized from benzene and gave 1.32 g (77%) of *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (9): mp 172–174° dec; ir (KBr) 1705 (>C=O), 1330, and 1150 cm^{-1} (<SO_2); nmr (CD_3COCD_3) δ 7.65–8.18 (m, 4, aromatic H's), 5.74 (dd, $J_{C_4-C_{3x}} = 5.5$, $J_{C_4-C_{3y}} = 9.5$ Hz, 1, $-CO_2CHCl-$), 5.23 (dd, $J_{C_2-C_{3x}} = 3.5$, $J_{C_2-C_{3y}} = 10.5$ Hz, 1, $-SO_2CHCl-$), 3.37 (two dd, $J_{C_{3x}-C_{3y}} = 14$, $J_{C_{3x}-C_4} = 5.5$, $J_{C_{2y}-C_2} = 3.5$ Hz, 1, $-SO_2CHClCH_xH_yCHCl$), 2.49 (two dd, $J_{C_{3y}-C_{3x}} = 14$, $J_{C_{3y}-C_4} = 9.5$, $J_{C_{3y}-C_2} = 11$ Hz, 1, $-SO_2CHClCH_xH_yCHCl-$).

Anal. Calcd for $C_{10}H_8Cl_2O_3S$: C, 43.03; H, 2.89; O, 17.20. Found: C, 43.21; H, 2.71; O, 17.11.

trans-2,4-Dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (7).—Hydrogen chloride gas was bubbled into a solution of 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one[2] (8) (2.00 g, 9.50 mmol) in $CHCl_3$ (10 ml) for 20 min at room temperature. The excess HCl gas was removed under a stream of N_2 and evaporation of the solvent gave a white solid, mp 106–109°. An nmr spectrum of this crude product showed the absence of the cis-dichloro isomer 6. Recrystallization of the crude solid from hexane–$CHCl_3$ afforded 2.15 g (92%) of *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (7), as long, fluffy needles: mp 108–109°; ir (CCl_4) 1700 cm^{-1} (>C=O); nmr ($CDCl_3$) δ 7.91–7.40 (m, 4, aromatic H's), 5.29 (dd, $J_{C_4-C_{3x}} = 7.5$, $J_{C_4-C_{3y}} = 7$ Hz, 1, $-COCHCl-$), 5.09 (dd, $J_{C_2-C_{3x}} = 7$, $J_{C_2-C_{3y}} = 7$ Hz, 1, $—SCHCl$), 2.98 (t, $J_{C_3-C_4} = 7$, $J_{C_3-C_2} = 7$ Hz, 2, $-SCHClCH_xH_yCHCl$). A mixture melting point of *trans*- and *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one, mp 108–109° for each, was depressed to 81–89°.

Anal. Calcd for $C_{10}H_8Cl_2OS$: C, 48.60; H, 3.26; Cl, 28.69. Found: C, 48.40; H, 3.34; Cl, 28.78.

The same result was obtained when the above reaction was carried out in benzene instead of $CHCl_3$.

A solution of concentrated HCl (5 ml), 7a-chlorocyclopropa[*b*][1]benzothiapyran-7-one[2] (8) (1.59 g, 7.60 mmol), dioxane (17 ml), and H_2O (2 ml) was stirred at room temperature for 1 hr and poured onto crushed ice and gave 1.43 g of crude dichloro ketone 7, mp 103–108°. Recrystallization of the crude solid from hexane–$CHCl_3$ provided 1.25 g (68%) of the trans dichloro ketone 7, mp 107.5–109°.

trans-2,4-Dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-Dioxide (10). Method A.—A solution of triethylamine (2.50 ml, 18 mmol), *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (9) (0.50 g, 1.79 mmol), and $CHCl_3$ (20 ml) was warmed on a steam bath for 1 min and allowed to remain at room temperature for 30 min. The $CHCl_3$ solution was washed with 10% HCl (5 × 15 ml) and washed with H_2O, the organic layer was dried (Na_2SO_4), and the solvent was removed to give a solid, mp 173–177°. Recrystallization of this solid from benzene gave 0.30 g (60%) of *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (10): mp 178.5–180°; ir (KBr) 1710 (>C=O), 1328 and 1129 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 8.17 (m, 1, C_9H), 7.90–7.51 (m, 3, C_6, C_7, C_8H's), 5.29 (t, $J_{C_4-C_3} = 5.5$ Hz, 1, $-COCHCl$), 5.00 (t, $J_{C_2-C_3} = 5.5$ Hz, 1, $-SO_2CHCl-$), 3.09 (t, $J_{C_3-C_2} = J_{C_3-C_4} = 5.5$ Hz, 2, $-SO_2CHClCH_2CHCl-$). A mixture melting point of the cis and trans dichloro sulfones was depressed, 163–172°.

Anal. Calcd for $C_{10}H_8Cl_2O_3S$: C, 43.03; H, 2.89; Cl, 25.40. Found: C, 42.80; H, 2.79; Cl, 25.19.

Method B.—Using the procedure for the preparation of *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide, the reaction of *m*-chloroperbenzoic acid (0.96 g, 5.59 mmol) and *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (7) (0.70 g, 2.43 mmol) gave, after recrystallization from benzene, 0.55 g (81%) of *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (10), mp 179–180°.

Method C.—Sulfuryl chloride (338 mg, 2.5 mmol) in $CHCl_3$ (3 ml) was added dropwise to a stirred solution of 2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (16) (122 mg, 0.5 mmol) in $CHCl_3$ (6 ml). After the reaction mixture was refluxed for 24 hr, the solvent was removed and the residue was recrystallized from benzene to give 60 mg (43%) of *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (10), mp 180–182°. The nmr spectrum was identical with that of the above sample and a mixture melting point with the above sample was not depressed.

Nmr analysis of the crude reaction product indicated that *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide was not formed.

Reaction of 3,4-Dihydro-1-benzothiepin-5(2*H*)-one with SO_2Cl_2 (1 Equiv).—After a solution of sulfuryl chloride (2.70 g, 20 mmol) and 3,4-dihydro-1-benzothiepin-5(2*H*)-one (1) (3.56 g, 20 mmol) in CH_2Cl_2 (40 ml) was stirred and heated at 50–55° for 3 hr, the solvent was removed under vacuum and gave 4.1 g of a yellow oil. Thin layer chromatography of the crude oil on silica G_{254} using benzene–ethanol (12:3) and hexane–benzene (9:3) as eluents indicated three components in the mixture. Spectral analysis of the crude oil suggested the presence of 3,4-dihydro-1-benzothiepin-5(2*H*)-one (1) [ir 1680 cm^{-1} (>C=O), nmr ($CDCl_3$) δ 2.2 ($-SCH_2CH_2CH_2C=O$)], *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (6) [ir 1690–1700 cm^{-1} (>C=O); nmr ($CDCl_3$) δ 4.87 (dd, J = 4, 11 Hz)], and 2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (15) (identified below). The absence of *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (7) in the crude mixture was established by adding a sample of trans dichloro ketone 7 and observing the appearance of new bands for the trans isomer in the nmr spectrum.

A solution of the above crude product mixture (4.1 g) and *m*-chloroperbenzoic acid (8.28 g, 48 mmol) in $CHCl_3$ (45 ml) was allowed to remain at room temperature overnight. After the reaction mixture was filtered, the filtrate washed with Na_2CO_3 solution (10%) and water, and the organic layer dried ($MgSO_4$), the $CHCl_3$ was removed and gave 4.5 g of a solid, mp 97–103°. Fractional crystallization of the crude solid (4.2 g) from $CHCl_3$ and 95% ethanol led to the isolation of 0.52 g (13%) of 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (3), mp 159.5–160.5° (lit.[16] mp 157–158°), the nmr of which was identical with that of an authentic sample and the mixture melting point was not depressed; 0.22 g (4.3%) of *trans*-2,4-dichloro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (10), mp 180–183°, the nmr of which was identical with that of an authentic sample and the mixture melting point was not depressed; and 1.64 g (35%)[17] of 2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (16): mp 149–150°; ir ($CHCl_3$) 1700 (>C=O), 1330, 1280, 1190, 1140, and 1120 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 8.07 (m, 1, C_9H), 7.87–7.50 (m, 3, C_6, C_7, C_8H's), 5.20–4.99 (m, 1, $-SO_2CHCl-$), 3.22–1.87 (m, 4, $-SO_2CHClCH_2CH_2C=O$).

Anal. Calcd for $C_{10}H_9ClO_3S$: C, 49.08; H, 3.71; Cl, 14.49. Found: C, 49.21; H, 3.68; Cl, 14.31.

A second experiment was performed in which sulfuryl chloride was added in increments until 2 equiv was introduced. A solution of sulfuryl chloride (337 mg, 2.5 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one (1) (890 mg, 5 mmol) in CH_2Cl_2 (7 ml) and the reaction was stirred at room temperature for 100 min. After the reaction mixture was dried (Na_2SO_4), the solvent was removed and the residue (943 mg), *via* nmr analysis, contained *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (6) (3%), 2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (15) (24%), and 3,4-dihydro-1-benzothiepin-5(2*H*)-one (1) (73%).

The above residue in CH_2Cl_2 (7 ml) was treated with sulfuryl chloride (337 mg, 2.5 mmol) in CH_2Cl_2 (3 ml) and the mixture was refluxed for 1 hr. After the solvent was removed, analysis of the residue by its nmr spectrum showed the following compounds: cis-dichloro ketone 6 (17.5%), 2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (45%), and unchlorinated ketone 1 (37.5%).

The preceding residue was mixed with sulfuryl chloride (674 mg, 5 mmol) in CH_2Cl_2 and the mixture was refluxed for 2.5 hr. The solvent was removed and the nmr spectrum of the residue showed a mixture of the cis dichloro ketone 6 (50%), 2-chloro ketone 15 (40%), and unchlorinated ketone 1 (10%).

(17) The per cent yields were calculated from 3,4-dihydro-1-benzothiepin-5(2*H*)-one and are corrected to represent the total sample (4.5 g) isolated in the oxidation reaction.

4-Chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (17).—After a mixture of 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (2) (7.0 g, 27.2 mmol), lithium chloride (11.5 g, 272 mmol), and dimethylformamide (50 ml) was allowed to stir for 3 days at ambient temperatures, the reaction mixture was poured into 300 ml of water. The resulting precipitate was filtered and dried to give 5.7 g (98%) of 4-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (17). Recrystallization of the crude product from ethanol gave 4.99 g (86%) of pure, colorless, crystalline 17: mp 84.5–85.5°; ir ($CHCl_3$) 1690 cm^{-1} (>C=O); nmr ($CDCl_3$) δ 7.7–8.0 (m, 1, C_9 H), 7.1–7.6 (m, 3, C_6, C_7, C_8 H's), 5.2–5.5 (m, 1, –COCHCl–), 2.2–3.4 (m, 4, $-SCH_2CH_2-$).

Anal. Calcd for $C_{10}H_9ClOS$: C, 56.46; H, 4.27; Cl, 16.67. Found: C, 56.21; H, 4.08; Cl, 16.53.

Reaction of 4-Chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (17) with SO_2Cl_2.—A solution of sulfuryl chloride (1.35 g, 0.01 mol) in methylene chloride (5 ml) was added dropwise to a stirred solution of 4-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (17) (2.13 g, 0.01 mol) in methylene chloride (20 ml). After the mixture was refluxed gently for 1 hr, the solvent was removed *in vacuo* and the remaining clean yellow oil (2.4 g, 96% monochlorination) solidified upon standing in the refrigerator. An nmr analysis of the crude product showed the presence of *cis*- and *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one in a ratio of 40:60.[18]

Fractional crystallization of the mixture from $CHCl_3$–hexane led to the separation into the trans isomer 7 (750 mg, 30%, mp 103–105°) and the cis isomer 6 (190 mg, 8%, mp 104–107°). These compounds had nmr spectra identical with those of authentic samples. The combined mother liquor from the fractional crystallization showed the presence of both isomers which could not be separated further.

4-Chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-Dioxide (18). Method A.—Sulfuryl chloride (1.20 ml, 14.7 mmol) in methylene chloride (10 ml) was added dropwise over a 15-min period to a stirred solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (3) (1.00 g, 4.90 mmol) in methylene chloride (15 ml). After the reaction mixture was refluxed for 24 hr, the solvent was removed and the remaining white solid, mp 128–135°, was recrystallized from 95% ethanol to give 0.85 g (72%) of 4-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (18): mp 139–142°; ir (KBr) 1695 (>C=O), 1300, 1110 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 8.07 (m, 1, C_9 H), 7.66 (m, 3, C_6, C_7, C_8 H's), 4.90 (dd, J = 2.5 and 7 Hz, 1, >CHCl), 3.9–2.5 (m, 4, $-SO_2CH_2CH_2-$). An analytical sample melted at 143–144°.

Anal. Calcd for $C_{10}H_9ClO_3S$: C, 49.08; H, 3.77; Cl, 14.49. Found: C, 48.91; H, 3.49; Cl, 14.67.

Method B.—A solution of 4-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (17) (137 mg, 0.64 mmol) in $CHCl_3$ (4 ml) was added dropwise to a solution of *m*-chloroperbenzoic acid (330 mg, 1.9 mmol) in $CHCl_3$ (6 ml) maintained at −20° and the reaction mixture was allowed to come to room temperature and stirred overnight. The reaction solution was washed with 10% $NaHCO_3$ and H_2O and dried, and the solvent was removed. The residue (157 mg, mp 110–120°) was recrystallized from ethanol and gave 105 mg (66%) of 4-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (18), mp 143–144°. A mixture melting point with a sample from method A was not depressed and the nmr spectra of both samples were identical.

***cis*- and *trans*-4-Bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (11 and 12). Method A.**—After a mixture of 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (2) (5.00 g, 19.50 mmol), *N*-chlorosuccinimide (2.67 g, 20.00 mmol), and CCl_4 (60 ml), placed in a flask protected with a $CaCl_2$ drying tube, was stirred at room temperature for 24 hr, the succinimide was filtered and removal of the solvent under vacuum left 1.58 g of solid. The crude solid was placed in $CHCl_3$ (5 ml) and the insoluble cis isomer was filtered. The filtrate was cooled and gave an additional amount of cis isomer. Recrystallization of the combined solids from hexane–$CHCl_3$ gave 0.40 g (7%) of *cis*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (11): mp 134–135°; ir (KBr) 1685 cm^{-1} (>C=O); nmr ($CDCl_3$) δ 7.71–7.40 (m, 4, aromatic H's), 5.37 (dd, 1, $J_{C_4-C_{3x}}$ = 6, $J_{C_4-C_{3y}}$ = 8 Hz, –COCHBr–), 4.72 (dd, 1, $J_{C_2-C_{3x}}$ = 4, $J_{C_2-C_{3y}}$ = 12 Hz, –SCHCl–), 3.18 (two dd, 1, $J_{C_{3x}-C_{3y}}$ = 14, $J_{C_{3x}-C_4}$ = 6, $J_{C_{3x}-C_2}$ = 4 Hz, $-SCHClCH_xH_yCHBr$), 2.57 (two dd, 1, $J_{C_{3y}-C_{3x}}$ = 14, $J_{C_{3y}-C_2}$ = 12, $J_{C_{3y}-C_4}$ = 8 Hz, $-SCHClCH_xH_yCHBr$).

The above chloroform solution was evaporated to dryness and the residue was recrystallized from hexane–$CHCl_3$ to give 1.00 g (18%) of *trans*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (12): mp 98–99°; ir (KBr) 1695 cm^{-1} (>C=O); nmr ($CDCl_3$) δ 7.75–7.28 (m, 4, aromatic H's), 5.25 (dd, 1, $J_{C_4-C_{3x}}$ = 6.5, $J_{C_4-C_{3y}}$ = 8.5 Hz, –COCHBr–), 5.02 (dd, 1, $J_{C_2-C_{3x}}$ = 6.5, $J_{C_2-C_{3y}}$ = 5.5 Hz, –SCHCl), 2.96 (dd, C_{3x} and C_{3y} overlap, $J_{C_{3x}-C_4}$ = 6.5, $J_{C_{3x}-C_2}$ = 6.5 Hz, $-SCHClCH_x-H_yCHBr$–), 2.92 (dd, C_{3y} and C_{3x} overlap, $J_{C_{3y}-C_4}$ = 8.5, $J_{C_{3y}-C_2}$ = 5.5 Hz, $-SCHClCH_xCH_yCHBr$–).

Anal. Calcd for $C_{10}H_8BrClOS$: C, 41.19; H, 2.76; Br, 27.41. Found for cis isomer C: 41.43; H, 2.83; Br, 27.35. Found for trans isomer C: 41.00; H, 2.66; Br, 27.74.

Method B.—Sulfuryl chloride (1.08 g, 8.00 mmol) was added dropwise over a period of 10 min to a stirred solution of 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (2) (2.00 g, 7.80 mmol) in CH_2Cl_2 (25 ml) at room temperature. The reaction mixture was refluxed (opening fitted with a $CaCl_2$ drying tube) for 1 hr, and the solvent was removed under vacuum to give 1.42 g (63%) of a mixture of the cis and trans isomers. A trace amount of the cis isomer was removed by treating the crude material with cold $CHCl_3$ (3 ml) and filtering off the insoluble cis isomer 11. The solvent was removed from the filtrate and recrystallization of the residue from hexane–$CHCl_3$ gave 1.35 g (61%) of *trans*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (12), mp 98–99°. The ir and nmr spectra and mixture melting point were identical with those of the trans isomer isolated by method A.

***cis*-4-Bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-Dioxide (13).**—A solution of *cis*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (11) (0.37 g, 1.27 mmol) in $CHCl_3$ (6 ml) was added to a stirred solution of *m*-chloroperbenzoic acid (0.50 g, 2.29 mmol) in $CHCl_3$ (8 ml) maintained at −10 to −15°. The reaction mixture was allowed to warm to room temperature and stirred for 9 hr. Work-up by the procedure described for the cis dichloro ketone sulfone 9 and recrystallization of the crude product from 95% ethanol gave 0.36 g (87%) of *cis*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (13): mp 167–169°; ir (KBr) 1700 (>C=O), 1330 and 1170, 1120 cm^{-1} (three strong bands) (>SO_2); nmr (CD_3COCD_3) δ 8.13–7.65 (m, 4, aromatic H's), 5.65 (dd, 1, $J_{C_4-C_2}$ = 10, $J_{C_4-C_3}$ = 6 Hz, –COCHBr–), 5.23 (dd, 1, $J_{C_2-C_3}$ = 12, $J_{C_2-C_3}$ = 3 Hz, $-SO_2CHCl-$), 3.74–3.20 (m, 2, $-SO_2CHClCH_2CHBr-$).

Anal. Calcd for $C_{10}H_8BrClO_3S$: C, 37.11; H, 2.49; O, 14.83. Found: C, 37.09; H, 2.42; O, 14.51.

***trans*-4-Bromo-1-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-Dioxide (14). Method A.**—Using the preceding procedure (*cis*-4-bromo-2-chloro sulfone 13,) *m*-chloroperbenzoic acid (1.35 g, 7.86 mmol) in $CHCl_3$ (20 ml) and *trans*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (12) (1.00 g, 3.43 mmol) in $CHCl_3$ (10 ml) gave after recrystallization from 95% ethanol 0.92 g (83%) of *trans*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (14): mp 161–163° dec; ir (KBr) 1705 (>C=O), 1330, 1145, and 1120 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 8.13 (m, 1, C_9 H), 7.91–7.50 (m, 3, C_6,C_7,C_8 H's), 5.22 (dd, 1, $J_{C_4-C_3}$ = 5, $J_{C_4-C_3}$ = 6 Hz, –COCHBr–), 5.00 (dd, 1, $J_{C_2-C_3}$ = 6, $J_{C_2-C_3}$ = 5 Hz, $-SO_2CHCl-$), 3.06 (dd, 2, J = 5, 6 Hz, $-SO_2-CHClCH_2CHBr-$).

Anal. Calcd for $C_{10}H_8BrClO_3S$: C, 37.11; H, 2.49; O, 14.83. Found: C, 37.43; H, 2.56; O, 15.02.

Method B.—Using the procedure described under *trans*-2,4-dichloro keto sulfone 10 (method A), *cis*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (13) (200 mg, 0.62 mmol) and triethylamine (0.72 g, 7.2 mmol) in $CHCl_3$ (5 ml) gave 190 mg of crude solid, mp 160–163°. Recrystallization of the crude solid from 95% ethanol gave 183 mg (92%) of *trans*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (14), mp 161–163°. The ir and nmr spectra and mixture melting point were identical with those of the trans isomer isolated by method A.

4-Iodo-3,4-dihydro-1-benzothiepin-5(2*H*)-one.—A solution of 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (2) (9.5 g, 0.036 mol), KI (15 g, 0.10 mol), and acetone (60 ml) was refluxed for 90 min, poured into water, and extracted with ether and the extract was dried (anhydrous K_2CO_3). After the solvent was

(18) The nmr peaks used to calculate this ratio involved a comparison of the low-field triplet (δ 5.5) for the cis isomer **6** with the entire absorption (δ 5.7–4.7) of the C_2 H and C_4 H of both **6** and **7**. The trans isomer **7** was clearly the more abundant component from comparison of its low-field doublets of doublets (δ 5.29) with that of the cis **6** low field triplet (δ 5.5). Overlapping C_2 H and C_4 H protons of the trans isomer **7** precluded a more accurate analysis of the isomer composition.

removed, the red solid was recrystallized twice from methanol and gave 7.5 g (65%) of faintly yellow 4-iodo-3,4-dihydro-1-benzothiepin-5(2*H*)-one, mp 98–99°.

Anal. Calcd for $C_{10}H_9IOS$: C, 39.49; H, 2.98. Found: C, 39.93; 39.75; H, 3.10, 3.09.

Registry No. —**1**, 21609-70-1; **2**, 21609-66-5; **3**, 22710-97-0; **3**, 22710-97-0; **4**, 21609-67-6; **5**, 40322-27-8; **6**, 40322-28-9; **7**, 40322-29-0; **7**, 40322-29-0; **8**, 40322-30-3; **9**, 40322-31-4; **10**, 40322-32-5; **11**, 40322-33-6; **12**, 40322-34-7; **13**, 40322-35-8; **14**, 40322-36-9; **15**, 40322-37-0; **16**, 40322-38-1; **17**, 40322-39-2; **18**, 40322-63-2; bromine, 7726-95-6; *N*-chlorosuccinimide, 128-09-6; sulfuryl chloride, 7791-25-5; *m*-chloroperbenzoic acid, 937-14-4; lithium chloride, 7447-41-8; dimethylformamide, 68-12-2; 4-iodo-3,4-dihydro-1-benzothiepin-5(2*H*)-one, 40322-40-5.

Seven-Membered Heterocycles. VI. 4-Alkylidene-1-benzothiepin-5(2*H*)-ones and the Reaction of Halogenated 3,4-Dihydro-1-benzothiepin-5(2*H*)-ones with Base[1-3]

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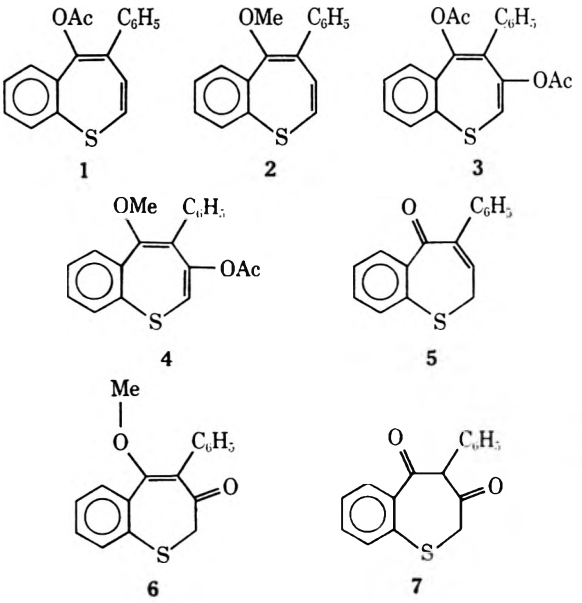
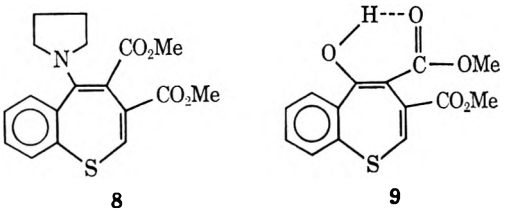
The Mannich reaction with 3,4-dihydro-1-benzothiepin-5(2*H*)-one (**15**) and dimethylamine hydrochloride provided 4-[(dimethylamino)methyl]-3,4-dihydro-1-benzothiepin-5(2*H*)-one hydrochloride (**16**) and a dimer **17** of 4-methylene-1-benzothiepin-5(2*H*,3*H*)-one, while base-catalyzed condensation of benzaldehyde with **15** gave 4-(α-hydroxybenzyl)-3,4-dihydro-1-benzothiepin-5-(2*H*)-one (**19**), 4-benzylidene-1-benzothiepin-5(2*H*,3*H*)-one (**20**), or 4,4′-benzylidenebis[3,4-dihydro-1-benzothiepin-5(2*H*)-one] (**18**) depending on temperature and solvent. Condensation of **15** and ethyl formate produced the hydroxymethylene derivative **21** which formed an enamine **22** with morpholine. Reaction of the enamine **22** with phenylmagnesium bromide and methylmagnesium iodide formed **20** and 4-ethylidene-1-benzothiepin-5(2*H*,3*H*)-one (**23**), respectively. Attempts to isomerize the exocyclic double bond in **20** and **23** using Pd/C were unsuccessful. Reaction of 4-bromo- (**12**, X = Br) or 4-iodo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**12**, X = I) with a variety of bases failed to produce 1-benzothiepin-5(2*H*)-one (**13**), while reaction of *cis*- or *trans*-2,4-dichloro-1-benzothiepin-5(2*H*)-one (**27a** and **27b**, respectively) with base rapidly formed 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one (**28**). Base-catalyzed elimination of hydrogen chloride from *cis*- and *trans*-2-chloro-4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**29a**, and **29b**, respective) gave the corresponding bromocyclopropyl ketone (**30**). The effect of base and solvent on the 1,3 elimination is reviewed and the enolate ion was trapped as the enol acetate **34**. The acid-catalyzed ring opening of the chlorocyclopropyl ketone **28** with acetic anhydride provided 2,5-diacetoxy-4-chloro-2,3-dihydro-1-benzothiepin (**39**) and similar ring-opening reactions with 7a-chloro-7-hydroxycyclopropa[*b*][1]benzothiopyran (**41**) and hydrogen chloride or acetic anhydride and *p*-toluenesulfonic acid gave 2,4-dichloro- (**45**) or 2-acetoxy-4-chloro-2,3-dihydro-1-benzothiepin (**43**). The formation of these compounds is explained *via* homoallylic cations **40** and **47**. Compound **45** and its derivatives are useful intermediates in the synthesis of 1-benzothiepin.

The stable 1-benzothiepin derivatives, reported in the literature,[5,6] have been highly substituted on the thiepin ring and contained one or more methoxy and/or acetoxy groups (compounds **1**–**4**). These derivatives were prepared by the methylation or acetylation of the corresponding enols of compounds **5**–**7**. A recent addition to the class of isolable 1-benzothiepins was dimethyl 5-pyrrolidino-1-benzothiepin-3,4-dicarboxylate (**8**) and the corresponding 5-hydroxy derivative **9**.[7]





It is interesting to note that compounds **5**–**7** existed in the keto form while **9** was exclusively enolic. A sta-

(1) For part V in this series see V. J. Traynelis, J. C. Sih, Y. Yoshikawa, R. F. Love, and D. M. Borgnaes, *J. Org. Chem.*, **38**, 2623 (1973).

(2) Presented in part before the Organic Division at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

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(4) (a) Abstracted from a portion of the Ph.D. Dissertation submitted by J. C. S. in Dec 1971 at West Virginia University. (b) Abstracted from a portion of the Ph.D. Dissertation submitted by D. M. B. in Aug 1968 at the University of Notre Dame.

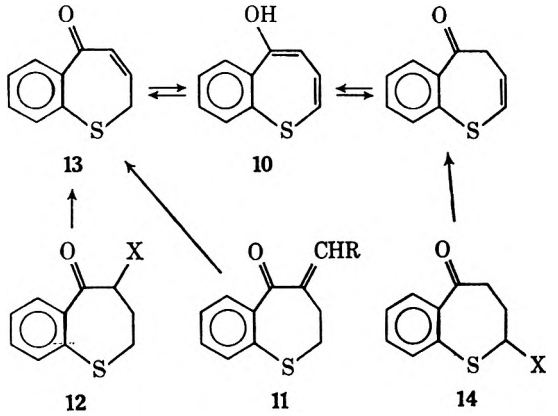
(5) H. Hofmann and H. Westernacher, *Chem. Ber.*, **102**, 205 (1969).

(6) H. Hofmann, B. Meyer, and P. Hofmann, *Angew. Chem., Int. Ed. Engl.*, **11**, 423 (1972).

(7) D. N. Reinhoudt and C. G. Kouwenhoven, *Chem. Commun.*, 1233 (1972).

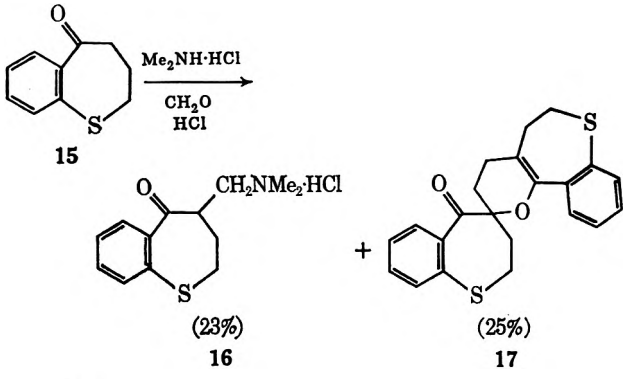
bilizing feature in **9** has been ascribed to intramolecular H bonding.[7]

In this report we wish to describe our studies directed toward unsaturated ketones in the 1-benzothiepin system. The three types of precursors (**11**, **12**, **14**) which can ultimately lead to derivatives of 5-hydroxy-1-benzothiepin (**10**) are outlined below. Although we

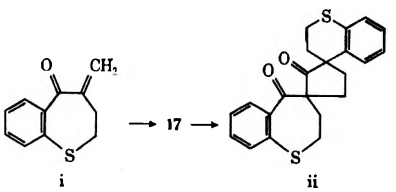


were not successful in producing and trapping **10** *via* a derivative, some unexpected reactions of the halogenated ketones led to intermediates which were subsequently converted to 1-benzothiepins.

The Mannich reaction of 3,4-dihydro-1-benzothiepin-5(2*H*)-one (**15**) and dimethylamine hydrochloride provided the expected product **16** in low yield along with a white, crystalline substance assigned structure **17**.[8-10] When the reaction was performed in acetic acid, only **17** was formed (86% yield). The use of **16** as a source of 4-methylene-1-benzothiepin-5(2*H*,3*H*)-one was precluded owing to the ease of dimerization of the unsaturated ketone to **17**.



(8) 2′,3,3′,4,5′,6′-Hexahydrospiro[1-benzothiepin-4,2′-(1-benzothiepino-[5,4-*b*]-4H-pyran)]-5(2*H*)-one. Compound **17** is also available by heating the free base 4-[(dimethylamino)methyl]-3,4-dihydro-1-benzothiepin-5-(2*H*)-one. The proposed formation of compound **17** entailed a Diels–Alder dimerization of 4-methylene-1-benzothiepin-5(2*H*,3*H*)-one (i),[9,10] which can form by elimination of dimethylamine from the Mannich product. An alternate structure ii has been suggested[10] which arises from an acid-catalyzed rearrangement of i. Thus the structural assignment for **17** remains unsettled.

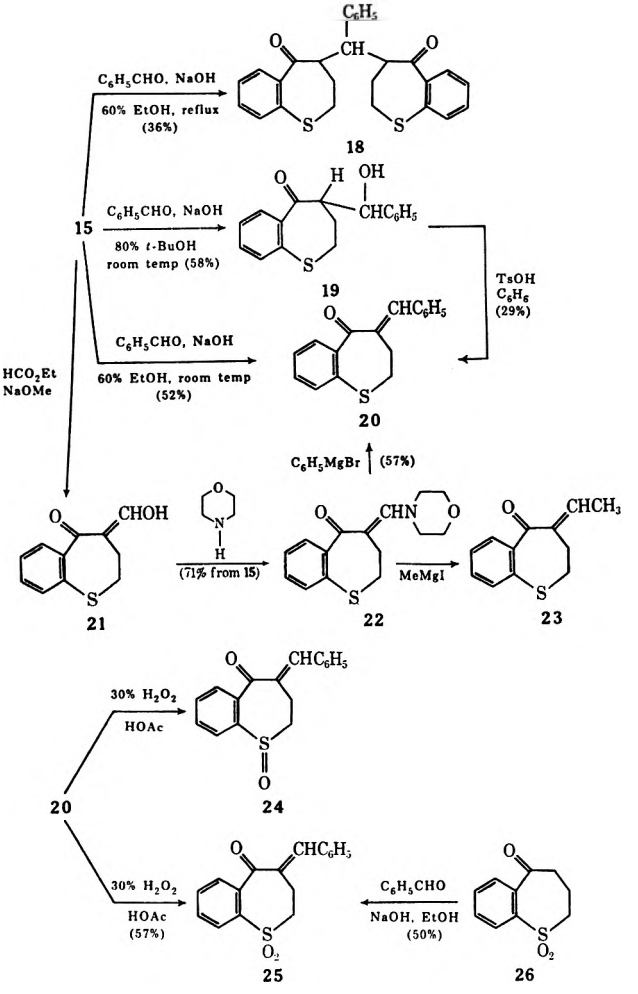


(9) R. J. Mohrbacher, U. S. Patent 3,287,369 (1966); *Chem. Abstr.*, **66**, 28754k (1967).

(10) K. Sindelar and M. Protiva, *Collect. Czech. Chem. Commun.*, **33**, 4315 (1968).

The base-catalyzed reaction of **15** and benzaldehyde gave 4-(α-hydroxybenzyl)-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**19**), 4-benzylidene-1-benzothiepin-5(2*H*,3*H*)-one (**20**), or 4,4′-benzylidenebis[3,4-dihydro-1-benzothiepin-5(2*H*)-one] (**18**) which depended on the reaction temperature and solvent. An acid-catalyzed dehydration of **19** also provided **20**, although in low yield. An alternative sequence used to prepare **20** employed the method of Ireland[11] for generating α-alkylidene ketones. The condensatiou of **15** and ethyl formate produced the hydroxymethylene derivative **21**, which showed a strong, broad ir absorption with peaks at 1629 and 1585 cm^{-1}, characteristic for α,β-unsaturated β-hydroxy ketones,[11,12] Reaction of **21** with morpholine gave enamine **22** which, when treated with phenylmagnesium bromide, was converted to **20**. This enamine synthesis was also utilized in the preparation of 4-ethylidene-1-benzothiepin-5(2*H*,3*H*)-one (**23**).

Oxidation of **20** with hydrogen peroxide at room temperature gave the corresponding sulfoxide **24**, while more vigorous oxidizing conditions led to sulfone **25**, which was also prepared by the base-catalyzed condensation of benzaldehyde and 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (**26**).



Structural assignments for the above condensation products and their oxidized derivatives were based on uv (see Table I), ir, and nmr spectral data. The uv

(11) R. Ireland and P. Schiess, *J. Org. Chem.*, **28**, 6 (1963).

(12) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, pp 142–143.

TABLE I
UV SPECTRAL DATA[a]

Compd	λ_{max}, nm	Log ε
4-Benzylidene-1-benzothiepin-5(2*H*,3*H*)-one (**20**)	235	4.07
	304	4.20
4-Benzylidene-1-benzothiepin-5(2*H*,3*H*)-one 1-oxide (**24**)	233	4.22
	316	4.16
4-Benzylidene-1-benzothiepin-5(2*H*,3*H*)-one 1,1-dioxide (**25**)	232	4.04
	305	4.16
4-Ethylidene-1-benzothiepin-5(2*H*,3*H*)-one (**23**)	251	4.16
4-(Morpholinomethylene)-1-benzothiepin-5-(2*H*,3*H*)-one (**22**)	247	4.06
4-(α-Hydroxybenzyl)-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**19**)	240	4.28
	263	3.75
trans-Benzalacetophenone	227[b]	
	305	4.40
	226[c]	4.23
	300	4.30
Phenylvinyl ketone	247[d]	4.00

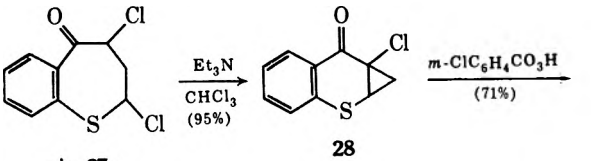
[a] Measurements were made in 95% ethanol unless stated otherwise. [b] Methanol solvent. J. F. Thomas and G. Branch, *J. Amer. Chem. Soc.*, **75**, 4793 (1953). [c] Cyclohexane solvent. C. L. Stevens, R. C. Church, and V. J. Traynelis, *J. Org. Chem.*, **19**, 522 (1954). [d] K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946).

data supported the α,β-unsaturated ketone structure, while ir absorptions were consistent with functional group changes. In addition the exocyclic nature of the double bond was confirmed by ozonolysis of **25**, which gave benzaldehyde. The other expected ozonolysis product, the α diketone, was not isolated or characterized.

Isomerization of the exocyclic double bonds in **20** and **23** into the ring was studied using the method reported by Leonard[13,14] for isomerization of 3,5-dibenzylidenetetrahydropyrone[13] and α,α′-dibenzylidenecycloheptanone[14] into 3,5-dibenzylpyrone and 2,7-dibenzyltropone, respectively. When **20** or **23** was heated with 10% Pd/C in ethylene glycol at various temperatures and times, no isomerization was observed and the starting material was recovered in 80–88% yields. Even at temperatures of 300° and in the absence of solvent, no isomerization in **20** or **23** occurred; however, some decomposition was noted. Thus, one is led to conclude that no strong driving force exists for relocating the double bond into the ring and generating the enolic structure **10** even when the exocyclic double bond lacks further conjugation as in **23**.

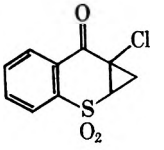
A second approach directed toward the formation of **13** or its derivatives involved the study of the reaction of halogenated ketones with base. The reaction of 4-bromo-[1,15] (**12**, X = Br) or 4-iodo-3,4-dihydro-1-benzothiepin-5-(2*H*)-one[1,4b] (**12**, X = I) with a variety of bases [triethylamine, tetramethylquanidine, potassium *tert*-butoxide, LiBr and dimethylformamide (DMF) or LiCl, Li_2CO_3 in DMF] gave either unreacted starting material or, under more vigorous conditions, resinification. Although hydrogen halide was eliminated in some reactions, no identifiable products could be isolated. The difficulty encountered in the elimination of hydrogen halide in **12** to generate **13** is not surprising in view of the conformational preference in **12**[1] and the high energy state required for a trans coplanar elimination in **12**. The use of **14**, X = Cl, in reactions with base was precluded since it was not possible to obtain **14**, X = Cl, free from the dichloro ketone **27**[1] and thus we directed our studies to **27**.

The reaction of either *cis*- or *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**27a** and **27b**, respectively) with triethylamine in chloroform at room temperature resulted in a rapid 1,3 elimination of hydrogen chloride to give 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one (**28**) in near-quantitative yields. The



cis, **27a**
trans, **27b**

28



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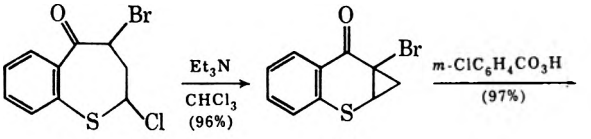
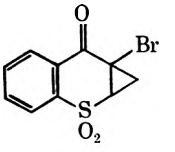


cis, **29a**
trans, **29b**

30



32

direction of ring closure, namely abstraction of the C_4 proton and elimination of the C_2 chlorine, was established by reaction of *cis*- or *trans*-2-chloro-4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**29a** and **29b**, respectively) with triethylamine to give 7a-bromocyclopropa[*b*][1]benzothiopyran-7-one (**30**). The cyclopropyl ketones **28** and **30** were oxidized to the corresponding sulfones **31** and **32**, respectively, and the structures were assigned on the basis of elemental analysis, ir, and their unique nmr spectra.

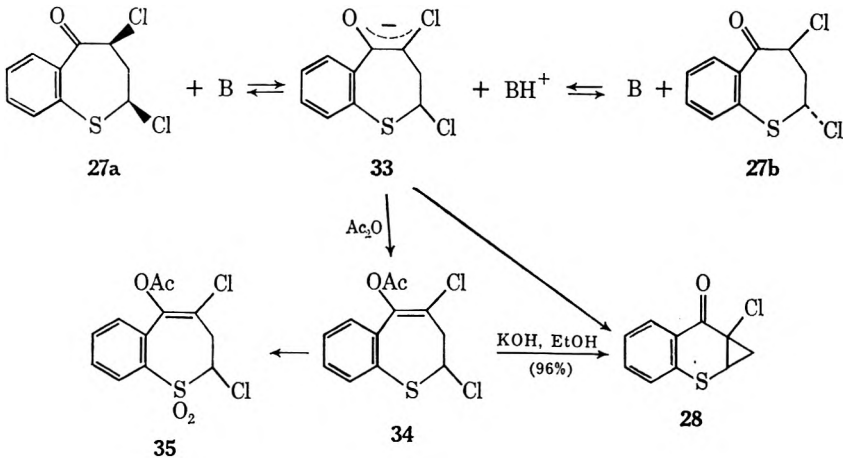
The influence of solvent and base strength on the conversion of the dichloro ketones **27** to the cyclopropyl ketone **28** are summarized in Table II. One finds that an increase in basicity or solvent polarity enhances ring closure to the cyclopropyl ketone **28**. The initial step entails abstraction of the C_4 proton and the formation of enolate ion **33**. With triethylamine in chloroform the elimination of the C_2 chloride from **33** becomes so rapid that the 1,3 elimination resembles an E2 process. Even when limited quantities of triethylamine were used, no isomerization of **27a** to **27b** or vice versa or deuterium exchange in **27** was observed.

(13) N. J. Leonard and D. Choudhury, *J. Amer. Chem. Soc.*, **79**, 156 (1957).
(14) N. J. Leonard, L. A. Miller, and J. W. Berry, *ibid.*, **79**, 1482 (1957).
(15) R. F. Love, Ph.D. Dissertation, University of Notre Dame, May 1960.

TABLE II
REACTIONS OF *cis*- AND *trans*-2,4-DICHLORO-3,4-DIHYDRO-1-BENZOTHIEPIN-5(2*H*)-ONE WITH BASE AT ROOM TEMPERATURE

Isomer (mmol)	Base (mmol)	Solvent (ml)	Reaction time	Yield,[a] % (compd)
cis **27a** or *trans*-**27b** (4.05)	Et_3N (25)	$CHCl_3$ (20)	17 min[b]	100 (**28**)[c]
cis-**27a** (2.22)	Et_3N (1.00)	$CHCl_3$ (10)	5 min	32 (**28**) 68 (**27a**)[d]
trans-**27b** (2.22)	Et_3N (1.00)	$CHCl_3$ (10)	5 min	34 (**28**) 66 (**27b**)
cis-**27a** (5.00)	Pyridine (5.00)	Benzene (17)	21 hr	0 (**28**) Equilibrium mixture of **27a** and **27b**[e]
trans-**27b** (5.00)	Pyridine (5.00)	Benzene (17)	21 hr	0 (**28**) Equilibrium mixture of **27a** and **27b**[e]
cis-**27a** (5.00)	Pyridine (5.00)	$CHCl_3$ (17)	21 hr	72 (**28**) 27 (**27a** and **27b**)
cis-**27a** or *trans*-**27b** (5.00)	Et_3N (5.00)	$CHCl_3$ (17)	21 hr	100 (**28**)
cis-**27a** (4.05)	Et_3N (25)	Benzene (20)	30 min	40 (**28**) 60 (**27a** and **27b**)
cis-**27a** (4.05)	Et_3N (25)	Benzene (20) Ethanol (2)	30 min	100 (**28**)

[a] Yields were determined by nmr analysis. [b] When the reaction was followed by nmr, complete conversion to **28** resulted immediately after addition of triethylamine. [c] 7a-Chlorocyclopropa[*b*][1]benzothiopyran-7-one. [d] No isomerization of **27a** to **27b** occurred during the reaction as determined by nmr; no deuterium exchange was observed when the reaction was performed in the presence of deuterio ethanol. [e] When aliquots of the reaction mixture were quenched at the end of 17, 21, or 48 hr, the relative peak heights (nmr) used for analysis of the mixture of **27a** and **27b** remained constant and represented a 50:50 mixture.

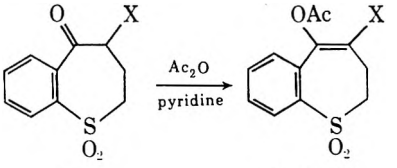


27a 33 27b 35 34 28

On the other hand the reaction of **27a** or **27b** with pyridine in benzene led only to isomerization and formation of an equilibrium mixture of **27a** and **27b**, while the use of pyridine in chloroform or triethylamine in benzene provided some cyclopropyl ketone **28** and the isomerized equilibrium mixture of **27a** and **27b**, thus approaching an E1cB type process.

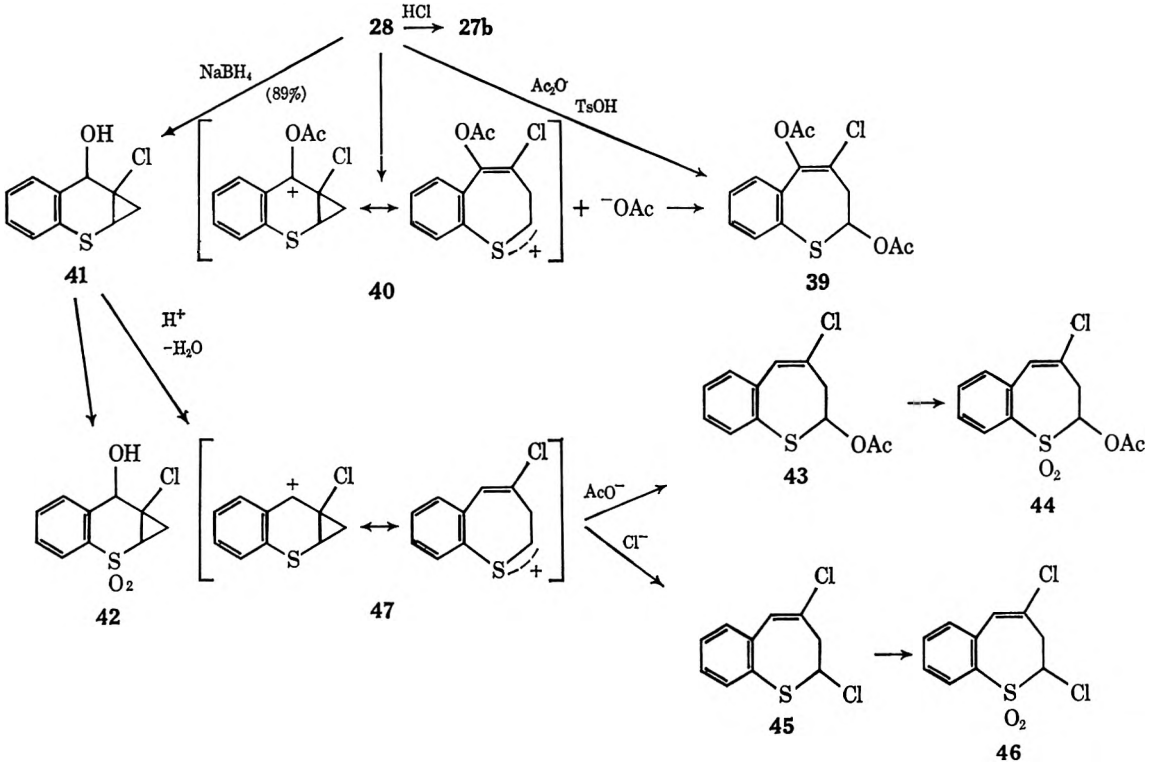
The initial appearance of enolate ion **33** was established by acetylation and isolation of enol acetate **34**, characterized as its sulfone **35**. When **34** was treated with triethylamine, no reaction took place; however, reaction with potassium hydroxide in 95% ethanol rapidly generated the cyclopropyl ketone **28**, most likely *via* **33**.

Sulfone **35** was also obtained from reaction of *cis*- or *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide[1] with acetic anhydride and pyridine. Other α-halo keto sulfones **36** were readily converted to enol acetates, 5-acetoxy-4-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (**37**), and 5-acetoxy-4-bromo-2,3-dihydro-1-benzothiepin 1,1-dioxide (**38**), by action of acetic anhydride and pyridine, while the corresponding α-halo keto sulfides **12** and **15** did not react even under more vigorous conditions.



36 37, X = Cl 38, X = Br

Ring opening of the cyclopropane ring in **28** occurred quite readily under acid catalysis to regenerate the 1-benzothiepin system. The reaction of **28** with HCl in chloroform proceeded steroselectively to produce *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one (**27b**).[1] The absence of the cis isomer (**27a**) (which is stable under the experimental conditions for adding HCl to **28**) excludes the enol intermediate and thus requires a cis addition of HCl across the cyclopropane ring. In contrast the addition of acetic anhydride to **28** in the presence of *p*-toluenesulfonic acid gave 2,5-diacetoxy-4-chloro-2,3-dihydro-1-benzothiepin (**39**), which can be rationalized by a similar pathway to the addition of HCl followed by enol acetate formation or by the steps outlined below *via* the homoallylic cation **40**.



Reduction of **28** with sodium borohydride gave 7a-chloro-7-hydroxycyclopropa[*b*][1]benzothiopyran (**41**), which was characterized as it sulfone **42**. The cyclopropyl alcohol **41**, like **28**, underwent facile ring opening under acidic conditions with acetic anhydride and hydrogen chloride to produce **43** and **45**, respectively, which were characterized by their corresponding sulfone **44** and **46**. The formation of the 2,3-dihydro-1-benzothiepins **43** and **45** is readily rationalized *via* cation **47**.

The use of **28** and **41** in the synthesis of substituted 2,3-dihydro-1-benzothiepins can be extended to 5-alkyl or 5-aryl derivatives by application of the Grignard reaction with **28** and HCl ring opening of the resulting cyclopropyl alcohol.[16] These 2-chloro-2,3-dihydro-1-benzothiepins, such as **45**, have been key intermediates in the synthesis of 1-benzothiepin and its chlorinated derivatives. The preparation and properties of 1-benzothiepin will be reported in the subsequent publication.

Thus the general method for preparing 2-chloro-2,3-dihydro-1-benzothiepin derivatives serves as a good synthetic approach in generating a variety of 1-benzothiepin derivatives.

Experimental Section[17]

4-[(Dimethylamino)methyl]-3,4-dihydro-1-benzothiepin-5(2*H*)-one Hydrochloride (16).—A mixture of 3,4-dihydro-1-benzothiepin-5(2*H*)-one[18] (8.9 g, 0.050 mol), dimethylamine hydrochloride (4.2 g, 0.052 mol), paraformaldehyde (2.3 g, 0.075 mol), isoamyl alcohol (40 ml), and concentrated HCl (0.5 ml) was refluxed for 3.5 hr, concentrated, diluted with H_2O, and extracted with ether. The extract was dried and upon removal of the ether gave 2.4 g (25%) of 2′,3,3′,4,5′,6′-hexahydrospiro-[1-benzothiepin-4,2′-(1-benzothiepino[5,4-*b*]-4*H*-pyran)]-5(2*H*)-one (**17**), mp 152–154°.

The aqueous layer was evaporated, leaving 3.1 g (23%) of crude 4-[(dimethylamino)methyl]-3,4-dihydro-1-benzothiepin-5-(2*H*)-one hydrochloride, mp 169–172°. An analytical sample, mp 176–179°, ir ($CHCl_3$) 2320 (>NH)$^+$, 1695 cm^{-1} (>C=O), nmr (DMSO-d_6) δ 7.86–7.28 (m, aromatic H's), 4.0–1.70 [broad multiplet with overlapping solvent peaks and a singlet at δ 2.67 for the $N(CH_3)_2$ includes all aliphatic protons], was obtained by repeated crystallization from ethanol–ethyl acetate.

Anal. Calcd for $C_{13}H_{18}ClNOS$: C, 57.45; H, 6.67. Found: C, 57.55, 57.43; H, 6.51, 6.74.

2′,3,3′,4,5′,6′-Hexahydrospiro[1-benzothiepin-4,2′-(1-benzothiepino[5,4-*b*]-4*H*-pyran)]-5(2*H*)-one (17).—A solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one[18] (17.8 g, 0.10 mol), ethanol (15 ml), acetic acid (14.0 g, 0.233 mol), aqueous dimethylamine solution (6.75 g, 0.15 mol), and formalin (7.50 g, 0.25 mol) was refluxed for 3 hr and cooled. The resulting solid was filtered, washed with H_2O, and dried, giving 16.5 g (86%) of **17**, mp 152–154°, ir (CCl_4) 1720 (>C=O), 1625 cm^{-1} (>C=C<). An analytical sample of **17**, mp 154.5–155°, was prepared by repeated crystallization from mixed octanes.

Anal. Calcd for $C_{22}H_{20}O_2S_2$: C, 69.44; H, 5.30; mol wt, 380.5. Found: C, 69.44, 69.62; H, 5.41, 5.40; mol wt, 398.

4-(α-Hydroxybenzyl)-3,4-dihydro-1-benzothiepin-5(2*H*)-one (19).—A solution of 80% aqueous *tert*-butyl alcohol (100 ml), NaOH (0.2 g, 0.005 mol), 3,4-dihydro-1-benzothiepin-5(2*H*)-one[18] (8.9 g, 0.050 mol), and benzaldehyde (5.3 g, 0.050 mol) was stirred and, on four occasions at 30-min intervals, the precipitated solid was filtered. The solids were combined and crystallization from benzene gave 15.5 g (58%) of 4-(α-hydroxybenzyl)-3,4-dihydro-1-benzothiepin-5(2*H*)-one: mp 164–166°; ir ($CHCl_3$) 3600 (free OH) 3500 (associated OH), 1680 cm^{-1} (>C=O); uv max (95% EtOH) 240 nm (log ϵ 4.28), 263 (3.75); nmr ($CDCl_3$) δ 7.95–7.17 (m, 4, aromatic H's), 5.25–5.0 [m, 1, –CH(OH)C_6H_5], 3.93 {two t, 1, J = 7, 11 Hz, –COCH[CH(OH)C_6H_5]–}, 3.20–1.57 (m, 5, remainder of the aliphatic protons and OH). An analytical sample, mp 168.5–169°, was obtained by repeated crystallization from benzene.

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67. Found: C, 71.92; H, 5.55.

4,4′-Benzylidenebis[3,4-dihydro-1-benzothiepin-5(2*H*)-one] (18).—After a solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one[18] (8.9 g, 0.050 mol), benzaldehyde (5.3 g, 0.050 mol), NaOH (0.2 g, 0.005 mol), and 60% aqueous ethanol (100 ml) was refluxed for 12 hr, the reaction mixture was cooled and filtered.

(16) V. J. Traynelis and D. Cassis, unpublished results.

(17) All melting points and boiling points are uncorrected. Elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind., or Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined on a Perkin-Elmer Model 137-B or a Beckman IR-8 spectrometer, uv spectra were measured on a Bausch and Lomb 505 spectrometer, and nmr spectra were obtained on a Varian Associates Model HA-60 or Model T-60 spectrometer.

(18) V. J. Traynelis and R. F. Love, *J. Org. Chem.*, **26**, 2728 (1961).

The resulting solid was recrystallized from dioxane–H_2O and gave 4.0 g (36%) of 4,4'-benzylidenebis[3,4-dihydro-1-benzothiepin-5(2*H*)-one], mp 204–205°.

Anal. Calcd for $C_{27}H_{24}O_2S_2$: C, 72.92; H, 5.44; mol wt, 444.62. Found: C, 72.82; H, 5.81; mol wt, 444.

4-Benzylidene-1-benzothiepin-5(2*H*,3*H*)-one (20). Method A.—A solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one[18] (8.9 g, 0.050 mol), benzaldehyde (5.3 g, 0.050 mol), NaOH (0.2 g, 0.005 mol), and 60% aqueous ethanol (100 ml) was allowed to remain for 30 min at room temperature with occasional swirling. The resulting solid was filtered, washed (H_2O), and dried and recrystallization from methanol gave 7.0 g (52%) of 4-benzylidene-1-benzothiepin-5(2*H*,3*H*)-one as yellow needles: mp 82–84°; uv max (95% EtOH) 235 nm (log ϵ 4.07), 304 (4.20); ir (CCl_4) 1675 (C=O), 1610 cm^{-1} (C=C); nmr (CCl_4) δ 8.06 (s, 1, C=CHC_6H_5), 7.35 (m, 9, aromatic H's), 3.02 (m, 4, -SCH_2-CH_2-). Repeated crystallization from methanol gave an analytical sample, mp 88.5–89°.

Anal. Calcd for $C_{17}H_{14}OS$: C, 76.66; H, 5.30. Found: C, 76.82; H, 5.26.

Method B.—To a stirred solution of phenylmagnesium bromide, prepared from bromobenzene (28.6 g, 0.167 mol) and magnesium (4.0 g, 0.17 g-atom) in ether (150 ml), was added solid 4-(morpholinomethylene)-1-benzothiepin-5(2*H*,3*H*)-one (see below for preparation) (10.0 g, 0.0364 mol) and the reaction mixture was stirred at reflux for 4 hr. The solution was hydrolyzed cautiously with 9.1 g of NH_4Cl in 30 ml of H_2O; After the ether layer was separated and dried ($MgSO_4$) and the solvent was removed, the residue was crystallized from methanol and give 5.5 g (57%) of 4-benzylidene-1-benzothiepin-5(2*H*,3*H*)-one, mp 86.5–88°. An ir spectrum of this material was identical with that of the preceding sample.

Method C.—A solution of 4-(α-hydroxybenzyl)-3,4-dihydro-1-benzothiepin-5(2*H*)-one (10.0 g, 0.035 mol) and *p*-toluenesulfonic acid (0.20 g) in benzene (50 ml) was refluxed for 48 hr, after which time 0.42 ml of H_2O was collected in a Dean–Stark trap. The benzene solution was extracted with $NaHCO_3$ solution and washed with water, and after the solvent was removed, the residue was crystallized from methanol. The yield of 4-benzylidene-1-benzothiepin-5(2*H*,3*H*)-one, mp 86–88°, was 2.7 g (29%). A mixture melting point with an authentic sample was not depressed.

4-Benzylidene-1-benzothiepin-5(2*H*,3*H*)-one 1-Oxide (24).—A solution of 4-benzylidene-1-benzothiepin-5(2*H*,3*H*)-one (2.7 g, 0.010 mol), 30% hydrogen peroxide (2.0 g, 0.030 mol), and acetic acid (20 ml) was allowed to stand for 12 hr at room temperature and poured onto cracked ice. The oil which separated crystallized after addition of a few drops of Skelly B. The solid precipitate was filtered, dried, and recrystallized from benzene–Skelly B to give 4-benzylidene-1-benzothiepin-5(2*H*,3*H*)-one 1-oxide: mp 137–140°; uv max (95% EtOH) 233 nm (log ϵ 4.22), 316 (4.16); ir (CCl_4) 1673 (>C=O), 1070 cm^{-1} (>S=O); nmr ($CDCl_3$) δ 8.20–7.30 (m, 10, aromatic H's and >C=C-HC_6H_5), 4.20–2.40 (m, 4, -$SOCH_2CH_2$-).

Anal. Calcd for $C_{17}H_{14}O_2S$: C, 72.31; H, 5.00. Found: C, 72.07; H, 4.93.

4-Benzylidene-1-benzothiepin-5(2*H*,3*H*)-one 1,1-Dioxide (25). Method A.—After a solution of 30% hydrogen peroxide (2.0 g, 0.030 mol) and 4-benzylidene-1-benzothiepin-5(2*H*,3*H*)-one (2.7 g, 0.010 mol) in glacial acetic acid (20 ml) remained at room temperature for 12 hr, a second portion of 30% hydrogen peroxide (2.0 g, 0.030 mol) was added and the reaction mixture was heated on a steam bath for 3 hr. The reaction mixture was cooled, poured on ice, and extracted with $CHCl_3$ and the extract was dried ($MgSO_4$). After the solvent was removed, crystallization of the residue from methanol gave 1.7 g (57%) of 4-benzylidene-1-benzothiepin-5(2*H*,3*H*)-one 1,1-dioxide: mp 153–155°; uv max (95% EtOH) 232 nm (log ϵ 4.04), 305 (4.16); ir ($CHCl_3$) 1678 (>C=O), 1332 and 1149 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 8.10 (s, 1, >C=CHC_6H_5), 8.00–7.40 (m, 9, aromatic H's), 3.57 (t, 2, J = 6 Hz, -$SO_2CH_2CH_2$-), 2.88 (t, 2, J = 6 Hz, -SO_2-CH_2CH_2-). Several recrystallizations from methanol gave the analytical sample, mp 156–157°.

Anal. Calcd for $C_{17}H_{14}O_3S$: C, 68.44; H, 4.73. Found: C, 68.48; H, 4.92.

Method B.—A solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide[18] (12.4 g, 0.059 mol), benzaldehyde (6.25 g, 0.059 mol), and NaOH (0.80 g, 0.020 mol) in ethanol (50 ml) was kept at room temperature for 1 hr and then neutralized with hydrochloric acid. The solvent was removed from the reaction mixture and the residue was recrystallized three times from ethanol to give 7.0 g (50%) of 4-benzylidene-1-benzothiepin-5-(2*H*,3*H*)-one 1,1-dioxide, mp 148–150°. Two additional recrystallizations raised the melting point to 154–155°. A mixture melting point with the above sample was not depressed.

Ozonolysis of 4-Benzylidene-1-benzothiepin-5(2*H*,3*H*)-one 1,1-Dioxide.—Ozone (1%) in a stream of oxygen was bubbled into a Dry Ice–acetone-cooled solution of 4-benzylidene-1-benzothiepin-5(2*H*,3*H*)-one 1,1-dioxide (1.0 g, 0.0034 mol) in methylene chloride (100 ml) and pyridine (2 ml) for 3 hr. After the reaction mixture was warmed to room temperature and washed with 10% HCl, $NaHCO_3$ solution, and then H_2O, the organic layer was allowed to react for 2 hr with a solution of sodium metabisulfite (5.0 g) in H_2O (20 ml). The water layer was separated and neutralized with NaOH and the solution was extracted with ether. After the ether solution was dried ($MgSO_4$) and the solvent removed, the residue was treated with 2,4-dinitrophenylhydrazine. The yield of the 2,4-dinitrophenylhydrazone of benzaldehyde, mp 236–238°, was 0.57 g (60%). A mixture melting point with an authentic sample was 236–238°.

A red oil which was isolated from the organic phase of the bisulfite reaction was not identified.

4-Morpholinomethylene-1-benzothiepin-5(2*H*,3*H*)-one (22).—A solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one[18] (7.65 g, 0.0430 mol) and ethyl formate (18.5 g, 0.280 mol) in dry benzene (50 ml) was added slowly to an ice-cooled suspension of sodium methoxide (8.90 g, 0.165 mol) in dry benzene (150 ml). The reaction mixture was stirred overnight at room temperature, H_2O (75 ml) was added, and the aqueous layer was separated. The benzene solution was extracted with 5% NaOH (2 × 25 ml) and the combined alkaline aqueous solutions were washed with ether, cooled, acidified with cold 10% HCl, and extracted with ether. The combined ether extracts were washed with H_2O and saturated NaCl solution and dried (Na_2SO_4). After the ether was removed, the residue was 4-hydroxymethylene-1-benzothiepin-5-(2*H*,3*H*)-one (21), an oil, ir (neat) 3400 (-OH), 1730 (medium) (>C=O), 1629 and 1585 cm^{-1} (>C=CHOH).

Without further purification 21 was combined with morpholine (4.35 g, 0.0512 mol) in benzene (120 ml) and the solution was refluxed for 2 hr, during which time H_2O (0.8 ml) was collected in the Dean–Stark trap. The reaction mixture was concentrated to half the original volume and *n*-hexane (50 ml) was added. The resulting solid was filtered and dried and gave 8.4 g (71% based on starting 3,4-dihydro-1-benzothiepin-5(2*H*)-one) of 4-morpholinomethylene-1-benzothiepin-5(2*H*,3*H*)-one, mp 165–167°, ir ($CHCl_3$) 1650 cm^{-1} (>C=O). An analytical sample was prepared by repeated crystallizations from benzene–*n*-hexane, mp 166–167°.

Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22. Found: C, 65.66; H, 6.25.

4-Ethylidene-1-benzothiepin-5(2*H*,3*H*)-one (23).—To a solution of methylmagnesium iodide, prepared from magnesium (4.0 g, 0.17 g-atom) and methyl iodide (25.8 g, 0.182 mol) in ether (100 ml), was added in small increments solid 4-morpholinomethylene-1-benzothiepin-5(2*H*,3*H*)-one (10.0 g, 0.0364 mol). After the reaction mixture was stirred for 4.5 hr, NH_4Cl (9.1 g) in H_2O (30 ml) was added followed by more H_2O (100 ml). The organic layer was separated and dried (Na_2SO_4) and the solvent was removed. The residue was crystallized from Skelly B and gave 5.3 g (72%) of 4-ethylidene-1-benzothiepin-5(2*H*,3*H*)-one, mp 75–79°. An analytical sample was obtained by recrystallization from Skelly B and had the following constants: mp 79–79.5°; uv max (95% EtOH) 251 nm (log ϵ 4.16); ir (neat) 1675 cm^{-1} (>C=O); nmr (CCl_4) δ 7.39 (m, 4, aromatic H's), 6.94 (q, 1, J = 7.5 Hz, C=CHCH_3), 2.75 (m, 4, -SCH_2CH_2-), 1.89 (d, 3, J = 7.5 Hz, C=CHCH_3).

Anal. Calcd for $C_{12}H_{12}OS$: C, 70.55; H, 5.92. Found: C, 70.42, 70.29; H, 5.91, 5.85.

Attempted Isomerization of 4-Benzylidene-1-benzothiepin-5-(2*H*,3*H*)-one and 4-Ethylidene-1-benzothiepin-5(2*H*,3*H*)-one. Method A.—A mixture of 4-benzylidene-1-benzothiepin-5(2*H*,-3*H*)-one (2.66 g, 0.0100 mol), 10% Pd/C (1.3 g), and ethylene glycol (75 ml) was refluxed for 15 min and filtered hot. After the filtrate was diluted with water and extracted with ether, the ether extract was washed with H_2O and saturated NaCl solution and dried ($MgSO_4$). The ether was removed and the residue upon recrystallization from methanol gave 2.10 g (80%) of recovered starting material, mp 85–87°.

The same procedure was used with 4-ethylidene-1-benzothiepin-5(2*H*,3*H*)-one (1.70 g, 0.00833 mol) and 10% Pd/C (1.00 g) in

ethylene glycol (50 ml) and a 90-min reflux. Starting material was recovered in 88% yield.

Method B.—A mixture of 4-benzylidene-1-benzothiepin-5-(2*H*,3*H*)-one (1.00 g, 0.00376 mol) and 10% Pd/C (0.200 g) was heated in a Wood's metal bath at 250° for 15 min. The reaction mixture was cooled, dissolved in methanol, and filtered and, after the methanol was removed, 0.82 g (82%) of the starting material, mp 85–88°, was recovered. When the reaction was repeated at 300°, 83% of the starting material was recovered.

Similar experiments performed with 4-ethylidene-1-benzothiepin-5(2*H*,3*H*)-one at 250 and 300° gave recovered starting material in 75 and 76% yields, respectively.

7a-Chlorocyclopropa[*b*][1]benzothiopyran-7-one (28).[19] **Method A.**—After a solution of triethylamine (13.1 g, 0.128 mol) and *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one[1] (5.00 g, 0.020 mol) in $CHCl_3$ (70 ml) was allowed to stand at room temperature for 1 hr, the reaction mixture was washed with 10% HCl and H_2O, and the organic layer was dried ($MgSO_4$). The solvent was removed under vacuum and the residual oil solidified upon the addition of ice water. The solid was filtered, dried, and recrystallized from 60% ethanol to give 4.03 g (95%) of 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one: mp 61–62°; ir (KBr) 3040 (w), 1680 (s, >C=O), 1585 (s), 1310 (s), 1145 (s), 940 (s), 740 (s), 675 cm^{-1} (s); nmr ($CDCl_3$) δ 8.06–7.88 (m, 1, C_3 H), 7.50–7.10 (m, 3, C_4, C_5, C_6 H's), 3.24 (dd, 1, $J_{C_{1a}-C_{1x}}$ = 8 Hz, $J_{C_{1a}-C_{1y}}$ = 7 Hz, C_{1a} H), 2.23 (dd, 1, $J_{C_{1x}-C_{1a}}$ = 8 Hz, $J_{C_{1x}-C_{1y}}$ = 7 Hz, C_1 H_x), 1.73 (t, 1, $J_{C_{1y}-C_{1x}}$ = $J_{C_{1y}-C_{1a}}$ = 7 Hz, C_1 H_y).

Anal. Calcd for $C_{10}H_7ClOS$: C, 57.00; H, 3.36; Cl, 16.83. Found: C, 57.25; H, 3.33; Cl, 16.80.

Using the same procedure as above, *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one[1] (1.00 g, 4.05 mmol) and triethylamine (3.50 ml, 25 mmol) in $CHCl_3$ (20 ml) gave after recrystallization from 60% ethanol 0.80 g (95%) of **28**, mp 61–62°. A mixture melting point with the above sample was not depressed and the ir and nmr spectra of both samples were identical.

Method B.—A mixture of 5-acetoxy-2,4-dichloro-2,3-dihydro-1-benzothiepin (1.00 g, 3.46 mmol), KOH (1.00 g, 18 mmol), and 95% ethanol (35 ml) was heated at 55° for 10 min. The excess KOH was removed by filtration, $CHCl_3$ (60 ml) was added, and the organic layer was washed with 10% HCl and H_2O and dried ($MgSO_4$). After the solvent was removed, the residual oil solidified upon addition of ice water and recrystallization from 60% ethanol gave 0.70 g (96%) of **28**, mp 61–62°. The ir and nmr spectra of this sample were identical with those of the above sample.

Method C.—Using the quantities and employing the reaction conditions listed in Table II, the reactions of **27** with base were quenched with 10% HCl. The organic layer was washed with H_2O, separated, and dried ($MgSO_4$). Analysis of the reaction mixture by nmr ($CDCl_3$) was performed on the residual oil which remained after removal of the solvent under vacuum.

7a-Chlorocyclopropa[*b*][1]benzothiopyran-7-one 2,2-Dioxide (31).—After a solution of 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one (0.68 g, 3.18 mmol) in $CHCl_3$ (10 ml) was added over a 15-min period to a stirred solution of *m*-chloroperbenzoic acid (1.26 g, 7.31 mmol) in $CHCl_3$ (15 ml) maintained at −10 to −16°, the reaction mixture was allowed to warm to room temperature and kept overnight at ambient temperature. *m*-Chlorobenzoic acid was removed by filtration, and the filtrate was washed with 10% Na_2CO_3 solution, dried ($MgSO_4$), and filtered. The solvent was removed and recrystallization of the residue from 95% ethanol gave 0.55 g (71%) of 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one 2,2-dioxide: mp 176.5–178°; ir (KBr) 1695 (>C=O), 1305, 1155 cm^{-1} (>SO_2); nmr ($CDCl_3$)[19] δ 8.20–7.75 (m, 4, aromatic H's), 3.82 (dd, 1, $J_{C_{1a}-C_{1x}}$ = 8 Hz, $J_{C_{1a}-C_{1y}}$ = 8.5 Hz, C_{1a} H), 2.31 [dd, 1+ (overlap with 1y), $J_{C_{1x}-C_{1a}}$ = 8 Hz, $J_{C_{1x}-C_{1y}}$ = 11.5 Hz, C_1 H_x), 2.16 [dd, 1+ (overlap with 1x), $J_{C_{1y}-C_{1a}}$ = 8.5 Hz, $J_{C_{1y}-C_{1x}}$ = 11.5 Hz, C_1 H_y).

Anal. Calcd for $C_{10}H_7ClO_3S$: C, 49.49; H, 2.91; Cl, 14.61; O, 19.78. Found: C, 49.50; H, 2.76; Cl, 14.94; O, 19.88.

7a-Bromocyclopropa[*b*][1]benzothiopyran-7-one (30).—A solution obtained by the addition of triethylamine (0.70 ml, 5 mmol) to *trans*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one[1] (200 mg, 0.70 mmol) in $CHCl_3$ (10 ml) was kept at room temperature for 17 min and neutralized with 10% HCl, and the organic layer was separated, washed with H_2O, and dried ($MgSO_4$). The solvent was removed and gave 168 mg (96%) of 7a-bromocyclopropa[*b*][1]benzothiopyran-7-one as a red oil: ir (neat) 3045 (w), 1685 (s, >C=O), 1590 (s), 1140 (m), 935 (s), 740 cm^{-1} (s); nmr ($CDCl_3$) δ 8.07–7.90 (m, 1, C_3 H), 7.50–7.10 (m, 3, C_4, C_5, C_6 H's), 3.26 (dd, 1, $J_{C_{1a}-C_{1x}}$ = 8 Hz, $J_{C_{1a}-C_{1y}}$ = 7 Hz, C_{1a} H), 2.25 (dd, 1, $J_{C_{1x}-C_{1a}}$ = 8 Hz, $J_{C_{1x}-C_{1y}}$ = 7.5 Hz, C_1 H_x), 1.79 (t, 1, $J_{C_{1y}-C_{1x}}$ = $J_{C_{1y}-C_{1a}}$ = 7 Hz, C_1H_y); mass spectrum (70 eV) *m/e* (rel intensity) 256 (20), 254 (20) [254/256 intensity ratio 0.97], 175 (100), 147 (100), 108 (32), 103 (20).

Thin layer chromatography of the red oil using benzene and benzene–ethanol (17:3) as eluents showed only one component present. Although **30** was obtained as a low-melting solid, mp 39–42°, elemental analysis was performed on the sulfone derivative (see below).

Compound **30** was also prepared from *cis*-4-bromo-2-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one[1] using the above procedure.

7a-Bromocyclopropa[*b*][1]benzothiopyran-7-one 2,2-Dioxide (32).—Using the procedure described for the preparation of **31**, the oxidation of 7a-bromocyclopropa[*b*][1]benzothiopyran-7-one (0.55 g, 2.16 mmol) with *m*-chloroperbenzoic acid (0.85 g, 4.97 mmol) gave, after crystallization from 95% ethanol, 0.60 g (97%) of 7a-bromocyclopropa[*b*][1]benzothiopyran-7-one 2,2-dioxide: mp 187.5–189.5°; ir (KBr) 1690 (>C=O), 1300 and 1150 cm^{-1} (>SO_2); nmr (DMSO-d_6),[19] δ 8.05 (s, 4, aromatic H's), 4.97 (t, 1, *J* = 8 Hz, C_{1a} H), 2.55 (m, 2, methylene bridge hydrogens, C_1 H's, appear in the same region as the solvent; subtracting the contribution of the solvent gave the correct integration for 2 H's).

Anal. Calcd for $C_{10}H_7BrO_2S$: C, 41.83; H, 2.46; Br, 27.83. Found: C, 41.50; H, 2.41; Br, 27.68.

5-Acetoxy-2,4-dichloro-2,3-dihydro-1-benzothiepin (34).—A solution of *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one[1] (1.00 g, 4.05 mmol), acetic anhydride (25 ml), and pyridine (4 ml) was allowed to stand at room temperature for 90 min, warmed on a steam bath for 30 min, cooled, and poured onto crushed ice. The resulting oil was extracted into $CHCl_3$ (60 ml); the extract was neutralized with 10% $NaHCO_3$ solution, washed with H_2O, and dried (Na_2SO_4). The solvent was removed under vacuum and gave 0.85 g (75%) of 5-acetoxy-2,4-dichloro-2,3-dihydro-1-benzothiepin as a reddish oil: ir (neat) 3065 (w), 1775 (s, >C=O), 1645 (m), 1370 (m), 1185 (broad, strong), 940 (m), 755 cm^{-1} (s); nmr ($CDCl_3$) δ 7.72–7.22 (m, 4, aromatic H's), 5.97 (dd, 1, $J_{C_2-C_{3a}}$ = 5.5 Hz, $J_{C_2-C_{3b}}$ = 11 Hz, –SCHCl–), 3.11 (dd, 1, $J_{C_{3a}-C_2}$ = 5.5 Hz, $J_{C_{3a}-C_{3b}}$ = 14.5 Hz, –SCHClCH_aH_b–), 2.68 (dd, 1, $J_{C_{3b}-C_2}$ = 11 Hz, $J_{C_{3b}-C_{3a}}$ = 14.5 Hz, –SCHClCH_aH_b–); mass spectrum (70 eV) *m/e* (rel intensity) 289 (2), 254 (3), 212 (16), 185 (100), 176 (17), 164 (17), 148 (40).

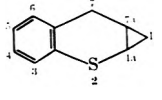
Thin layer chromatography of this oil using benzene, benzene–ethanol (17:3), and $CHCl_3$ as eluents indicated only one component. Elemental analysis was performed on the corresponding sulfone (see below).

5-Acetoxy-2,4-dichloro-2,3-dihydro-1-benzothiepin 1,1-Dioxide (35). Method A.—Employing the procedure described for the preparation of **31**, the oxidation of 5-acetoxy-2,4-dichloro-2,3-dihydro-1-benzothiepin (0.65 g, 2.24 mmol) with *m*-chloroperbenzoic acid (1.15 g, 6.67 mmol) in $CHCl_3$ (12 ml) gave, after crystallization from 95% ethanol, 0.31 g (41%) of 5-acetoxy-2,4-dichloro-2,3-dihydro-1-benzothiepin 1,1-dioxide: mp 147–148°; ir (KBr) 1770 (>C=O), 1330, and 1130 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 8.13–7.98 (m, 1, C_9 H), 7.68–7.30 (m, 3, C_6, C_7, C_8 H's), 5.30 (dd, 1, $J_{C_2-C_{3a}}$ = 5.5 Hz, $J_{C_2-C_{3b}}$ = 9 Hz, –SO_2CHCl–), 3.26 [dd, 1+ (overlaps with C_{3b} H), $J_{C_{3a}-C_2}$ = 5.5 Hz, $J_{C_{3a}-C_{3b}}$ = 14.5 Hz, –SO_2CHClCH_aH_b–], 2.94 [dd, 1+ (overlaps with C_{3a} H), $J_{C_{3b}-C_2}$ = 9 Hz, $J_{C_{3b}-C_{3a}}$ = 15 Hz, –SO_2CHClCH_aH_b–], 2.28 (s, 3, –O_2CCH_3).

Anal. Calcd for $C_{12}H_{10}Cl_2O_4S$: C, 44.88; H, 3.14; Cl, 22.08. Found: C, 44.57; H, 3.28; Cl, 22.33.

Method B.—A solution of *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide[1] (0.40 g, 1.43 mmol), acetic anhydride (18 ml), and pyridine (4 ml) was allowed to stand at room temperature for 50 min and the resulting yellow solution was poured onto ice. An oil separated, slowly solidified, and was collected, and recrystallization from 95% ethanol gave 0.40 g (90%) of **35**, mp 147–148.5°.

(19) For the numbering of **28** and related compounds see A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd ed, American Chemical Society, Washington, D. C., 1960, p 275.



In a second experiment *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide[1] (0.20 g, 0.72 mmol), acetic anhydride (12 ml), and pyridine (3 ml) were processed as above and gave 0.9 g (85%) of **35**, mp 147–148°. The ir and nmr spectra of these two samples were identical with those of **35** from method A.

5-Acetoxy-4-chloro-2,3-dihydro-1-benzothiepin 1,1-Dioxide (37).—A solution of 4-chloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide[1] (0.50 g, 2.04 mmol) in acetic anhydride (15 ml) and pyridine (4 ml) was allowed to stand at room temperature for 9 hr and poured onto crushed ice. An oil separated and slowly solidified upon stirring. Recrystallization of the solid from 95% ethanol gave 0.46 g (80%) of 5-acetoxy-4-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide: mp 147.5–149°; ir (KBr) 1770 (>C=O), 1305, and 1120 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 8.27–8.10 (m, 1, C_9 H), 7.78–7.33 (m, 3, C_6, C_7, C_8 H's), 3.85 (t, 2, J = 7 Hz, $-SO_2CH_2CH_2-$), 2.94 (t, 2, J = 7 Hz, $-SO_2CH_2-CH_2-$), 2.30 (s, 3, $-O_2CCH_3$).

Anal. Calcd for $C_{12}H_{11}ClO_4S$: C, 50.27; H, 3.87; Cl, 12.37. Found: C, 50.36; H, 3.93; Cl, 12.21.

5-Acetoxy-4-bromo-2,3-dihydro-1-benzothiepin 1,1-Dioxide (38).—Using the preceding procedure 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide[1] (1.00 g, 3.50 mmol), acetic anhydride (20 ml), and pyridine (4 ml) were allowed to react at room temperature for 12 hr and gave, after recrystallization from 95% ethanol, 0.77 g (66%) of 5-acetoxy-4-bromo-2,3-dihydro-1-benzothiepin 1,1-dioxide: mp 161–162°; ir (KBr) 1775 (>C=O), 1640 (strong), 1300, 1170, and 1120 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 8.21–8.05 (m, 1, C_9 H), 7.73–7.40 (m, 3, C_6, C_7, C_8 H's), 3.83 (t, 2, J = 6 Hz, $-SO_2CH_2CH_2-$), 3.01 (t, 2, J = 6 Hz, $-SO_2CH_2CH_2-$), 2.29 (s, 3, $-O_2CCH_3$).

Anal. Calcd for $C_{12}H_{11}BrO_4S$: C, 43.52; H, 3.35; Br, 24.13. Found: C, 43.75; H, 3.38; Br, 24.11.

Reaction of 3,4-Dihydro-1-benzothiepin-5(2*H*)-one 1,1-Dioxide with Acetic Anhydride and Pyridine.—A solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide[18] (1.00 g), acetic anhydride (20 ml), and pyridine (5 ml) was warmed on a steam bath for 30 min and allowed to stand at room temperature for 28 hr. After the reaction solution was poured onto crushed ice and the colorless oil solidified, recrystallization of the solid gave 0.90 g (90%) of recovered starting material, mp 155–156°; its mixture melting point with starting material was not depressed and its ir spectrum was identical with that of an authentic sample.

When 3,4-dihydro-1-benzothiepin-5(2*H*)-one[18] and 4-bromo-3,4-dihydro-1-benzothiepin-5(2*H*)-one[1] were treated as above, no enol acetates were isolated, and only starting material was recovered.

4-Chloro-2,5-diacetoxy-2,3-dihydro-1-benzothiepin (39).—After a solution of 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one (1.30, 6.20 mmol) and a catalytic amount of *p*-toluenesulfonic acid in acetic anhydride (15 ml) was warmed on a steam bath for 5 min and allowed to remain at room temperature for 75 min, the reaction mixture was poured onto ice and the oil, which separated, slowly solidified to give a brown solid, mp 89–93°. Recrystallization of the brown solid from 95% ethanol gave 1.73 g (90%) of 4-chloro-2,5-diacetoxy-2,3-dihydro-1-benzothiepin: mp 104–105°; ir (neat) 3030 (w), 1775 (>C=O), 1750 (>C=O), 1650 (w), 1470 (s), 1200 (broad, strong), 1015 (s), 870 (m), 755 cm^{-1} (s); nmr ($CDCl_3$) δ 7.75–7.40 (m, 4, aromatic H's), 6.67 [dd, 1, $J_{C_2-C_{3a}}$ = 6 Hz, $J_{C_2-C_{3a}}$ = 11 Hz, $-SCH(OAc)CH_aH_b-$], 2.93 [dd, 1+ (overlaps with C_{3b} H), $J_{C_{3a}-C_2}$ = 6 Hz, $J_{C_{3a}-C_{3b}}$ = 14.5 Hz, $-SCH(OAc)CH_aH_b-$], 2.60 [dd, 1+ (overlaps with C_{3a} H), $J_{C_{3b}-C_2}$ = 11 Hz, $J_{C_{3b}-C_{3a}}$ = 14.5 Hz, $-SCH(OAc)CH_aH_b-$].

Anal. Calcd for $C_{14}H_{13}ClO_4S$: C, 53.76; H, 4.19; O, 20.46. Found: C, 53.48; H, 4.34; O, 20.48.

7a-Chloro-7-hydroxycyclopropa[*b*][1]benzothiopyran (41).—7a-Chlorocyclopropa[*b*][1]benzothiopyran-7-one (4.00 g, 19 mmol) in 95% ethanol (20 ml) was added over a 10-min period with stirring to a slurry of sodium borohydride (0.72 g, 20 mmol) in 95% ethanol (14 ml) and the reaction mixture was heated in an oil bath at 75° for 30 min and stirred at room temperature for 1 hr. The reaction mixture was poured onto an ice–hydrochloric acid mixture, the resulting oil was extracted into $CHCl_3$ (2 × 70 ml), and the extract was washed with H_2O and dried ($MgSO_4$). The solvent was evaporated under vacuum and gave 3.59 g (89%) of 7a-chloro-7-hydroxycyclopropa[*b*][1]benzothiopyran as a colorless oil: ir (neat) 3410 (broad, strong, –OH), 3070 (w), 1590 (m), 1129 (s), 1035 (s), 910 (m), 755 cm^{-1} (s); nmr ($CDCl_3$)[19] δ 7.83–7.09 (m, 4, aromatic H's), 5.02 (s, 1, –CHOH), 3.30 (s, 1, –CHOH), 2.60 (dd, 1, $J_{C_{1a}-C_{1x}}$ = 7 Hz, $J_{C_{1a}-C_{1y}}$ = 7.5 Hz, C_{1a} H), 1.26 [d, 2 (combined value of both C_{1x} H and C_{1y} H, a doublet with shoulders), $J_{C_{1x}-C_{1a}}$ = 7 Hz, C_1 H_x], 1.24 [d, 2 (combined value of both C_{1x} H and C_{1y} H), $J_{C_{1y}-C_{1a}}$ = 7.5 Hz, C_1 H_y]; mass spectrum (70 eV) *m/e* (rel intensity) 212 (38), 195 (52), 177 (67), 175 (42), 163 (38), 147 (100), 134 (48).

Thin layer chromatography of this oil using benzene and benzene–ethanol (9:1) as eluents indicated only one compound. Elemental analysis was performed on the corresponding sulfone (see below).

7a-Chloro-7-hydroxycyclopropa[*b*][1]benzothiopyran 2,2-Dioxide (42).—Using the procedure described for the preparation of **31**, the oxidation of 7a-chloro-7-hydroxycyclopropa[*b*][1]benzothiopyran (1.00 g, 5.0 mmol) with *m*-chloroperbenzoic acid (1.86 g, 11 mmol) in $CHCl_3$ (23 ml) over a 12-hr period gave, after recrystallization from 95% ethanol, 0.90 g (80%) of 7a-chloro-7-hydroxycyclopropa[*b*][1]benzothiopyran 2,2-dioxide: mp 122–123°; ir (KBr) 3440 (broad, strong, OH), 1300, 1160, and 1110 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 7.92–7.45 (m, 4, aromatic H's), 5.37 (d, 1, J = 5 Hz, –CHOH), 3.69 (d, 1, J = 5 Hz, –CHOH), 3.20 (dd, 1, $J_{C_{1a}-C_{1x}}$ = 6.5 Hz, $J_{C_{1a}-C_{1y}}$ = 9.0 Hz, C_{1a} H), 1.75–1.10 (m, 2, C_1 H_xH_y).

Anal. Calcd for $C_{10}H_9ClO_3S$: C, 49.08; H, 3.77; O, 19.61. Found: C, 49.12; H, 3.67; O, 19.57.

2-Acetoxy-4-chloro-2,3-dihydro-1-benzothiepin (43).—After a solution of 7a-chloro-7-hydroxycyclopropa[*b*][1]benzothiopyran (1.00 g, 4.70 mmol) and *p*-toluenesulfonic acid (0.85 g, 4.75 mmol) in acetic anhydride (10 ml) was warmed on a steam bath for 10 min and cooled, the reaction mixture was poured onto crushed ice and the oil was extracted with $CHCl_3$ (35 ml). The $CHCl_3$ extract was washed with 5% $NaHCO_3$ solution and H_2O and dried ($MgSO_4$) and, after the solvent was removed under vacuum, gave 1.00 g (84%) of 2-acetoxy-4-chloro-2,3-dihydro-1-benzothiepin as a yellow oil: ir (neat) 3060 (w), 1750 (>C=O), 1635 (m), 1730 (m), 1220 (s), 950 (m), 750 cm^{-1} (m); nmr ($CDCl_3$) δ 7.72–7.10 (m, 4, aromatic H's), 6.86 (s, 1, C_5 H), 6.52 (dd, 1, $J_{C_2-C_{3a}}$ = 7 Hz, $J_{C_2-C_{3b}}$ = 9 Hz, –SCHOAc), 2.80 [d, 2 (overlap of C_{3a} H and C_{3b} H), J = 7 Hz, $-SCH(OAc)CH_aH_b-$], 2.78 [d, 2 (overlap of C_{3a} H and C_{3b} H), J = 9 Hz, $-SCH(OA)-CH_aH_b-$], 2.04 (s, 3, $-O_2CCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 254 (4.1), 193 (39), 175 (19), 167 (19), 158 (19), 145 (100), 133 (24).

Elemental analysis was performed on the sulfone derivative (see following experiment).

2-Acetoxy-4-chloro-2,3-dihydro-1-benzothiepin 1,1-Dioxide (44).—Employing the procedure described for the preparation of **31**, the oxidation of 2-acetoxy-4-chloro-2,3-dihydro-1-benzothiepin (0.75 g, 2.95 mmol) with *m*-chloroperbenzoic acid (1.17 g, 6.78 mmol), after reaction overnight, gave after crystallization from 95% ethanol 0.65 g (82%) of 2-acetoxy-4-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide: mp 163–165°; ir (KBr) 1770 (>C=O), 1375, 1300, 1200, 1150 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 8.13–8.08 (m, 1, C_9 H), 7.83–7.31 (m, 3, C_6, C_7, C_8 H's), 6.98 (s, 1, C_5 H), 6.19 [t, 1, J = 7 Hz, $-SO_2CH(OAc)CH_2-$], 3.22 [d, 2, J = 7 Hz, $-SO_2CH(OAc)CH_2-$], 2.08 (s, 3, O_2CCH_3).

Anal. Calcd for $C_{12}H_{11}ClO_4S$: C, 50.26; H, 3.86; O, 22.32. Found: C, 50.43; H, 3.90; O, 22.16.

2,4-Dichloro-2,3-dihydro-1-benzothiepin (45).—HCl gas was bubbled into a solution of 7a-chloro-7-hydroxycyclopropa[*b*][1]-benzothiopyran (1.00 g, 4.72 mmol) in $CHCl_3$ (5 ml) for 5 min at room temperature. After addition of $CHCl_3$ (15 ml) to the reaction mixture, the excess HCl was removed from the solution under a stream of nitrogen and the $CHCl_3$ solution was dried ($MgSO_4$). The solvent was removed under vacuum and gave 1.00 g (92%) of 2,4-dichloro-2,3-dihydro-1-benzothiepin: mp 55–57°; ir ($CHCl_3$) 3070 (w), 3010 (w), 1630 (s), 1470 (s), 1280 (m), 1174 (m), 1030 (s), 850 cm^{-1} (m); nmr ($CDCl_3$) δ 7.67–7.03 (m, 4, aromatic H's), 6.80 (s, 1, C_5 H), 5.75 (dd, 1, $J_{C_2-C_{3a}}$ = 6 Hz, $J_{C_2-C_{3b}}$ = 10 Hz, $-SCHClCH_aH_b-$), 3.03 [d, 2 (overlap of C_{3a} H and C_{3b} H), J = 6 Hz, $-SCHClCH_aH_b-$], 2.99 [d, 2 (overlap of C_{3a} H and C_{3b} H), J = 10 Hz, $-SCHClCH_aH_b-$]; mass spectrum (70 eV) *m/e* (rel intensity) 230 (11), 196 (38), 169 (100), 160 (51), 148 (64), 135 (64), 116 (83).

Attempts to recrystallize **45** from a variety of solvent systems led to an oil. Elemental analysis was obtained for its sulfone derivative (see following experiment).

2,4-Dichloro-2,3-dihydro-1-benzothiepin 1,1-Dioxide (46).—Using the procedure described for the preparation of **31**, the oxidation of 2,4-dichloro-2,3-dihydro-1-benzothiepin (0.50 g, 2.16 mmol) by *m*-chloroperbenzoic acid (0.86 g, 5.00 mmol) over

a 20-hr period gave, after recrystallization from 95% ethanol, 0.48 g (85%) of 2,4-dichloro-2,3-dihydro-1-benzothiepin 1,1-dioxide: mp 187–188.5°; ir ($CHCl_3$) 1635 (m), 1325, and 1150 cm^{-1} (>SO_2); nmr ($CDCl_3$) δ 8.38–8.24 (m, 1, C_9 H), 7.93–7.37 (m, 3, C_6, C_7, C_8 H's), 7.05 (s, 1, C_5 H), 5.22 (t, 1, J = 5 Hz, $-SO_2CHClCH_aH_b-$), 3.83 (dd, 1, $J_{C_{3a}-C_2}$ = 5 Hz, $J_{C_{3a}-C_{3b}}$ = 19 Hz, $-SOCHClCH_aH_b-$), 3.33 (dd, 1, $J_{C_{3b}-C_2}$ = 5.5 Hz, $J_{C_{3b}-C_{3a}}$ = 19 Hz, $-SO_2CHClCH_aH_b-$).

Anal. Calcd for $C_{10}H_8Cl_2O_2S$: C, 45.64; H, 3.06; Cl, 26.95; O, 12.16. Found: C, 45.51; H, 3.18; Cl, 26.67; O, 12.21.

Registry No.—**15**, 21609-70-1; **16**, 19373-31-0; **17**, 14171-33-6; **18**, 40322-44-9; **19**, 40322-45-0; **20**, 40322-46-1; **21**, 40322-47-2; **22**, 40322-48-3; **23**, 40322-49-4; **24**, 40322-50-7; **25**, 40322-51-8; **26**, 22710-97-0; **27a**, 40322-28-9; **27b**, 40322-29-0; **28**, 40322-30-3; **29a**, 40322-33-6; **29b**, 40322-34-7; **30**, 40322-58-5; **31**, 40322-59-6; **32**, 40322-60-9; **34**, 40322-61-0; **35**, 40322-62-1; **36** (X = Cl), 40322-63-2; **36** (X = Br), 21609-67-6; **37**, 40322-65-4; **38**, 40322-66-5; **39**, 40322-67-6; **41**, 40322-68-7; **42**, 40322-69-8; **43**, 40322-70-1; **44**, 40322-71-2; **45**, 40322-72-3; **46**, 40322-73-4; dimethylamine hydrochloride, 506-59-2; paraformaldehyde, 30525-89-4; isoamyl alcohol, 123-51-3; ethanol, 64-17-5; acetic acid, 64-19-7; formalin, 50-00-0; *tert*-butyl alcohol, 75-65-0; sodium hydroxide, 1310-73-2; benzaldehyde, 100-52-7; *p*-toluenesulfonic acid, 104-15-4; ozone, 10028-15-6; benzaldehyde 2,4-dinitrophenylhydrazone, 1157-84-2; ethyl formate, 109-94-4; morpholine, 110-91-8; triethylamine, 121-44-8; *m*-chloroperbenzoic acid, 937-14-14; acetic anhydride, 108-24-7; pyridine, 110-86-1; *cis*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide, 40322-31-4; *trans*-2,4-dichloro-3,4-dihydro-1-benzothiepin-5-(2*H*)-one 1,1-dioxide, 40322-32-5.

Synthesis of Thiabicyclo[2.2.2]octenes. Carbon-13 Nuclear Magnetic Resonance Spectra of Bicyclic Sulfides

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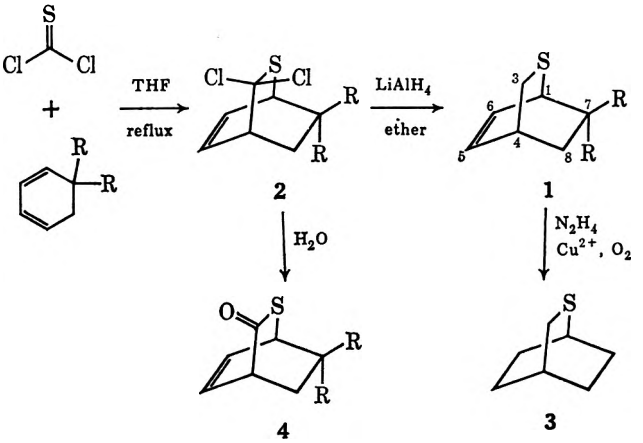
2-Thiabicyclo[2.2.2]oct-5-ene (**1a**) was synthesized by 1,4 addition of thiophosgene to 1,3-cyclohexadiene giving 3,3-dichloro-2-thiabicyclo[2.2.2]oct-5-ene (**2a**) followed by reduction with lithium aluminum hydride. 7,7-Dimethyl-2-thiabicyclo[2.2.2]oct-5-ene (**1b**) and 4,6,7,7-tetramethyl-2-thiabicyclo[2.2.2]oct-5-ene (**8**) were synthesized similarly from 5,5-dimethyl- and 1,3,5,5-tetramethyl-1,3-cyclohexadiene. Compound **1a** was characterized by diimide reduction to the known 2-thiabicyclo[2.2.2]octane which was shown not to be the photolysis product of 3-cyclohexenylmethanethiol (**5**) as previously reported. Compound **8** was characterized by oxidation to the sulfoxide **9** and sulfone **10**. Hydrolysis of the thiophosgene–cyclohexadiene adducts **2a**, **2b**, and **7** gave the corresponding δ-thiolactones **4a**, **4b**, and **12** (3-oxo-2-thiabicyclo[2.2.2]oct-5-enes). ^{13}C nmr was used to establish the structures of **1a**, **8**, **9**, **10**, and **12**.

Published synthetic approaches to the thiabicyclo[2.2.2]octene system have usually involved either cyclization of substituted cyclohexanes[1] or the cycloaddition of cyclohexadienes with thiocarbonyl compounds.[2] None of the reported syntheses is easily modified for the preparation of 2-thiabicyclo[2.2.2]-octene (**1a**) which we required for photochemical studies. In particular, reported examples of the latter method have involved substituted thiocarbonyl compounds (cyanothioformyl halides,[2a] perfluorinated thioketones,[2b] thiofluorenone,[2c] and thiobenzophenone[2d]) such that substituents are not easily replaced by hydrogen, and in any event have often proceeded in synthetically unattractive yields.

Middleton[2b] reported the cycloaddition of thiophosgene with cyclopentadiene to give 3,3-dichloro-2-thiabicyclo[2.2.1]hept-5-ene, and Johnson, Keiser, and Sharp[3] subsequently accomplished the reductive removal of the chlorine substituents, although only with difficulty and in low yield. The *S*-oxide of thiophosgene also undergoes cycloaddition with cyclopentadiene.[4] We have examined the reaction of thiophosgene with several cyclohexadienes and would like to report that this is a general route to the desired ring system, as well as to the saturated analog.

The reaction of cyclohexadiene with thiophosgene proceeded exothermically to give 3,3-dichloro-2-thiabicyclo[2.2.2]oct-5-ene (**2a**). Since the dichloride is moisture sensitive, reduction with lithium aluminum



(1) (a) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, **22**, 1590 (1957); (b) A. W. Weitkamp, *J. Amer. Chem. Soc.*, **81**, 3430 (1959); (c) J. Plešek, S. Heřmánek, and B. Štíbr, *Collect. Czech. Chem. Commun.*, **33**, 2336 (1968); (d) J.-M. Surzur, R. Nouguier, M.-P. Crozet, and C. Dupuy, *Tetrahedron Lett.*, 2035 (1971).

(2) (a) S. Proskow, U. S. Patent 3,026,304 (Mar 20, 1962); *Chem. Abstr.*, **58**, P11032*b* (1962); (b) W. J. Middleton, *J. Org. Chem.*, **30**, 1390 (1965); (c) A. Schoenberg and B. Koenig, *Tetrahedron Lett.*, 3361 (1965); (f) Y. Omote, M. Yoshioka, K. Yamada, and N. Sugiyama, *J. Org. Chem.*, **32**, 3676 (1967).

(3) C. R. Johnson, J. E. Keiser, and J. C. Sharp, *ibid.*, **34**, 860 (1969).

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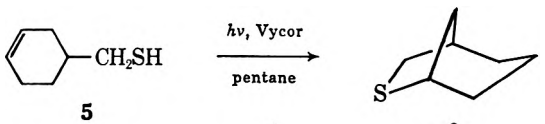
hydride[5] to give **1a** was best carried out on the crude product, and resulted in 45% yield overall from cyclohexadiene. The spectral data for **1a** and **2a** were as anticipated, with the possible exception of the CH_2–S geminal coupling constant of 7.5 Hz in **1a**. Geminal coupling for such protons in thiabicyclo-[2.2.1]heptanes of 9 Hz has been reported,[3] and Liberatore, *et al.*, have reported a 9.5-Hz geminal coupling in a complex 2-azabicyclo[2.2.2]octene.[6]

Compound **1a** was further characterized by diimide reduction to the known saturated sulfide **3**, which had identical melting point and ir spectrum with those given by Birch, *et al.*[1a] Our nmr spectrum of **3** did not match that reported for the product of photocyclization of 3-cyclohexenylmethanethiol (**5**) to which Surzur, *et al.*,[1d] also had assigned structure **3**. Unambiguous proof of the correctness of our structural assignment for the reduction product of **1a** was provided by the ^{13}C nmr spectrum, which gave only five peaks [δ^{TMS} ($CDCl_3$)[7] 23.2, d; 24.5, t; 29.3, t; 30.33; 30.37] in a 1:2:2:1:1 ratio as required for the symmetric structure. We have repeated the photolysis of **5** and find that it leads to a compound with the nmr spectrum reported,[1d] but with the ir and melting point identical with those of 6-thiabicyclo[3.2.1]octane[1a] (**6**). The ^{13}C nmr spec-



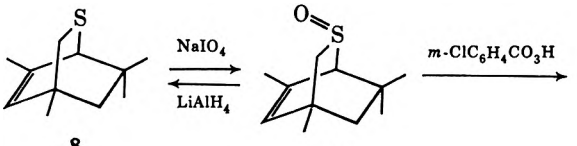
5 **6**

trum has seven resonances [δ^{TMS} ($CDCl_3$)[7] 18.5, t; 32.0, t; 33.5, t; 35.7, t; 36.9, d; 42.9, t; 45.7, d] supporting this assignment and conclusively ruling out structure **3**. The photolysis of **5** leads to no detectable formation of **3** (2% would have been observed).

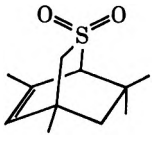
Chromatography on silica gel converted **2a** into the thiolactone **4a**, which was characterized by the nmr spectrum and ir carbonyl frequency of 1680 cm^{-1},[8] as well as by a major mass spectral fragmentation involving loss of COS (*m/e* 80, base peak).

Substituted cyclohexadienes are also accessible by this route. 5,5-Dimethylcyclohexadiene[9] forms with thiophosgene the adduct **2b**. This compound could be reduced to **1b** or hydrolyzed to the thiolactone **4b**. The orientation of the cycloaddition is shown by the nmr spectra of the thiolactone and of the sulfoxide prepared by sodium metaperiodate oxidation of **1b**. The bridgehead protons of both compounds appear as a broad triplet [H_4, for **4b**: δ (CCl_4) 3.44; decoupling experiments showed $J_{4,5}$ = 6 Hz, $J_{4,6}$ = 1.5 Hz, $J_{4,8}$ = 4 Hz, and $J_{4,8'}$ = 2 Hz] and a broad doublet [H_1, for **4b**: δ (CCl_4) 3.59, $J_{1,6}$ = 6 Hz, $J_{1,5}$ = 2 Hz] which must be the bridgehead proton next to the *gem*-dimethyl group. In the presence of shift reagent [Eu(fod)$_3$] the broad triplet resonance is shifted downfield about three times as far as the doublet resonance in the thiolactone, whereas the reverse is true for the sulfoxide. Since complexation occurs at carbonyl oxygen in the thiolactone[10] and at sulfoxide oxygen in the sulfoxide, the cycloadducts of 5,5-dimethylcyclohexadiene must have the orientation shown.

1,3,5,5-Tetramethylcyclohexadiene[11] reacted with thiophosgene to give the cycloadduct **7**, which could be reduced to **8**. Apart from the allylic and vinyl protons, all of the pmr absorptions of **8** fall in the region δ 0.8–



8 **9**



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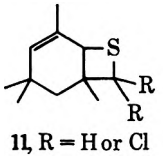
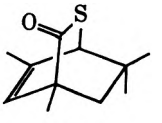
1.3, including the methylene group next to sulfur, which is normally found near 2.5. The CH_2–S protons are shifted to lower field in the corresponding sulfoxide **9** (which gives a broadened AB quartet at δ 1.69 and 2.98) and the sulfone **10** (singlet at δ 2.58), although these shifts are still at somewhat higher field than normal. We have no rationale for the unusual CH_2–S chemical shift of **8**, particularly in view of the fact that **1a** (2.42, H-syn; 2.91, H-anti) and **1b** (2.34, H-syn; 2.81, H-anti) show normal shifts for these protons. We have been unable to devise another structure to better fit the spectroscopic and chemical data. The only reasonable grouping which could be expected to give upfield shifts of this magnitude is a thiirane. Thiiranes are reduced by lithium aluminum hydride[12] and the ability to prepare **8** from **7** or the sulfoxide **9** rules out the presence of such a function in these compounds. Furthermore, the sulfone **10** is stable to at least 190°, whereas thiirane *S,S*-dioxides usually decompose near room temperature.[13]

A thietane structure for **7** and **8** (*e.g.*, **11**, the product of a [$2_\pi + 2_\pi$] cycloaddition) can be ruled out by considering the hydrolysis product **12**, which is formed



11, R = H or Cl



12

from **7** under both basic (aqueous pyridine) and acidic (chromatography on silica gel) conditions. The compound has a carbonyl frequency (1680 cm^{-1}) identical with that of **4a** and **4b**, for which there is little doubt

(5) Other reducing agents such as $NaBH_4$ in ethylene glycol [H. C. Brown and H. M. Bell, *J. Org. Chem.*, **27**, 1928 (1962)], diglyme, and dimethyl sulfoxide did not give the desired product.

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(7) The multiplicities reported for the ^{13}C nmr peaks were determined by single frequency off-resonance decoupling. Chemical shifts were measured using noise-modulated decoupling: R. A. Archer, R. D. G. Cooper, and P. V. Demarco, *Chem. Commun.*, 1291 (1970).

(8) Monocyclic δ-thiolactones absorb near 1665 cm^{-1}: F. Korte and H. Christoph, *Chem. Ber.*, **94**, 1966 (1961).

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(11) M. S. Kharasch and P. O. Tawney, *J. Amer. Chem. Soc.*, **63**, 2308 (1941). A mixture of exo- and endocyclic dienes was used; these apparently equilibrated during the cycloaddition.

(12) M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 1042 (1952); D. A. Lightner and C. Djerassi, *Chem. Ind. (London)*, 1236 (1962).

(13) F. G. Bordwell, J. M. Williams, Jr., E. B. Hoyt, Jr., and B. B. Jarvis, *J. Amer. Chem. Soc.*, **90**, 429 (1968).

about the structure. β-Thiolactones are reported to have carbonyl frequencies near 1775 cm^{-1}.[14]

The ^{13}C nmr spectra (Table I) clearly require the presence of two carbons bonded to sulfur, since these

TABLE I

CARBON-13 NMR CHEMICAL SHIFTS[a] OF 2-THIABICYCLO[2.2.2]OCTENES

Compd	C_1	C_2	C_4	C_5	C_6	C_7	C_8
1a	32.7 d[b]	33.4 t	29.1 d	131.5 d*	134.5 d*	30.3 t**	23.3 t**
8[d]	50.8 d	39.5 t	37.1 s*	127.0 d	142.7 s	36.1 s*	48.0 t
9[d]	68.3 d	61.1 dd[c]	36.3 s*	129.3 d	135.6 s	34.0 s*	47.2 t
10[d]	70.0 d	59.6 t	37.3 s*	129.0 d	138.7 s	36.1 s*	46.8 t
12[d]	59.1 d	*e*	53.2 s	126.3 d	146.5 s	37.5 s	46.4 t

[a] Chemical shifts reported downfield from TMS. Assignments for peak positions marked with an asterisk may be reversed. [b] See ref 7. [c] A doublet of doublets is observed for the C-3 methylene of **7** because of the large chemical shift difference between the geminal protons, resulting in different residual C–H couplings. [d] Methyl quartets at (**8**) 21.0, 26.6, 30.0, 30.8; (**9**) 24.8, 25.5, 28.8, 32.1; (**10**) 22.5, 25.6, 29.1, 31.9; (**12**) 19.9, 21.5, 30.1, 31.0. [e] Not observed.

are shifted strongly downfield as the sulfur is oxidized. The downfield shifted carbons in **8**, **9**, and **10** were shown to be a methyne and methylene by single frequency off-resonance decoupling,[7] thus demonstrating that the orientation of the cycloaddition must be as depicted. This is supported by the δ-thiolactone (**12**) ^{13}C shifts, where a quaternary carbon (C-4) is shifted downfield.

Only one cycloaddition product was observed in each case, but the isolated adducts may not be the result of kinetic control. The orientation of the cycloaddition for 5,5-dimethyl- and 1,3,5,5-tetramethylcyclohexadienes can be explained as a result of steric control by the *gem*-dimethyl group, although for the latter compound electrophilic attack by sulfur also can be used to rationalize the observed mode of addition.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian XL-100, Varian A-60A, or Jeol MH-100 spectrometer. Carbon-13 (Fourier transform) nmr spectra were measured on the XL-100 system using noise modulated proton decoupling. Infrared spectra were obtained on a Beckman IR-8 spectrophotometer, and mass spectra on an AEI MS-902 spectrometer.

3,3-Dichloro-2-thiabicyclo[2.2.2]oct-5-ene (2a).—To a refluxing solution of 0.80 g (10 mmol) of 1,3-cyclohexadiene in 5 ml of pentane under nitrogen was added in one portion 0.76 ml (10 mmol) of thiophosgene. This mixture was refluxed for 2 hr and cooled to Dry Ice temperature. The orange liquid was decanted, and the pale yellow precipitate was recrystallized four times from pentane at −78° to give 0.98 g (50%) of a white, waxy, odiferous, hydrolysis-sensitive solid: mp 98–100°; nmr δ (CCl_4) 1.0–2.5 (m, 4 H), 3.4–3.9 (m, 2 H), 6.5 (td, J = 9, 2 Hz, 1 H), 6.65 (td, J = 8, 1.2 Hz, 1 H).

Anal. Calcd for $C_7H_8Cl_2S$: *m/e* 193.97238. Found: *m/e* 193.97160.

2-Thiabicyclo[2.2.2]oct-5-ene (1a).—To a solution of 5.9 g (73.5 mmol) of 1,3-cyclohexadiene in 50 ml of dry tetrahydrofuran heated to 35° was added dropwise 5.6 ml (73 mmol) of thiophosgene. The mixture was refluxed for 1 hr, and unreacted starting materials were removed by evaporating the solution to two-thirds its volume in a stream of N_2. The remaining tetrahydrofuran solution of the adduct was added dropwise with stirring to a slurry of 4 g (105 mmol) of $LiAlH_4$ in 400 ml of ether over a period of 1 hr. The reduction mixture was refluxed an additional 30 min, cooled, and quenched with saturated NH_4Cl solution. The ether layer was decanted, washed with 10% KOH solution, washed with water, and dried (Na_2SO_4). The ether was evaporated and the white solid residue was sublimed to give 4.2 g (45%) of white waxy crystals: mp 138–141° (mp 142–143° after gc purification); nmr δ (CCl_4) 1.2–1.8 (m, 3 H), 2.0 (m, 1 H), 2.42 (m, H-3-syn), 2.91 (d, J = 7.5 Hz, H-3-anti), 2.94 (m, H-4), 3.31 (m, H-1), 6.12 (td, J = 7, 1 Hz, H-5), 6.46 (td, J = 7, 1 Hz, H-6). (The spectrum of 3,3-dideuterio-**1a** (prepared by reduction of **2a** with $LiAlD_4$) and homonuclear decoupling experiments on **1a** confirm the above assignments and following couplings: $J_{5,6} = J_{4,5} = J_{1,6} = 7$ Hz, $J_{1,5} = J_{4,6} = 1$ Hz, $J_{3s,3a} = 7.5$ Hz, $J_{3s,4} = J_{3s,8} = 2$ Hz); mass spectrum *m/e* (rel intensity) 126 (55), 98 (35), 97 (30), 80 (85), 79 (100), 78 (30), 77 (35); ir (CCl_4) 3020, 2920, 2860, 1680 (w), 850 cm^{-1}.

Anal. Calcd for $C_7H_{10}S$: C, 66.61; H, 7.99. Found: C, 66.50; H, 7.81.

2-Thiabicyclo[2.2.2]octane (3).—To 1.0 g (7.8 mmol) of **1a** in 10 ml of absolute ethanol was added 4 g (80 mmol) of 100% hydrazine hydrate and a small amount of $CuSO_4$.[15] Oxygen was bubbled through the solution for 3 hr. The solution was filtered, diluted with 10 ml of water, and extracted with 2 × 10 ml of pentane. The pentane solution was washed twice with 10 ml of water and dried ($MgSO_4$). Evaporation gave 0.50 g (49%) of waxy solid: mp 200–205° (208–209° after sublimation; lit.[1a] 210–212°); nmr δ (CCl_4) 1.77 (m, 4 H), 1.92 (m, 3 H), 2.01 (m, 2 H), 2.45 (m, 1 H), 2.70 (d, J = 3 Hz, 2 H).

3-Oxo-2-thiabicyclo[2.2.2]oct-5-ene (4a).—A CCl_4 solution of **2a** prepared by refluxing 160 mg (2 mmol) of 1,3-cyclohexadiene with 0.15 ml (2 mmol) of thiophosgene for 1 hr and reducing the resulting mixture to one-half its volume in a stream of N_2 was hydrolyzed by preparative thin-layer silica gel chromatography. Sublimation gave 101 mg (36%) of colorless crystals: mp 65–67°; nmr δ (CCl_4) 1.5–2.4 (m, 4 H), 3.58 (m, 1 H), 4.15 (m, 1 H), 6.30 (td, J = 7.5, 2 Hz, 1 H), 6.67 (td, J = 7, 1.5 Hz, 1 H); ir (CCl_4) 3050 (w) 2960, 2940, 2870, 1680, 1615 (w) cm^{-1}.

Anal. Calcd for C_7H_8OS: *m/e* 140.02954. Found: *m/e* 140.02980.

7,7-Dimethyl-2-thiabicyclo[2.2.2]oct-5-ene (1b).—Using the method for preparing **1a**, 2.7 g (25 mmol) of 5,5-dimethyl-1,3-cyclohexadiene[9] and 1.9 ml (25 mmol) of thiophosgene on reduction with 1.9 g (50 mmol) of $LiAlH_4$ and purification by sublimation gave 1.2 g (31%) of solid **4a**: mp 60–63° (mp 67–68° after gc purification); nmr δ (CCl_4) 0.89 (s, 3 H), 1.25 (s, 3 H), 0.8–1.5 (m, 2 H), 2.34 (td, J = 9, 3 Hz, H-3-syn), 2.81 (dd, J = 9, 3 Hz, H-3-anti), 2.88 (d, J = 7 Hz, 1 H), 2.95 (m, 1 H), 6.07 (td, J = 7, 1 Hz, 1 H), 6.55 (br t, J = 7 Hz, 1 H).

Anal. Calcd for $C_9H_{14}S$: *m/e* 154.08162. Found: *m/e* 154.08168.

3-Oxo-7,7-dimethyl-2-thiabicyclo[2.2.2]oct-5-ene (4b).—The cycloadduct of 5,5-dimethyl-1,3-cyclohexadiene[9] (216 mg, 2 mmol) and thiophosgene (0.15 ml, 2 mmol) on hydrolysis by silica gel chromatography and purification by sublimation gave 112 mg (33%) **4b**: mp 106–109°; nmr δ (CCl_4) 1.11 (s, 3 H), 1.35 (s, 3 H), 1.49 (dd, J = 13.5, 4 Hz, 1 H), 1.87 (dd, J = 13.5, 2 Hz, 1 H), 3.44 (br t, J = 6 Hz, 1 H), 3.59 (br d, J = 6 Hz, 1 H), 6.26 (td, J = 7, 2 Hz, 1 H), 6.75 (td, J = 7, 1.5 Hz, 1 H); ir (CCl_4) 3070 (w), 2960, 2880, 1680, 1610 (w), 1380, 1360 cm^{-1}. Homonuclear decoupling experiments established the following couplings: $J_{1,6} = J_{4,5} = 6$ Hz, $J_{4,5} = 4$ Hz, $J_{1,5} = J_{4,5'} = 2$ Hz, $J_{4,6} = 1.5$ Hz, $J_{5,6} = 8$ Hz, $J_{8,5'} = 13.5$ Hz.

Anal. Calcd for $C_9H_{12}OS$: *m/e* 168.06082. Found: *m/e* 168.06095.

7,7-Dimethyl-2-thiabicyclo[2.2.2]oct-5-ene 2-Oxide.—By the method of Leonard and Johnson,[16] 154 mg (1 mmol) of **1b** gave on sublimation 141 mg (83%) of the sulfoxide: mp 125–127°; nmr δ (CCl_4) 0.98 (s, 3 H), 1.12 (s, 3 H), 0.8–1.6 (m, 2 H), 1.88 (br d, J = 13 Hz, 1 H), 3.1 (m, 1 H), 3.24 (dd, J = 13, 2.5 Hz, 1 H), 3.84 (br d, 6.5 Hz, 1 H), 6.18 (br t, 7 Hz, 1 H), 6.54 (br t, 7.5 Hz, 1 H).

Anal. Calcd for $C_9H_{14}OS$: *m/e* 170.07646. Found: *m/e* 170.07609.

4,6,7,7-Tetramethyl-2-thiabicyclo[2.2.2]oct-5-ene (8).—By the method used for the preparation of **1a**, 6.8 g (50 mmol) of 1,3,5,5-tetramethylcyclohexadiene[11] and 3.7 ml (48 mmol) of thiophosgene on reduction with 3.8 g (100 mmol) of $LiAlH_4$ gave after distillation [bp 68° (20 mm)] 3.0 g (33%) of **8**: nmr δ (CCl_4) 0.88 (s, 3 H), 1.18 (s, 3 H), 1.25 (s, 3 H), 0.8–1.3 (m, 4 H), 1.90 (d, J = 1.5 Hz, 3 H), 2.59 (m, 1 H), 5.42 (m, 1 H);

(14) P. Y. Johnson and G. A. Berchtold, *J. Org. Chem.*, **35**, 584 (1970).

(15) M. Ohno and M. Okamoto, *Org. Syn.*, **49**, 30 (1969).

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mass spectrum *m/e* (rel intensity) 182 (55), 136 (25), 126 (93), 121 (100), 111 (85).

Anal. Calcd for $C_{11}H_8S$: C, 72.46; H, 9.95. Found: C, 72.44; H, 10.01.

4,6,7,7-Tetramethyl-2-thiabicyclo[2.2.2]oct-5-ene 2-Oxide (9).—By the method of Leonard and Johnson,[16] 100 mg (0.55 mmol) of **8** gave 98 mg (90%) of colorless crystals from pentane (at −78°): mp 70–73°; nmr δ (CCl_4) 0.93 (s, 3 H), 1.05 (s, 3 H), 1.25 (s, 3 H), 0.85–1.3 (m, 2 H), 1.90 (d, J = 1.5 Hz, 3 H), 1.69 (br d, J = 13 Hz, 1 H), 2.98 (d, J = 13 Hz, 1 H), 3.52 (m, 1 H), 5.85 (m, 1 H).

Anal. Calcd for $C_{11}H_{18}OS$: *m/e* 198.10783. Found: *m/e* 198.10802.

A sample of **9** was reduced with $LiAlH_4$ in refluxing ether to give pure **8** by nmr comparison.

4,6,7,7-Tetramethyl-2-thiabicyclo[2.2.2]oct-5-ene 2,2-Dioxide (10).—Using the procedure of Johnson, Keiser, and Sharp,[3] 100 mg (0.55 mmol) of **8** gave 77 mg (65%) of colorless crystals from CCl_4: mp 116–118°; nmr δ (CCl_4) 0.98 (s, 3 H), 1.22 (s, 3 H), 1.43 (s, 3 H), 1.20 and 1.58 (ABq, J = 13.5 Hz, 2 H), 1.95 (d, J = 1.5 Hz, 3 H), 2.58 (br s, 2 H), 2.92 (br s, 1 H), 5.58 (m, 1 H).

Anal. Calcd for $C_{11}H_{18}O_2S$: *m/e* 214.10274. Found: *m/e* 214.10345.

3-Oxo-4,6,7,7-tetramethyl-2-thiabicyclo[2.2.2]oct-5-ene (12).—Compound **12** was prepared in 39% yield (155 mg) by the method used for **4a** and **4b** from the cycloadduct obtained from 272 mg (2 mmol) of 1,3,5,5-tetramethylcyclohexadiene[11] and 0.15 ml (2 mmol) of thiophosgene: mp 45–47° (48–49° after sublimation); nmr δ (CCl_4) 1.07 (s, 3 H), 1.21 (s, 3 H), 1.28 (d, J = 13 Hz, 1 H), 1.30 (s, 3 H), 1.68 (d, J = 13 Hz, 1 H), 1.95 (d, J = 1.5 Hz, 3 H), 3.12 (m, 1 H), 5.45 (m, 1 H); ir (CCl_4) 3030 (w), 2980, 2935, 2860, 1680, 1655 (sh), 1375, 1360 cm^{-1}.

Anal. Calcd for $C_{11}H_8OS$: C, 67.30; H, 8.22. Found: C, 67.46; H, 8.18.

Compound **12** was also obtained by basic hydrolysis (addition of pyridine followed by H_2O) of the diene–thiophosgene cycloadduct.

Registry No.—**1a**, 40168-94-3; **1b**, 40168-95-4; **1b** 2-oxide, 40317-79-1; **2a**, 40168-96-5; **3**, 280-41-1; **4a**, 40168-97-6; **4b**, 40168-98-7; **8**, 40168-99-8; **9**, 40169-00-4; **10**, 40169-01-5; **12**, 40169-02-6; 1,3-cyclohexadiene, 592-57-4; thiophosgene, 463-71-8; 5,5-dimethyl-1,3-cyclohexadiene, 33482-80-3; 1,3,5,5-tetramethylcyclohexadiene, 4724-89-4.

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Nuclear Magnetic Resonance Studies on *cis*-Bicyclo[3.3.0]oct-7-en-2-yl Derivatives. A Long-Range Magnetic Anisotropic Effect on Olefinic Protons by Endo Carbonyl Group

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Considerable chemical shift differences (Δτ 0.29–0.37) of olefinic protons were observed in the nmr of some esters of *endo-cis*-bicyclo[3.3.0]oct-7-en-2-ols, while the olefinic protons of the corresponding exo esters did not show such chemical shift differences. This difference was considered to result from a remote through-space magnetic anisotropic effect of the endo acyl residue; *i.e.*, the remote effect in the present system was attributable to the rigid structure of the bicyclo[3.3.0]octene skeleton which allowed the endo carbonyl group to move to the position in close proximity to H_8 and to cause the considerable deshielding effect on H_8 (and also the shielding effect on H_7 to some extent), but did not allow the exo carbonyl group to do so. The conformations of *exo*- and *endo-cis*-bicyclo[3.3.0]octan-2-ols, *exo*- and *endo*-bicyclo[3.3.0]octan-3-ols, and *exo*- and *endo-cis*-bicyclo[3.3.0]oct-7-en-2-ols were assigned as *W* and *S*, *W* and *W*, and *H-C* and *S* type, respectively, on the ground of the coupling constants of α proton to hydroxy group according to the Karplus equation.

In the previous report, we have discussed the conformations of *exo*- and *endo-cis*-bicyclo[3.3.0]oct-2- and -3-yl derivatives (hereafter abbreviated as the *exo*- and *endo-3.3.0*-2 and -3 derivatives, respectively) on the basis of the calculations of the shielding effects in nmr spectroscopy by means of McConnell's equation.[1] In the present manuscript, we wish to report the investigation of the nmr coupling pattern of the α proton to the hydroxyl group in the *3.3.0*-2-ols which is in accord with our previous conclusion.[1] We also wish to describe an interesting observation of chemical shift difference of olefinic protons of some esters of *endo-cis*-bicyclo-[3.3.0]oct-7-en-2-ol (hereafter abbreviated as the *endo-3.3.0*-7-en-2-ol, and so on). Such a difference was not observed in nmr of the *exo-3.3.0*-7-ene-2 derivatives. These observations seem to be useful to determine the stereochemistry at C_2 position in the *cis*-bicyclo[3.3.0]-oct-7-en-2-yl derivatives and related compounds. The coupling patterns of the olefinic protons were investigated by the decoupling technique, and the substituent effect on the difference was also evaluated. This difference was considered to result from a remote through-space magnetic anisotropic effect of the carbonyl group of the acyl residue on the olefinic protons.

(1) I. Tabushi, K. Fujita, and R. Oda, *J. Org. Chem.*, **35**, 2383 (1970).

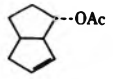
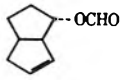
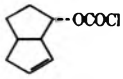
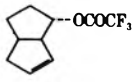
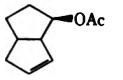
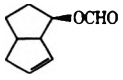
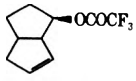
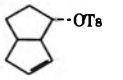
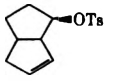
Results and Discussion

Chemical Shift Difference of Olefinic Protons of *endo-cis*-Bicyclo[3.3.0]oct-7-en-2-ol Derivatives.—Nmr measurements were carried out in carbon tetrachloride where τ values were determined on the basis of a TMS–chloroform internal double standard, using 60-MHz and 100-MHz nmr spectrometers. A spectrum of olefinic protons of the *endo-3.3.0*-7-en-2 formate is shown in Figure 1 as a typical example. As is shown in the figure, a remarkable chemical shift difference was observed for the esters of the *endo-3.3.0*-7-en-2-ol, while it was not observed for the exo esters (the signals of olefinic protons of the exo

esters as well as the exo and endo alcohols were observed to be singlet-like). The downfield or upfield signal showed ABK_1 or ABK_2K_3 pattern, respectively, though the patterns were fairly complex by virtue of additional remote couplings. In order to gain further insights, the bridgehead allyl methine proton (H_1; see Figure 1), which appeared at τ 6.65 as a broad multiplet, was irradiated. The downfield signal (H_8) was simplified to the AB pattern with fine structure by the decoupling from H_1, while upfield signal (H_7) kept ABK_2K_3 pattern with fine structure although it was slightly simplified by the removal of the remote coupling with H_1. The result of the decoupling is shown in Figure 2. Thus the upfield or downfield signal was assigned to the proton at C_7 (H_7) or at C_8 (H_8), respectively. In order to investigate the substituent effect on the splitting, locations and coupling patterns of olefinic proton signals of the *endo-3.3.0*-7-en-2-yl esters were measured (Table I). Coupling constants,

TABLE I

COUPLING PARAMETERS OF VINYL PROTONS OF *cis*-BICYCLO[3.3.0]OCTENE DERIVATIVES

Registry no.		τ_7[a]	τ_8[a]	$\Delta\tau$[b]	$J_{H_7H_8}$[c]	J_{AK_i}[d]
40132-71-6		4.63	4.34	0.293	6.0	~1.6
40132-72-7		4.59	4.28	0.307	6.0	~1.6
40132-73-8		4.62	4.30	0.318	5.9	~1.6
40132-74-9		4.61	4.23	0.377	~6.0	~1.6
40132-75-0		4.36	4.36	~0	~6.0[f]	2.0[f]
40132-76-1		4.36	4.36	~0	~6.0[f]	2.0[f]
40132-77-2		4.29	4.29	~0	~6.0[f]	2.0[f]
40132-78-3		4.64	4.36	0.283	~6.0	~1.6
40132-79-4		4.59	4.38	0.213[e]	~6.0	~1.6

[a] τ value of H_7 or H_8 with TMS–$CHCl_3$ standard. [b] Chemical shift difference between two olefinic protons ($\tau_7 - \tau_8$) in ppm unit. [c] Observed coupling constant of two olefinic protons in cps units. [d] Observed coupling constants between an allylic proton and an olefinic one in cps units; these are observed to be almost equal. [e] The splitting seems to be attributable to the magnetic anisotropic effect of the tosyl residue. [f] From the comparison of the observed spectrum of the olefinic protons with the theoretical one calculated for the 5 spin system (H_1, H_{6x}, H_{6N}, H_7, and H_8) with the computer program, these couplings constants were obtained on the assumption that $\Delta\tau \approx 0$ cps, $J_{6x6N} = -13.50$ cps, and that all J_{Ak_i} were equal to each other.

J_{AK_1}, J_{BK_2}, and J_{BK_3}, of the esters were observed to be practically equal (1.6 Hz). Coupling parameters of the AB pattern were obtained from the chemical shifts of

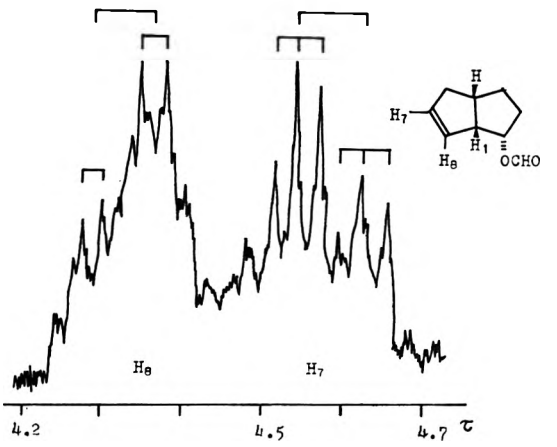


Figure 1.—Nmr spectrum of H_7 and H_8 of *endo-cis*-bicyclo[3.3.0]oct-7-en-2-yl formate measured at 60 MHz, with TMS–$CHCl_3$ internal standard.

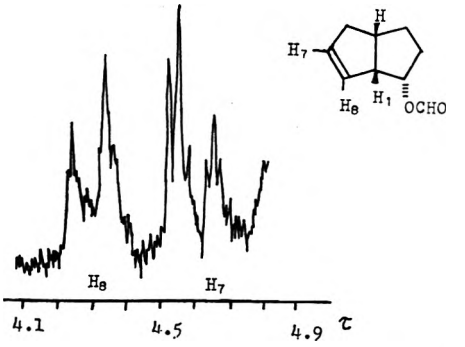


Figure 2.—Decoupled spectrum of H_7 and H_8 of *endo-cis*-bicyclo[3.3.0]oct-7-en-2-yl formate, from H_1 at τ 6.65.

band centers of the four peaks by the ordinary procedure.[2] Neither coupling constant nor chemical shift showed appreciable temperature dependency from 0 up to 100°. The temperature insensitivity seems to show that the carbonyl group actually rotates around the single bond under the condition of the nmr measurements (*i.e.*, even at 0°).[3] The chemical shift of H_8 in the *endo-3.3.0*-7-en-2-yl ester was most sensitive to the nature of acyl residue (Figure 3). This finding suggests not only that H_8 is in closer proximity to the substituent than H_7 in the endo ester consistently with the assignment made from the decoupling experiment, but also that the chemical shift difference ($\tau_7 - \tau_8$) results mainly from the deshielding of H_8, even though it is also probable that the shielding of H_7 contributes to the chemical shift difference to some extent. The chemical shift difference, $\Delta\tau$ 0.28 − 0.38, seems to indicate that the through-space magnetic anisotropic effect is the major factor of the observed chemical shift difference rather than the through-bond effect (the acyl residue is separated from H_7 or H_8 by five or six bonds, respectively), by considering that such a large chemical shift difference, $\Delta\tau$ 0.28 − 0.38, is neither seen in the open-chain analog, *trans*-hept-5-en-2-one, with the chemical shift difference of the olefinic protons to be far less than $\Delta\tau$ 0.1, nor in ω-substituted alkanes.

(2) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Oxford, 1965, p 310.

(3) Two other rationalizations are possible: (1) rotation is highly restricted even at room temperature and (2) the chemical shifts are insensitive to various rotomer species.

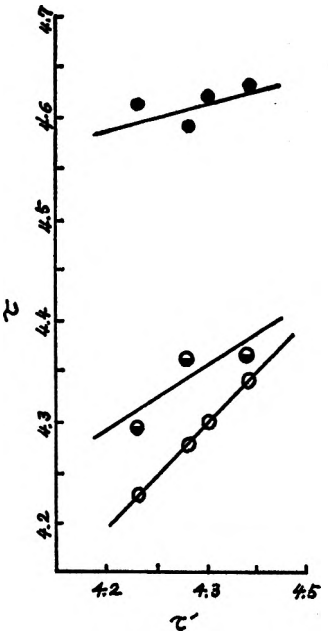


Figure 3.—Chemical shift of the olefinic proton of *endo-* or *exo-cis*-bicyclo[3.3.0]oct-7-en-2-yl ester (τ) *vs.* that of H_8 of *endo-cis*-bicyclo[3.3.0]oct-7-en-2-yl ester as a standard (τ); H_7 and H_8 of *exo-cis*-bicyclo[3.3.0]oct-7-en-2-yl ester (●), H_7 of *endo-cis*-bicyclo[3.3.0]oct-7-en-2-yl ester (◒), and H_8 of *endo-cis*-bicyclo[3.3.0]oct-7-en-2-yl ester (○).

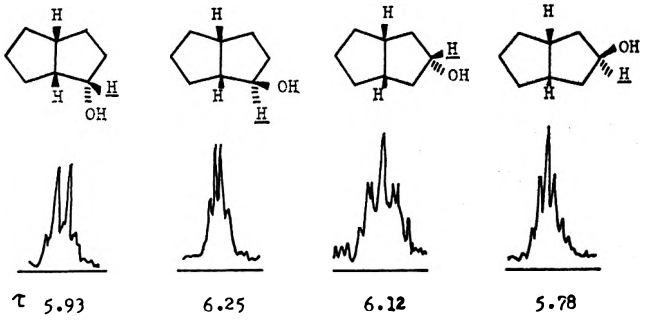


Figure 4.—Coupling patterns and chemical shifts of α protons of *cis*-bicyclo[3.3.0]octanols.

The enhanced through-space magnetic effect in the present system is largely attributable to its rigid structure. By assuming that the conformation of the *endo-3.3.0*-7-en-2-yl derivative is constructed with an envelope cyclopentane and a near-planar cyclopentene and has the substituent at C_2 quasiequatorial position, one may notice that the carbonyl group of the acyl residue can move to the position in close proximity to H_8 during the rotation and that the average effect of the magnetic anisotropy of the rotating carbonyl group causes a considerable deshielding of H_8 on the basis of a molecular model. While, for the conformation of C_2 quasiaxial substituent on the envelope cyclopentane ring or that of a half-chair cyclopentane ring, the anisotropic effect is expected to be small. For the esters of the *exo-3.3.0*-7-en-2-ol, the carbonyl group is expected to locate far from the two olefinic protons from the investigation of the molecular model. Therefore, no appreciable anisotropic effect is expected in these systems.

Conformations of *cis*-Bicyclo[3.3.0]oct-2-ols and *cis*-Bicyclo[3.3.0]oct-7-en-2-ols.—Karplus predicted that the coupling of vicinal protons ($J_{HH'}^{vic}$) should vary

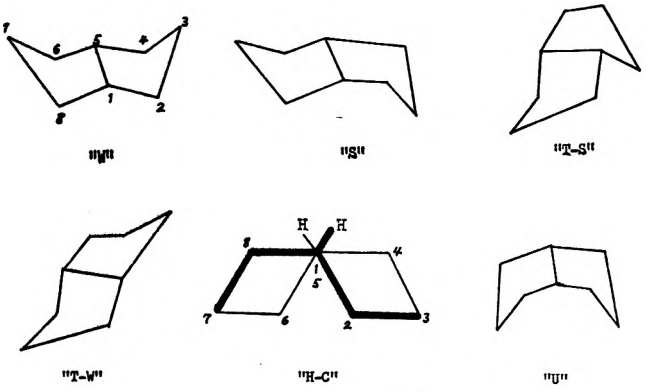


Figure 5.—Typical conformations of *cis*-bicyclo[3.3.0]octane framework.

with dihedral angle (ψ) according to the following equation.[4]

$$J_{HH'}^{vic} = 8.5\cos^2\psi - 0.28 \qquad 0° \leqq \psi \leqq 90°$$
$$= 9.5\cos^2\psi - 0.28 \qquad 90° \leqq \psi \leqq 180°$$

This equation was verified in many cases and used to identify configurational and conformational isomers.[5] Especially, the equation was shown to be successfully applied to six-membered ring;[6] but the factors other than the dihedral angle such as substituent effects were often shown to affect coupling constants.[7] Although the Karplus equation may not be strictly (numerically) applied to a five-membered ring, it seems to be allowed qualitatively to investigate the conformation or the configuration of the five-membered ring by means of the Karplus equation. We wish to discuss the conformations of the *cis*-bicyclo[3.3.0]-octane and the *cis*-bicyclo[3.3.0]oct-2-ene frameworks on the grounds of coupling constants of the α proton to hydroxyl group of the *3.3.0*-2- or -3-ols and the *3.3.0*-7-en-2-ols analyzed according to the equation. The observed nmr spectra of the α proton to hydroxyl group of the alcohols are shown in Figure 4. In order to analyze the coupling patterns in Figure 4, a reasonable assumption was made that each five-membered ring has envelope or half-chair conformation.[8] Five typical conformational models names as "*S*," "*W*," "*T-S*," "*T-W*," and "*H-C*" in Figure 5[1] were selected because of their expected stabilities. Other unstable conformers such as "*U*" were omitted, where C_3 and C_7 locate so close to suffer an unfavorable repulsive interaction between two nonbonded hydrogens (*endo-*

(4) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); H. Conroy, *Advan. Org. Chem.*, **2**, 265 (1960).

(5) (a) For carbohydrate of six-membered ring: R. V. Lemieux, R. K. Kulling, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **79**, 1005 (1957); *ibid.*, **80**, 6098 (1958). (b) For steroids: J. N. Shooley and M. T. Rogers, *ibid.*, **80**, 5121 (1958). (c) For halocyclohexanes: R. U. Lemieux and J. W. Lown, *Can. J. Chem.*, **42**, 893 (1964), and many other references.

(6) A. A. Bothner-By, "Advances in Magnetic Resonance," Vol. 1, Academic Press, New York, N. Y., 1965, p 195.

(7) (a) K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 516 (1963); (b) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963); (c) E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1166 (1964); (d) P. Laszol and P. v. R. Schleyer, *ibid.*, **86**, 1964 (1964).

(8) Pitzer suggested that the envelope conformer was the most stable; later, Brutcher and Hoffmann claimed that the half-chair conformer was more stable than the envelope. See K. S. Pitzer and W. E. Donath, *J. Amer. Chem. Soc.*, **81**, 3213 (1959); E. V. Brutcher, Jr., and W. Bauer, Jr., *ibid.*, **84**, 2232 (1962); R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).

H_3 and *endo*-H_7).[9] In the conformational models, dihedral angles between the α proton and the adjacent protons were varied, the corresponding $J_{HH'}{}^{vic}$'s were estimated by the Karplus equation, and then coupling patterns were reconstructed. By this "trial and error" procedure, conformations with the best agreement with the observed patterns were found out as shown in Table II. The best agreement was obtained by assuming "*W*" conformations for the *exo*-*3.3.0*-2-ol, the *endo*-*3.3.0*-3-ol and the *endo*-*3.3.0*-3-ol and "*S*" conformation for the *endo*-*3.3.0*-2-ol. The result is the same as that obtained from our previous investigation of the nmr shielding effect, where the other five-membered ring ($C_1C_5C_6C_7C_8$) was assumed to have an envelope conformation as shown in Figure 5. The change of the favorable conformation from "*W*" to "*S*" is explicable by steric repulsion between 2-*endo*-hydroxyl group and *endo*-H_8 proton in the *endo*-*3.3.0*-2-ol. This repulsion is minimized by the conformational change of the 2-*endo*-hydroxyl group from the quasiaxial position to the quasiequatorial one. This result is consistent with the investigation for the conformation of 2-*endo*-ethyl-*cis*-bicyclo[3.3.0]octane-2,3-diol reported by E. Ghera,[10] where the bicyclooctane framework has "*S*" conformation due to the repulsion between bulky 2-*endo*-ethyl group. Chemical shifts and coupling patterns of the α proton (H_2) observed in the spectra of the *3.3.0*-7-en-2-ols are listed in Figure 6, respectively. The results of the conformational investigation of the *3.3.0*-7-en-2-ols by the similar procedure as that of the *3.3.0*-2- and -3-ols are shown in Table III, where the unsaturated ring ($C_1C_5C_6C_7C_8$) was assumed to have nearly planar conformation. "*S*" conformation was again concluded to be favored for the *endo*-*3.3.0*-7-en-2-ol, while the best agreement with the observation was obtained for "*H-C*" conformation in the case of the *exo*-*3.3.0*-7-en-2-ol (Figure 5).

TABLE II

OBSERVED COUPLING CONSTANTS AND ROUGHLY ESTIMATED DIHEDRAL ANGLES OF *cis*-BICYCLO[3.3.0]OCT-2- AND -3-OLS

endo-*3.3.0*-2-Ol[a] (24454-38-4)	*exo*-*3.3.0*-2-Ol[a] (23359-88-8)	*endo*-*3.3.0*-3-Ol[a] (24454-40-8)	*exo*-*3.3.0*-3-Ol[a] (24454-39-5)
$H_{2x}H_1$ ~20° (J ~ 7.0 cps)	$H_{2N}H_1$ ~130° (J ~ 4.4 cps)	$H_{3x}H_{2x(4x)}$ ~35° (J ~ 5.4 cps)	$H_{3N}H_{2x(4x)}$ ~110° (J ~ 3.5 cps)
$H_{2x}H_{3x}$ ~30° (J ~ 5.6 cps)	$H_{2N}H_{3N}$ ~25° (J ~ 6.5 cps)	$H_{3x}H_{2N(4N)}$ ~155° (J ~ 7.5 cps)	$H_{3N}H_{2N(4N)}$ ~10° (J ~ 8.0 cps)
$H_{2x}H_{3N}$ ~150° (J ~ 7.4 cps)	$H_{2N}H_{3x}$ ~145° (J ~ 6.0 cps)		
"*S*"[a]	"*W*"[a]	"*W*"[a]	"*W*"[a]

[a] With respect to the abbreviation, see text. Registry numbers are in parentheses.

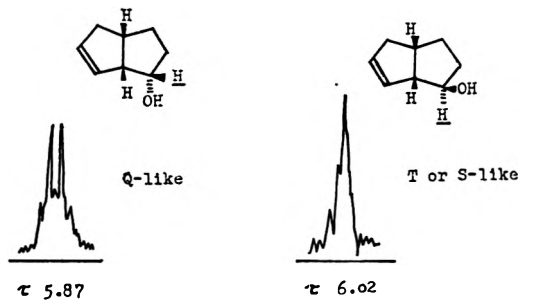


Figure 6.—Coupling patterns and chemical shifts of *cis*-bicyclo[3.3.0]oct-7-en-2-ols.

TABLE III

OBSERVED COUPLING CONSTANTS AND ROUGHLY ESTIMATED DIHEDRAL ANGLES OF *cis*-BICYCLO[3.3.0]OCT-7-EN-2-OLS

endo-*3.3.0*-7-En-2-ol[a]	*exo*-*3.3.0*-7-En-2-ol[a]
$H_{2x}H_1$ ~20° (J ~ 7.2 cps)	$H_{2N}H_1$ ~45° (J ~ 4.3 cps)
$H_{2x}H_{3x}$ ~25° (J ~ 6.3 cps)	$H_{2N}H_{3x}$ ~95° (J ~ 0.2 cps)
$H_{2x}H_{3N}$ ~145° (J ~ 6.3 cps)	$H_{2N}H_{3N}$ ~25° (J ~ 6.8 cps)
"*S*"[a]	"*H-C*"[a]

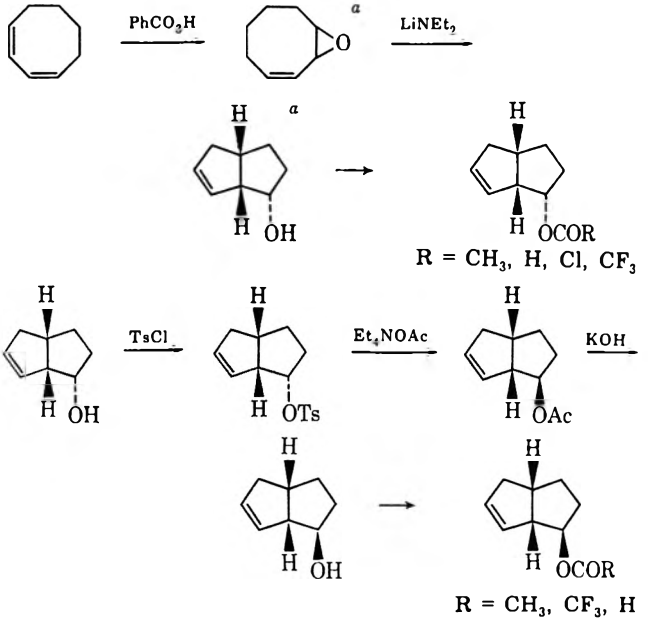
[a] With respect to the abbreviation, see text.

Experimental Section

Preparation of the Compounds for Nmr Measurements *exo*- and *endo*-*cis*-Bicyclo[3.3.0]octan-2- and -3-ols and Their Acetates.—The preparation of the alcohols and their acetates were described elsewhere.[1] A general scheme of the preparation of the *3.3.0*-7-en-2-yl derivatives is described in Scheme I.

SCHEME I

PREPARATION OF DERIVATIVES OF *cis*-BICYCLO[3.3.0]OCT-2-ENE



[a] See ref 10.

***endo*-*cis*-Bicyclo[3.3.0]oct-7-en-2-ol.**—This alcohol was prepared from 3,4-epoxycyclooctene by isomerization with lithium diethylamide,[11] bp 90–95° (20 mm) [lit.[11] bp 93–96 (20 mm)].

***exo*- and *endo*-*cis*-Bicyclo[3.3.0]oct-7-en-2-yl Tosylates.**—A solution of 8 g (0.065 mol) of the *endo*-*3.3.0*-7-en-2-ol in 53.0 ml of pyridine was added to a solution of 22.9 g (0.120 mol) of *p*-toluenesulfonyl chloride with ice cooling and stirring. Then the mixture was stirred for 20 hr at room temperature. The reaction was quenched by the addition of 2 ml of cold water under ice cooling. The mixture was poured into 200 ml of cold water and extracted with seven portions of 200 ml of ether. The ether extracts were combined and washed with 1 *N* hydrochloric

(9) For example, bicyclo[3.3.1]nonane framework was reported to have a serious repulsion between two endo protons attached to C_7 and C_3. See M. Dolber and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964); W. A. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965); W. D. K. Macrosson, J. D. Lark, C. A. Flegal, and L. M. Honing, *J. Org. Chem.*, **32**, 1372 (1967). Our calculation according to the extended Hückel method shows that "*U*" conformation is less stable than "*W*" one for *cis*-bicyclo[3.3.0]octane. Raman and ir spectra of the hydrocarbon suggested that "*S*" conformation was more stable than "*W*" and "*U*" ones: R. Granger, L. Bardet, C. Sablayrolles, and J.-P. Girard, *Bull. Soc. Chim. Fr.*, 4454 (1971).

(10) E. Ghera, *J. Org. Chem.*, **33**, 1042 (1948).

(11) J. K. Crandall and L.-H. Chang, *J. Org. Chem.*, **32**, 532 (1967).

acid and then saturated aqueous sodium bicarbonate solution. The ether layer was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was the practically pure tosylate (17.2 g). The ir spectrum (neat) did not show the absorption of OH stretching but the characteristic absorption of a tosylate: 1363 and 1177 cm^{-1}. The *exo-3.3.0*-7-en-2-yl tosylate was prepared by a similar procedure, ir 1360 and 1170 cm^{-1}.

exo-cis-**Bicyclo[3.3.0]oct-7-en-2-yl Acetate.**—A mixture of 10.5 g of the *endo-3.3.0*-7-en-2-yl tosylate, 11.3 g of tetraethylammonium acetate, and 250 ml of acetone was refluxed for 22 hr. After evaporation of acetone, the residue was poured into 400 ml of water. Then the mixture was extracted five times with 200 ml portion of ether. The ether extracts were combined, washed with water, dried (Na_2SO_4), and concentrated. Distillation afforded 6.7 g of the *exo-3.3.0*-7-en-2-yl acetate: bp 69–73° (5 mm); ir, 1730, 1020, and 720 cm^{-1}, mass spectrum *m/e* 106 ($M^+ - CH_3CO_2H$) (the molecular peak, 166, was not observed).

exo-cis-**Bicyclo[3.3.0]oct-7-en-2-ol.**—A mixture of 6.7 g of the *exo-3.3.0*-7-en-2-yl acetate, 2 g of sodium hydroxide, 2 drops of water, and 20 ml of methanol was refluxed for 10 hr. On cooling, the mixture was neutralized with concentrated hydrochloric acid. The precipitated sodium chloride was filtered off and the filtrate was concentrated. Distillation gave 3.8 g of the *exo-3.3.0*-7-en-2-ol: bp 79–83° (5 mm) [lit.[12] bp 71–72° (3 mm)]; ir (neat) 3360 cm^{-1}.

endo-cis-**Bicyclo[3.3.0]oct-7-en-2-yl Acetate.**—A solution of 0.5 g of the *endo-3.3.0*-7-en-2-ol in 0.85 g of acetic anhydride was fluxed for 6 hr. The mixture was poured into 50 ml of saturated aqueous sodium bicarbonate solution and extracted with five 50-ml portions of ether. The ether extracts were combined, washed with water, dried (Na_2SO_4), and concentrated. Distillation afforded 0.6 g of the *endo-3.3.0*-7-en-2-yl acetate: bp 69–73° (6 mm); ir (neat) 1723, 790, and 765 cm^{-1}, mass spectrum *m/e* 106 ($M^+ - CH_3CO_2H$) (the molecular peak, 166, was not observed).

exo- **and** *endo-cis*-**Bicyclo[3.3.0]oct-7-en-2-yl Trifluoroacetates.**—Each trifluoroacetate was prepared from trifluoroacetic anhydride (1.5 ml) and the corresponding alcohol (0.2 g) by the similar procedure described above. The dried ether extract was concentrated under reduced pressure and used for nmr measurement without isolation. The ir spectrum of the nmr sample showed the absence of hydroxyl group and the presence of carbonyl group of trifluoroacetate: the exo isomer, 1775 cm^{-1}; the endo isomer, 1779 cm^{-1}.

exo- **and** *endo-cis*-**Bicyclo[3.3.0]oct-7-en-2-yl Formates.**—A mixture of 0.2 g of the corresponding alcohol, 3 ml of formic acid, and 0.2 g of anhydrous sodium sulfate was heated at 80° for 4 hr. Then the mixture was poured into 150 ml of saturated aqueous sodium bicarbonate solution, extracted with four 50-ml portions of ether. The ether layer was washed with water, dried (Na_2SO_4), and concentrated. Distillation of the formate afforded the *exo-3.3.0*-7-en-2-yl formate, bp 84–86° (20 mm), ir (neat) 1718 cm^{-1}, mass spectrum *m/e* 106 ($M^+ - HCO_2H$) (the molecular peak, 152, was not observed), and the *endo-3.3.0*-7-en-2-yl formate, bp 73–74° (12 mm), $n^{22}D$ 1.4852, ir (neat) 1716 cm^{-1}, mass spectrum *m/e* (rel intensity) 152 (1.59, M^+), 106 (100, $M^+ - HCO_2H$).

endo-cis-**Bicyclo[3.3.0]oct-7-en-2-yl Chloroformate.**—Dry phosgene gas was bubbled into a solution of 0.1 g of the *endo-3.3.0*-7-en-2-ol in 1 ml of carbon tetrachloride during 20 min at 15°. The solution was kept standing for 30 min at room temperature. Then dry nitrogen was bubbled for 15 min in order to purge excess phosgene and hydrogen chloride formed. The mixture was used for nmr measurement without isolation.

(12) N. A. LeBel and L. A. Spurlock, *Tetrahedron*, **20**, 215 (1964).

Nuclear Magnetic Resonance Spectroscopy. The Carbon-13 Spectra of Some Cyclic Alkynes, Allenes, and Alkenes[1]

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The ^{13}C nuclear magnetic resonance (cmr) spectra of selected examples of cyclic alkynes, allenes, and alkenes are reported and discussed. The possible effects of diamagnetic anisotropy on the differences of carbon chemical shifts between cyclic and acyclic alkynes are considered. Other possible sources of carbon chemical-shift differences in these compounds are discussed.

The chemical shifts of sp-hybridized carbons have been of interest to nuclear magnetic resonance (nmr) spectroscopists for several years.[2-5] More recently, technological advances in the maintenance of stable magnetic fields and proton decoupling have made possible the resolution of the carbon resonances of the entire alkyne molecule, so that the substituent effects of the alkyne moiety on the chemical shift of neighboring carbons could be studied.[6,7] It was evident from these last studies that the triple bond appears to have a larger effect upon carbon than proton chemical shifts. The present study seeks to extend our knowledge of the effect of diamagnetic anisotropy in carbon chemical shifts, and to investigate the differences in the responses of protons and carbons to neighboring multiple bonds.

Experimental Section

The compounds used in this study were obtained from commercial sources or were prepared by known literature procedures. Data for the compounds are presented in Table I.

Carbon-13 chemical shifts were measured under conditions of full proton decoupling on a Varian digital frequency sweep spectrometer described previously.[8] Spectra were obtained in benzene solution. Chemical shifts were measured relative to internal cyclohexane (*ca.* 5%) and later referenced to external carbon disulfide by the relation $\delta_{CS_2} = \delta_{C_6H_{12}} + 166.2$ ppm.

Results

The carbon-13 chemical shifts are summarized in Table II. The assignments of resonances were based

(1) Supported by the National Science Foundation, and by the Public Health Service, Research Grant No. GM-11072 from the Division of General Medical Sciences.

(2) P. C. Lauterbur in "Determination of Organic Structures by Physical Methods," F. C. Nachod and W. D. Phillips, Ed., Academic Press, New York, N. Y., 1963.

(3) R. A. Friedel and H. L. Retcofsky, *J. Amer. Chem. Soc.*, **85**, 1300 (1963).

(4) K. Frei and H. J. Bernstein, *J. Chem. Phys.*, **38**, 1216 (1963).

(5) D. D. Traficante and G. E. Maciel, *J. Phys. Chem.*, **69**, 1348 (1965).

(6) (a) S. Rang, T. Pehk, E. Lippmaa, and O. Eisen, *Eesti NSV Tead. Akad. Toim. Keem. Geol.* **16**, 346 (1967); (b) *ibid.*, **17**, 210, 294 (1968).

(7) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36**, 2757 (1971).

(8) (a) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 2967 (1967); (b) F. J. Weigert, M. Jautelat, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, **60**, 1152 (1968).

TABLE I

PREPARATIONS AND PHYSICAL PROPERTIES

Compd	Mp or bp, °C (mm)	Ref
1,7-Octadiyne	93–95 (190)	*a*
4,6-Decadiyne	*i*	
Cyclotridecyne	84–86 (3)	*b*
Tetradeca-1,7,13-triyne	*i*	
Cyclotetradeca-1,8-diyne	*i*	
Tetradeca-1,6,8,13-tetrayne		*c*
Cyclotetradeca-1,3,8,10-tetrayne	115–120 dec	*c*
Hexadeca-1,7,9,15-tetrayne	15–17	*d*
Cyclohexadeca-1,3,9,11-tetrayne	160–162 dec	*d*
Octadeca-1,8,10,17-tetrayne		*c, e*
Cyclooctadeca-1,3,10,12-tetrayne	210–212	*c, e*
Cycloheptacosa-1,3,10,12,19,21-hexayne	125	*c, e*
Cyclohexatriaconta-1,3,10,12,19,21,28,30-octayne	135	*c, e*
Cyclohexa-1,4-diene	*i*	
Cycloocta-1,5-diene	*i*	
cis,cis-Cyclotetradeca-1,8-diene	43	*f*
Cyclonona-1,2-diene	62–63 (16)	*g*
Cyclonona-1,2,6-triene	61–62 (13)	*g*
Cyclodeca-1,2,6,7-tetraene	48–50 (0.7)	*g*
Cyclotrideca-1,2-diene	90 (5)	*b, g, h*
Cyclohexadeca-1,2,9,10-tetraene	80	*g*

[a] H. Bader, L. C. Cross, I. Heilbron, and E. R. H. Jones, *J. Chem. Soc.*, 619 (1949). [b] H. Nozaki, S. Kato, and R. Noyori, *Can. J. Chem.*, **44**, 1021 (1966). [c] F. Sondheimer, Y. Amiel, and R. Wolovsky, *J. Amer. Chem. Soc.*, **79**, 6263 (1957). [d] F. Sondheimer and Y. Amiel, *ibid.*, **79**, 5817 (1957). [e] F. Sondheimer, Y. Amiel, and R. Wolovsky, *ibid.*, **81**, 4600 (1959). [f] D. J. Cram and N. L. Allinger, *ibid.*, **78**, 2518 (1956). [g] L. Skattebol, *Acta Chem. Scand.*, **17**, 1683 (1963). [h] H. Nozaki, T. Aratane, and R. Noyori, *Tetrahedron*, **23**, 3645 (1967). [i] Product commercially available from Farchan and used without prior purification or analysis.

upon the following criteria: (1) molecular symmetry which, in many cases, gives rise to differing peak heights; (2) coherent proton decoupling frequencies for the various carbon resonances which could be compared with the partially resolved proton nmr spectra; (3) nuclear Overhauser enhancements which were expected to be attenuated in cases of carbons which have no proximal protons.[9] The last criterion is useful in assignment of the resonances of conjugated diyne systems, in which the resonances of the inner pair of carbons are of smaller peak height than those of this outer pair. It should be noted that this assignment of these resonances is in accord with the finding that carbons which are α to a triple bond are shielded by some 10–15 ppm.[6,7] Thus, in conjugated diyne systems, the inner pair of carbons is shielded by adjacency of the other triple bond, while the outer carbons are not.

In many cases, the above criteria were not sufficient and many of the resonances within a spectrum could not be surely assigned. Such instances are denoted by asterisks in Table II. This problem becomes particularly acute when the ring contains only one functional group (*cf.* cyclotridecyne), and has prevented the assessment of substituent effects of unsaturated groups in medium and large rings.[10,11]

(9) A. J. Jones, D. M. Grant, and K. F. Kuhlman, *J. Amer. Chem. Soc.*, **91**, 5013 (1969).

(10) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 1347 (1970).

(11) J. Graefe, K. Herwig, D. E. Dorman, and J. D. Roberts, in preparation.

Discussion

The Cycloalkynes.—The simplest cycloalkyne examined in this study is cyclotridecyne (**3**). It is interesting to note that any strain in the triple-bonded carbons resulting from the cyclic nature of **3** appears to have a negligible effect on the chemical shift of the sp-hybridized carbons. Thus, the unsaturated carbons of **3** come into resonance at 112.4 ppm,[12] while carbons 7 and 8 of tetradeca-1,7,13-triyne (**4**), the closest acyclic model in this study, resonate at 112.7 ppm.[13] This conclusion is in accord with other studies of the cmr spectra of cis and trans cycloalkenes,[11] in which differences in ring strain were found to have only small effects upon the chemical shifts of the unsaturated carbons.

Except for the α carbons (C-3, -13), the effect of the triple bond on the chemical shifts of the saturated carbons of **3** is difficult to assess because of problems in assigning the resonances to particular carbons. The α carbons are shifted strongly upfield, occurring at almost 10 ppm higher field than the remaining sp^3-hybridized carbons. Again, this is in general accord with previous results.[6,7] The resonance of carbon 8, which, in principle, is identifiable because of the molecular symmetry, apparently falls beneath the overlapping resonances at 167.3 ppm. The remaining resonances range over about 2 ppm and are centered at about 166 ppm. The chemical shift of the single resonance of cyclotridecane is reported to be approximately 167 ppm.[14] The spectra of *cis*- and *trans*-cyclotridecene[11] show a spread similar to that for **3**, although the spectrum of **3** compares most closely to that of the trans example. In the absence of specific assignments, however, the origins of these chemical-shift differences cannot be dissected further.

Better success is possible in comparisons of the spectra of compounds **5**–**11**, for which the principles discussed in the Results section of this paper suffice to give complete assignments. The spectra of closely related cyclic and acyclic polyynes are compared in Table III. For the pair A, there are some very large and obvious differences. Thus, the sp-hybridized carbons (7) are deshielded by approximately 2.5 ppm relative to the analagous carbons of the conjugated diyne moiety of **6**. From what was said earlier, these differences seem larger than would be the case for ring-strain effects. Furthermore, there are changes of comparable magnitude in the chemical shifts of the sp^3-hybridized carbons. Because of the possible importance of the diamagnetic anisotropy of the triple bond,[6,15] it seems appropriate to see if these chemical-shift changes can be attributed to this phenomenon.

Diamagnetic anisotropy associated with the triple bond arises from interactions between the magnetic

(12) All chemical shifts in this paper are related to external carbon disulfide, with positive numbers representing upfield shifts. The chemical shift of external carbon disulfide on the TMS scale is approximately −193.7 ppm: G. C. Levy and J. D. Cargioli, *J. Magn. Resonance*, **6**, 143 (1972).

(13) It will be noted that the chemical shifts of the cycloalkynes reported in this paper differ in some regards from those reported previously.[7] These disparities are probably due to the different solvents used in the two studies. A deshielding solvent effect has already been noted for benzene: J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, **92**, 1338 (1970).

(14) J. J. Burke and P. C. Lauterbur, *ibid.*, **86**, 1870 (1964).

(15) (a) H. M. McConnell, *J. Phys. Chem.*, **27**, 226 (1956). (b) A number of modifications of the McConnell procedure have also been suggested; *cf.* J. A. Pople, *J. Amer. Chem. Soc.*, **88**, 4811 (1966), R. S. Macomber, *J. Org. Chem.*, **37**, 1205 (1972), and J. W. ApSimon, *Tetrahedron*, **23**, 2339 (1967).

TABLE II

CARBON CHEMICAL SHIFTS[a] IN SELECTED ALKYNES, CYCLOALKYNES, CYCLOALLENES, AND CYCLOALKENES

Compd	1	2	3	4	5	6	7	8	9	10
1,7-Octadiyne (1)	124.0	109.2	175.3	165.6						
4,6-Decadiyne (2)	180.1	171.1	172.2	117.0	127.3					
Cyclotridecyne (3)	112.4	112.4	174.4	165.5*	166.6*	167.1*	167.3*	167.3*		
Tetradeca-1,7,13-triyne (4)	124.6	109.6	175.2	165.1*	165.5*	174.9	112.7			
Cyclotetradeca-1,8-diyne (5)	112.7	112.7	174.6	165.0	166.3					
Tetradeca-1,6,8,13-tetrayne (6)	124.0	110.4	175.8	165.9	175.1	116.9	126.7			
Cyclotetradeca-1,3,8,10-tetrayne (7)	114.5	123.8	123.8	114.5	173.3	168.9				
Hexadeca-1,7,9,15-tetrayne (8)	124.5	109.7	175.4	165.7*	165.7*	174.6	116.5	127.1		
Cyclohexadeca-1,3,9,11-tetrayne (9)	115.4	126.0	126.0	115.4	173.9	166.3				
Octadeca-1,8,10,17-tetrayne (10)	124.7	109.3	175.1	165.3*	165.3*	165.3*	174.3	116.4	126.9	
Cyclooctadeca-1,3,10,12-tetrayne (11)	116.7	125.8	174.3	165.9	166.5					
Cycloheptacosa-1,3,10,12,19,21-hexayne (12)	116.0	126.4	174.2	165.5	165.8					
Cyclohexatriaconta-1,3,10,12,19,21,28,30-octayne (13)	116.0	126.6	174.3	165.4	165.4					
Cyclohexa-1,4-diene (14)	69.0	69.0	167.4							
Cycloocta-1,5-diene (15)	64.8	64.8	165.1							
cis,cis-Cyclotetradeca-1,8-diene (16)	63.3	63.3	166.8	165.0*	165.6*					
Cyclonona-1,2-diene (17)	101.0	−12.8	101.0	165.8	167.7*	165.1*				
Cyclonona-1,2,6-triene (18)	103.2	−13.0	103.2	166.3*	164.6*	63.3				
Cyclodeca-1,2,6,7-tetraene (19)	103.5	−14.6	103.5	166.9						
Cyclotrideca-1,2-diene (20)	101.9	−11.5	101.9	165.7	166.0*	166.0*	166.4*	166.6*		
Cyclohexadeca-1,2,9,10-tetraene (21)	103.1	−12.0	103.1	163.9	164.8	165.9				

[a] In parts per million, relative to external carbon disulfide.[12] The figures for chemical shifts marked with asterisks represent uncertain assignments.

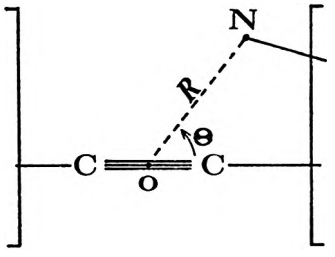
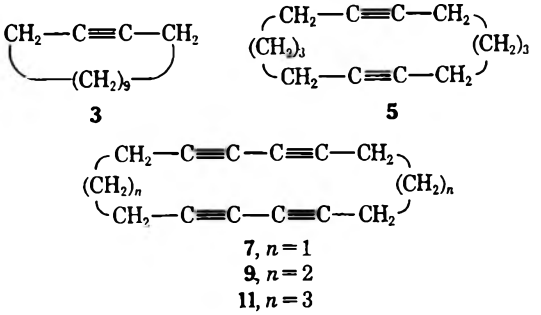


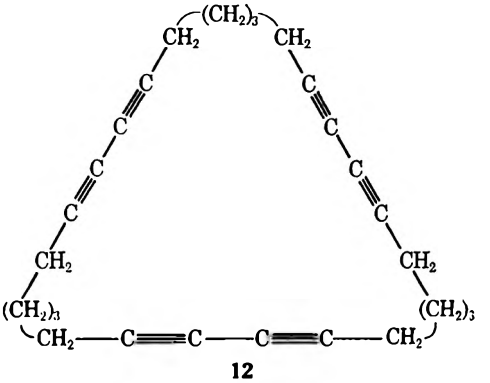
Figure 1.—A definition of the parameters of the McConnel equation.[15b] The brackets represent the remainder of the molecule in generalized form. O is the electrical center of gravity of the triple bond; R is the distance between O and the nucleus N, which is also in the same molecule; and θ is the angle between the symmetry axis of the triple bond and the ray R.

field (H_0) and the motion of the π electrons of the triple bond. An induced magnetic field results, the character of which, in the simplest case, may be approximated by point dipole at O (Figure 1).[15a] If N is a nucleus in the same molecule, it experiences the small field of this point dipole and the effective magnetic field at N is thereby altered. The strength of the field of the point dipole is dependent on the angle between the applied external magnetic field and the symmetry axis of the triple bond, but in liquids rapid molecular tumbling average this last effect so that the effective field at N is dependent only on R, θ, and a constant which represents the anisotropy of the triple bond, $\Delta\chi$. The dependence of σ_g, the screening of N owing to the anisotropy of the triple bond, is given by the following relation.[15a]

$$\sigma_g = \frac{\Delta\chi}{3R^3}(1 - 3\cos^2\theta) \qquad (1)$$

A polar plot of $(1 - 3\cos^2\theta)/R^3$ (Figure 2) shows that, for θ angles of less than approximately 54.7°, σ_g is positive and the nucleus N is shielded. For larger angles, however, the effect of the triple bond will be deshielding in character. The single point dipole





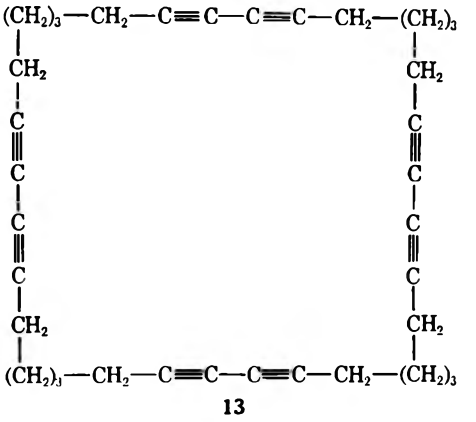


TABLE III

COMPARISON OF CARBON CHEMICAL SHIFTS IN SOME CLOSELY RELATED CYCLIC AND ACYCLIC POLYYNES[a]

$$-CH_2CH_2C\overset{\alpha}{\equiv}C\overset{\beta}{C}\equiv\overset{\gamma}{C}\overset{\delta}{C}H_2CH_2-$$

	Compd	α	β	γ	δ	ε
A	Cyclotetradeca-1,3,8,10-tetrayne (7)	−2.9	−2.4	−1.9	+2.0	
	Tetradeca-1,6,8,13-tetrayne (6)					
B	Cyclohexadeca-1,3,9,11-tetrayne (9)	−1.1	−1.1	−0.7	+0.6	
	Hexadeca-1,7,9,15-tetrayne (8)					
C	Cyclooctadeca-1,3,10,12-tetrayne (11)	−1.1	+0.3	0.0	+0.5	+1.2
	Octadeca-1,8,10,17-tetrayne (10)					
D	Cycloheptacosa-1,3,10,12,19,21-hexayne (12)	−0.5	−0.4	−0.1	+0.2	+0.5
	Octadeca-1,8,10,17-tetrayne (10)					
E	Cyclohexatriaconta-1,3,10,12,19,21,28,30-octayne (13)	−0.3	−0.4	0.0	+0.1	+0.1
	Octadeca-1,8,10,17-tetrayne (10)					
F	Cyclotetradeca-1,8-diyne (5)	0.0	0.0	−0.3	−0.1	
	Tetradeca-1,7,13-triyne (3)					

[a] Pairs of compared compounds are enclosed in brackets. The tabulated shift differences were obtained by subtracting the cmr spectrum of the second member of the pair from that of the first.

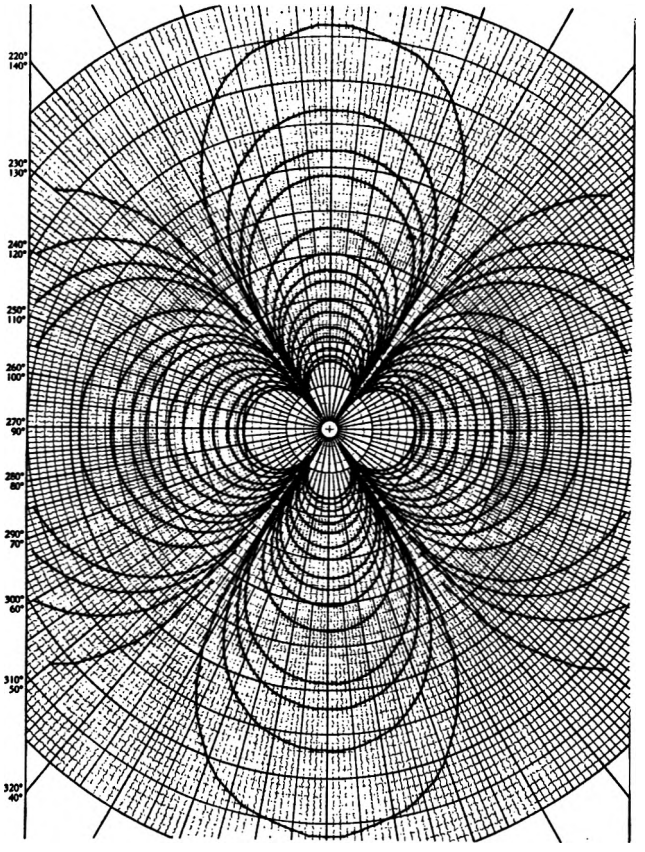


Figure 2.—Polar plot of constant values of $(1 - 3\cos^2\theta)/R^3$, where θ is 0° or 180° when R lies along the bond axis and R is the distance from the center of the bond. The contours from the inside out are at 1.0, 0.8, 0.6, 0.4, 0.3, 0.2, 0.15, 0.1, 0.08, 0.06, 0.04, 0.02, 0.015, 0.01, 0.005. The contours are negative for the horizontal lobes and positive for the vertical lobes. The bond axis is in the horizontal direction. The outer-most circle is 10 Å from the bond center. The figures printed along the side are values of $\theta - 90°$ or $\theta + 90°$. In using these plots it is very convenient to sketch the pattern of the molecule on a transparent overlay which can be positioned so as to easily see where particular atoms fall in the shielding or deshielding zones.

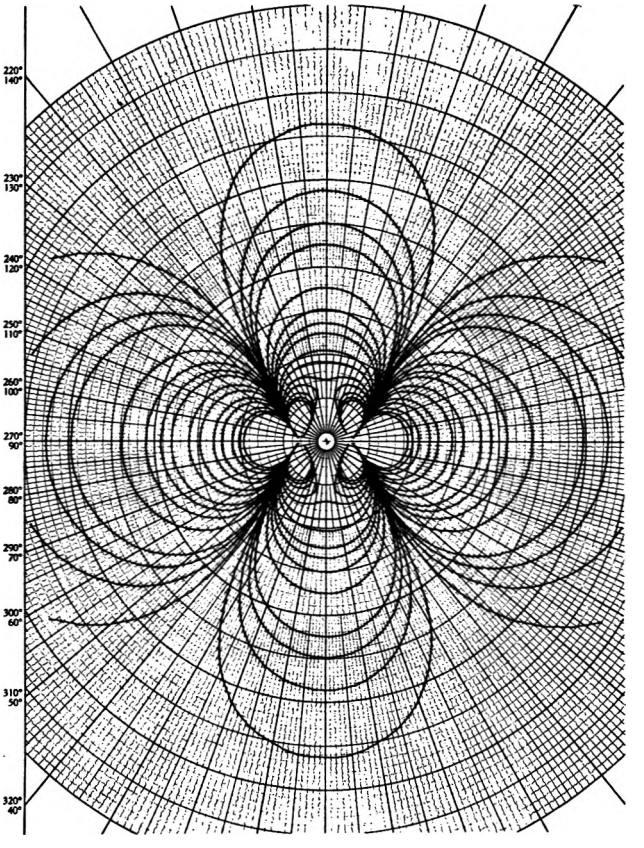


Figure 3.—Polar plot of constant values of $(1 - 3\cos^2\theta_1)R_1^2 + (1 - 3\cos^2\theta^2)/R_2^2$, where the distance between the point dipoles is 1.20 Å. The other features are as in Figure 1.

approximation has obvious shortcomings for calculating magnetic shielding produced by triple bonds in that it does not well reflect the over-all electron distributions of such bonds. Better results would be expected from Pople's procedure,[15b] where the shielding could be simulated by two point dipoles (1,2) centered on each end of the bond (1.20 Å apart). A polar plot of $(1 - 3\cos^2\theta_1)/R_1^3 + (1 - \cos^2\theta_2)/R_2^3$ is shown in Figure 3. The important conclusions that can be derived from a comparison of Figures 2 and 3 are (1) that the shielding and deshielding regions have roughly similar angular dependences once one gets about 1.5 Å away from the center of the double bond, and (2) that the shielding and deshielding effects are predicted to fall off rather *faster* with distance from the bond center for the split dipole model. This means that the calculated shielding (or deshielding) effects will be generally *smaller* for the split dipole model, other things being the same.

Calculation of magnetic anisotropy effects with many of the substances considered here is complicated

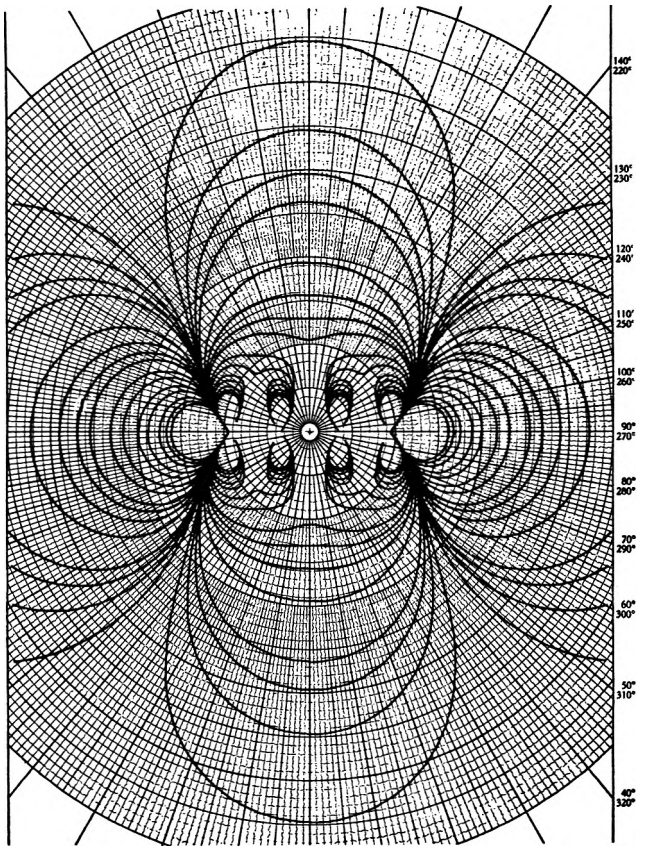
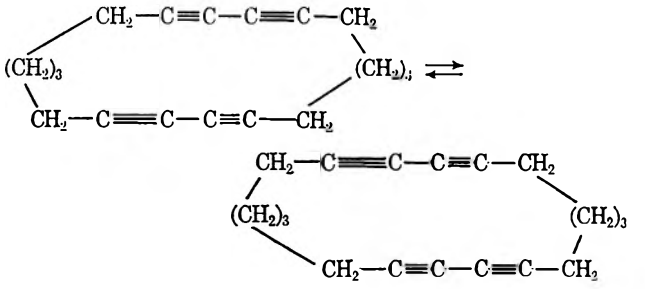


Figure 4.—Polar plot of constant values of $\Sigma(1 - 3\cos^2\theta_i)/R_i^3$ for four split dipoles corresponding to two triple bonds, each 1.20 Å in length and separated by 1.38 Å. The other features are as in Figure 2.

by the fact that it is not clear how the shielding and deshielding volumes will be changed by conjugation of triple bonds. We will assume here that two conjugated triple bonds can be approximated by assuming that there are two point dipoles, one at the center of each of the triple bonds, or else by four point dipoles centered on each carbon. The former case is represented by Figure 3, if it is rescaled so that the distance between the dipoles is about 2.6 Å instead of 1.2 Å and considered to be for two bonds, not one. The latter case with four point dipoles is shown in Figure 4, on the assumption that all of the dipoles are equivalent. With either of these approximations it is clear that carbons marked α and β (see Table III) should be deshielded by the pair of triple bonds across the ring in the cyclic structure **7** relative to **6** and, indeed, deshielding effects are observed. The chair conformation proposed for **7** on the basis of models and X-ray crystallography[16] makes it possible to compute the parameters R and θ with rather good accuracy. The carbons marked γ fall in the shielding zone where the contours are narrowly spaced and close to the boundary where deshielding should begin. As a result, one cannot very confidently predict what should happen. That a substantial deshielding should occur is plausible, even if not gratifying. Strong shielding is predicted for the carbons marked δ of **7** from the triple bonds across the ring, and this is in accord with experiment. However, it is predicted from the curves of Figure 4 that the across-ring deshielding of the carbons marked α and β would be substantially smaller in magnitude than the shielding of the carbons marked δ.

Turning now to the next pair (B) of Table III, we see that the differences between the chemical shifts of carbons α, β, and γ in the cyclic (**9**) and acyclic (**8**) examples fall in the same pattern but are smaller than in the first pair above. This attenuation would be expected from increasing R.

Pair C (Table III) is somewhat different. Here, molecular models suggest that R could be so large that neighboring-group anisotropy effects would be quite small for **11**. In fact, however, there is only a small effect on $^{\beta}$C and it is difficult to find a reasonable arrangement of the triple bonds which gives slight shielding for $^{\beta}$C, deshielding for $^{\alpha}$C, and nothing at $^{\gamma}$C. Something approximating this is possible if the cross-ring triple bonds on the average lie parallel to one another, equilibrating between two (quite reasonable) conformations with the centers of the pairs of multiple bonds staggered by about 2 Å. It is also possible that



the conjugated bonds of **11** are skewed with respect to one another. In the absence of detailed conformational data, these explanations are at best speculative.

The carbons labeled δ and ϵ in Table III show considerable shielding effects for $^{\delta}$C of **7** and $^{\epsilon}$C of **11** and this is in accord with the predictions of Figure 4. The other pairs of Table II, as expected, show little differences in shift between the cyclic and acyclic substances because in the cyclic cases, the triple-bond segments are either away from one another or held at angles such that effects will be small.

Finally, we should note an additional problem evident in earlier studies.[5-7] Numerous proton nmr studies of alkynes have been used to derive empirical values for $\Delta\chi$ of eq 1.[17] These values predict carbon chemical-shift differences that are rather too small[6,7] and the same problem is encountered here. Similar difficulties have been found for fluorine shifts,[18] and it has been suggested that electric fields should be taken into considerations in theoretical evaluations of fluorine chemical shifts.[18] Certainly, electric-field effects appear to be important in carbon chemical shifts, but they have been involved only in cases where there exists a large electric dipole within the molecule.[19,20]

Cycloalkenes.—Also included in Table II are some preliminary data for three cycloalkadienes. These substances have the advantage that their corresponding cmr spectra are frequently easier to interpret than those of corresponding acyclic compounds. However,

(16) Footnote c, Table I.

(17) H. Heel and W. Zeil, *Z. Elektrochem.*, **64**, 962 (1960); W. Zeil and H. Buchert, *Z. Phys. Chem.*, **38**, 47 (1963).

(18) J. W. Emsley and L. Phillips in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. 7, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, Elmsford, N. Y., 1971.

(19) W. McFarlane, *Chem. Commun.*, 418 (1970).

(20) P. S. Pregosin and E. W. Randall, *ibid.*, 399 (1971).

it is apparent from Table II that even the resonances of the cyclic diene spectra are difficult to assign when the ring is large. In the case of *cis,cis*-cyclotetradeca-1,8-diene (16), for example, only the resonances of the trigonal and the adjacent sp^3 carbons could be assigned.

In Table IV, the cmr spectra of the cyclic dienes and model compounds are compared in the same way as for

TABLE IV

COMPARISON OF SPECTRA OF CYCLOALKADIENES AND CYCLOALKENES[a]

$[C{=}\overset{\alpha}{C}{-}\overset{\beta}{C}]$

		$\delta\alpha$	$\delta\beta$
A	Cyclohexa-1,4-diene (14) / Cyclohexene[b]	+2.7	−0.6
B	Cycloocta-1,5-diene (15) / *cis*-Cyclooctene	+1.5	−2.6
C	Cycloocta-1,5-diene (15) / *cis,cis*-Octa-2,6-diene[a]	+1.8	−1.3
D	*cis,cis*-Cyclotetradeca-1,8-diene (16) / *cis*-Cyclotridecene[c]	+1.1	−0.7

[a] Tabulated shift differences were obtained by subtracting the cmr spectrum of the second member of a pair from the first. [b] Reference 21. [c] Reference 11.

the alkynes. It is seen that in cyclohexa-1,4-diene, for example, the trigonal carbons have shifts at rather higher fields than is normal for cis alkenes.[21] Specifically, these carbons come into resonance at a position 2.7 ppm upfield from the analogous carbons of cyclohexene. The effect at the adjacent sp^3 carbon, on the other hand, is deshielding. Comparisons of the spectra of larger cycloalkadienes with model compounds show that the shielding effect at the trigonal carbons is attenuated, while the shift differences at the directly connected sp^3 carbons are irregular.

The available evidence indicates that the diamagnetic anisotropy of the double bond results in shielding in the regions above and below the plane of the trigonal carbons, as well as possible deshielding within the plane.[22] Such anisotropy should result in deshielding at the immediately adjacent sp^3 carbons. In fact, such an effect has been noted only for trans alkenes, and the deshielding in these cases could be an effect of electronegativity. In cis examples, the chemical shifts of the α carbons show a strong shielding tendency, presumably owing to steric effects.[21] At the present time, it is not possible to identify with certainty any anisotropy effect on the α-carbon resonances.

The data in Table IV are consistent, however, with the postulated shielding effect in the region perpendicular to the plane of the double bond. Thus, the unusually high field resonance of the trigonal carbons of cyclohexa-1,4-diene could result from such an effect. This shielding effect is attenuated in the larger rings, but still seems to persist in cyclotetra-1,8-diene (16).

Cycloallenes.—The cyclic allenes have been studied previously by both infrared and proton nmr spectroscopy.[23] It was concluded in this earlier work that the nine-membered cyclic allene 17 was significantly more strained than the higher homologs. The greatest differences were found to occur in the chemical shift of the protons attached to the trigonal carbons, and in the infrared band assigned to the torsional movement of the terminal carbons of the allenic unit. There appeared to be little change in the infrared band assigned to stretching vibrations of the allene.

The carbon chemical shifts reported in the present work provide some information regarding the effects of such strain on the central carbon of the allene. Thus, comparison of the spectrum of 17 with that of cyclotrideca-1,2-diene (20), which is considered to be relatively strain-free,[23] shows that all three carbons of the allene unit are deshielded by the effects of strain (pair A, Table V). As in the cases of cis and trans cyclo-

TABLE V

COMPARISON OF THE CMR SPECTRA OF SELECTED CYCLIC ALLENES[a]

$C{-}\overset{A}{C}{=}\overset{B}{C}{=}\overset{C}{C}{-}C$

		δ_A	δ_B	δ_C
A	Cyclononа-1,2-diene (17) / Cyclotrideca-1,2-diene (20)	−1.3	−0.9	0.1
B	Cyclonona-1,2,6-diene (18) / Cyclotrideca-1,2-diene (20)	−1.5	+1.3	
C	Cyclodeca-1,2,6,7-tetraene (19) / Cyclononа-1,2-diene (17)	−1.8	+2.5	+1.1
D	Cyclodeca-1,2,6,7-tetrane (19) / Cyclohexadeca-1,2,9,10-tetraene (21)	−2.6	+0.4	+3.0
E	Cyclohexadeca-1,2,9,10-tetraene (21) / Cyclotrideca-1,2-diene (20)	−0.5	+1.2	−1.8

[a] Tabulated shift differences were obtained by subtracting the cmr spectrum of the second member of the pair from the first.

alkenes,[11] the effects of strain on carbon chemical shifts seem to be small.

Ring strain may also be an important effect in the remaining comparisons shown in Table V. Unfortunately, these comparisons are further complicated by the possibility of the anisotropic shift effects arising from the alkene and allene units. The effects of the diamagnetic anisotropy of the double bond was considered above. It is possible that the increased shielding of the terminal carbons of the alkene unit of cyclonona-1,2,6-triene (18) relative to the simple allene 17 is due to the diamagnetic anisotropy of the double bond. Such an explanation does not account, however, for the rather little change observed in the chemical shift of the quaternary carbon (*cf.* Table II). Again, it is necessary to recognize that the additional double bond of 18 may add significantly to the strain of the ring.

The anisotropy of the allene moiety is also difficult to assess. On the basis of recently reported data for the acyclic allenes,[24,25] one can predict that the ^{13}C chemical shifts of the sp and sp^2 carbons of the allene group would be about −12 and 104 ppm, respectively. From Table II it can be seen that the chemical shifts for cyclic allenes are similar to these estimates. The case of cyclodeca-1,2,6,7-tetraene (19) suggests the possibility of deshielding regions immediately surrounding the sp-hybridized carbons. This idea is supported by comparisons C–E of Table V, which also suggest a complementary shielding region around the remainder of the allene unit. There are two indications, however,

(21) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36**, 2757 (1971).

(22) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, pp 72–73.

(23) G. C. Joshi, G. Negridrappa, and D. Devaprobhakara, *Indian J. Chem.*, **7**, 296 (1969).

(24) R. Sleur, J. P. C. M. van Dongen, M. J. A. de Bie, and W. Drenth, *Tetrahedron Lett.*, 3307 (1971).

(25) J. K. Crandall and S. J. Sojka, *J. Amer. Chem. Soc.*, **94**, 5084 (1972).

that the effect of diamagnetic anisotropy in allenes is small. First, there appears to be no large effect which can be ascribed to anisotropy at the α position. Indeed, the rather irregular chemical-shift changes which do occur at this position may be due largely to the effects of the conformation of the ring. Second, the chemical shift of the alkene carbons of *cis*-cyclononene[11] do not differ significantly from that of the alkene unit of cyclonona-1,2,6-triene.

Conclusions

The present results generally confirm and extend earlier conclusions[5-7] regarding the magnetic anisotropy of the triple bond. The shifts observed show variations which are in general accord with the McConnell equation. However, the observed shifts are several times larger than those observed in proton chemical shifts.

The carbon spectra of the alkenes and allenes do not show large effects which can unambiguously be assigned to magnetic anisotropy. Owing to limitations of the theoretical models of such systems and to the sparse data from proton nmr studies of these compounds, the recognizable effects which do occur are difficult to evaluate and assign to specific causes.

Registry No.—**1**, 871-84-1; **2**, 16387-71-6; **3**, 5601-68-3; **4**, 872-21-9; **5**, 1540-80-3; **6**, 39805-79-3; **7**, 7158-20-5; **8**, 14538-94-4; **9**, 4634-66-6; **10**, 39805-82-8; **11**, 39805-83-9; **12**, 6675-65-6; **13**, 39805-85-1; **14**, 628-41-1; **15**, 111-78-4; **16**, 6108-60-7; **17**, 1123-11-1; **18**, 1502-42-7; **19**, 3451-55-6; **20**, 5601-67-2; **21**, 7129-53-5.

Cycloaddition of Diphenylketene to Some C=N Heterocycles. Structural Assignment and Reactions of Adducts[1]

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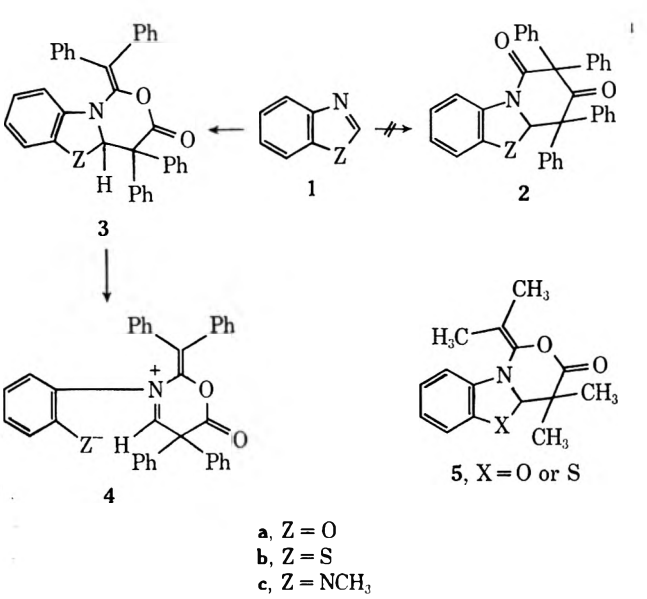
The cycloaddition reactions of diphenylketene to some C=N heterocycles have been reexamined and the adducts are assigned oxazinone (**3** or **4**) rather than amido ketone structures **2**. The reaction of **4** with hydrazine yielded pyrazolinone **7**, whereas sodium methoxide produced the ring-opened ester **6**.

As part of our interest in the cycloaddition reactions of ketenes to olefins and to heterocycles,[2] we investigated the reaction of some heterocyclic imines with diphenylketene.

The cycloaddition of ketenes to imines is known to proceed with formation of 1:1 or of 2:1 adducts. In the latter case six-membered ring products were isolated and assigned structures that ranged from amido ketones[3] or lactones (oxazinones)[4] to dioxazines.[2d] The factors influencing the type of cycloadduct formed have not been examined.

The reactions of diphenylketene with 2-methylthiazoline, *N*-methylimidazole, benzoxazole, benzothiazole, and *N*-methylbenzimidazole were reported by Kimbrough,[3] who found that these heterocycles added to diphenylketene in a 1:2 ratio to give adducts to which he assigned an amido ketone structure, *e.g.*, **2**. These results are surprising in view of the formation of oxazinones from the cycloaddition of dimethylketene with C=N heterocycles.[4] The infrared bands at 1770 cm^{-1} reported by Kimbrough for the adducts from benzoxazole and benzothiazole do not agree with an amido ketone structure **2**. Such adducts are expected to show two strong carbonyl bands at 1710 and 1680 cm^{-1}. In the course of our cycloaddition studies of diphenylketene we reexamined the reported reactions and would like to correct the previous structure assignment and to shed light on some interesting ring-opening reactions that occur in these heterocyclic systems.



Results and Discussion

We were able to reproduce the cycloaddition of diphenylketene to the heterocycles stated above including the infrared data. The diphenylketene adducts from benzoxazole and benzothiazole (**1**, Z = O and S) showed strong carbonyl absorptions at 1770 cm^{-1} and medium bands at 1665 and 1640 cm^{-1}, in addition to strong bands at 1130 cm^{-1} indicative of a

(1) Cycloadditions. XI. For paper X in this series see A. Hassner, A. S. Miller, and M. J. Haddadin, *J. Org. Chem.*, **37**, 2682 (1972).

(2) (a) A. Hassner, V. R. Fletcher, and D. P. G. Hamon, *J. Amer. Chem. Soc.*, **93**, 264 (1971); (b) A. Hassner, and V. R. Fletcher, *Tetrahedron Lett.*, 1071 (1970); (c) *ibid.*, 5053 (1970); (d) A. Hassner, A. S. Miller, and M. J. Haddadin, *ibid.*, 1353 (1972).

(3) R. D. Kimbrough, Jr., *J. Org. Chem.*, **29**, 1242 (1964).

(4) (a) J. C. Martin, K. C. Brannock, R. D. Burpitt, P. Glenn Gott, and V. A. Hoyle, Jr., *J. Org. Chem.*, **36**, 2211 (1971); (b) M. A. Shah and G. A. Taylor, *J. Chem. Soc. C*, 1651 (1970), and other papers in the series; (c) R. Huisgen, B. A. Davis, and M. Morikam, *Angew. Chem., Int. Ed. Engl.*, **7**, 826 (1968).

vinyl ester. The adduct from imidazole or *N*-methylbenzimidazole displayed strong absorptions at 1750 cm^{-1} and very weak bands at 1600 cm^{-1}.

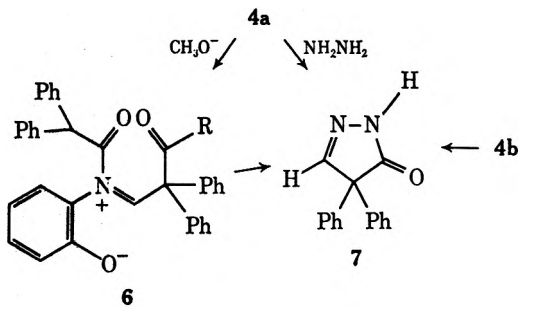
The above facts lead us to conclude that the cycloaddition adducts from **1** and diphenylketene have an oxazinone structure **3**. Analogous oxazinone structures (*e.g.*, **5**) have been assigned to the adducts of dimethylketene to **1a** and **1b**[4a] as well as to ketene adducts of imines and C=N heterocycles.[4]

Interestingly, the nmr spectra of the adducts of **1a** and **1b** with diphenylketene did not show a singlet for the proton at the ring junction in the expected region of τ 4.5–6,[5] whereas the spectrum of the diphenylketene adduct from **1c** and that from *N*-methylimidazole each gave a singlet (1 H) near τ 4.9. A careful inspection of the aromatic region of the adducts from **1a** and **1b** revealed a sharp singlet (1 H) at τ 3.2, which retained its sharpness and shifted downfield on addition of $Eu(fod)_3$ reagent. This low-field absorption strongly suggests that the structure of the diphenylketene adducts to **1a** and **1b** are best represented by the ylides **4a** and **4b**. The adduct derived from **1c** is assigned the ring-closed structure **3c**. These assignments are further corroborated by the position of the methine absorption in the nmr spectra of related systems (see below).[5] The ^{13}C nmr spectrum of **4a** showed two signals at 164 and 156 ppm (downfield from TMS), whereas the adduct **3c** showed one signal at 170 ppm (C=O), with the rest of the signals between 30 and 140 ppm. The low-field singlet at 156 ppm, which was more intense than that at 164 ppm (C=O), is attributable to the iminium carbon in **4**.

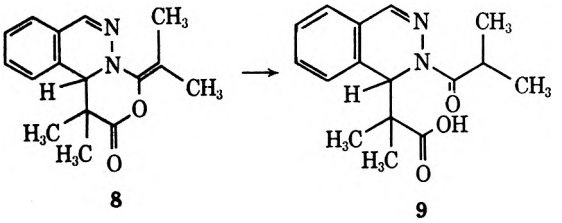
An examination of the molecular model of **3** indicates that, in practically all conformations, there exists a most severe interaction between the ortho-disubstituted aromatic ring and the vinylic phenyl system. Such interaction is markedly minimized in structure **4** owing to increased flexibility. Moreover, the conversion of **3** into **4** is facilitated by the good leaving group property of the phenoxide and thiophenoxide anions. It appears that ring cleavage of **3** to product **4** requires that both of the above factors be operative. Such an assumption is supported by the fact that adduct **3c**, which lacks good leaving group, exists entirely in the tricyclic structure (singlet at τ 4.9) in spite of the presence of steric interaction among the phenyl groups. Secondly, the adducts of dimethylketene to benzoxazole and benzothiazole[4a,5b] showed a singlet (1 H) at τ 4.5–4.8 and therefore possess structure **5**. In this case, less steric interference is experienced by the smaller methyl substituents. The mass spectra of adducts **3c**, **4a**, and **4b** showed weak peaks at $M^+ - CO$ and strong peaks at $M^+ - Ph_2C{=}C{=}O$ (194).

The structure of adduct **4a** was corroborated by the following chemical transformations. Pyrolysis of the adduct yielded benzoxazole and diphenylketene. Whereas treatment of **4a** with methanolic sodium methoxide gave methyl ester **6** (R = OCH_3); reaction with hydrazine afforded diphenylacetylhydrazide and pyrazolinone **7**. The latter was also obtained by refluxing a methanolic solution of **6** (R = OCH_3) with hydrazine, or by treatment of **4b** with hydrazine.

(5) (a) T. A. Crabb and R. F. Newton, *Tetrahedron Lett.*, 3361 (1971). (b) We are grateful to Dr. J. C. Martin for supplying us with the nmr spectra of these adducts.



The formation of **7** most likely involves an attack of hydrazine on the carbonyl carbon of **4a** followed by another attack on the iminium carbon, resulting in ring closure. The possibility that the reaction proceeded by a reverse of the above order was ruled out on the basis of the fact that **4a** reacted with *unsym*-dimethylhydrazine to give **6** [R = $NHN(CH_3)CH_3$]. Treatment of the latter with hydrazine gave **7**. Product **6** (R = OCH_3) showed an M^+ peak at *m/e* 539 and two carbonyl bands at 1735 and 1680 cm^{-1} in the infrared. Its nmr spectrum exhibited three singlets at τ 6.3, 4.3, and 2.08, assigned to the methyl, benzylic hydrogen, and the iminium hydrogen, respectively. It is interesting to note that the iminium hydrogen in ester **6** has shifted downfield by about 1.1 ppm with respect to the proton in **4a**. This effect is probably analogous to the observation of Shah and Taylor,[4b] who reported that the ring junction proton in **8**, which appears at τ 5.2, shifts to 3.6 in the ring-opened **9**. The



structure of pyrazolone **7** was consistent with its spectroscopic data.

Experimental Section[6]

4,4-Diphenyl-1-benzhydrylidene-5 methyl-4*H*-[1,3]oxazino-[4,3-*b*]benzimidazol-3-one (3c).—The title compound was prepared from *N*-methylbenzimidazole (**1c**) and diphenylketene according to ref 3: ir 1750 (s), 1600 (w), 1495, 1390, 1330, 1310, 1245, 1190, 1120 (s), 1080, 1070, 970, 780, 750, and 700 cm^{-1}; pmr τ 6.7 (s, 3 H), 4.9 (s, 1 H), 2.6–2.9 (m, 23 H), 2.05–2.2 (m, 1 H); ^{13}C nmr δ 170, 142, 136, 135.5, 132, 127, 126.8, 125.5, 120, 60.5, 30; mass spectrum M^+ 520, 492, 326, 297, 281, 215, 194, 166, 165, 152, 83, 77.

5,5-Diphenyl-2-benzhydrylidene-*N*-(*o*-phenoxide)-5*H*-[1,3]oxazonia-6-one (4a).—The title compound was prepared from **1a** according to Kimbrough's method:[3] ir 1770 (s), 1670 (m), 1600 (w), 1482, 1230, 1120, 1010, 760, and 705 cm^{-1}; pmr τ 3.2 (s, 1 H), 2.5–3.75 (m, 24). Addition of 45 and 90 mg of $Eu(fod)_3$ to a saturated solution of **4a** in $CDCl_3$ (1.5 ml) shifted the singlet at τ 3.2 to 3 and 2.9, respectively: ^{13}C nmr δ 164, 156.5, 140,

(6) All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were measured in Nujol on a Perkin-Elmer 457 grating spectrometer. Pmr spectra were taken in deuterated chloroform with TMS as an internal reference using a Varian A-60A spectrometer. ^{13}C nmr were measured in chloroform solution with TMS as an internal reference on a JEOL high-resolution JNM-PS-100 instrument. Mass spectra were determined on a Varian M. A. T. CH-5 instrument. Elemental analyses were performed at the Galbraith Laboratories, Inc.

136.5, 136, 135, 134.5, 128, 127, 126, 123.3, 120.5, 117.5, 108.6, 108, 95, 60; mass spectrum M+ 507, 479, 463, 333, 313, 285, 194, 178, 164, 165, 166, 152, 149, 119, 92, 83, 63.

5,5-Diphenyl-2-benzhydrylidene-*N*-(*o*-phenothioxide)-5*H*-[1,3]oxazonia-6-one (4b).—The title compound was prepared from **1b** according to ref 3: ir 1772 (s), 1640 (s), 1480, 1225, 1145, 1020, 760, and 710 cm^{-1}; pmr τ 3.82–4.02 (m, 1 H), 3.15 (s, 1 H), 2.5–3.52 (m, 23 H); ^{13}C nmr δ 166.9, 141.9, 140, 138.1, 137.9, 126.8, 127.0, 127.5, 128.0, 128.5, 129.5, 130.3, 124.9, 122.4, 121.3, 114.8, 112.8, 70.50, 62.54; mass spectrum M+ 523, 507, 495, 301, 195, 194, 163, 164, 165, 166, 167, 139, 135, 126, 115, 108, 97, 92, 77.

***o*-[*N*-(2,2-Diphenylacetyl)-2,2-diphenyl-2-carbomethoxy-*N*-acetiminium] Phenoxide (6).**—Oxazinone **4a** (0.3 g) was dissolved in hot dioxane (20 ml). Methanol (5 ml) containing sodium methoxide (0.3 g) was added to the solution, which turned yellowish. After heating on the steam bath for 5 min, the solution was filtered and the filtrate was diluted with water. The precipitated white solid was collected and treated with hot methanol. The dried white solid weighed 0.28 g, mp 174–176°. The analytical sample that melted at 180° was recrystallized from chloroform–methanol: ir 1738 (s), 1680 (2), 1490, 1265, 1235, 1215, 1180, 1160, 1100, 1025, 760, and 700 cm^{-1}; pmr τ 6.3 (s, 3 H), 4.3 (s, 1 H), 2.5–3.5 (m, 24 H), 2.1 (s, 1 H); mass spectrum M+ 539, 508, 480, 420, 314, 215, 197, 194, 165, 166, 167, 152, 119, 105, 85, 83, 77. *Anal.* Calcd for $C_{36}H_{29}O_4N$ (539.60): C, 80.13; H, 5.42; N, 2.60. Found: C, 80.14; H, 5.45; N, 2.75.

***o*-[*N*-(2,2-Diphenylacetyl)-2,2-diphenyl-2-(*N'*,*N'*-dimethylacylhydrazyl)-*N*-acetiminium] Phenoxide (6).**—Oxazinone **4a** (50 mg) was dissolved in excess *unsym*-dimethylhydrazine (3 ml) and the solution was heated on the steam bath until the solvent evaporated. The gummy residue was treated with ether and the resulting solid was collected (45 mg). The analytical sample was recrystallized from methanol–water and melted at 215°: ir 1680, 1650, 1485, 1260, 1220, 1150, 1030, 1020, 955, 770, and 710 cm^{-1}; pmr τ 7.6 (s, 6 H), 4.2 (s, 1 H), 2.5–3.6 (m, 24 H), 2.15 (s, 1 H); mass spectrum M+ 567, 508, 481, 448, 314, 287, 286, 255, 254, 225, 210, 194, 187, 167, 166, 165, 164, 152, 119, 77. *Anal.* Calcd for $C_{37}H_{33}O_3N_3$ (567.66): C, 78.28; H, 5.86; N, 7.40. Found: C, 78.36; H, 5.92; N, 7.14.

4,4-Diphenyl-5-pyrazolone (7) from 4a.—Oxazinone **4a** (1 g) was placed in hot methanol (15 ml). Hydrazine (95%, 5 ml) was added and the mixture was heated on the steam bath until all the solid (**4a**) dissolved. Water was added and the resulting white solid was collected by suction filtration, washed with water and methanol, and dried: 0.45 g; mp 207°; ir 3420, 1705, 1500, 1360, 840, 760, and 700 cm^{-1}; pmr τ 2.67 (s, 10 H), 2.05 (broad s, 1 H); mass spectrum M+ 236, 207, 194, 179, 166, 165, 152, 139, 102, 77.

Anal. Calcd for $C_{15}H_{12}ON_2$ (236.26): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.06; H, 5.18; N, 11.76.

The mother liquor from the above reaction was left to stand overnight at room temperature. Diphenylacetylhydrazide precipitated, and was identified by comparison with an authentic sample: mp 134°; ir 3420, 1650, 1500, 1370, 1250, 1020, 1010, 750, 730, 700 cm^{-1}; nmr τ 2.6 (m, 2 H), 5.1 (s, 1 H), 3.7, (s, 10 H), 2.35 (m, 1 H).

Conversion of 6 into 4,4-Diphenyl-5-pyrazolone (7).—Product **6** [R = OCH_3 or $NHN(CH_3)_2$] (45 mg) was dissolved in hot methanol (10 ml). Hydrazine (95%, 2 ml) was added to the solution, which was left to stand at room temperature for 24 hr. Dilution with water and neutralization with hydrochloric acid resulted in the precipitation of 4,4-diphenyl-5-pyrazolone (10 mg), mp 207°.

The above procedure was also applied to the conversion of product **4b** into pyrazolone **7**.

Pyrolysis of Oxazinone 4a.—A sample of oxazinone **4a** was placed in a test tube and heated until it melted. The yellow liquid was shown (ir) to be a mixture of diphenylketene and benzoxazole by comparison with an authentic mixture. The identity of benzoxazole was confirmed by tlc on silica gel.

1-Methyl-5-benzhydrylidene-8,8-diphenyl-5*H*,8*H*-imidazo-[3,2-c]-1,3-oxazin-7-one (10).—The title compound was prepared from *N*-methylimidazole and diphenylketene according to ref 3. The product entraps solvent of crystallization (methanol): ir 1748 (s), 1600 (w), 1500, 1315, 1235, 1188, 1125 (s), 1050, 760, 750, and 710 cm^{-1}; pmr τ 6.9 (s, 3 H), 4.9 (s, 1 H), 3.35 (m, 1 H), 2.6–3.18 (m, 21 H); mass spectrum M+ 470, 276, 247, 194, 167, 165, 152, 83, 82.

Registry No.—**1a**, 273-53-0; **1b**, 95-16-9; **1c**, 1632-83-3; **3c**, 40110-18-7; **4a**, 40110-19-8; **4b**, 40110-20-1; **6** (R = OMe), 40317-83-7; **6** (R = $NHNMe_2$), 40110-21-2; **7**, 40110-22-3; **10**, 40110-23-4; diphenylketene, 525-06-4; sodium methoxide, 124-41-4; *unsym*-dimethylhydrazine, 57-14-7; hydrazine, 302-01-2; diphenylacetylhydrazide, 6636-02-8; *N*-methylimidazole, 616-47-7.

Acknowledgment.—Support of this research by PHS Grant CA4474 from the National Cancer Institute is gratefully acknowledged.

The Chemistry of a Ketene–Sulfur Dioxide Adduct. II. Reactions with Heterocumulenes

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The reaction of ketenimines with ketene in anhydrous liquid sulfur dioxide gave substituted 1,2-oxathiane-4-one 2-oxides. The structures of these compounds were verified by both chemical and spectral methods. *p*-Tolylsulfonyl isocyanate reacted with ketene in liquid sulfur dioxide to yield *N*-(*p*-tolylsulfonyl)-3-thiazolidine-2,4-dione 1,1-dioxide. In addition, substituted 2,1,5-benzothiadiazepin-4-one 2-oxides were obtained from the corresponding *o*-phenylenediamine, ketene, and sulfur dioxide. The mechanisms of these reactions were believed to involve a ketene–sulfur dioxide adduct as a common intermediate. This reactive species was isolated and intercepted at low temperatures. During the course of this investigation, ketene was also found to react with *N*-sulfinylaniline to give *N*-phenyl-1,2-thiazetidin-3-one 1-oxide.

The cycloaddition of imines with ketene in liquid sulfur dioxide was described in earlier publications.[1,2] The mechanisms of the reactions discussed were believed to involve an intermediate formed from ketene and sulfur dioxide Although the isolation of the presumed adduct was not accomplished, its existence was detected by a low-temperature nmr study. Recently, we have observed other cycloadditions involving the ketene–sulfur dioxide adduct and certain heterocumulenes such as ketenimines. In addition, we offer further proof for the existence of such an adduct by its low-temperature isolation and interception with appropriate reagents.

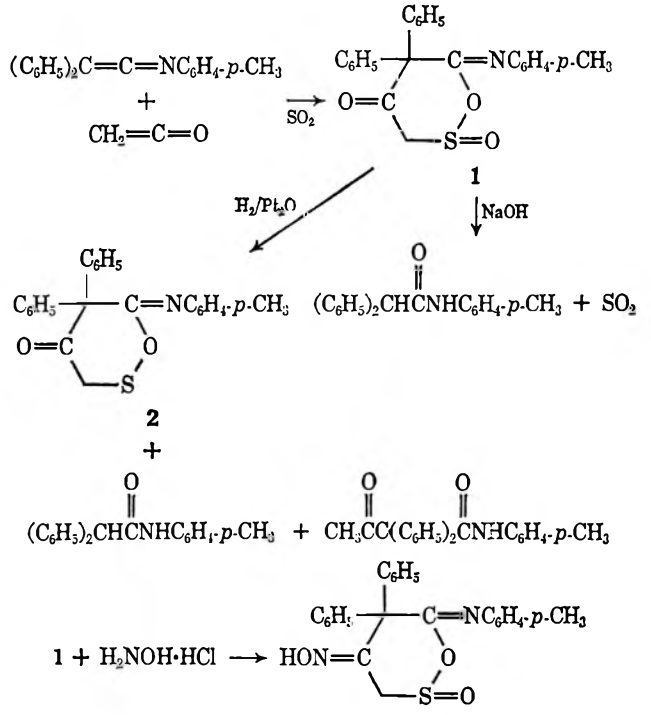
(1) A. S. Gomes and M. M. Joullié, *Chem. Commun.*, 935 (1967).
(2) A. S. Gomes and M. M. Joullié, *J. Heterocycl. Chem.*, **6**, 729 (1969).

Results and Discussion

The first investigation required the preparation of various ketenimines. These compounds were synthesized by the linear dehydration of substituted amides by either one of two methods. One procedure utilized a mixture of phosphorus pentoxide and alumina in pyridine[3] while the other employed triphenylphosphine dibromide and triethylamine in dichloromethane[4] as the dehydrating agents.

When diphenylketene-*N*-(*p*-tolyl)imine was treated with ketene in liquid sulfur dioxide, a white, crystalline product was obtained and postulated to be 5,5-diphenyl-6-(*p*-tolylimino)-1,2-oxathian-4-one 2-oxide (**1**). This structure was established by both instrumental and chemical methods (Scheme I).[5]

SCHEME I

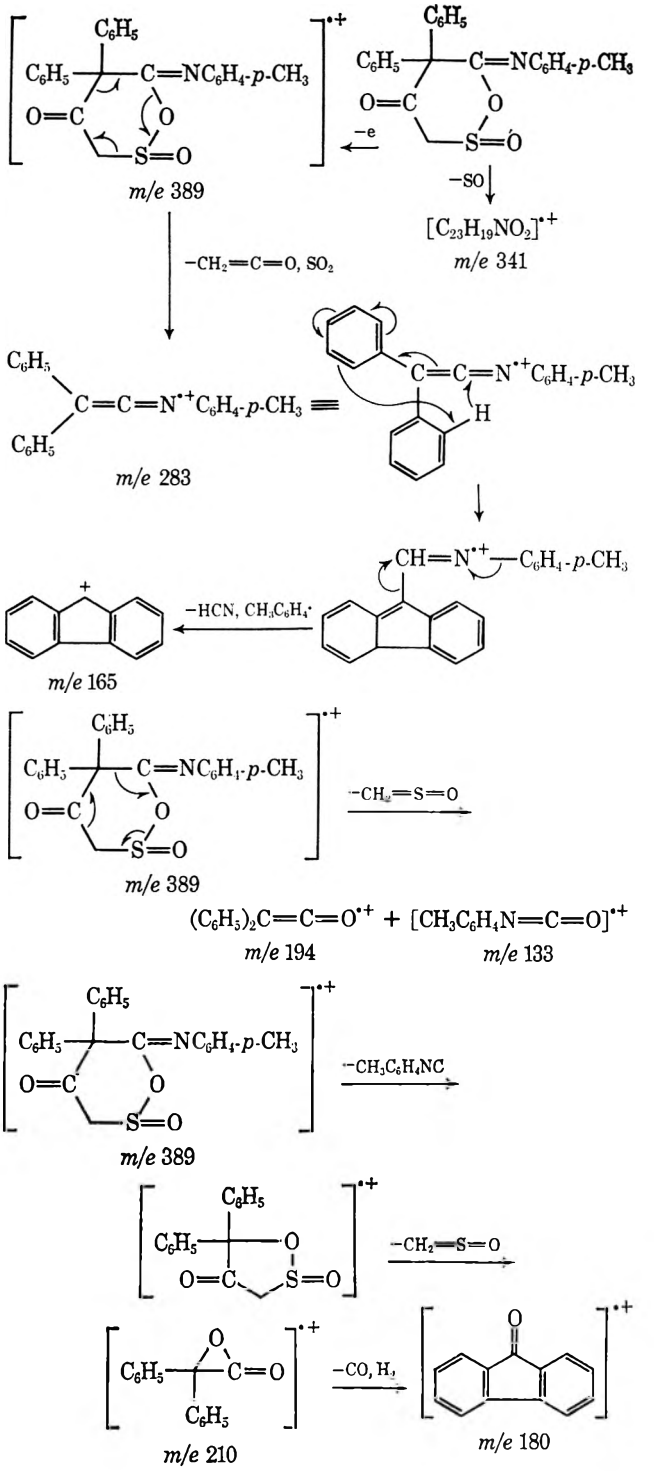


In addition to ir and nmr data, the mass spectral fragmentation of **1** was very useful in confirming the postulated structure (Scheme II).

The molecular ion (*m/e* 389), once generated, may undergo three modes of decomposition. The loss of both a molecule of ketene and a molecule of sulfur dioxide gives the ion radical (*m/e* 283) which undergoes further decomposition to form the fluorenyl cation (*m/e* 165). Both the diphenylketene (*m/e* 194) and the isocyanate (*m/e* 133) ion radicals may result from loss of a sulfene molecule from the molecular ion. Another fragmentation path may involve the loss of an isonitrile and subsequent elimination of sulfene to give the ion radical at *m/e* 210, which gives rise by further decomposition to the ion radical at *m/e* 180.

The mass spectrum of diphenylketene-*N*-(*p*-tolyl)-imine helped to elucidate the fragmentation pattern of **1**. The two major peaks in this spectrum appeared at the following *m/e* ratios: 283 (molecular ion) and 165

SCHEME II



due to $C_{13}H_9$. This observation established the fragmentation of the ketenimine as a possible source of the fluorenyl cation. The proposed mechanism for the formation of this ion is similar to the one postulated for the fragmentation of the anil of benzophenone.[6]

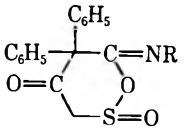
To further clarify the decomposition route of **1**, the mass spectrum of 5,5-diphenyl-6-(*p*-tolylimino)-1,2-oxathian-4-one (**2**) was also investigated. The spectrum of **2** exhibited peaks at *m/e* 373 (molecular ion), 331 (loss of $CH_2{=}C{=}O$), 198 [$(C_6H_5)_2C{=}S\cdot^+$], and 194 [$(C_6H_5)_2C{=}C{=}O\cdot^+$]. However, a peak at *m/e*

(3) C. L. Stevens and G. H. Singhal, *J. Org. Chem.*, **29**, 34 (1963).
(4) H. G. Bestmann, J. Lienert, and L. Mott, *Justus Liebigs Ann. Chem.*, **718**, 24 (1968).
(5) J. M. Bohen and M. M. Joullié, *Tetrahedron Lett.*, 1815 (1971).
(6) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

283 corresponding to $(C_6H_5)_2C{=}C{=}NC_6H_4\text{-}p\text{-}CH_3\cdot^+$ was conspicuously missing from the spectrum. In the case of **1**, both ketene and sulfur dioxide can be lost to generate the *m/e* 283 peak. This type of fragmentation is not possible with **2**.

Additional reactions were performed with various ketenimines in order to establish the general nature of the ketene–sulfur dioxide cycloaddition. The results of these reactions are summarized in Table I.

TABLE I
SUBSTITUTED 1,2-OXATHIAN-4-ONE 2-OXIDES



Compd	R	Mp, °C[a]	Yield, %
1	$C_6H_4\text{-}p\text{-}CH_3$	207–208	57
3	$C_6H_4\text{-}p\text{-}Br$	206–207	64
4	$C_6H_4\text{-}p\text{-}SCH_3$	177–178	40
5	$C_6H_4\text{-}p\text{-}SO_2CH_3$	247–248	51
6	C_6H_5	212–213	37

[a] All compounds decomposed at their melting point.

Each of the synthesized 1,2-oxathianes (**3–6**) exhibited strong absorptions in the following regions of the infrared spectrum: 1736–1720 (>C=O), 1695–1675 (>C=N–), and 1070–1060 cm^{-1} (>S=O). The nmr spectra of the 1,2-oxathianes displayed the characteristic AB quartet for the nonequivalent methylene ring protons. Finally, the same fragmentation pattern (see Scheme II) was observed in the mass spectra of each of the synthesized compounds. Peak shifts were encountered owing to the difference of substituents on R.

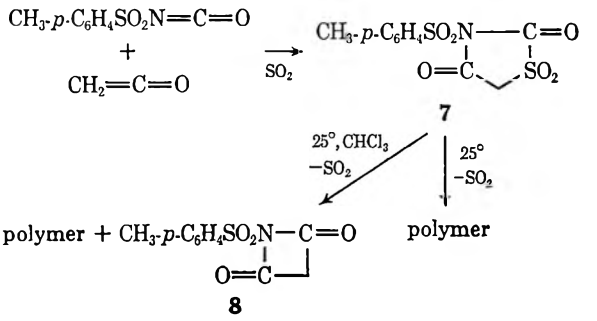
The reaction of ketenimines with the ketene–sulfur dioxide adduct was successful only when the heterocumulene was substituted with three aryl groups. Neither electron-donating nor electron-withdrawing groups on R seemed to have a pronounced effect on the cycloaddition. No 1,2-oxathianes were isolated from dimethylketene-*N*-phenylimine, diphenylketene-*N*-(*n*-butyl)imine, and isopropylketene-*N*-phenylimine, since these ketenimines resinified under the reaction conditions.

To extend our study of cycloadditions, we investigated the reaction of the isocyanates with the ketene–sulfur dioxide adduct. Both aryl and alkyl isocyanates were found to be unreactive. However, when the highly active *p*-tolylsulfonyl isocyanate was treated with ketene in anhydrous liquid sulfur dioxide at −10°, a white solid (**7**) resulted. This product was found to be unstable at room temperature and slowly decomposed to polymeric material with evolution of sulfur dioxide. When the decomposition was allowed to occur in chloroform, *N*-(*p*-tolylsulfonyl)malonimide (**8**) was isolated (Scheme III).

The ir spectrum ($CHCl_3$) of **7** exhibited a strong carbonyl absorption at 1705 cm^{-1}. This absorption is consistent with the value of 1700 cm^{-1} reported for the carbonyls of five-membered cyclic imides.[7] As **7** decomposed, the peak at 1705 cm^{-1} disappeared with the concurrent formation of a small peak at 1770 cm^{-1} (characteristic of the carbonyls of **8**).

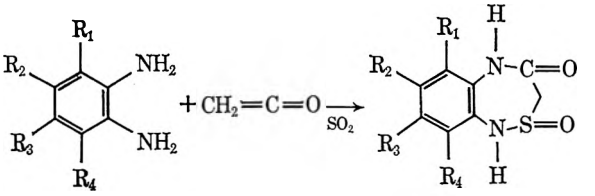
(7) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965.

SCHEME III



The reactions of the ketene–sulfur dioxide adduct with aromatic amines were extended to substituted *o*-phenylenediamines. When 3,6-dimethoxy-*o*-phenylenediamine and 4,5-dimethyl-*o*-phenylenediamine were treated with ketene in liquid dioxide, the corresponding 2,1,5-benzothiadiazepin-4-one 2-oxides resulted (Scheme IV).

SCHEME IV



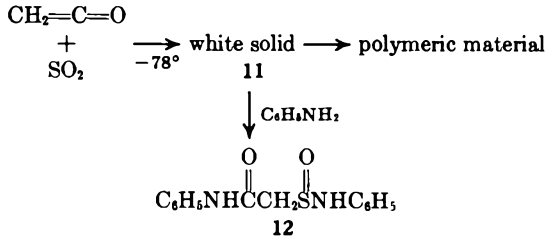
9, $R_1 = R_4 = H$; $R_2 = R_3 = CH_3$
10, $R_1 = R_4 = OCH_3$; $R_2 = R_3 = H$

Compounds **9** and **10** are both derivatives of a new ring system, 2,1,5-benzothiadiazepine, first synthesized in our laboratory.[2] The structures assigned to **9** and **10** were supported by analytical and spectral data. The ir spectra of both compounds showed the characteristic absorptions of an amide, 3200–3190 (>NH) and 1670–1664 cm^{-1} (>C=O), in addition to the strong absorption of a sulfinamide at 1075–1063 cm^{-1} (>S=O). The nmr spectra of both compounds exhibited an AB quartet for the nonequivalent methylene ring protons.

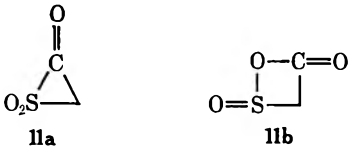
Since the cycloadditions discussed were believed to involve a ketene–sulfur dioxide adduct, the isolation of this adduct was attempted. When sulfur dioxide was mixed with an excess of ketene at −78° *in vacuo*, a white solid (**11**) formed. The excess ketene was removed by distillation, leaving only **11** in the reaction cell. When the solid was warmed to room temperature, decomposition occurred with evolution of sulfur dioxide. When **11** was treated with aniline in acetone at −78°, 2-(phenylsulfinamoyl)acetanilide (**12**) was formed (Scheme V).

The nmr spectrum of **11** in liquid sulfur dioxide at −67° exhibited a singlet at δ 2.30. This value was in agreement with the one observed in our first nmr study.[2] When the sample was allowed to decompose at higher temperatures, this peak disappeared. The chemical shift of the protons of **11** is more consistent with a three-

SCHEME V



rather than a four-membered ring structure (**11a** or **11b**).

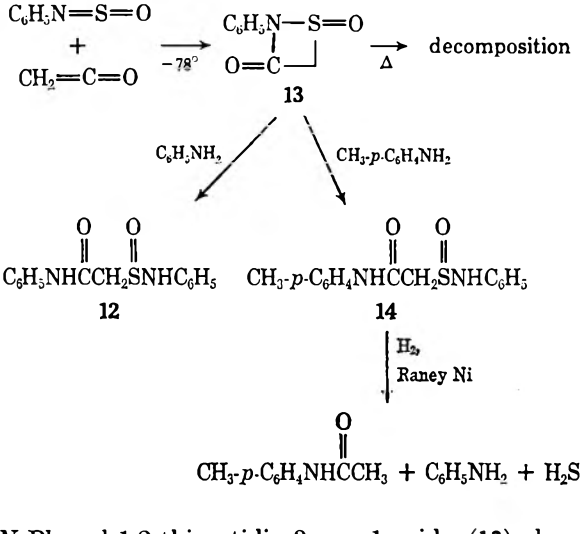


11a **11b**

This is supported by a low-temperature (−77°) nmr study of the nitrogen analog (**13**) of **11b**. The methylene protons of *N*-phenyl-1,2-thiazetidin-3-one 1-oxide (**13**) appeared as a singlet at δ 4.58. As the temperature was decreased slowly, this singlet began to broaden into a multiplet. The singlet observed for the ketene–sulfur dioxide adduct was not affected by a temperature decrease.

Although the cycloaddition of aromatic ketenes with both aliphatic and aromatic *N*-sulfinylamines and *N*-sulfinylsulfonamides has been previously described,[8-10] no products have been isolated from the reaction of these compounds with ketene. We have prepared **13** by the reaction of *N*-sulfinylaniline and ketene at −78° (Scheme VI).

SCHEME VI



N-Phenyl-1,2-thiazetidin-3-one 1-oxide (**13**) decomposed when warmed to room temperature. However, when it was treated with aniline at −78°, 2-(phenylsulfinamoyl)acetaniline (**12**) was obtained. The reaction of **13** with *p*-toluidine gave 2-(phenylsulfinamoyl)-*p*-acetotoluidide (**14**) exclusively. The structure of **14** was supported by its reduction with Raney nickel, which yielded only *N*-(*p*-tolyl)acetamide and aniline.

(8) G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Trede, *Angew. Chem., Int. Ed., Engl.*, **1**, 89 (1962).

(9) H. Beecken and F. Korte, *Tetrahedron*, **18**, 1527 (1962).

(10) G. Kresze and W. Wucherpfennig, *Angew. Chem., Int. Ed. Engl.*, **6**, 149 (1969).

Experimental Section

All microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Midwest Microlab, Ltd., Indianapolis, Ind. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were taken on a Perkin-Elmer 521 double beam recording spectrophotometer. Nmr spectra were determined on a Varian A-60A spectrometer. Chemical shifts are expressed in δ (parts per million) downfield from TMS. Mass spectra were obtained on a Consolidated Electrodynamics Corp. CEC-110 (double focusing) mass spectrometer. Brinkmann aluminum oxide F-254 (1.5 mm) and silica gel F-254 (2.0 mm) precoated 20 × 20 mm glass plates were employed for preparative thin layer chromatography.

Materials.—Ketene was prepared by the pyrolysis of acetone in a ketene generator. When necessary, samples of ketene were purified on a vacuum system by the following method. Both stopcocks on a gas collection trap were closed. The exit port was connected to a calcium chloride drying tube and the inlet to the generator. The stopcocks were opened and ketene was allowed to pass through the trap for a few minutes. The trap was then immersed into a dewar flask containing a Dry Ice–acetone mixture (−78°). When a sample of ketene had been collected, the stopcocks were closed and the trap was disconnected from the generator. The sample was cooled to −195° in a liquid nitrogen bath and evacuated on the vacuum system to a pressure of less than 10^{-3} mm. The collection trap was slowly warmed to −78° and the gas was distilled through a trap cooled to −78° and collected in a second trap at −195°. The distillation was repeated. The pure sample of ketene was stored at −195° *in vacuo* until it was used.

The cell used for low-temperature reactions consisted of a 28 × 180 mm Pyrex tube joined to a stopcock. A 18/7 ball joint was attached to the stopcock in order to connect the vessel to the vacuum system.

All low-temperature nmr studies were performed on samples sealed in evacuated nmr tubes.

Synthesis of Ketenimines.—The yields, principal ir absorptions (>C=C=N–),[11] and melting or boiling points of the cumulenes are indicated in parentheses. The following ketenimines were synthesized by the method of Stevens and Singhal:[3] diphenylketene-*N*-(*p*-tolyl)imine (86.5%, 1990 cm^{-1}, mp 82–83°), diphenylketene-*N*-(*p*-bromophenyl)imine (71.5%, 2000 cm^{-1}, mp 79–80.5°), and diphenylketene-*N*-(*p*-methylthiophenyl)-imine (83.5%, 1960 cm^{-1}, mp 79–81°). Diphenylketene-*N*-(*p*-methylsulfonylphenyl)imine (66.7%, 1980 cm^{-1}, mp 138.5–139.5°), diphenylketene-*N*-phenylimine (80.5%, 2005 cm^{-1}, mp 54–56°), diphenylketene-*N*-*n*-butylimine [25.0%, 2015 cm^{-1}, bp 136–140° (0.1 mm)], dimethylketene-*N*-phenylimine [27.3%, 2010 cm^{-1}, 47–48° (0.1 mm)], and isopropylketene-*N*-phenylimine [66.1%, 2010 cm^{-1}, bp 47–48° (0.1 mm)] were prepared by the method of Bestmann, *et al.*[4]

5,5-Diphenyl-6-(*p*-tolylimino)-1,2-oxathian-4-one 2-Oxide (1).—The general procedure for the reaction of ketene with ketenimines in anhydrous sulfur dioxide is described in the preparation of this compound.

Diphenylketene-*N*-(*p*-tolyl)imine (2.8 g, 0.01 mol) was placed in a 50-ml, two-necked, round-bottomed flask fitted with a gas inlet tube, Dry Ice condenser, and a calcium chloride drying tube. Anhydrous sulfur dioxide (25 ml) was condensed into the reaction flask. The reaction mixture was cooled to −78°. Ketene was generated and bubbled through the solution at a rate of 0.408 mol per 1 hr for 20 min. At the end of the ketene addition, the delivery tube was replaced with a stopper. The amber solution was stirred for 45 min without the use of the Dry Ice–acetone bath. The excess sulfur dioxide was removed *in vacuo* and the resulting brown tar was dissolved in 75 ml of methanol. The solution was allowed to stand overnight at room temperature. The solid that formed was collected by filtration, washed with cold methanol, and then recrystallized from absolute methanol. The yield of I was 1.6 g (57.2%): mp 207–208° dec; ir (KBr) 1720 (>C=O), 1675 (>C=N–), and 1063 cm^{-1} (>S=O); nmr ($CDCl_3$) δ 2.38 (s, 3 H), 3.57 (d, 1 H, J = 17.0 Hz), 4.08 (d, 1 H, J = 17.0 Hz), and 7.34 (m, 14 H); mass spectrum m/e 389, 341, 283, 210, 194, 180, 165, and 133.

Anal. Calcd for $C_{23}H_{19}NSO_3$: C, 70.93; H, 4.92; N, 3.60; S, 8.24. Found: C, 70.72; H, 4.96; N, 3.72; S, 8.40.

(11) Spectra were determined as solutions in $CHCl_3$.

Reduction of 5,5-Diphenyl-6-(*p*-tolylimino)-1,2-oxathian-4-one 2-Oxide.—A catalytic amount of platinum oxide was added to a solution of 0.5 g (1.2×10^{-3} mol) of 1 dissolved in 250 ml of ethanol. The suspension was shaken for 4 hr under 60 psi of hydrogen on a Parr hydrogenator. The ethanolic solution was filtered to remove the catalyst and then concentrated. The solution was allowed to stand overnight at room temperature. The solid that formed was collected by filtration, washed with cold methanol, and then recrystallized from absolute methanol. The yield of 5,5-diphenyl-6-(*p*-tolylimino)-1,2-oxathian-4-one (2) was 385 mg (82.5%): mp 208–209° dec; ir (KBr) 1725 (>C=O) and 1690 cm^{-1} (>C=N–); nmr ($CDCl_3$) δ 2.36 (s, 3 H), 3.55 (s, 2 H), and 7.17 (m, 14 H); mass spectrum *m/e* 373, 331, 198, and 194.

Anal. Calcd for $C_{23}H_{19}NSO_2$: C, 73.97; H, 5.15; N, 3.75; S, 8.58. Found: C, 73.97; H, 5.28; N, 3.71; S, 8.66.

A second sample of 0.5 g was reduced under the conditions described above for 9 hr. Concentration of the ethanolic solution yielded 230 mg (63.7%) of *N*-(*p*-tolyl)diphenylacetamide, which was collected by filtration: mp 178–179° (lit.[3] mp 178–179°); ir (KBr) 3300, 3260 (>NH), and 1660 cm^{-1} (>C=O); nmr (DMSO-d_6) δ 2.18 (s, 3 H), 5.15 (s, 1 H), 7.28 (m, 14 H), and 10.3 (s, 1 H). The ethanol filtrate was chromatographed on a preparative alumina thin layer plate with benzene. A white solid (8 mg) was isolated and identified as *N*-(*p*-tolyl)-α,α-diphenylacetoacetamide: ir (KBr) 3318, 3200 (>NH), 1690 (>C=O), and 1671 cm^{-1} (>C=O amide); nmr (DMSO-d_6) δ 2.37 (s, 3 H), 2.39 (s, 3 H), 7.00 (m, 14 H), and 7.92 (s, 1 H).

Hydrolysis of 5,5-Diphenyl-6-(*p*-tolylimino)-1,2-oxathian-4-one 2-Oxide (1).—A solution of 0.5 g (0.014 mol) of sodium hydroxide in 5 ml of water was added slowly to a stirred solution of 1.0 g (2.4×10^{-3} mol) of 1 dissolved in 150 ml of methanol. The reaction mixture turned yellow with evolution of sulfur dioxide. The solution was stirred for 20 min at room temperature. The reaction mixture was concentrated *in vacuo* and the resulting solid was collected by filtration. The solid was washed with water until the washings were neutral to litmus. The crude solid was recrystallized from methanol. The yield of *N*-(*p*-tolyl)-diphenylacetamide was 450 mg (62.3%): mp 178–179° (lit.[3] mp 178–179°); ir (KBr) 3300, 3260 (>NH), and 1660 cm^{-1} (>C=O); nmr (DMSO-d_6) δ 2.18 (s, 3 H), 5.15 (s, 1 H), 7.28 (m, 14 H), and 10.3 (s, 1 H).

5,5-Diphenyl-6-(*p*-bromophenylimino)-1,2-oxathian-4-one 2-Oxide (3).—Compound 3 was obtained in 63.7% yield: mp 206–207° dec; ir (KBr) 1726 (>C=O), 1683 (>C=N–), and 1070 cm^{-1} (>S=O); nmr ($CDCl_3$) δ 3.56 (d, 1 H, *J* = 17.0 Hz), 4.05 (d, 1 H, *J* = 17.0 Hz), and 7.38 (m, 14 H); mass spectrum *m/e* 455, 453, 407, 405, 349, 347, 210, 194, 180, and 165.

Anal. Calcd for $C_{22}H_{16}NSO_3Br$: C, 58.16; H, 3.55; N, 3.09; S, 7.06; Br, 17.59. Found: C, 57.91; H, 3.42; N, 3.20; S, 7.16; Br, 17.80.

5,5-Diphenyl-6-(*p*-methylthiophenylimino)-1,2-oxathian-4-one 2-Oxide (4).—Compound 4 was obtained in 40.4% yield: mp 177–178° dec; ir (KBr) 1725 (>C=O), 1684 (>C=N–), and 1063 cm^{-1} (>S=O); nmr ($CDCl_3$) δ 2.48 (s, 3 H), 3.62 (d, 1 H, *J* = 17.0 Hz), 4.10 (d, 1 H, *J* = 17.0 Hz), and 7.81 (m, 14 H); mass spectrum *m/e* 421, 373, 315, 210, 194, 180, and 165.

Anal. Calcd for $C_{23}H_{19}NS_2O_3$: C, 65.53; H, 4.54; N, 3.32; S, 15.21. Found: C, 65.34; H, 4.58; N, 3.25; S, 15.46.

5,5-Diphenyl-6-(*p*-methylsulfonylphenylimino)-1,2-oxathian-4-one 2-Oxide (5).—Compound 5 was obtained in 50.6% yield: mp 247–248° dec; ir (KBr) 1736 (>C=O), 1693 (>C=N–), and 1068 cm^{-1} (>S=O); nmr (DMSO-d_6) δ 3.27 (s, 3 H), 3.84 (d, 1 H, *J* = 17.0 Hz), 4.52 (d, 1 H, *J* = 17.0 Hz), and 7.81 (m, 14 H); mass spectrum *m/e* 453, 405, 347, 210, 194, 180, and 165.

Anal. Calcd for $C_{23}H_{19}NS_2O_5$: C, 60.91; H, 4.22; N, 3.09; S, 14.14. Found: C, 61.19; H, 4.27; N, 2.96; S, 14.18.

5,5-Diphenyl-6-phenylimino-1,2-oxathian-4-one 2-Oxide (6).—Compound 6 was obtained in 37.4% yield: mp 212–213° dec; ir (KBr) 1729 (>C=O), 1687 (>C=N–), and 1068 cm^{-1} (>S=O); nmr ($CDCl_3$) δ 3.57 (d, 1 H, *J* = 17.0 Hz), 4.05 (d, 1 H, *J* = 17.0 Hz), and 7.35 (m, 15 H); mass spectrum *m/e* 375, 327, 269, 210, 194, 180, and 165.

Anal. Calcd for $C_{22}H_{17}NSO_3$: C, 70.38; H, 4.56; N, 3.73; S, 8.54. Found: C, 70.10; H, 4.72; N, 3.75; S, 8.38.

***N*-(*p*-Tolylsulfonyl)-thiazolidine-2,4-dione 1,1-Dioxide (7).**—*p*-Tolylsulfonyl isocyanate (10.0 g, 0.05 mol) was placed in a 250-ml, two-necked, round-bottomed flask fitted with a gas inlet tube, Dry Ice condenser, and a calcium chloride drying tube. Sulfur dioxide (100 ml) was condensed into the reaction flask and the resulting solution was cooled to −78°. Ketene was generated and bubbled through the reaction mixture at a rate of 0.408 mol per 1 hr for 30 min. When the addition was completed, the delivery tube was replaced with a stopper. The solution was stirred for 1 hr at −78°. The reaction mixture was slowly warmed to −10° and stirred at this temperature for an additional 20 min. The solution was concentrated and the resulting white solid was collected by filtration. The dry solid started to decompose with evolution of sulfur dioxide. When a portion of the solid was dissolved in chloroform, decomposition continued. When gas evolution ceased, the chloroform was evaporated under reduced pressure and a white solid was isolated. The solid was recrystallized from ethyl acetate and identified as *N*-(*p*-tolylsulfonyl)malonimide (8): mp 139–141° dec (lit.[12] mp 144–147° dec); ir (KBr) 1780 (>C=O), 1300, and 1170 cm^{-1} ($-SO_2-$); nmr (acetone-d_6) δ 2.62 (s, 3 H), 4.14 (s, 2 H), 7.92 (d, 2 H, *J* = 9.2 Hz), and 8.36 (d, 2 H, *J* = 9.2 Hz).

2,1,5-(4,5-Dimethyl)benzothiadiazepin-4-one 2-Oxide (9).—The apparatus and procedure used were the same as those described for the preparation of compound 8. Pure 4,5-dimethyl-*o*-phenylenediamine (5.0 g, 0.036 mol) was mixed with 100 ml of liquid sulfur dioxide. The yellow solid that resulted was attributed to an adduct formed from the amine and sulfur dioxide. Ketene was generated and bubbled through the suspension at a rate of 0.408 mol per 1 hr for 45 min. When the addition was completed, the delivery tube was replaced with a stopper. The suspension was stirred for 45 min without the use of the Dry Ice–acetone bath. The excess sulfur dioxide was removed *in vacuo* and the resulting brown residue was dissolved in 100 ml of methanol. The solid that formed was collected by filtration, washed with cold methanol, and recrystallized from absolute methanol. The yield of 9 was 4.1 g (50.8%): mp 226–227° dec; ir (KBr) 3190 (>NH), 1670 (>C=O), and 1060 cm^{-1} (>S=O); nmr (DMSO-d_6) δ 2.17 (s, 6 H), 3.17 (d, 1 H, *J* = 12.0 Hz), 3.90 (d, 1 H, *J* = 12.0 Hz), 6.93 (m, 2 H), 8.62 (s, 1 H), and 9.43 (s, 1 H).

Anal. Calcd for $C_{10}H_{12}N_2SO_2$: C, 53.55; H, 5.39; N, 12.49; S, 14.30. Found: C, 53.77; H, 5.44; N, 12.64; S, 14.20.

2,1,5-(3,6-Dimethoxy)benzothiadiazepin-4-one 2-Oxide (10).—The apparatus and procedure used were the same as those described for the preparation of compound 8. Pure 3,6-dimethoxy-*o*-phenylenediamine (5.0 g, 0.037 mol) yielded 3.6 g (51.6%) of 10: mp 230–231° dec; ir (KBr) 3200, 3120 (>NH), 1664 (>C=O), and 1063 cm^{-1} (>S=O); nmr (DMSO-d_6) δ 3.17 (d, 1 H, *J* = 12.2 Hz), 3.77 (s, 6 H), 3.90 (d, 1 H, *J* = 12.2 Hz), 6.90 (s, 2 H), 8.40 (s, 1 H), and 9.30 (s, 1 H).

Anal. Calcd for $C_{10}H_{12}N_2SO_4$: C, 46.86; H, 4.72; N, 10.93; S, 12.51. Found: C, 46.96; H, 4.68; N, 10.83; S, 12.31.

Isolation and Interception of the Ketene–Sulfur Dioxide Adduct (11).—On a vacuum system, a pure sample of anhydrous sulfur dioxide was distilled into an evacuated reaction cell cooled to −195°. Ketene was generated, collected, and purified as previously described. The pure sample of ketene was distilled into the reaction vessel in excess. The stopcock on the cell was closed when the addition of the ketene was completed. The temperature of the mixture was slowly raised to −78°. The solution was maintained at this temperature for 1 hr. During this period, a white solid formed in the vessel. The excess ketene was removed by distillation. The stopcock was closed and the cell was removed from the vacuum system. The temperature of the cell was slowly raised to 25°. The white solid decomposed with evolution of gases and formation of a brown tar.

A second sample of the ketene–sulfur dioxide adduct was prepared as described above. Freshly distilled aniline (1.0 g) was dissolved in 10 ml of anhydrous acetone and the resulting solution was cooled to −78°. The aniline solution was slowly added to the adduct. The reaction mixture was maintained at −78° for 1 hr, when the addition of the aniline was completed. The solution was then warmed to room temperature. Methanol was added and the resulting white solid was collected by filtration. The solid was recrystallized from absolute methanol. The yield of 2-(phenylsulfinamoyl)acetanilide (12) was 127 mg: mp 172–173° dec (lit.[2] mp 167–168° dec); ir (KBr) 3280, 3250 (>NH), 1655 (>C=O), and 1062 cm^{-1} (>S=O); nmr (DMSO-

(12) J. C. Martin, R. D. Burpitt, P. G. Goth, M. Harris, and R. H. Meen, *J. Org. Chem.*, **36**, 2205 (1971).

d_6) δ 4.55 (s, 2 H), 7.28 (m, 10 H), 9.08 (s, 1 H), and 10.3 (s 1 H).

N-Phenyl-1,2-thiazetidin-3-one 1-Oxide (13).—In a reaction cell, 0.5 g (3.7×10^{-3} mol) of pure sulfinylaniline was dissolved in 25 ml of dry acetone. The mixture was cooled to −195° and the vessel was evacuated to a pressure of less than 10^{-3} mm on the vacuum system. Ketene was generated, collected, and purified as previously described. The pure ketene was distilled into the reaction cell. The temperature of the mixture was slowly raised to −78°. The solution was stirred at this temperature for 2 hr. During this period, the orange solution became colorless and a white solid formed. The reaction mixture was slowly warmed to room temperature. The solid decomposed with evolution of ketene. The acetone was evaporated under reduced pressure and the resulting oil was chromatographed on a dry column of silica gel with benzene. Only sulfinylaniline and polymeric materials were isolated.

Interception of *N*-Phenyl-1,2-thiazetidin-3-one 1-Oxide (13) with Aniline and *p*-Toluidine.—A sample of *N*-phenyl-1,2-thiazetidin-3-one 1-oxide (13) was prepared as described above. A solution of aniline (1.0 g) in 10 ml of dry acetone was cooled to −78° and then added slowly to the reaction mixture. The solution was allowed to stand at −78° overnight. It was then warmed to room temperature and the white solid was collected by filtration. The solid was recrystallized from methanol. The yield of 2-(phenylsulfinamoyl)acetanilide was 463 mg (45.8%): mp 172–173° dec (lit.[2] mp 167–168° dec); ir (KBr) 3280, 3250 (>NH), 1655 (>C=O), and 1062 cm^{-1} (>S=O); nmr (DMSO-d_6) δ 4.55 (s, 2 H), 7.28 (m, 10 H), 9.08 (s, 1 H), and 10.3 (s, 1 H).

A second sample of 13 prepared as described above was treated with a solution of *p*-toluidine (1.0 g) dissolved in 10 ml of dry acetone. The yield of 2-(phenylsulfinamoyl)-*p*-acetotoluidide (14) was 1.45 g (58.3%): mp 181–182° dec; ir (KBr) 3225, 3185 (>NH), 1650 (>C=O), and 1049 cm^{-1} (>S=O); nmr (DMSO-d_6) δ 2.27 (s, 3 H), 4.12 (s, 2 H), 7.25 (m, 9 H), 9.23 (s, 1 H), and 10.3 (s, 1 H).

Anal. Calcd for $C_{15}H_{16}N_2SO_2$: C, 62.48; H, 5.59; N, 9.71; S, 11.12. Found: C, 62.70; H, 5.82; N, 9.58; S, 11.05.

Reduction of 2-(Phenylsulfinamoyl)-*p*-acetotoluidide (14).—A solution of 70 mg (2.4×10^{-4} mol) of 14 dissolved in 30 ml of absolute ethanol was placed in a 50-ml, round-bottomed flask, fitted with a condenser. Raney nickel W-4 (500 mg) was added to the solution. The reaction mixture was heated under reflux overnight. The hot solution was filtered to remove the catalyst. The ethanol was evaporated under reduced pressure and the residue was chromatographed on a preparative alumina thin layer plate with ether. The major band (R_f 0.49) was isolated and the alumina was leached with acetone. The acetone was evaporated under reduced pressure and the resulting white solid was recrystallized from chloroform. The yield of *N*-(*p*-tolyl)-acetamide was 16 mg (44.5%): mp 155–156° (lit.[13] mp 155–156°); ir (KBr) 3215 (>NH) and 1660 cm^{-1} (>C=O); nmr ($CDCl_3$) δ 2.12 (s, 3 H), 2.30 (s, 3 H), 7.09 (d, 2 H, J = 8.0 Hz), 7.39 (d, 2 H, J = 8.0 Hz), and 8.05 (s, 1 H).

Registry No.—**1**, 32720-35-7; **2**, 32720-36-8; **3**, 40328-72-1; **4**, 40328-73-2; **5**, 40328-74-3; **6**, 40328-75-4; **7**, 40328-76-5; **8**, 1888-29-5; **9**, 40328-78-7; **10**, 40328-79-8; **11a**, 27393-94-8; **12**, 23990-58-1; **13**, 40328-82-3; **14**, 40328-83-4; ketene, 463-51-4; diphenylketene-*N*-(*p*-tolyl)imine, 5110-45-2; diphenylketene-*N*-(*p*-bromophenyl)imine, 29376-76-9; diphenylketene-*N*-(*p*-methylthiophenyl)imine, 40328-86-7; diphenylketene-*N*-(*p*-methylsulfonylphenyl)imine, 40328-87-8; diphenylketene-*N*-phenylimine, 14181-84-1; diphenylketene-*N*-*n*-butylimine, 21843-89-0; dimethylketene-*N*-phenylimine, 14016-34-3; isopropylketene-*N*-phenylimine, 34621-16-4; sulfur dioxide, 7446-09-5; *N*-(*p*-tolyl)diphenylacetamide, 4107-01-1; *N*-(*p*-tolyl)-α,α-diphenylacetoacetamide, 40328-93-6; 4,5-dimethyl-*o*-phenylenediamine, 3171-45-7; 3,6-dimethoxy-*o*-phenylenediamine, 40328-95-8; *N*-(*p*-tolyl)acetamide, 103-89-9.

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The Solvolysis of Pyridine Analogs of Cumyl Chloride. The Determination of the Brown Electrophilic Substituent Constants for Pyridine Derivatives[1a]

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Rates of solvolysis in 80% ethanol have been determined for 2-(2-pyridyl)-2-chloropropane, 2-(3-pyridyl)-2-chloropropane, and 2-(4-pyridyl)-2-chloropropane, and for 2-(2-pyridyl)-2-chloropropane *N*-oxide and 2-(4-pyridyl)-2-chloropropane *N*-oxide. From these rates and the rates of solvolysis of cumyl chlorides bearing electron-withdrawing substituents, σ^+ values appropriate for the replacement of the benzene ring by a pyridine moiety have been calculated.

There have been numerous studies in recent years aimed at relating pyridine derivatives to benzene derivatives. As a determination of the Hammett substituent constant, σ, appropriate for substitution of the aza =N for =CH in benzene by the primary defining reaction (ionization of an aromatic carboxylic acid) is fraught with some difficulty because of zwitterion formation, such σ values have generally been evaluated by secondary reactions. A summary by Blanch[2] evaluates a number of such reactions, and lists preferred σ values. A more recent study by Campbell, *et al.*,[3] derives similar though slightly modified values from ester saponification rates. Katritzky and Swinbourne[4] have derived substituent constants for the pyridine *N*-oxide moiety from spectroscopic studies. There has been less attention to determination of Brown's electrophilic substituent constants, σ^+.[5] An early study by Taylor[6] derives σ^+ values from the high-temperature pyrolysis of 1-(X-pyridyl)ethyl acetates. Extensive studies of the nitration, bromination, and hydrogen exchange reactions of pyridine derivatives

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by Katritzky, *et al.*,[7] have led to several derived σ^+ constants for pyridyl moieties.

In conjunction with studies from these laboratories of the transmission of substituent effects in heterocyclic systems,[3] we have had occasion to examine the solvolysis rates of some 2-(pyridyl)-2-chloropropanes. These reactions are easily followed kinetically at constant (and neutral) pH. This provides a much more direct measure of the Brown electrophilic substituent constants for these systems, as there is less need for the severe extrapolations which Katritzky found necessary, and there is no ambiguity about the nature of the species undergoing reaction; it is the neutral species. In order to assign σ^+ constants from these measured rates, it is necessary to determine the ρ value for the solvolysis reaction of the cumyl chlorides at 75°, and to have rates for appropriate cumyl chlorides in 80% ethanol. Okamoto, Inukai, and Brown[9] have reported extensive data for the solvolysis of cumyl chlorides at a number of temperatures. Extrapolating the data for deactivating substituents to 75° gives a ρ in 90% acetone of −4.00. They also report[9b] that ρ is relatively insensitive to the change of solvent to ethanol. However, calculation of expected rates in 80% ethanol by use of mY[10] correlations and the data of Okamoto, Inukai, and Brown[9] proved to be unsatisfactory. Both Fainberg and Winstein[11] and Swain, Mosely, and Bown[12] have noted that mY correlations involving α-phenylethyl chloride and benzhydryl chloride show much dispersion as between aqueous acetone and aqueous ethanol. Rates in aqueous acetone are invariably less than mY correlations predict.

In view of these considerations we have made rate measurements in 80% ethanol on a limited number of cumyl chlorides bearing electron-withdrawing substituents. These rate measurements are summarized in Table I. Rates for cumyl chlorides in 80% ethanol at 75° are satisfactorily predicted by eq 1.

$$\log k = -4.0\sigma^+ + 0.18 \quad (1)$$

Measured rates for the pyridyl analogs of cumyl chlorides are given in Table II, and Table III summarizes σ^+ values, both as herein determined and related values from other studies.

Although it seemed likely that these were typical solvolytic reactions, we examined the plausible alternative that an intramolecularly assisted E2 pathway was involved in the reaction of 2-(2-pyridyl)-2-chloropropane (1). The rate of solvolysis of α-(2-pyridyl)-benzyl chloride (6) (in which an elimination pathway is impossible) was measured. Compound 6 gave a rate of solvolysis quite comparable to that of 3, Table IV. As Streitwieser[13] has pointed out, a phenyl group is roughly as effective as two methyl groups in stabilizing a carbonium ion. Additionally, 2-(2-pyridyl)-2-bromopropane (7) was solvolyzed, and its rate was 40 times that of compound 1, again a typical result.[14] Incidentally, Olah and Calin[15] have demonstrated the formation of a number of substituted pyridinylcarbonium ions in superacid solutions, though the cation from 2-(2-pyridyl)-2-propanol was not observed owing to the rapidity of subsequent reactions.

TABLE I

RATES OF SOLVOLYSIS OF SUBSTITUTED *tert*-CUMYL CHLORIDES IN 80% ETHANOL AT VARIOUS TEMPERATURES

Registry no.	Compd	Temp, °C	k, sec^{-1}
14276-98-3	*p*-Br	0.0	$2.18 \pm 0.05 \times 10^{-4}$
		24.96	$4.71 \pm 0.04 \times 10^{-3}$
		75.00[a]	5.92×10^{-1}
40473-10-7	*m*-Cl	44.80	$2.43 \pm 0.02 \times 10^{-3}$
		60.09	$9.92 \pm 0.1 \times 10^{-3}$
		75.00	$3.51 \pm 0.05 \times 10^{-2}$
		75.00[b]	3.54×10^{-2}
2924-89-2	*p*-CF_3	75.0	$5.22 \pm 0.1 \times 10^{-3}$

[a] Extrapolated from rates at lower temperatures. [b] Extrapolated from rates at 45 and 60°.

TABLE II

RATES OF SOLVOLYSIS OF 2-HETEROARYL-2-CHLOROPROPANES IN 80% ETHANOL AT 75.0°

Compound solvolyzed	k, sec^{-1}	k_{rel}
2-(2-Pyridyl)-2-chloropropane (1)	1.51×10^{-3}	46.9
2-(3-Pyridyl)-2-chloropropane (2)	1.08×10^{-2}	335
2-(4-Pyridyl)-2-chloropropane (3)	3.22×10^{-5}	1.0
2-(2-Pyridyl)-2-chloropropane *N*-oxide (4)	2.85×10^{-3}	88
2-(4-Pyridyl)-2-chloropropane *N*-oxide (5)	2.31×10^{-2}	717

Experimental Section[16]

2-(2-Pyridyl)-2-chloropropane (1).—The preparation of 2-(2-pyridyl)-2-propanol followed the procedure of Emmert and Asendorf[17] incorporating modifications suggested by Bachman and Micucci,[18] mp 49–50° (lit.[18] mp 49–50°).

To a stirred solution of 2-(2-pyridyl)-2-propanol (3.0 g, 0.022 mol) in 100 ml of methylene chloride was added dropwise 5.0 g (0.042 mol) of thionyl chloride. The solution was stirred for 30 min and the methylene chloride and excess thionyl chloride were removed on a rotary evaporator. The oil was redissolved in 100 ml of methylene chloride, washed with aqueous sodium carbonate, and dried ($MgSO_4$). The methylene chloride was removed on a rotary evaporator. The nmr spectrum of the resulting oil showed it to be 50% 2-(2-pyridyl)-2-chloropropane and 50% 2-(2-pyridyl)propene. This mixture of chloride and olefin was used

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TABLE III

SUBSTITUENT CONSTANTS DETERMINED FOR AZA REPLACEMENT IN BENZENE DERIVATIVES, FOR PYRIDYL, PYRIDINIUM, AND PYRIDYL *N*-OXIDE GROUPS

	2-Py	3-Py	4-Py	2-Py$^+$	3-Py$^+$	4-Py$^+$	2-Py$_{NO}$	3-Py$_{NO}$	4-Py$_{NO}$	Ref
σ	0.71	0.55	0.94	3.11	2.10	2.57				2
σ	0.75	0.65	0.96							3
σ	1.0	0.6	0.8	2.2	1.9	1.3	(1.5)	0.7	0.4	4
σ^+	0.80	0.30	0.87							6
σ^+		0.63						0.8		*a*
σ^+	0.75	0.54	1.16				0.68		0.45	*b*

[a] References 7a, 7d, 7e. [b] This study.

TABLE IV

RATES OF SOLVOLYSIS OF SELECTED PYRIDYLALKYL HALIDES IN 80% ETHANOL

Compound solvolyzed	Temp, °C	k, sec^{-1}
1	45.0	$7.45 \pm 0.20 \times 10^{-5}$
	60.0	$3.74 \pm 0.04 \times 10^{-4}$
	75.0[a]	$1.51 \pm 0.03 \times 10^{-3}$
7	25.0	2.53×10^{-4}
	45.0	2.94×10^{-3}
6	45.0	9.80×10^{-5}
	60.0	5.80×10^{-4}
	75.0	1.94×10^{-3}

[a] From Table II.

directly for the kinetic measurements without further purification.

2-(4-Pyridyl)-2-chloropropane (3) and 2-(3-Pyridyl)-2-chloropropane (2).—Reaction of methylmagnesium bromide and methyl isonicotinate afforded 2-(4-pyridyl)-2-propanol, mp 133–134° (lit. mp 132°,[19] 136°[14]). Conversion to a mixture of the chloride, 2-(4-pyridyl)-2-chloropropane (3), and 2-(4-pyridyl)-propene was carried out as above. The nmr spectrum showed that the mixture contained 33% chloride and 67% olefin.

In an analogous fashion methyl nicotinate afforded 2-(3-pyridyl)-2-propanol.[20] Conversion to the chloride with thionyl chloride as above gave a mixture, which was shown by nmr to consist of 63% 2-(3-pyridyl)-2-chloropropane and 37% 2-(3-pyridyl)propene. The mixture of chloride and olefin was used without further purification for the kinetic measurements.

2-(2-Pyridyl)-2-propanol *N*-Oxide.—To a stirred solution of 10.0 g (0.073 mol) of 2-(2-pyridyl)-2-propanol in 20 ml of acetic acid, 30 ml of 40% peracetic acid was added dropwise. After the solution was stirred for 15 min at room temperature the mixture was heated at 45° for 20 hr and then at 75° for 5 hr. After cooling, the solution was poured over crushed ice and made alkaline with a concentrated aqueous solution of sodium hydroxide. The aqueous solution was extracted with 3 × 150 ml of methylene chloride. The combined extracts were dried ($MgSO_4$, plus a small amount of Na_2CO_3), filtered, and concentrated. The resulting colorless oil was shaken with 25 ml of mixed hexanes and the *N*-oxide was crystallized. There was isolated 7.6 g (68%) of 2-(2-pyridyl)-2-propanol *N*-oxide: mp 68–71°; ir (neat) 3400 (s), 1295 (m), 965 (m), 972 (m), and 783 cm^{-1} (s); nmr (CCl_4) δ 1.57 (s, 6), 7.33 (m, 4), and 8.10 (m, 1).

2-(2-Pyridyl)-2-chloropropane *N*-Oxide (4).—A solution of 2-(2-pyridyl)-2-propanol *N*-oxide (1.0 g, 0.007 mol) and phosphorus pentachloride (1.36 g, 0.007 mol) in 200 ml of methylene chloride was stirred for 5 days. The solution was concentrated on a rotary evaporator. The oil was redissolved in 100 ml of methylene chloride, and sodium carbonate and water were added to form a slurry. After stirring for 15 min the methylene chloride was dried ($MgSO_4$), filtered, and concentrated. The oil was dissolved in 100 ml of mixed hexanes and cooled in the refrigerator for 4 hr. The mixed hexanes solution was decanted from a small amount of residue and concentrated on a rotary evaporator to yield 0.80 g (67%) of 2-(2-pyridyl)-2-chloropropane *N*-oxide: nmr (CCl_4) δ 2.15 (s, 6), 7.34 (m, 2), 7.87 (m, 1) and 8.16 (m, 1).

Anal. Calcd for $C_8H_{10}ClNO$: C, 56.00; H, 5.83; N, 8.16; Cl, 20.69. Found: C, 56.20; H, 5.83; N, 8.29; Cl, 20.52.

2-(4-Pyridyl)-2-propanol *N*-Oxide.—A solution of 10.0 g (0.073 mol) of 2-(4-pyridyl)-2-propanol in 35 ml of 40% peracetic acid was heated at 75° for 12 hr. The reaction mixture was neutralized by dissolving the mixture in 300 ml of methylene chloride and adding water and sodium carbonate in small portions to form a slurry (note: the *N*-oxide is very soluble in water). After stirring for 1 hr, the methylene chloride was dried ($MgSO_4$), filtered, and concentrated to yield a white solid. The solid was washed with CCl_4 to yield 4.0 g (37%) of 2-(4-pyridyl)-2-propanol *N*-oxide: nmr (CCl_4) δ 1.55 (s, 6), 4.54 (broad s, 1), 7.40 (broad d, 2, J = 6.2 Hz), and 8.02 (broad s, 2, J = 6.2 Hz).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.25; N, 9.15. Found: C, 62.62; H, 7.12; N, 9.05.

2-(4-Pyridyl)-2-chloropropane *N*-Oxide (5).—A solution of 1.7 g (0.011 mol) of 2-(4-pyridyl)-2-propanol *N*-oxide and 2.31 g (0.011 mol) of phosphorus pentachloride in 100 ml of methylene chloride was stirred for 5 days. The methylene chloride was removed on a rotary evaporator. The oil was redissolved in 100 ml of methylene chloride, and sodium carbonate and water were added to form a slurry. After the mixture was stirred for 15 min the methylene chloride was dried ($MgSO_4$), filtered, and concentrated. The nmr spectrum of the red oil showed that the 2-(4-pyridyl)-2-chloropropane *N*-oxide was mixed with 2-(4-pyridyl)propene *N*-oxide. The nmr spectrum of the mixture (CCl_4) showed resonances at δ 1.96 (s), 7.42 (m), and 8.20 (m) for the chloride and resonances for the olefin at δ 2.13 (broad s, 3), 5.25 (broad s, 1), 5.53 (s, 1), 7.42 (m), and 8.20 (m).

The mixture was used for the kinetic measurements without further purification.

α-(2-Pyridyl)benzyl Chloride (6).—The procedure of Tilford, Shelton, and Van Campen,[21] which is a modification of that of Emmert and Asendorf,[17] was followed for the preparation of α-(2-pyridyl)benzyl alcohol, bp 120° (0.7 mm) [lit.[21] bp 127–129° (0.3 mm)], mp 70–72° (lit.[21] mp 76–78°).

Phosphorus pentachloride (3.4 g, 0.016 mol) was added in small portions to a stirred solution of α-(2-pyridyl)benzyl alcohol in 100 ml of methylene chloride. After the solution was stirred for 30 min, 300 ml of diethyl ether was added. The solution was extracted with 3 × 100 ml of aqueous sodium carbonate. The ether was dried over anhydrous magnesium sulfate and removed on a rotary evaporator. The residual oil was purified by chromatography on a silica gel column using initially 1 l. of mixed hexanes followed by 10% ether–90% hexane, which eluted 2.16 g (71%) of α-(2-pyridyl)benzyl chloride (6): ir (neat) 3010 (w), 1695 (m), 1430 (m), 748 (m), and 696 cm^{-1} (m); nmr (CCl_4) δ 6.06 (s, 1 H), 7.37 (m, 8 H), and 8.35 (m, 1 H).

Anal. Calcd for $C_{12}H_{10}NCl$: C, 70.78; H, 4.91. Found: C, 70.66; H, 5.16.

2-(2-Pyridyl)-2-bromopropane (7).—Bromine (1.3 ml, 0.025 mol) was added dropwise to a stirred solution of phosphorus tribromide (2.4 ml, 0.025 mol) in 300 ml of methylene chloride. The mixture was stirred for 5 min and 2-(2-pyridyl)-2-propanol (1.0 g, 0.0073 mol) was added dropwise. After the addition was complete, 20 ml of pyridine was added very cautiously owing to a very exothermic reaction. The solution was stirred for 2 days and the liquid was decanted from a trace of solid material into 500 ml of mixed hexanes. Anhydrous magnesium sulfate and

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3 ml of water were added and the solution was stirred until it became clear (5 min). The solid was removed by filtration and the solvent was removed on a rotary evaporator to yield 0.65 g (45%) of 2-(2-pyridyl)-2-bromopropane (7): nmr (CCl_4) δ 2.16 (s, 6 H), 7.04 (m, 1 H), 7.60 (m, 2 H), and 8.38 (m, 1 H). Upon attempted distillation of the bromide, hydrogen bromide was eliminated; hence the crude bromide was used directly for the kinetic measurements.

Kinetic Measurements.—Rate measurements were made using a Radiometer automatic titration assembly as has been described previously[8d] at constant pH (apparent pH 7.5 in 80% ethanol).

Registry No.—**1**, 6581-08-4; **2**, 40472-84-2; **3**, 40473-14-1; **4**, 40473-15-2; **5**, 40473-16-3; **6**, 40473-17-4; **7**, 40473-18-5; 2-(2-pyridyl)-2-propanol, 37988-38-8; methylmagnesium bromide, 75-16-1; methyl isonicotinate, 2459-09-8; 2-(4-pyridyl)-2-propanol, 15031-78-4; methyl nicotinate, 93-60-7; 2-(3-pyridyl)-2-propanol, 15031-77-3; 2-(2-pyridyl)-2-propanol *N*-oxide, 40473-22-1; 2-(4-pyridyl)-2-propanol *N*-oxide, 40473-23-2; α-(2-pyridyl)benzyl alcohol, 14159-57-0; bromine, 7726-95-6.

Transmission of Substituent Effects in Heterocyclic Systems. The Solvolysis of Some Substituted Chloroalkylpyridines[1]

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The rates of solvolysis for a number of substituted 2-(pyridyl)-2-chloropropanes have been determined. It is shown that Brown's electrophilic substituent constants give a good representation of the relative reactivities for these compounds, when the substituents are in the 4 and 5 positions in the pyridine ring. The reactivities of 6-substituted pyridines are not satisfactorily correlated with σ^+ constants; it appears that a new set of constants is needed for this structural situation.

The applicability of the Hammett equation to a number of series of pyridine derivatives has been explored by several authors.[2-5] Jaffe and Doak[2] first pointed out that the original Hammett σ constants appropriately reproduce changes in dissociation constants for pyridines and pyridine oxides. Applicability to ester hydrolysis has also been examined more recently.[4] However, when the substituent is adjacent to the nitrogen (*e.g.*, 6-substituted pyridine derivatives), poor correlations result, both with respect to pK_a's[3,5] and with respect to rates of ester hydrolysis.[4]

There has been much less attention given to the application of Brown's electrophilic substituent constants to series of pyridine derivatives. Katritzky[6,7,8] and his coworkers have examined aromatic substitution reactions for a number of pyridine derivatives.

In conjunction with studies from these laboratories of the solvolysis reaction as a probe for the evaluation of the transmission of substituent effects in diverse heterocyclic systems, we have had occasion to determine the rates of solvolysis of a number of substituted pyridine derivatives. We wish to report those results here, and to examine the usefulness of σ^+ constants as applied to pyridine derivatives.

The solvolysis of 2-(2-pyridyl)-2-chloropropane (**1**) is conveniently followed at constant pH in 80% ethanol at somewhat elevated temperatures. Introduction of substituents in the 4 or the 5 position of the pyridine moiety results in sharply modified rates of solvolysis. For a set of such substituted pyridines, the rates which we have measured are recorded in Table I, part A. We compare these rates with the calculated rates, presuming that σ is −4.0, as determined by extrapolation of the data of Brown, *et al.*,[9,10] to 75° and by our independent measurements.[11]

Column 7 of Table I gives the difference between the calculated and the observed rates on this basis.

Likewise for 2-(3-pyridyl)-2-chloropropanes, similar comparative results for a smaller number of compounds are given in Table I, part B. The results for 4- and 5-substituted 2-(2-pyridyl)-2-chloropropanes, compounds **1**, **3**, **5**, **7**, **9**, **11**, and **13**, and for 5-substituted 2-(3-pyridyl)-2-chloropropanes, compounds **14**, **17**, and **19**, show satisfactory correlation with the σ^+ constants.

However, examination of the data for the 6-substituted compounds, compounds **23**, **25**, **27**, **29**, and **31** (Table I, part C), shows that there is little correspondence between the predicted and the observed rate of solvolysis. Each of these compounds shows a very markedly enhanced rate of solvolysis. The set of compounds which we had in hand are all substances where there may be substantial resonance donation to the pyridine nitrogen.

Such a result is perhaps not unexpected. Charton[3] has observed similar "abnormalities" in the pK_a's of pyridine derivatives. Deady, *et al.*,[4] observed that the rates of saponification for 6-substituted pyridine carboxylates deviated from the behavior predicted on the basis of Hammett substituent constants and, moreover, that the magnitude of the deviation was related to σ_{R^0}, *i.e.*, to the resonance capabilities of the substituent.

An alternative and very useful way of correlating

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TABLE I

RATES OF SOLVOLYSIS OF SUBSTITUTED 2-(PYRIDYL)-2-CHLOROPROPANES IN 80% ETHANOL

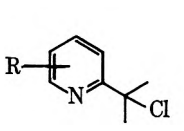
Substituent	Compd	Temp, °C	σ^+	k_1, sec^{-1}	Log k/k_H	Calcd Log k/k_H[a]	Δ log k[b]
			A. Substituted 2-Pyridyl Systems				
H	1	75.0	0.00	1.51×10^{-3} [c]	0.00	0.00	0.0
4-CH_3	3	60.0		6.22×10^{-4}			
		75.0	−0.066	2.52×10^{-3}	0.22	0.264	−0.04
5-CH_3	5	25.0		1.36×10^{-4}			
		45.0		1.30×10^{-3}			
		60.0		5.70×10^{-3}			
		75.0	−0.311	2.13×10^{-2}	1.15	1.24	−0.09
4-Cl	7	75.0	0.399	5.38×10^{-5} [d]	−1.45	−1.59	+0.14
5-Cl	9	45.0	0.114	7.04×10^{-5}			
		75.0		1.13×10^{-3}	−0.13	−0.45	+0.32
4-Cl, 5-OCH_3	11	25.0		7.53×10^{-4}			
		45.0		6.42×10^{-3}			
		60.0		2.63×10^{-2}			
		75.0	−0.379	9.80×10^{-2} [e]	1.81	1.51[f]	+0.31
5-OCH_3	13	0.12		5.30×10^{-3}			
		9.1		1.54×10^{-2}			
		25.0		8.7×10^{-2} [e]			
		75.0	−0.778	7.2×10^{-2} [e]	3.67 ± 0.3	3.11	0.5
			B. Substituted 3-Pyridyl Systems				
H	14	75.0		1.08×10^{-2} [c]	0.00	0.00	0.00
			0.00	1.04×10^{-2} [d]			
5-CH_3	17	25.0		1.20×10^{-4}			
		45.0		1.16×10^{-3}			
		60.0		5.15×10^{-3}			
		75.0	−0.066	1.80×10^{-2}	0.22	0.264	−0.04
5-Br	19	45.0		3.09×10^{-5}			
		75.0	0.405	6.47×10^{-4}	−1.22	−1.62	0.40
6-CH_3	21	25.0		1.38×10^{-3}			
		45.0		1.26×10^{-2}			
		75.0	−0.311	2.14×10^{-1} [e]	1.29	1.24	0.05
			C. 6-Substituted 2-Pyridyl Systems				
6-CH_3	23	45.0		3.77×10^{-4}			
		60.0		1.76×10^{-3}			
		75.0	−0.066	6.28×10^{-3}	0.62	0.264	0.36
6-OCH_3	25	25.0		1.15×10^{-4}			
		45.0		1.17×10^{-3}			
		75.0	0.047	1.52×10^{-2}	1.003	−0.19	−1.19
6-OC_2H_5	27	25.0		1.15×10^{-4}			
		45.0		1.09×10^{-3}			
		75.0		1.55×10^{-2}	1.01	−0.19	1.20
6-C_6H_5	29	75.0	0.109	2.54×10^{-3}	0.23	−0.44	0.67
6-Cl	31	75.0	0.399	2.14×10^{-4}	−0.85	−1.59	0.74

[a] Calculated using $\rho = -4.00$; *cf.* ref 11. [b] Column 5 − column 6. [c] From ref 11. [d] Not at constant pH; using ampoules. [e] Extrapolated from data at lower temperatures. [f] Assuming additivity of substituent constants.

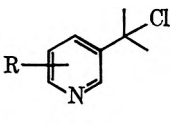
these results is with the $\mathcal{F}$ and $\mathcal{R}$ values for substituents, introduced by Swain and Lupton.[12] This approach quantifies the greater response of the methyl 6-X-picolinates to resonance than of the methyl 4-X-picolinates.

We have examined our data from this point of view (which is closely related, of course, to that used by Charton[13]) and note that our data imply a resonance component of nearly 60% $\mathcal{R}$ for what is formally a meta relationship between the reaction site and the substituent.

Though our data are of somewhat limited extent, they clearly show that a different defined substituent



1, R = H
3, R = 4-CH_3
5, R = 5-CH_3
7, R = 4-Cl
9, R = 5-Cl
11, R = 4-Cl, 5-OCH_3
13, R = 5-OCH_3
23, R = 6-CH_3
25, R = 6-OCH_3
27, R = 6-OEt
29, R = 6-C_6H_5
31, R = 6-Cl



14, R = H
17, R = 5-CH_3
19, R = 5-Br
21, R = 6-CH_3

constant other than σ_m, σ_p, σ_m^+, or σ_p^+ is needed for application to situations where the substituent is adjacent to the pyridine nitrogen. The Swain and

(12) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

(13) Charton, ref 3, expresses the total substituent effect as $\sigma_T = \lambda\sigma_I + \delta\sigma_R$.

Lupton treatment offers a promising basis upon which to proceed; with the information we have in hand, there is sufficient information for making intelligent projections of solvolysis rates of 2-(2-X-4-pyridyl)-2-chloropropanes. These would be interesting to test.

Experimental Section[14]

Standard Procedures. A. Chloride Formation from Alcohol.—To a stirred solution of the alcohol in methylene chloride a slight excess of thionyl chloride was added dropwise. The solution was stirred for 30 min and the methylene chloride and excess thionyl chloride were removed with a rotary evaporator. The residue was redissolved in 100 ml of methylene chloride, and sodium carbonate and water were added to form a slurry. After stirring for 15 min the solution was dried ($MgSO_4$), filtered, and concentrated. Owing to the instability of the chloride, the resulting oils were used in kinetic measurements without further purification. The contaminant in these oils was olefin, which does not affect the kinetic measurements. The relative concentrations of olefin and chloride were determined by comparison of proton areas of appropriate nmr spectra.

B. Alcohol Formation from Esters.[15]—The ester was added dropwise to a 2.5 *M* excess of methylmagnesium bromide in dry ether. The solution was stirred at room temperature overnight. Saturated ammonium chloride solution was added cautiously. The ether phase was separated and the saturated ammonium chloride solution was extracted with 3 × 200 ml of ether. The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated to yield the desired product.

C. Alcohol Formation from Bromopyridines.—To a stirred solution of the bromopyridine in absolute ether under nitrogen in a Dry Ice–acetone bath was added dropwise a slight excess (*ca.* 5%) of *n*-butyllithium (1.6 *M* in hexane). After the addition was complete the solution was stirred for 15 min and acetone (2.5 *M* excess) was added. The mixture was allowed to warm to room temperature and 100 ml of water was added cautiously. The ether phase was separated, washed twice with 100 ml of water, dried ($MgSO_4$), filtered, and concentrated to yield the desired product.

2-(2-Pyridyl)-2-chloropropane (1) and 2-(3-pyridyl)-2-chloropropane (14) have been reported previously.[11]

2-(4-Methyl-2-pyridyl)-2-propanol (2).—The procedure of Emmert and Asendorf[11,16] was used with γ-picoline substituted for pyridine. After work-up in the usual manner, the combined ether extracts were dried ($MgSO_4$), concentrated, and distilled to yield 21% alcohol **2**: bp 65° (0.1 mm);[17] nmr (CCl_4) δ 1.45 (s, 6), 2.30 (s, 3), 4.87 (broad s, 1), 6.80 (d, 1, J = 5.0 Hz), 7.10 (s, 1), and 8.12 (d, 1, J = 5.0 Hz).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.63; H, 8.74; N, 9.07.

2-(4-Methyl-2-pyridyl)-2-chloropropane (3).—Chloride **3** was synthesized by standard procedure A. The nmr spectrum of the red oil (2.8 g) showed it to be 50% **3** and 50% 2-(4-methyl-2-pyridyl)propene. The nmr spectrum of the chloride (CCl_4) showed resonances at δ 1.92 (s), 2.21 (s), 6.85 (d), 7.21 (s), and 8.32 (m), The same spectrum showed resonances for the olefin at δ 2.21 (s), 2.32 (broad), 5.21 (broad, 1), 5.76 (broad, 1), 6.85 (d), 7.55 (s), and 8.32 (m).

2-(5-Methyl-2-pyridyl)-2-propanol (4).—2-Bromo-5-methylpyridine was prepared by the method of Case,[18] from 2-amino-5-methylpyridine in 85% yield, mp 49–50° (lit.[18] mp 49–50°). For the preparation of the alcohol **4**, standard procedure C using 2-bromo-5-methylpyridine (17.29 g, 0.10 mol) was followed. Distillation afforded 7 g (47% yield) of alcohol **4** as a viscous, colorless oil: bp 58° (0.1 mm); nmr (CCl_4) δ 1.45 (s, 6), 2.12 (s, 3), 4.78 (s, 1), 7.24 (m, 2), and 8.13 (s, 1).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.40; H, 8.90; N, 9.49.

Compound **4** has previously been reported as one component of the mixture resulting from the Emmert reaction on β-picoline.[16,17]

2-(5-Methyl-2-pyridyl)-2-chloropropane (5).—Chloride **5** was synthesized in the usual manner (procedure A). The nmr spectrum of the red oil (1.8 g) showed it to be 60% chloride **5** and 40% 2-(5-methyl-2-pyridyl)propene. The nmr spectrum of the chloride (CCl_4) showed resonances at δ 1.83 (s), 2.20 (s), 7.30 (m), and 8.10 (broad s). The same spectrum showed resonances for the olefin at δ 2.12 (broad s, 3), 2.20 (s), 5.08 (m, 1), 5.63 (broad s, 1), 7.30 (m), and 8.10 (m).

2-(4-Chloro-2-pyridyl)-2-propanol (6).—Methyl 4-chloropicolinate, prepared by the method of Mosher and Look,[19] was treated with excess methylmagnesium bromide in ether (standard procedure B). Alcohol **6** was isolated in 80% yield: bp 73° (0.2 mm); nmr (CCl_4) δ 1.48 (s, 6), 4.54 (broad s, 1), 7.00 (2 d, 1, J = 2 and 5 Hz), 7.41 (d, 1, J = 2 Hz), and 8.22 (d, 1, J = 5 Hz).

Anal. Calcd for $C_8H_{10}ClNO$: C, 56.00; H, 5.87; N, 8.16; Cl, 20.66. Found: C, 56.03; H, 5.63; N, 8.19; Cl, 20.48.

2-(4-Chloro-2-pyridyl)-2-chloropropane (7).—The standard procedure was followed. The nmr spectrum of the red oil (1.5 g) showed it to be 40% chloride **7** and 60% 2-(4-chloro-2-pyridyl)-propene. The nmr spectrum (CCl_4) of the chloride showed resonances at δ 1.95 (s), 7.07 (m), 7.78 (d, J = 2 Hz), and 8.35 (m). The same spectrum showed resonances for the olefin at δ 2.18 (broad s, 3), 5.28 (broad s, 1), 5.85 (broad s, 1) 7.07 (m), 7.40 (d, J = 2 Hz), and 8.35 (m).

2-(5-Chloro-2-pyridyl)-2-propanol (8).—5-Amino-2-bromopyridine was converted to 2-bromo-5-chloropyridine,[20] mp 69–70° (lit.[21] mp 70–71°). Standard procedure C was followed to afford alcohol **8** in 38% yield: bp 78° (0.2 mm); nmr (CCl_4) δ 1.49 (s, 6), 4.32 (broad s, 1), 7.53 (m, 2), and 8.37 (broad s, 1).

Anal. Calcd for $C_8H_{10}ClNO$: C, 56.00; H, 5.87; N, 8.16; Cl, 20.66. Found: C, 56.22; H, 6.04; N, 7.97; Cl, 20.48.

2-(5-Chloro-2-pyridyl)-2-chloropropane (9).—Standard procedure A yielded 1.1 g of a red oil. The nmr spectrum showed it to be 40% chloride **9** and 60% 2-(5-chloro-2-pyridyl)propene. The nmr spectrum of the chloride (CCl_4) showed resonances at δ 1.92 (s), 7.60 (m), and 8.42 (m). The same spectrum showed resonances for the olefin at δ 2.17 (broad s, 3), 5.28 (broad s, 1), 5.80 (broad s, 1), 7.60 (m), and 8.42 (m).

Ethyl 4-Chloro-5-methoxypicolinate.—2-Hydroxymethyl-5-methoxy-1,4-pyrone[22] was converted to 2-hydroxymethyl-5-methoxy-4-pyridone.[23] Oxidation to 5-methoxy-4-pyridone-2-carboxylic acid followed the procedure of Beyerman, mp 254–256° (lit.[24] mp 251–253°). Thence treatment with thionyl chloride, followed by ethanol, afforded ethyl 4-chloro-5-methoxypicolinate, mp 147–148° (lit.[24] mp 145–146°).

2-(4-Chloro-5-methoxy-2-pyridyl)-2-propanol (10).—Alcohol **10** was synthesized by procedure B using 7.8 g of ethyl 4-chloro-5-methoxypicolinate. The thick yellow oil was distilled to yield 4.7 g (64%) of alcohol **10**: bp 90° (0.1 mm); mp 71.0–72.5°; nmr (CCl_4) δ 1.45 (s, 6), 3.91 (s, 3), 4.13 (broad s, 1), 7.35 (s, 1), and 7.99 (s, 1).

Anal. Calcd for $C_9H_{12}ClNO_2$: C, 53.59; H, 6.00; N, 6.94; Cl, 17.60. Found: C, 53.79; H, 6.12; N, 6.74; Cl, 17.35.

2-(4-Chloro-5-methoxy-2-pyridyl)-2-chloropropane (11).—Alcohol **10** was converted to chloride **11** by procedure A. The nmr spectrum of the red oil (1.7 g) showed it to be 78% chloride **11** and 22% 2-(4-chloro-5-methoxy-2-pyridyl)propene. The nmr spectrum of the chloride showed resonances at δ 1.93 (s), 3.95 (s), 7.85 (s), and 8.02 (s). The same spectrum showed resonances for the olefin at δ 2.16 (broad s, 3), 3.95 (s), 5.16 (broad s, 1), 5.62 (broad s, 1), 7.85 (s), and 8.05 (s).

Ethyl 5-Methoxypicolinate.—Ethyl 4-chloro-5-methoxypicolinate (15.0 g, 0.067 mol) was added to 9.0 g of zinc dust suspended in 75 ml of glacial acetic acid. After a short induction period a vigorous reaction began and the solution was stirred for 1 hr. The solution was heated in an oil bath at 90° for an additional 1 hr. After the mixture cooled to room temperature, the glacial acetic acid was decanted from excess zinc dust onto approximately 200 g of ice. The solution was neutralized with con-

(14) Elemental analyses were determined by the Chemical Analytical Services Laboratory, College of Chemistry, Berkeley, Calif. Melting points and boiling points are uncorrected. Routine infrared spectra were recorded using a Perkin-Elmer Infracord Model 137. Nmr spectra were obtained using a Varian Associates Model T-60 spectrometer.

(15) G. B. Bachman and D. D. Micucci, *J. Amer. Chem. Soc.*, **70**, 2381 (1948).

(16) E. Emmert and E. Asendorf, *Ber.*, **72**, 1188 (1939).

(17) Lochte, Kruse, and Wheeler report bp 119–121° (23 mm): H. L. Lochte, P. F. Kruse, Jr., and E. N. Wheeler, *J. Amer. Chem. Soc.*, **75**, 4477 (1953).

(18) F. N. Case, *J. Amer. Chem. Soc.*, **68**, 2574 (1946).

(19) H. S. Mosher and M. Look, *J. Org. Chem.*, **20**, 283 (1955).

(20) L. C. Craig, *J. Amer. Chem. Soc.*, **56**, 232 (1934).

(21) F. H. Case, *J. Amer. Chem. Soc.*, **68**, 2574 (1946).

(22) K. N. Campbell, J. E. Ackerman, and B. K. Campbell, *J. Org. Chem.*, **15**, 221 (1950).

(23) J. W. Armit and T. J. Nolan, *J. Chem. Soc.*, 3023 (1931).

(24) H. C. Beyerman, *Recl. Trav. Chim. Pays-Bas*, **77**, 249 (1958).

centrated ammonium hydroxide and extracted with 3 × 200 ml of diethyl ether. The combined extracts were dried ($MgSO_4$), filtered, concentrated, and distilled to yield 7.0 g (58%) of ethyl 5-methoxypicolinate: bp 90° (0.3 mm); nmr (CCl_4) δ 1.57 (t, 3), 3.85 (s, 3), 4.30 (q, 2), 7.10 (2 d, 1, J = 10.0 and 2.8 Hz), 7.85 (d, 1, J = 10.0 Hz), and 8.17 (d, 1, J = 2.8 Hz).

2-(5-Methoxy-2-pyridyl)-2-propanol (12).—Ethyl 5-methoxypicolinate (7.0 g, 0.0387 mol) was converted to alcohol 12 by procedure B. The thick yellow oil was distilled to yield 2.2 g (34%) of alcohol 12: nmr (CCl_4) δ 1.47 (s, 6), 3.75 (s, 3), 4.65 (broad s, 1), 7.23 (m, 2), and 8.10 (d, 1, J = 3 Hz).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.83; N, 8.37. Found: C, 64.81; H, 7.60; N, 8.50.

2-(5-Methoxy-2-pyridyl)-2-chloropropane (13).—Alcohol 12 was converted to chloride 13 by procedure A. The nmr spectrum of the red oil (86% yield) showed it to be nearly 100% chloride 13 with only a trace of 2-(5-methoxy-2-pyridyl)propene. The nmr spectrum of the chloride (CCl_4) showed resonances at δ 1.96 (s, 6), 3.76 (s, 3), 7.03 (2 d, 1, J = 3 and 8.5 Hz), 7.60 (d, 1, J = 8.5 Hz), and 8.08 (d, 1, J = 3 Hz).

Ethyl 5-Methylnicotinate (15).—3,5-Lutidine was oxidized to 5-methylnicotinic acid with potassium permaganate.[25] The isolated 5-methylnicotinic acid hydrochloride was directly esterified with ethanol to give 15 in 25% overall yield: bp 76° (0.7 mm); nmr (CCl_4) δ 1.33 (t, 3), 2.28 (s, 3), 4.24 (q, 2) 7.87 (broad s, 1), 8.43 (broad s, 1), and 8.85 (broad s, 1).

2-(5-Methyl-3-pyridyl)-2-propanol (16).—Ester 15 (13.8 g, 0.0838 mol) was converted to alcohol 16 by procedure B. The thick yellow oil was distilled to yield 9.4 g (74%) of alcohol 16: bp 100° (0.7 mm); nmr (CCl_3) δ 1.50 (s, 6), 2.40 (s, 3), (broad s, 1), 7.55 (broad s, 1), 7.96 (broad s, 1), and 8.24 (broad s, 1).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.47; H, 8.45; N, 9.43.

2-(5-Methyl-3-pyridyl)-2-chloropropane (17).—Procedure A was used to yield 1.5 g of a red oil. The nmr spectrum showed it to be 60% chloride 17 and 40% 2-(5-methyl-3-pyridyl)propene. The nmr spectrum of the chloride (CCl_4) showed resonances at δ 2.00 (s, 6), 2.32 (s), 7.63 (broad s, 1), 8.28 (broad s, 1), and 8.58 (d, 1, J = 2.4 Hz). The same spectrum showed resonances for the olefin at δ 2.15 (broad s, 3), 2.32 (s), 5.12 (broad s, 1), 5.38 (broad s, 1), 8.28 (broad s, 1), and 8.47 (d, 1, J = 3 Hz).

2-(5-Bromo-3-pyridyl)-2-propanol (18).—Ethyl 5-bromonicotinate was prepared form nicotinic acid by the procedure of Bachman and Micucci,[15] and converted to alcohol 18: bp 110° (0.3 mm) [lit.[15] bp 135–140° (3 mm)]. The nmr spectrum was appropriate for this structure.

2-(5-Bromo-3-pyridyl)-2-chloropropane (19).—Standard procedure A was used. The nmr spectrum of the red oil (1.5 g) showed it to be a mixture of 37% chloride 19 and 63% 2-(5-bromo-3-pyridyl)propene. The nmr spectrum of the chloride (CCl_4) showed resonances at δ 1.95 (s), 7.92 (m), and 8.50 (m). The same spectrum showed resonances for the olefin at δ 2.15 (broad s, 3), 5.17 (broad s, 1), 5.41 (broad s, 1), 7.78 (m), and 8.50 (m).

2-(6-Methyl-3-pyridyl)-2-propanol (20).—The preparation of ethyl 6-methylnicotinate followed the procedure of Graf[25] involving the oxidation of 5-ethyl-2-methylpyridine and the direct esterification of the crude 6-methylnicotinic acid. Ethyl 6-methylnicotinate was converted to alcohol 20 by procedure B. The thick yellow oil was distilled to yield alcohol 20 in 76% yield: bp 93° (0.5 mm);[26] nmr (CCl_4) δ 1.38 (s, 6), 2.26 (s, 3), 5.16 (very broad s, 1), 6.82 (d, 1, J = 9 Hz), 7.58 (2 d, 1, J = 9 and 1.8 Hz), and 8.20 (broad s, 1).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.56; H, 8.66; N, 9.26.

2-(6-Methyl-3-pyridyl)-2-chloropropane (21).—Standard procedure A was used. The nmr spectrum of the red oil (2.9 g) showed it to be 55% chloride 21 and 45% 2-(6-methyl-3-pyridyl)-propene. The nmr spectrum of the chloride (CCl_4) showed resonances at δ 1.91 (s, 6), 2.45 (s), 7.00 (broad s, 1), 7.61 (m), and 8.59 (d, 1, J = 2.6 Hz). The same spectrum showed resonances for the olefin at δ 2.11 (broad s, 3), 2.45 (s), 4.98 (broad s, 1), 5.23 (broad s, 1), 6.83 (broad s, 1), 7.61 (m), and 8.43 (d, 1, J = 2.0 Hz).

(25) R. Graf, *J. Prakt. Chem.*, **133**, 19 (1932).

(26) Oparina reports mp 61–62° for alcohol 20: M. P. Oparina, *J. Russ. Phys. Chem. Soc.*, **61**, 2011 (1929); *Chem. Abstr.*, **24**, 4785 (1930).

2-(6-Methyl-2-pyridyl)-2-propanol (22) was prepared by the procedure of Emmert and Asendorf,[16] nmr (CCl_4) δ 1.43 (s, 6), 2.49 (s, 3), 4.84 (broad s, 1), and 7.20 (m, 3).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.72; H, 8.80; N, 9.41.

2-(6-Methyl-2-pyridyl)-2-chloropropane (23).—Standard procedure A was used. The nmr spectrum of the crude product showed it to be 50% chloride 23 and 50% 2-(6-methyl 2-pyridyl)-propene. The nmr spectrum of the chloride (CCl_4) showed resonances at δ 1.88 (s), 2.40 (s), 6.75 (m), and 7.24 (m). The same spectrum showed resonances for the olefin at δ 2.09 (broad s, 3), 2.40 (s), 5.03 (broad s, 1), 5.61 (broad s, 1), 6.75 (m), and 7.24 (m).

2-Bromo-6-methoxypyridine.—The method of Den Hertog and Wibaut[27] was used with methanol substituted for ethanol. The reaction yielded a mixture containing 20% 2,6-dimethoxypyridine and 80% 2-bromo-6-methoxypyridine. Separation by distillation was incomplete; hence, the mixture was used directly for the following reaction with *n*-butyllithium, as the 2-(6-methoxy-2-pyridyl)-2-propanol and 2,6-dimethoxypyridine were found easier to separate.

2-(6-Methoxy-2-pyridyl)-2-propanol (24).—The mixture above was used in procedure C. From 13.9 g of crude 2-bromo-6-methoxypyridine, containing about 2.1 g of 2,6-dimethoxypyridine, there was obtained 6.1 g (49%) of alcohol 24: bp 95° (0.5 mm); nmr (CCl_4) δ 1.55 (s, 6), 3.90 (s, 3), 4.33 (s, 1), 6.50 (d, 1, J = 8 Hz), 6.95 (d, 1, J = 8 Hz), and 7.43 (t, 1, J = 8 Hz).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.37. Found: C, 64.75; H, 7.68; N, 8.62.

2-(6-Methoxy-2-pyridyl)-2-chloropropane (25).—Alcohol 24 was converted to chloride 25 by procedure A. The nmr spectrum of the red oil (2.0 g) showed it to be 48% chloride 25 and 52% 2-(6-methoxy-2-pyridyl)propene. The nmr spectrum of the chloride (CCl_4) showed resonances at δ 1.90 (s), 3.87 (s), 6.55 (d), 7.23 (m), and 7.40 (m). The same spectrum showed resonances for the olefin at δ 2.15 (broad s, 3), 5.18 (broad s, 1), 4.87 (broad s, 1), 6.55 (d), 6.95 (m), and 7.40 (m).

2-(6-Ethoxy-2-pyridyl)-2-propanol (26).—2-Bromo-6-ethoxypyridine[27] (7.0 g, 0.347 mol) was converted to alcohol 26 by procedure C. The colorless oil was distilled to yield 3.0 g (48%) of alcohol 26: bp 72° (0.2 mm); nmr (CCl_4) δ 1.31 (t, 3), 1.39 (s, 6), 4.18 (broad s, 1 H), 4.28 (q, 2), 6.40 (d, 1, J = 8 Hz), 6.83 (d, 1, J = 8 Hz), and 7.40 (t, 1, J = 8 Hz).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.28; H, 8.33; N, 7.73. Found: C, 66.53; H, 8.43; N, 7.95.

2-(6-Ethoxy-2-pyridyl)-2-chloropropane (27).—Chloride 27 was synthesized by procedure A. The nmr spectrum of the red oil (2.0 g) showed it to be 40% chloride 27 and 60% 2-(6-ethoxy-2-pyridyl)propene. The nmr spectrum of the chloride (CCl_4) showed resonances at δ 1.34 (t), 1.90 (s), 4.32 (q), 6.44 (d), 6.82 (m), and 7.32 (m). The same spectrum showed resonances for the olefin at δ 1.34 (t), 2.13 (broad s, 3), 4.32 (q), 5.10 (broad s, 1), 5.82 (broad s, 1), 6.44 (d), 6.82 (m), and 7.32 (m).

2-(6-Phenyl-2-pyridyl)-2-propanol (28).—The procedure of Case and Kasper[28] was followed for the preparation of 2-bromo-6-phenylpyridine. Reaction with butyllithium followed by treatment with acetone afforded crude 28 as a pale yellow oil, bp 98–139° (0.2 mm). The nmr showed an excess of aromatic protons and the oil was chromatographed on a silica gel column using mixed hexanes followed by a 2% solution of ether–mixed hexanes which eluted 4.3 g (49%) of alcohol 28: nmr (CCl_4) δ 1.51 (s, 6), 5.83 (s, 1), 7.30 (m, 6), and 8.85 (m, 2).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.85; H, 7.08; N, 6.57. Found: C, 78.67; H, 7.05; N, 6.56.

2-(6-Phenyl-2-pyridyl)-2-chloropropane (29.)—Standard procedure A was used. A nmr spectrum of the red oil showed it to be a mixture of 37% chloride 29, 52% 2-(6-phenyl-2-pyridyl)-propene, and 11% of the initial 2-(6-phenyl-2-pyridyl)-2-propanol (28). The nmr spectrum of the chloride (CCl_4) showed resonances at δ 2.00 (s), 7.30 (m), and 7.95 (m). The same spectrum showed resonances for the olefin at δ 2.24 (broad s, 3), 5.23 (broad s, 1), 5.87 (broad s, 1), 7.30 (m), and 7.95 (m).

2-(6-Chloro-2-pyridyl)-2-propanol (30).—Methyl 6-chloropicolinate, mp 95–96° (lit.[29] mp 96–97°), was prepared by the

(27) H. J. Den Hertog and J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas*, **52**, 126 (1933).

(28) F. H. Case and T. J. Kasper, *J. Amer. Chem. Soc.*, **78**, 5842 (1956).

(29) M. P. Cava and N. K. Bhattacharya, *J. Org. Chem.*, **23**, 1287 (1958).

method of Cava and Bhattacharya,[29] involving diazotization (HCl) of 6-amino-2-methylpyridine, permanganate oxidation to 6-chloropicolinic acid, and esterification. The ester was treated with methylmagnesium bromide to afford **30** in 85% yield: bp 82–84° (2 mm); nmr (CCl_4) δ 1.52 (s, 6), 4.07 (s, 1), and 7.40 (m, 3).

Anal. Calcd for $C_8H_{10}ClNO$: C, 56.00; H, 5.87; N, 8.16; Cl, 20.66. Found: C, 55.89; H, 5.87; N, 7.94; Cl, 20.80.

2-(6-Chloro-2-pyridyl)-2-chloropropane (31).—Chloride **31** was synthesized by procedure A. The nmr spectrum of the red oil (2.5 g) showed it to be 30% chloride **31** and 70% 2-(6-chloro-2-pyridyl)propene. The nmr spectrum (CCl_4) showed resonances at δ 1.91 (s) and 8.31 (m). The same spectrum showed resonances for the olefin at δ 2.15 (broad s, 3 H), 5.21 (broad s, 1 H), 5.81 (broad s, 1 H), and 8.31 (m).

Kinetic Procedures.—Kinetic procedures have been reported previously.[11,30]

Registry No.—**1**, 6581-08-4; **2**, 40472-49-9; **3**, 40472-50-2; **4**, 40472-51-3; **5**, 40472-75-1; **6**, 40472-76-2; **7**, 40472-77-3; **8**, 40472-78-4; **9**, 40472-79-5; **10**, 40472-80-8; **11**, 40472-81-9; **12**, 40472-82-0; **13**, 40472-83-1; **14**, 40472-84-2; **15**, 20826-02-2; **16**, 40472-86-4; **17**, 40472-87-5; **18**, 40472-88-6; **19**, 40472-89-7; **20**, 40472-90-0; **21**, 40472-91-1; **22**, 40472-92-2; **23**, 40472-93-3; **24**, 40472-94-4; **25**, 40521-10-6; **26**, 40521-11-7; **27**, 40521-12-8; **28**, 40472-95-5; **29**, 40472-96-6; **30**, 40472-97-7; **31**, 40472-98-8; 2-bromo-5-methylpyridine, 3510-66-5; methyl 4-chloropicolinate, 24484-93-3; 2-bromo-5-chloropyridine, 40473-01-6; ethyl 4-chloro-5-methoxypicolinate, 40473-02-7; ethyl 5-methoxypicolinate, 40473-03-8; 5-methylnicotinic acid hydrochloride, 40473-04-9; ethyl 5-bromonicotinate, 20986-40-7; ethyl 6-methylnicotinate, 21684-59-3; 2-bromo-6-methoxypyridine, 40473-07-2; 2-bromo-6-ethoxypyridine, 4645-11-8.

(30) D. S. Noyce and R. W. Nichols, *J. Org. Chem.*, **37**, 4306 (1972).

CNDO–MO Exploration of Concerted and Stepwise Pathways for the Wittig and Peterson Olefination Reactions

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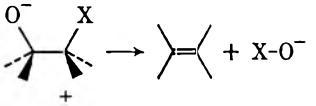
The decomposition of species of the type $XCH_2CH_2O^-$ to XO^- and $CH_2{=}CH_2$ was investigated with the aid of CNINDO calculations for the cases where X is H_3P^+– (Wittig reaction) and H_3Si– (Peterson reaction). Four-center intermediates **2a** (dihydrooxaphosphetane) and **2b** (dihydrooxasiletanide anion) were assumed and energies calculated for these and for the family of structures resulting from cleavage of the C–O and C–X bonds simultaneously (concerted fragmentation) or in separate stages (nonconcerted fragmentation). The calculations indicate that the energy surfaces are sharply skewed with C–X cleavage more advanced than C–O cleavage with the degree of skewing much greater for the Peterson reaction than for the Wittig reaction. The amount of stabilization of **2a** relative to its betaine precursor **1a** is calculated to be greater than that of **2b** relative to its precursor **1b** and it was concluded that dihydrooxaphosphetane **2a** is probably a true intermediate in the Wittig reaction but that dihydrooxasiletanide **2b** may be bypassed in the Peterson process with **1b** going directly to $H_3SiOCH_2CH_2^-$ (**3b**). Examples are given where theory and experiment are in harmony.

Four-center reactions involving intramolecular nucleophilic attack by alkoxide oxygen on a second-row element as a key step are common and provide the basis for a number of mechanistically interesting and synthetically useful olefin syntheses given in general terms by eq 1.



(1)

1a, X = $-PR_3^+$
b, X = $-SiR_3$
c, X = $-S(O)R$

The best known and most widely studied examples of these processes utilize phosphorus as the electrophilic center and include the Wittig reaction and its many modifications.[1] Less well known, but becoming increasingly useful for the synthesis of heteroatom-substituted olefins especially, are the base-catalyzed decomposition reactions of β-hydroxysilanes (the Peterson reaction).[2] In both the silicon and phosphorus cases decomposition of **1** (referred to as the "betaine" intermediate for **1a**) occurs under extremely mild conditions with the thermodynamic driving force being derived, in large part, from the formation of strong phosphorus–oxygen or silicon–oxygen bonds. The decomposition of β-hydroxy sulfoxides has also been observed[3,4] and a method developed for olefin synthesis employing thermal decomposition of β-hydroxy sulfinamides in benzene or toluene at 80–110°.[5] For each of these fragmentations a syn elimination is conceptually the most attractive and is supported by experiment in those cases which have been studied with respect to stereochemistry.[5,6]

An important question regarding the elimination pathways available to **1a–c** remains unanswered despite the number of studies, both synthetic and mechanistic, of the Wittig and related reactions. That question is concerned with whether thermal uncatalyzed decomposition of **1** is concerted or is rather a multistep process proceeding *via* initial formation of a four-membered ring intermediate. Further, if a four-membered ring species is an intermediate, does it

(1) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Inc., Menlo Park, Calif., 1972, pp 682–709, and references cited therein.

(2) (a) D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968); (b) T. H. Chan, E. Chang, and E. Vinokur, *Tetrahedron Lett.*, 1137 (1970); (c) F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 939, 1926 (1972), and references cited therein.

(3) (a) C. Walling and L. Bollyky, *ibid.*, **28**, 256 (1963); (b) E. J. Corey and M. Chaykovsky, *ibid.*, **28**, 254 (1963).

(4) For an analogous process see T. J. Wallace, *ibid.*, **30**, 4016 (1965).

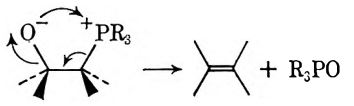
(5) (a) E. J. Corey and T. Durst, *J. Amer. Chem. Soc.*, **90**, 5548, 5553 (1968); (b) T. Durst, *Quart. Rep. Sulfur Chem.*, **3**, 113 (1968).

(6) E. Vedejs and P. L. Fuchs, *J. Amer. Chem. Soc.*, **93**, 4070 (1971).

fragment by a concerted or nonconcerted path? These possibilities are represented for the phosphorus case in Chart I. Analogous routes can be considered for the cases which result when X is silicon or sulfur.

CHART I

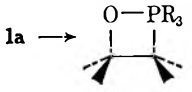
Concerted Decomposition of Betaine



(2)

1a

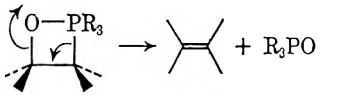
Initial Formation of a Dihydrooxaphosphetane Intermediate



(3)

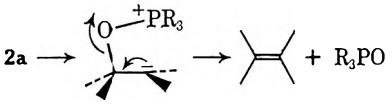
2a

Concerted Decomposition of Dihydrooxaphosphetane



(4)

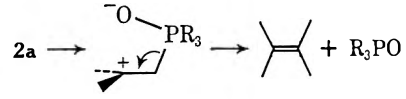
Nonconcerted Decomposition of Dihydrooxaphosphetane (P–C Cleavage)



(5)

3a

Nonconcerted Decomposition of Dihydrooxaphosphetane (C–O Cleavage)

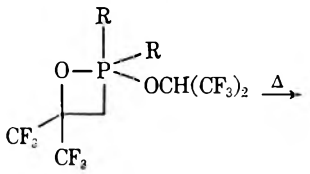


(6)

4a

Analogous structures (**1b–4b**) may be considered for the Peterson process by substituting silicon for phosphorus with appropriate formal charge adjustment.

The experimental evidence available at present does not permit a unique choice to be made among the alternative mechanisms outlined in Chart I. While the observed stereospecific nature of the eliminations[5,6] is readily accommodated by the concerted fragmentation of eq 2 and 4, it would also be possible from a nonconcerted process (eq 5 or 6) if decomposition of the zwitterionic intermediate (**3a** or **4a**) were faster than rotation around the carbon–carbon bond. The intermediacy of the dihydrooxaphosphetane 2a receives support from the recent isolation of such a species and the demonstration of its thermal conversion to olefins and phosphinate esters on heating (eq 7).[7]



5a, R = CH_3
b, R = Ph

$$(CF_3)_2C{=}CH_2 + R_2P(O)OCH(CF_3)_2 \quad (7)$$

(7) (a) F. Ramirez, C. P. Smith, and J. F. Pilot, *J. Amer. Chem. Soc.*, **90**, 6726 (1968); (b) M. U. Haque, C. N. Caughlan, F. Ramirez, J. F. Pilot, and C. P. Smith, *ibid.*, **93**, 5229 (1971).

While it could be argued that concerted fragmentation of a dihydrooxaphosphetane to an olefin and a phosphine oxide is similar to the thermally forbidden $[{}_\sigma 2_s + {}_\sigma 2_s]$[8] conversion of cyclobutane to two ethylenes, this would not appear to be an apt analogy. Theoretical[9] and experimental[10] results indicate that incorporation of heteroatoms into four-membered rings lowers the activation energy for certain concerted reactions. Further, the expanded coordination and the participation of d orbitals in the bonding scheme renders comparison of dihydrooxaphosphetanes and dihydrooxasiletanide anions with four-membered rings containing only first-row elements suspect. Accordingly, a theoretical study of the various mechanisms was undertaken to determine whether a choice could be made between them.

Results and Discussion

General Comments on the Computational Method.— The symmetry considerations developed by Woodward and Hoffmann are not directly applicable to the systems of this work since these systems lack suitable symmetry elements. The principle of phase continuity (which is an extension of the Woodward–Hoffmann methods requiring no symmetry) or a directly constructed correlation diagram show that a concerted passage from X=C + C=O to X=O and C=C is not forbidden (Figures 1 and 2). However, lower energy stepwise processes are not excluded, and the retention of stereochemistry in the alkene can be accommodated without presumption of a concerted process. Clearly, a more quantitative appreciation of the reaction surface is required. We chose to pursue CNDO estimates of the energy in order to determine the low energy path for these reactions. Calculations of the energy changes attending reaction of so complex a system as the Wittig betaine may be highly misleading if the geometry of each species along the reaction coordinate is not allowed to relax to its minimum energy. At the same time the size of the system (27 geometric parameters) and the number of variables which we wish to monitor (the distances between the heavy atoms) prohibit complete optimization of each parameter if a complicated function is chosen to represent the molecular energy. In this context the CNDO energy is a complicated function. The problem is to choose a geometry optimized in some very simple way before application of the CNDO method.

Geometry optimization of large systems has been given close attention by organic chemists[11] and more recently by physical biochemists.[12] If force constants for the several possible motions are available the Westheimer method[13] and its refinements become highly useful. Unfortunately the data are not complete for the systems in question, particularly for those configurations in which bonds are incompletely formed or broken.

(8) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, pp 65–73.

(9) D. R. Kearns, *J. Amer. Chem. Soc.*, **91**, 6554 (1969).

(10) L. E. Friedrich and G. B. Schuster, *ibid.*, **93**, 4602 (1971), and references cited therein.

(11) J. E. Williams, P. J. Stang, and P. v. R. Schleyer, *Ann. Rev. Phys. Chem.*, **19**, 531 (1968).

(12) D. G. Brant, *Ann. Rev. Biophys. Bioeng.*, **1**, 412 (1972).

(13) F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 12.

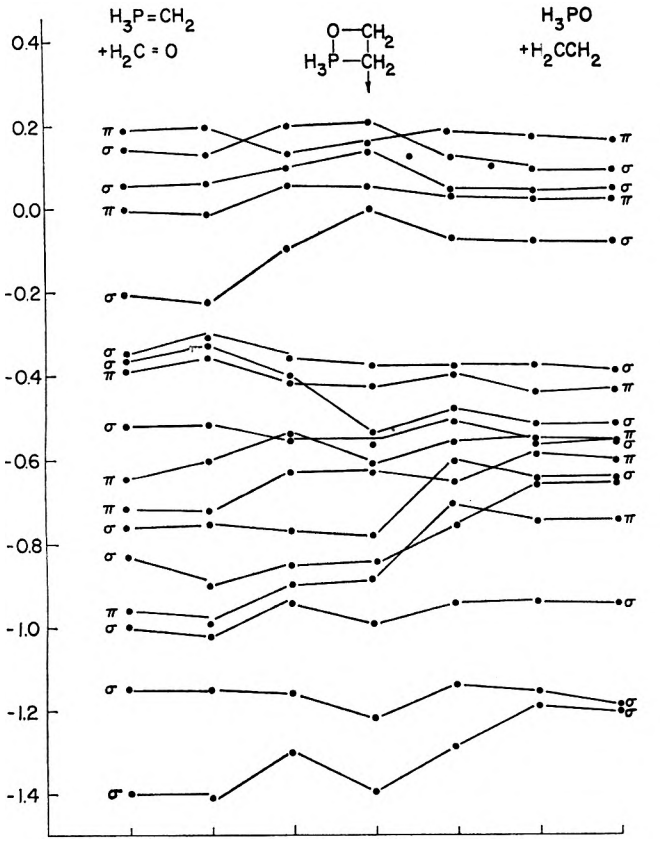


Figure 1.—Correlation diagram for conversion of methylene phosphorane and formaldehyde to ethylene and phosphine oxide *via* a dihydrooxaphosphetane intermediate. The 13 doubly occupied bonding orbitals and the four lowest unoccupied orbitals are shown with the ordinate giving the orbital energy in atomic units. The abscissa describes the separation of the dihydrooxaphosphetane to either starting materials or products. Because bonding orbitals of reactants correlate with bonding orbitals of products, the concerted process is allowed.

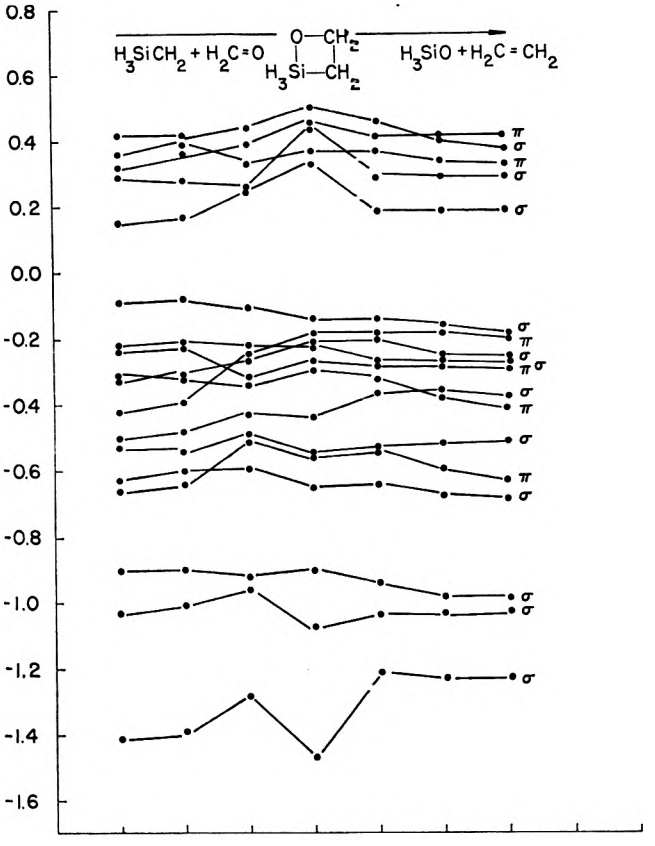


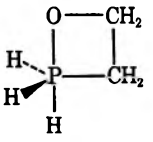
Figure 2.—Correlation diagram for conversion of silylmethyl anion and formaldehyde to ethylene and silanolate in a Peterson reaction. The diagram is constructed in a manner similar to that of Figure 1. The concerted process is allowed.

Geometric predictions based on point centers or repulsion are highly successful (Gillespie models for primary valence angles, "steric" models for long-range conformations) and can be refined by choosing point dipolar representations of heteronuclear bonds. In these models a careful appreciation of lone-pair effects is necessary for generally useful methods. However, if the configuration about atoms bearing lone pairs is immaterial or fixed by other considerations, angular geometries may be predicted merely by letting the nuclear repulsions be minimized. Our computation of the reaction paths of Chart I is composed of steps as follows: (1) choose a set of bond distances separating the heavy atoms; (2) find the angular arrangement which minimizes the repulsions among the nuclear cores; (3) perform the CNDO computation for that crudely optimized geometry.

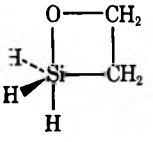
Each of these stages requires comment. The choice of bond distances involves an assignment of bond lengths for bonds unbroken in the course of reaction, and a choice of the lengths of breaking bonds. The latter are the variables which define the energy surfaces we report and are varied in steps of 0.5 Å. The bond lengths of unbroken bonds are almost certainly altered in the course of these eliminations; for example, the C–C separation changes from a length typical of a single bond to a length typical of a double bond. This bond length contributes a substantial driving force to the alkene formation which should not be neglected. However, for economic reasons we do not choose an optimum C–C bond length at each stage of the reaction but rather assign a fixed C–C bond length (Table I). This prejudice of our calculations must be kept in mind during the examination of the energy surfaces.

TABLE I

BOND LENGTHS FOR FOUR-CENTER INTERMEDIATES 2a AND 2b



2a



2b

Bond	Length, Å	Bond	Length, Å
P–O	1.63	Si–O	1.63
C–C	1.54	C–C	1.54
C–H	1.09	C–H	1.09
P–H	1.44	Si–H	1.48
P–C	1.84	Si–C	1.89
C–O	1.44	C–O	1.42

The values chosen for the bond lengths of 2a were idealized ones similar to those typically found for stable molecules and the geometry at phosphorus was assumed to be that of a trigonal bipyramid with the ring bonds apical to oxygen and equatorial to carbon.[14] The bond lengths of 1.63 Å for the apical P–O bond[15]

(14) D. E. Corbridge, *Top. Phosphorus Chem.*, **3**, 57 (1966).

(15) W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *J. Amer. Chem. Soc.*, **87**, 128 (1965).

and 1.44 Å for the C–O bond were selected rather than those reported for the stable oxaphosphetane **5b**, 1.79 and 1.36 Å, respectively.[7b] The stability of **5b** toward thermal fragmentation depends on the presence of the strongly electronegative trifluoromethyl substituents and is reflected by a rather long P–O bond and a short C–O bond. Use of this compound as a model would not appear to be so satisfactory as that of choosing more conventional bond lengths. This was also reinforced by the results of the calculations, which indicated an increase in the total energy of the molecule as either the P–O or C–O bond length was increased.

Minimization of the core repulsion with respect to all angular variables (presuming that bond lengths are fixed by other considerations) requires the scanning of a surface of 16 variables ($3N - 6 -$ number of bond lengths). Automation is of course essential and computer programs were employed for each of the problems of (1) varying angular features of the geometry only, and (2) systematically scanning the hypersurface defined by core repulsions. One of us (J.-T. H.) developed a program capable of varying the geometry by altering bond, torsional, and dihedral angles; a distinctive feature of this program is its ability to deal with ring systems. Rings may be constrained to be planar while being deformed in a plane or may be arbitrarily puckered. The scan of the surface was accomplished by a pattern search program STEPIT distributed by QCPE;[16] many of the optional abilities of STEPIT were removed for speed and compactness in this special application.

The CNDO computation was made possible by the program CNINDO distributed by QCPE[16] which can deal with second-row atoms bearing d orbitals. There seems to be a growing school of thought that d orbitals are not essential to the description of most chemical properties but do provide a convenient way to account for certain spectroscopic features of compounds containing second-row elements. We do not wish to maintain that d orbitals are a *sine qua non* in the Wittig and related systems but, noting that if d orbitals are suppressed it is often necessary to introduce excited p orbitals into the basis set, take the easy alternative and retain the d orbitals supplied by CNINDO. This algorithm may overestimate the population in d orbitals and may overstabilize the intermediate structures of trigonal bipyramidal geometry. CNINDO is known to underestimate strain energy and would overstabilize the crowded intermediate regardless of the use or refusal to use d orbitals. We will make some allowance for this source of error when we study the Wittig and Peterson surfaces.

Decomposition of the Betaine Intermediate in the Wittig Reaction.—For the purposes of analysis it is both convenient and instructive to prepare a three-dimensional potential surface for which the dihydrooxaphosphetane **2a** is the origin.[17] The vertical axis represents the energy calculated in atomic units for the species

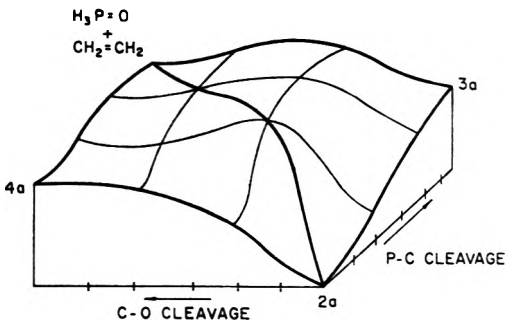


Figure 3.—Three-dimensional potential surface for conversion of a dihydrooxaphosphetane (**2a**) to ethylene and phosphine oxide.

which result when the internuclear separation between two atoms in **2a** is increased. The increase in internuclear separation in 0.5-Å increments is plotted along the two horizontal axes. Figure 3 shows the surface which is obtained when the reactions described by eq 5 and 6 are examined in this manner. The concerted decomposition of **2a** (eq 4) in which both the C–O and P–C bonds are equally stretched is then given by the energies which lie on the diagonal of the cube, while concerted reactions involving unequal C–O and P–C bond breaking are displaced from the diagonal toward the horizontal axes. Thus, Figure 3 depicts a continuum between the two limiting mechanisms expressed by eq 5 and 6 with the process expressed by eq 4 as the midpoint of that continuum.

The energies calculated for the limiting structures **1a–4a** are given in Table II. Simplification in this

TABLE II
CALCULATED ENERGIES OF VARIOUS INTERMEDIATES IN WITTIG AND PETERSON ELIMINATION

Wittig		Peterson	
Species	Energy, atomic units	Species	Energy, atomic units
$CH_2O + H_3PCH_3$	−42.6742	$CH_2O + H_3SiCH_2^-$	−39.9983
1a	−42.9183	**1b**	−40.3535
2a	−43.2832	**2b**	−40.4732
3a	−42.8706	**3b**	−39.9704
4a	−42.8000	**4b**	−39.8092
$CH_2CH_2 + H_3PO$	−42.8115	$CH_2CH_2 + H_3SiO^-$	−39.9740

and all succeeding calculations is achieved by specifying all substituents on carbon and phosphorus as being hydrogen.

Of the three zwitterionic intermediates, the betaine **1a** is calculated to be the most stable. Using the conversion factor 1 atomic unit is equal to 621 kcal/mol along with experience from similar calculations that the energy differences are exaggerated by a factor of 3–4, the data indicate that **1a** is more stable than **3a** by 7–10 kcal/mol and that **3a** is more stable than **4a** by 11–15 kcal/mol. Therefore, if dihydrooxaphosphetane **2a** is an intermediate in this reaction, it should exhibit a greater tendency to revert to betaine **1a** than to go on to products *via* **3a** or **4a**. Of the paths which lead to products, that proceeding through **3a** is much preferable to that proceeding through **4a**, not only on the basis of the energies of the limiting structures but also because the energy calculated at various points along the reaction coordinates for each process favors P–C cleavage over C–O cleavage. Completely concerted decomposition of oxaphosphetane

(16) Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, Ind. 47001.

(17) Three-dimensional potential surfaces have served as useful devices toward understanding the details of (a) elimination reactions, R. A. More O'Ferrall, *J. Chem. Soc. B*, 274 (1970), and (b) nucleophilic substitution reactions, E. R. Thornton, *J. Amer. Chem. Soc.*, **89**, 2915 (1967), and (c) have been suggested for reactions involving general acid–base catalysis, W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 4731 (1972); *Chem. Rev.*, **72**, 705 (1972).

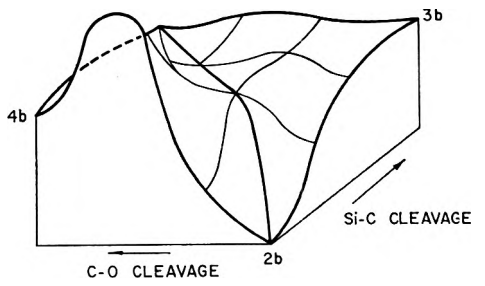


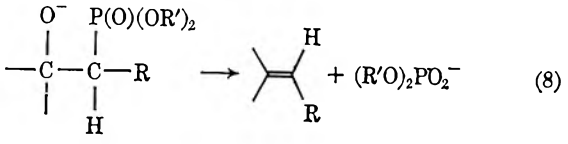
Figure 4.—Three-dimensional potential surface for conversion of a dihydrooxasiletanide anion to ethylene and silanolate.

2a is characterized by a rather steeply rising profile which reaches its maximum in potential energy at the point where each bond undergoing cleavage (P–C and C–O) has been stretched by *ca.* 1 Å. It would appear that the completely concerted process could only be favored if the second step of the competing stepwise process was disfavored This is not borne out by the calculations, which indicate that only modest energy expenditures are required to convert **3a** (or **4a**) to products.

A significant portion of the stabilization calculated for the oxaphosphetane **2a** (66–89 kcal/mol more stable than **1a**) reflects the bias of the computational method toward condensed structures. While this figure is certainly much too high, the distinct depression in the potential surface does allow the conclusion that **2a** is a permissible and reasonable intermediate in these reactions.

We believe that the most general description for the decomposition of the betaine intermediate in the Wittig reaction is that which proceeds through an initial, reversible formation of a dihydrooxaphosphetane, which in turn undergoes fragmentation to olefin and phosphine oxide by a process in which cleavage of the phosphorus–carbon bond is considerably advanced over cleavage of the carbon–oxygen bond.

This analysis coincides well with certain experimental observations. For example, the base-catalyzed decomposition of β-hydroxyalkylphosphonate esters as shown in eq 8 is a key step in the Horner–



(8)

6

Wadsworth–Emmons modification of the Wittig reaction but occurs readily only when R is an effective carbanion-stabilizing substituent such as phenyl, cyano, or carbethoxy.[1,18]

The effect of such substitution in **6** is to stabilize the zwitterionic intermediate analogous to **3a** lowering the energies along the right side of the energy surface in Figure 3.

The inclusion of a degree of C–O cleavage concurrent with P–C cleavage provides a reasonable rationalization for the relative stability of **5**. The presence of two electron-withdrawing trifluoromethyl groups

(18) The implication of this observation with respect to the question of concertedness in decomposition of an oxaphosphetane intermediate was perceived and alluded to briefly in a footnote to a Communication to the Editor by E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, **88**, 5654 (1966).

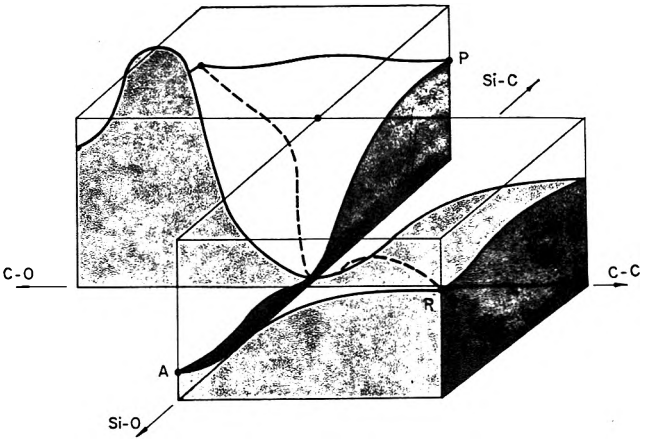
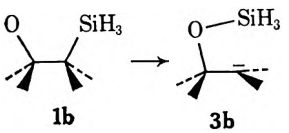


Figure 5.—A depiction of the potential surfaces for reaction of silylmethyl anion and formaldehyde (point R). Point A represents $H_3SiCH_2CH_2O^-$ and point P represents $^-CH_2CH_2OSiH_3$. The four-center species **2b** is a shallow minimum along the path A to P.

on the carbon atom which is undergoing C–O cleavage serves to strengthen the C–O bond and raise the energy of the left side of the potential surface. An increase in P–C cleavage is therefore required to achieve the transition state.

Decomposition of $H_3SiCH_2CH_2O^-$ in the Peterson Olefination.—A three-dimensional energy surface for the fragmentation of the hypothetical anionic dihydrooxasiletanide intermediate **2b** to ethylene and H_3SiO^- was constructed in a manner similar to that used for the Wittig reaction. This surface is shown in Figure 4 and is seen to be much more sharply skewed than that of the corresponding Wittig surface. In particular, cleavage of the C–O bond is characterized by a steep rise to an energy maximum of such magnitude as to be considered thermally inaccessible. The alternative mode which leads to products, cleavage of the Si–C bond, is much more favorable and suggests that Si–C cleavage is much more advanced than C–O cleavage in the transition state leading to olefin and silanolate. As in the Wittig case cleavage of the C–O bond subsequent to Si–C cleavage is a process of low energy and presumed to be rapid.

Another interesting and perhaps significant difference between the Wittig and Peterson surfaces is that formation of **2b** from **1b** (silicon case) is much less favorable than the corresponding formation of **2a** from betaine **1a** (phosphorus case). While **2a**, as determined by the calculations, is 66–89 kcal/mol more stable than **1a**, **2b** is only 18–25 kcal/mol more stable than **1b**. Given the bias toward condensed structures inherent in the calculations, this may mean that the dihydrooxasiletanide anion is bypassed as a true intermediate and may represent only an approximation of the transition state for conversion of **1b** to **3b** by nucleophilic attack of oxygen on silicon in an SNi–Si process (eq 9 and Figure 5).[19]



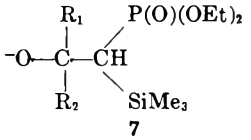
(9)

1b **3b**

(19) For terminology and general discussion of reaction mechanisms at silicon see L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill, New York, N. Y., 1965.

The same dependence on the electron-withdrawing capacity of substituents exists here as in the Horner–Wadsworth–Emmons modification of the Wittig reaction mentioned in the preceding section. Elimination of silanolate from **1b** to yield olefin is complete within minutes below 25° when the carbon atom bearing the silicon (as trimethylsilyl) also bears a substituent capable of delocalizing negative charge such as phenyl, methylthio or phenylthio, phenylsulfinyl, 1,3-dithianyl, diethylphosphonate, and diphenylphosphino.[2] Elimination is demonstrably slower when electron-withdrawing substituents are absent. Many of the above substituents are not only carbanion stabilizing but also may be considered to stabilize a developing double bond in the transition state. It is clear that this latter factor cannot be important because it has been established with certainty that a sulfinyl substituent tends to destabilize a double bond directly attached to it.[20] If stabilization of the double bond were the only factor which determined ease of elimination, then vinyl sulfoxides would be formed with great difficulty. Such is not the case; vinyl sulfoxide formation takes place with great ease.[21] This behavior is in accord with the results of the calculations, which indicate extreme skewing of the energy surface toward **3b** capable of being stabilized effectively by substitution with electron-withdrawing groups.

Skewing of the energy surfaces depicted in Figures 3 and 4 toward **3a** and **3b** also provides a reasonable rationalization for the observation that intermediates like **7** which have the capacity to form vinylphosphonates by loss of Me_3SiO^- or vinylsilanes by loss of $(EtO)_2PO^-{}_2$ yield only the product from elimination of silicon. Stabilization of **3b** by $-P(O)(OEt)_2$ is more effective than stabilization of **3a** by $-SiMe_3$, with the result that silicon migrates in preference to phosphorus.[22]



7

The tendency for silicon to migrate to oxygen in **7** because it leaves a more highly stabilized carbanion behind is sufficiently pronounced to overcome adverse steric effects when one of the R groups is isopropyl and the other hydrogen. The only products are the corresponding cis and trans diethyl vinylphosphonates with the cis predominating by 2.4:1.[2c] If a close balance existed between silicon migration and phosphorus migration a reasonable presumption would have been for stereoselective formation of a mixture of *trans*-vinylsilane and *trans*-vinylphosphonate.

In summary, the Peterson reaction differs from the Wittig reaction in that the four-center array represents, at most, an unstable intermediate during the passage of **1b** to **3b**. The preferential loss of Me_3SiO^- in species such as **7** results not so much from an intrinsically greater "migratory aptitude" on the part of silicon as from the greater stabilizing effect of phosphonate on the resulting carbanion.

Registry No.—**1a**, 16247-01-1; **1b**, 40110-49-4; **2a**, 40110-50-7; **2b**, 40330-42-5; **3a**, 20502-84-5; **3b**, 40110-53-0; **4a**, 40110-52-9; **4b**, 40140-15-6.

Acknowledgment.—Computational work was supported by a grant of access from the University Computer Science Center. Acknowledgment is made also to the A. P. Sloan Foundation, the National Science Foundation (Grant GP-30817), and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

(20) (a) D. E. O'Connor and W. I. Lyness, *J. Amer. Chem. Soc.*, **85**, 3044 (1963); (b) D. E. O'Connor and C. D. Broaddus, *ibid.*, **86**, 2267 (1964); (c) D. E. O'Connor and W. I. Lyness, *ibid.*, **86**, 3840 (1964).

(21) F. A. Carey and O. Hernandez, *J. Org. Chem.*, **38**, 2670 (1973).

(22) Quantitative data are not available on the relative carbanion-stabilizing abilities of $-SiMe_3$ and $-P(O)(OEt)_2$ but it seems likely that such data would coincide with expectation. In this context it is noteworthy that metalation of diethyl methylphosphonate occurs much more readily than metalation of tetramethylsilane; see ref 18 and D. J. Peterson, *J. Organometal. Chem.*, **9**, 373 (1967).

Silicon-Containing Carbanions. III. Synthesis of Vinyl Sulfoxides *via* 1-Trimethylsilyl-1-(phenylsulfinyl)methyllithium

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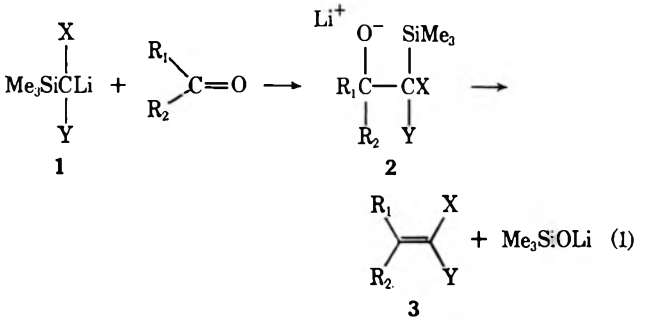
As part of a continuing study of trimethylsilyl-substituted organolithium reagents 1-trimethylsilyl-1-(phenylsulfinyl)methyllithium (**1d**) was prepared by metalation of trimethylsilylmethyl phenyl sulfoxide. Vinyl sulfoxides were formed in good yield by condensation of **1d** with the following carbonyl compounds: acrolein, adamantanone, benzaldehyde, benzophenone, cinnamaldehyde, cyclohexanone, cyclohexenone, and isobutyraldehyde. It was demonstrated that **1d** and related reagents can be prepared *in situ* by trimethylsilylation of, *e.g.*, (phenylsulfinyl)methyllithium and used for vinyl sulfoxide synthesis directly without ever isolating the thermally and hydrolytically sensitive trimethylsilylmethyl sulfoxide. Organolithium reagent **1d** reacted with ethyl benzoate to yield (phenylsulfinyl)acetophenone and with methyl iodide to yield 1-trimethylsilyl-1-(phenylsulfinyl)ethane as a single diastereomer which rearranged on heating in benzene at reflux to $Me_3SiOCH(SPh)CH_3$.

Elimination reactions proceeding through intramolecular attack on silicon by oxygen in a four-center process are common and provide the basis for a number of useful olefin syntheses.[1] Thus, 1-trimethylsilyl-1-alkyllithiums (**1**) add to aldehydes and ketones to give intermediates (**2**) which fragment to olefins and Me_3SiOLi under extremely mild conditions. The sequence depicted in eq 1 has been found to be broadly



(1)

a, X = H; Y = SPh
b, X = H; Y = $P(O)(OEt)_2$
c, X + Y = $-S(CH_2)_3S-$
d, X = H; Y = S(O)Ph
e, X = H; Y = H

applicable to the synthesis of vinyl phenyl thioethers (**3a**),[2] diethyl vinylphosphonates (**3b**),[2] and ketene thioacetals (**3c**).[3]

It was considered of interest to investigate the possibility of vinyl sulfoxide (**3d**) formation by the analogous process in which metalation of trimethylsilylmethyl phenyl sulfoxide (**4**) would serve to produce the required 1-trimethylsilyl-1-(phenylsulfinyl)methyllithium (**1d**). The reasons for this interest include the obvious one of extending the scope of what presently appears to be a general olefination reaction by providing a simple synthetic route to vinyl sulfoxides,[4] as well as the fact that silylmethyl sulfoxides themselves represent a potentially interesting class of compounds.

Brook[5] has described the synthesis of **4** by reaction of trimethylsilylmethylmagnesium chloride with methyl benzenesulfinate and found it to be both hydrolytically and thermally unstable. Hydrolytic instability with respect to silicon–carbon bond cleavage is a common feature of compounds of the type R_3SiCH_2X where X is a highly electronegative substituent.[6] The thermal instability results from a four-center elimination of Me_3SiO^- involving the sulfoxide oxygen and is conceptually related to the conversion of **2** to **3**. Recombination of the fragments produces the observed product, trimethylsiloxymethyl phenyl sulfide (eq 2).

$$\underset{\mathbf{4}}{Me_3SiCH_2S(O)Ph} \xrightarrow{60^\circ} Me_3SiO^- + CH_2{=}\overset{+}{S}Ph \longrightarrow Me_3SiOCH_2SPh \quad (2)$$

We have found that **4**, prepared by Brook's method, is sufficiently stable for study of its metalation provided care is taken in its preparation and it is stored at temperatures below 0°. The reactions of **1d**, resulting from metalation of **4**, are the subject of this report.

Results and Discussion

Metalation of **4** was accomplished at −70° in tetrahydrofuran using either *n*-butyllithium or *tert*-butyllithium to afford **1d**. The alternative mode of reaction, cleavage of the carbon–silicon bond to form butyltrimethylsilane and (phenylsulfinyl)methyllithium (**5**), did not occur to any measurable extent, as evidenced by the reaction of the resulting solution with benzophenone to afford 1-(phenylsulfinyl)-2,2-diphenylethylene (**6b**) as the exclusive product of carbonyl addition in 81–87% yield. Formation of the vinyl sulfoxide parallels the behavior of the other 1-trimethylsilylalkyllithium reagents depicted in eq 1. Had **5** rather than **1d** been formed from **4** the product would have been 1,1-diphenyl-2-(phenylsulfinyl)ethanol (**7**).[7] Independent generation of **5** from methyl phenyl sulfoxide and phenyllithium verified this and demonstrated

(1) (a) D. J. Peterson, *Organometal. Chem. Rev. A*, **7**, 295 (1972); (b) D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968); (c) T. H. Chan, E. Chang, and E. Vinokur, *Tetrahedron Lett.*, 1137 (1970).

(2) F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 939 (1972).

(3) F. A. Carey and A. S. Court, *ibid.*, **37**, 1926 (1972); D. Seebach, B. T. Grobel, A. K. Beck, M. Braun, and K. H. Geiss, *Angew. Chem., Int. Ed., Engl.*, **11**, 443 (1972); P. F. Jones and M. F. Lappert, *Chem. Commun.*, 526 (1972).

(4) For recent alternative syntheses of vinyl sulfoxides see (a) E. Block, *J. Amer. Chem. Soc.*, **94**, 642 (1972); (b) D. A. Evans, C. A. Bryan, and C. L. Sims, *ibid.*, **94**, 2891 (1972); (c) D. J. Abbott, S. Collona, and C. J. M. Stirling, *Chem. Commun.*, 471 (1971); (d) G. A. Russell and L. A. Ochrymowycz, *J. Org. Chem.*, **35**, 2106 (1970).

(5) A. G. Brook and D. G. Anderson, *Can. J. Chem.*, **46**, 2115 (1968).

(6) C. Eaborn and R. W. Bott in "Organometallic Compounds of the Group IV Elements," Vol. 1, A. G. MacDiarmid, Ed., Marcel Dekker, New York, N. Y., 1968, pp 367–378.

(7) For reactions of methylsulfinyl carbanion with benzophenone see E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

TABLE I

REACTION OF 1-TRIMETHYLSILYL-1-PHENYLSULFINYLMETHYLLITHIUM WITH CARBONYL COMPOUNDS

Aldehyde or ketone	Product	R_1	R_2	Metalating agent	Yield, %[a]
Benzaldehyde	**6a**	H	Ph	*n*-BuLi	87[b]
				t-BuLi	81[c]
Benzophenone	**6b**	Ph	Ph	*n*-BuLi	72
				t-BuLi	75
Cyclohexanone	**6c**		$-(CH_2)_4-$	*n*-BuLi	66
				t-BuLi	67
Isobutyraldehyde	**6d**	H	$(CH_3)_2CH$	*n*-BuLi	30[d]
				t-BuLi	66[e]
Acrolein	**6e**	H	$CH_2=CH-$	*n*-BuLi	67[f]
				t-BuLi	72[f]
trans-Cinnamaldehyde	**6f**	H	PhCH=CH	*n*-BuLi	70
Cyclohexenone	**6g**		$-CH=CH(CH_2)_3-$	*t*-BuLi	24
Adamantanone	**6h**			*t*-BuLi	82

[a] Isolated yield of purified product. [b] Cis/trans = 1. [c] Cis/trans = 0.5. [d] Cis/trans = 2. [e] Cis/trans = 0.8. [f] Cis/trans = 1.

that the product was stable under the reaction conditions.

$$\underset{\textbf{1d}}{PhS(O)CH(Li)SiMe_3} + R_1R_2CO \longrightarrow \underset{\textbf{6}}{R_1R_2C{=}CHS(O)Ph}$$

$$\underset{\textbf{5}}{PhS(O)CH_2Li} + R_1R_2CO \longrightarrow R_1R_2C(OH)CH_2S(O)Ph$$

7, $R_1 = R_2 = Ph$
8, $R_1 + R_2 = -(CH_2)_5-$

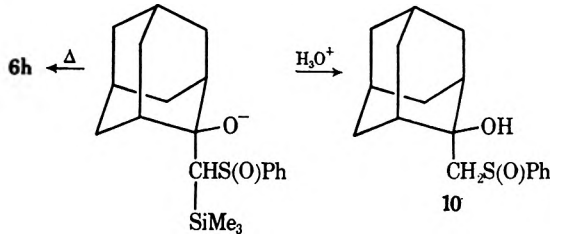
Similar results were found with cyclohexanone; vinyl sulfoxide **6c** was formed when **1d** was used while **8** was obtained on reaction with **5**.

A number of representative aldehydes and ketones reacted with **1d** to product vinyl sulfoxides in all cases and in generally good yields. These results are summarized in Table I. The structures of the products were established by the usual spectroscopic techniques and in certain instances (**6a** and **6e**) by comparison of physical properties with those previously reported (see Experimental Section for details). Most characteristic of the structures with respect to their nmr spectra was the signal for the vinyl proton on the carbon atom bearing the phenylsulfinyl group, which appeared at 1.1–1.5 ppm lower field than for the unsubstituted analog $R_2C{=}CH_2$.

As can be seen from Table I, vinyl sulfoxide formation is not stereoselective, mixtures of cis and trans isomers being formed from aldehydes. This has been previously observed in reaction of **1a** and **1b** and it is not yet clear as to the extent to which this reflects the stereoselectivity of addition of the unsymmetrical reagent to the carbonyl group *vs.* nonstereospecific elimination of Me_3SiOLi from the diastereomeric intermediate.

Conjugate addition did not occur when acrolein, cinnamaldehyde, or cyclohexenone was used, there being observed exclusively 1,2 addition to the carbonyl to afford dienyl phenyl sulfoxides **6e**, **6f**, and **6g**, respectively, as mixtures of cis and trans isomers in each case.

Addition of **1d** to 2-adamantanone has provided the only instance thus far in reactions of **1a–d** in which elimination of Me_3SiOLi is not spontaneous under the reaction conditions. When the experiment was performed in the normal way the isolated product was a mixture of **6h** and 2-(phenylsulfinyl)methyl-2-adamantanol (**10**). Since it seemed more likely that the formation of **10** resulted from **9** which hydrolyzed



during work-up rather than by addition of **5** (not observed in any other reactions of **4**) and that a reasonable explanation was that decomposition of the intermediate **9** was slow because of increased crowding in the transition state, the reaction was modified to the extent that the reaction mixture was refluxed for 0.5 hr prior to work-up. Under these conditions the vinyl sulfoxide **6h** was the sole product.

It is interesting to compare the relative ease of decomposition of various species having the structure represented by **2**. When X or Y is a substituent capable of stabilizing a carbanionic center, decomposition of **2** is spontaneous under the conditions of condensation of **1** and carbonyl compounds.[1-3] On the other hand, when X and Y are hydrogen, decomposition is rapid only at elevated temperatures.[1b,c] Such a dependence on carbanion-stabilizing power suggests an intermediate or transition state for the conversion of **2** to **3** in which considerable electron density is built up at the carbon atom from which the trimethylsilyl group is lost. This point is discussed in greater detail in the accompanying paper.[8]

The ready conversion of **2d** to **3d** not only is consistent with this description but also provides strong evidence against the alternative explanation that the effect of substituents is to stabilize a developing double bond in the transition state. It has been conclusively established that the conjugative effect of a sulfinyl group with a carbon–carbon double bond is negligible by observing that equilibration of α,β-unsaturated

(8) C. Trindle, J.-T. Hwang, and F. A. Carey, *J. Org. Chem.*, **38**, 2664 (1973).

sulfoxides leads to preferential formation of the β,γ isomer.[9] If stabilization of the developing double bond were important it reasonably follows that **2d** would be converted to **3d** less readily than **2e** to **3e**, in contrast to what is actually observed.

In situ generation of trimethylsilylmethyl sulfoxides was examined because, if successful, it would offer great advantages in convenience for synthetic purposes. When a solution containing 2 equiv of methylsulfinylmethyllithium (**11**) in tetrahydrofuran was treated with 1 equiv of trimethylchlorosilane followed by 1 equiv of benzophenone, 1-(methylsulfinyl)-2,2-diphenylethylene (**12**)[4d] was isolated in 50% yield. The reaction sequence described by eq 3–5 is proposed.

$$\underset{\mathbf{11}}{CH_3S(O)CH_2Li} + Me_3SiCl \longrightarrow CH_3S(O)CH_2SiMe_3 \quad (3)$$

$$CH_3S(O)CH_2Li + CH_3S(O)CH_2SiMe_3 \longrightarrow CH_3S(O)CH_3 + CH_3S(O)CH(Li)SiMe_3 \quad (4)$$

$$CH_3S(O)CH(Li)SiMe_3 + Ph_2CO \longrightarrow \underset{\mathbf{12}}{Ph_2C{=}CHS(O)CH_3} + Me_3SiOLi \quad (5)$$

Attempted *in situ* formation of **1d** by a similar process in which methyl phenyl sulfoxide was metalated with *n*-butyllithium, then allowed to react with trimethylchlorosilane and benzophenone, gave the mixture of products summarized in eq 6.

$$PhS(O)Me \xrightarrow[2.\ Me_3SiCl\ \ 3.\ Ph_2CO]{1.\ BuLi\ THF} \mathbf{6b}\ 34\% + \mathbf{7}\ 15\% + \underset{\mathbf{13},\ 32\%}{\text{Ph(H)C=C(Ph)S(O)Bu}} \quad (6)$$

Compounds **6** and **7** are presumably derived from **1d** and **5**, respectively, while the formation of 1-(*n*-butylsulfinyl)-2,2-diphenylethylene (**13**) suggests 1-trimethylsilyl-1-(*n*-butylsulfinyl)methyllithium (**14**) as its precursor. Since no **13** was observed when preformed **4** was metalated and treated with benzophenone, it follows that **14** results from reaction of trimethylchlorosilane with (*n*-butylsulfinyl)methyllithium formed in a prior step. The most plausible explanation involves the exchange process represented by eq 7–9.

$$PhS(O)Me + n\text{-}BuLi \longrightarrow \underset{\mathbf{5}}{PhS(O)CH_2Li} + BuH \quad (7)$$

$$\underset{\mathbf{5}}{PhS(O)CH_2Li} \longrightarrow CH_2{=}S{=}O + PhLi \quad (8)$$

$$CH_2{=}S{=}O + n\text{-}BuLi \longrightarrow n\text{-}BuS(O)CH_2Li \quad (9)$$

$$n\text{-}BuS(O)CH_2Li + Me_3SiCl \longrightarrow \underset{\mathbf{14}}{n\text{-}BuS(O)CH_2SiMe_3} \quad (10)$$

Such an exchange of ligands on sulfur by way of a sulfine intermediate has been suggested previously to rationalize the methyllithium-induced racemization of aryl methyl sulfoxides as well as a number of other reactions of sulfoxides.[10] It is of interest that the corresponding process (eq 11) does not occur with **1d**.

$$\mathbf{1d} \not\longrightarrow PhLi + Me_3SiCH{=}S{=}O \quad (11)$$

Simple steric considerations would predict a greater tendency for **1d** to fragment than for **5**. The decreased tendency of **1d** toward fragmentation can be most readily understood in terms of an enhanced stabilization of **1d** relative to **5**. Stabilization of carbanionic centers by adjacent silicon has been shown to be important in a number of cases, the most thorough studies being those of Schmidbaur,[11] who has observed appreciable stabilization of sulfur and phosphorus ylides by silicon and ascribes the stabilizing effect to either a "d-orbital π interaction or an altered charge distribution in the σ skeleton."

Other electrophilic substrates also reacted with **1d**. (Phenylsulfinyl)acetophenone was isolated in 76% yield from reaction with ethyl benzoate. Because cleavage of trimethylsilyl groups from β-ketosilanes occurs with extreme ease,[12] it is reasonable to believe that this results from hydrolysis of a benzoylated intermediate.

$$\underset{\text{COPh}}{\underset{|}{PhS(O)CHSiMe_3}} \xrightarrow{H_2O} \underset{\mathbf{15}}{PhS(O)CH_2COPh}$$

Alkylation of **1d** with methyl iodide produced 1-trimethylsilyl-1-(phenylsulfinyl)ethane (**16**) in 92%

$$\underset{\mathbf{16}}{\underset{|}{PhS(O)CHSiMe_3}} \xrightarrow{80^\circ} \underset{\mathbf{17}}{Me_3SiOCHSPh}$$

yield apparently as a single diastereomer judging from the clean nmr spectrum and sharp melting point of the product.[13]

This compound was more thermally stable than trimethylsilylmethyl phenyl sulfoxide but did rearrange in refluxing benzene (2 hr) to afford the *O*-trimethylsilyl *S*-phenyl thioacetal **17**. Such a rearrangement suggests a possible aldehyde synthesis in which **1d** functions as a latent or masked carbonyl equivalent.[14,15] This avenue has not been explored in detail but is not practical at present because **1d** did not prove sufficiently reactive toward other alkyl halides (butyl iodide, 1,5-dibromopentane) to justify further investigation.

Experimental Section

Nmr spectra were recorded on a Hitachi Perkin-Elmer R-20 spectrometer in $CDCl_3$ and chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Infrared spectra were measured on a Perkin-Elmer 337 grating instrument as KBr disks for solids and pressed films for liquids. Melting points are corrected and were determined on a Thomas-Hoover apparatus. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionizing potential of 70 eV.

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Microanalyses were performed by Alfred Bernhardt, Engelskirchen, West Germany.

All reactions were carried out in an atmosphere of dry nitrogen. Tetrahydrofuran was distilled from lithium aluminum hydride. *n*-Butyllithium in *n*-hexane, *tert*-butyllithium in pentane, and phenyllithium in benzene-ether were purchased from Alfa Inorganics.

General Procedure for Synthesis of Vinyl Sulfoxides.—Trimethylsilylmethyl phenyl sulfoxide (**4**, 500 mg, 2.35 mmol) was dissolved in 10 ml of purified tetrahydrofuran under a nitrogen atmosphere and cooled to −70°. A solution of *tert*-butyllithium in pentane (1.7 ml, 3.06 mmol) was added to form a clear yellow solution of **1d**. A solution of 2.35 mmol of the carbonyl compound in ~2 ml of tetrahydrofuran was added and the reaction mixture was stirred at −70° for 10 min and then allowed to warm to room temperature. After 2 hr at room temperature, 20 ml of saturated aqueous ammonium chloride solution was added, the tetrahydrofuran layer was separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$ or Na_2SO_4) and evaporated to afford the crude product.

An identical procedure was used for reactions in which *n*-butyllithium was the base. Yield data for these reactions can be found in Table I.

1-(Phenylsulfinyl)-2,2-diphenylethylene (6b).—The crude product crystallized on being washed with ether, yielding 535 mg (75%) of **6b**, mp 104.5–108.5°. After recrystallization from dichloromethane–ether the compound had mp 110–112°; ir (KBr) 1440, 1035, 1025, 805, 770, 750, 728, 710, 700, 690 cm^{-1}; nmr ($CDCl_3$) δ 7.2–7.9 (m, 15, aromatic) and 6.78 ppm (s, 1, C=CH); mass spectrum (70 eV) *m/e* (rel intensity) 304 (1), 288 (21), 257 (25), 256 (100), 195 (46), 179 (35), 178 (83), 167 (71), 165 (44), 152 (28), 77 (33).

The analytical sample was obtained from a previous preparation as a clear syrup by preparative tlc.

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.91; H, 5.30; S, 10.53. Found: C, 78.73; H, 5.39; S, 10.38.

Phenyl Styryl Sulfoxide (6a).—A mixture of *cis*- and *trans*-phenyl styryl sulfoxides was obtained in 81% yield by preparative tlc of the crude product on silica gel using benzene–ether as the solvent. The product composition was determined by nmr at 100 MHz to be cis/trans = 0.5.[16]

Anal. Calcd for $C_{14}H_{12}OS$: C, 73.65; H, 5.30; S, 14.04. Found: C, 73.46; H, 5.29; S, 13.91.

(1-Phenylsulfinyl)methylenecyclohexane (6c).—Preparative tlc of the crude product from 231 mg (2.35 mmol) of cyclohexanone on silica gel using benzene–ether (1:1) as the solvent gave 351 mg (67%) of **6c** as a colorless oil: nmr ($CDCl_3$) δ 7.5 (m, 5, aromatic), 5.95 (s, 1, C=CH), 2.7 and 2.2 (br m, 4, $C=CCH_2$), and 1.6 ppm (br, 6, CH_2); ir (neat) 1630, 1440, 1080, 1040, 1020, 800, 740, 690 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 220 (16), 204 (27), 203 (100), 110 (33), 93 (60), 91 (33), 77 (46), 67 (31), 55 (31), 41 (48).

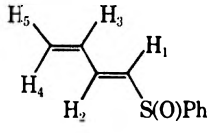
Anal. Calcd for $C_{13}H_{16}OS$: C, 70.87; H, 7.32; S, 14.55. Found: C, 70.87; H, 7.25; S, 14.67.

***cis*- and *trans*-2-Isopropylvinyl Phenyl Sulfoxide (6d).**—This reaction was carried out on a 4.7-mmol scale using *n*-butyllithium as the base at −70°. The crude product (563 mg) was chromatographed (preparative tlc) on silica gel using chloroform–ether (8:2) as the eluent to give two fractions. The less polar fraction (170 mg) consisted mainly of diphenyl disulfide and was discarded. The more polar fraction (287 mg, 30%) was a mixture of cis and trans vinyl sulfoxides. The analytical sample was prepared by rechromatography under the same conditions: ir (neat) 3060, 2980, 2940, 1630, 1480, 1450, 1085, 1040, 1000, 750, 730, 690 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 194 (11), 178 (27), 177 (100), 110 (24), 78 (33), 51 (24), 43 (30).

Anal. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26; S, 16.50. Found: C, 67.84; H, 7.08; S, 16.65.

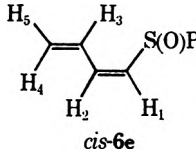
Analysis of the nmr spectrum at 100 MHz ($CDCl_3$) permitted the determination of the cis/trans ratio as 2:1. The spectrum showed, in addition to the aromatic multiplet at δ 7.4–7.8 and the methyl protons as a multiplet at δ 1, a doublet of doublets, J = 7, 15 Hz, centered at δ 6.7 which integrated for ~0.25 H and is assigned to *i*-PrC=CH of the trans isomer. The remaining vinyl protons appeared as a multiplet containing at least seven lines from δ 5.8 to 6.3 and integrated for ~1.75 H. Since the total area for vinyl protons is equivalent to 2 H, it follows that the trans isomer is only one-half as abundant as the cis isomer. This receives confirmation from consideration of the signals for $(CH_3)CH=C$, which appeared as two multiplets centered at δ 3.2 and 2.4 with areas in the relative ratio 2:1, respectively. The peak at lower field may be assigned to the $(CH_3)_2CH$ which is cis to the sulfoxide on the basis of the anisotropic effect of the sulfoxide group expected to be highly deshielding.[17]

Butadienyl Phenyl Sulfoxide (6e).—The crude product obtained from 0.17 ml (2.5 mmol) of freshly distilled acrolein was purified by preparative tlc on silica gel using benzene–ether (1:1) as the solvent to give 343 mg (82%) of **6e** as a pale yellow oil. The nmr spectrum of the product both at 60 and 100 MHz was extremely complex, as anticipated for a strongly coupled five-spin system. By comparing the 60 MHz spectrum (in CCl_4) with that of authentic *trans*-**6e** it could be ascertained that this compound was present.[18] Measuring the spectrum at 100 MHz of 60 mg of the product in 0.4 ml of $CDCl_3$ containing 50 mg of $Eu(fod)_3$ simplified the spectrum sufficiently so that it was possible to assign certain signals and not only verify that *cis*-**6e** was present but to determine that *cis*-**6e** and *trans*-**6e** were present in



trans-**6e**

H_1: 7.2, d, J_{12} = 15 Hz
H_2: 8.2, dd, J_{12} = 15, J_{23} = 10Hz
H_3: 6.4–6.9, dt, $J_{23} = J_{35}$ = 10, J_{34} = 17 Hz



cis-**6e**

H_1: overlaps with meta and para aromatic protons (7.3–7.5)
H_2: 6.7 (t) $J_{12} = J_{23}$ = 10 Hz

approximately equal amounts. The peak positions and assignments in the presence of the shift reagent are given below and are consistent with expectation. (δ values represent centers of multiplets.)

These nmr experiments were actually run on a sample obtained from a reaction in which *n*-butyllithium was used as the metalating agent, but there was no difference in the composition of the product obtained for the reaction when *tert*-butyllithium was the base, as evidenced from the appearance of the 60-MHz spectrum.

***cis*- and *trans*-1-(Phenylsulfinyl)-*trans*-4-phenylbutadiene (6f).**—Using *n*-butyllithium as the metalating agent, a solution of **1d** was prepared in tetrahydrofuran at −70° and treated with 310 mg (2.35 mmol) of *trans*-cinnamaldehyde. After hydrolysis and extraction 695 mg of product was obtained which was subjected to preparative tlc on silica gel using 1:1 benzene–ether as the eluent. The middle band was isolated as a yellow liquid (504 mg) and found to be mainly a mixture of *cis*- and *trans*-**6f** from its nmr spectrum. Rechromatography using 1:1 ethyl acetate–cyclohexane as the solvent gave a pure mixture of isomers (415 mg, 70%), ir (neat) 1630, 1580, 1440, 1090, 1040, 1000, 750, 730, 700 cm^{-1}. The nmr spectrum in $CDCl_3$ at 100 MHz revealed the presence of two doublets centered at δ 6.40 and 6.15 in the ratio 2:1, respectively. The low-field doublet had a coupling constant of 14 Hz and the one at higher field had a coupling constant of 10 Hz, leading to the assignment of *trans*-**6f** to the major product and *cis*-**6f** to the minor product. Together these two signals integrated for 1 proton out of a total area equivalent to 14 protons.

Anal. Calcd for $C_{16}H_{14}OS$: C, 75.56; H, 5.55; S, 12.61. Found: C, 75.32; H, 5.39; S, 12.48.

3-(1-Phenylsulfinyl)methylenecyclohexene (6g).—Addition of **1d** to cyclohexenone was carried out in the usual manner at −70° to yield 614 mg of an oil which purified with difficulty. Four separate preparative tlc steps were employed to afford, ultimately, 123 mg (24%) of **6g** as a colorless liquid: ir (neat) 3060, 3040, 2950 (CH), 1720, 1640, 1450, 1085, 1040 (S=O), 1000, 945, 870, 750, 740, 690 cm^{-1}; nmr ($CDCl_3$) δ 7.7–7.2 (m, 5, aromatic),

(16) The nmr spectra of the cis and trans isomers are sufficiently different in the region δ 6–7 to permit determination of composition; see T. H. Kinstle and W. R. Oliver, *Org. Mass Spectrom.*, **6**, 699 (1972).

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(18) This spectrum was kindly provided by Professor David A. Evans of UCLA. We acknowledge his assistance with thanks.

7.05–6.85 and 6.4–5.8 (m, 3, vinyl H), and 3–1.5 ppm (m, 6, ring CH_2).

Anal. Calcd for $C_{13}H_{14}OS$: C, 71.52; H, 6.46; S, 14.69. Found: C, 71.27; H, 6.54; S, 14.49.

2-(1-Phenylsulfinyl)methyleneadamantane (6h).—The general procedure was modified to the extent that the reaction mixture was refluxed for 0.5 hr prior to work-up. The crude product was recrystallized from ether–pentane to yield 521 mg (82%) of **6h**, mp 81.5–85°. Recrystallization from the same solvent mixture gave the analytical sample: mp 88–89°; ir (KBr) 3050, 2900, 2850, 1620, 1440, 1080, 1038, 1030, 800, 745, 720, 700, 690 cm^{-1}; nmr ($CDCl_3$) δ 7.5 (m, 5, aromatic), 5.92 (s, 1, C=CH), 3.6 and 2.5 (br, 2, C=CCH), and 2.0 ppm (br, 12); mass spectrum (70 eV) *m/e* (rel intensity) 272 (100), 256 (26), 255 (24), 224 (46), 223 (32), 167 (20), 105 (32), 93 (26), 91 (74), 79 (43), 77 (37), 67 (32), 41 (40).

Anal. Calcd for $C_{17}H_{20}OS$: C, 74.96; H, 7.40; S, 11.77. Found: C, 74.97; H, 7.26; S, 11.64.

In a previous experiment using *n*-butyllithium as the base and omitting the 0.5-hr reflux step, *i.e.*, standard conditions, the crude product was a yellow syrup (742 mg) from which was obtained by a combination of preparative tlc on silica gel and fractional recrystallization 97 mg of pure **6h** (mp 88.5–91.5°) and 47 mg of **10** (mp 142–143°): nmr ($CDCl_3$) δ 7.5 (m, s, aromatic), 4.18 (s, 1, OH), 3.1 [q, 2, J = 14 Hz, $CH_2S(O)$], 2.6–2.0 (br m, 3), and 2.0–1.5 ppm (br m, 11). The analytical sample had mp 143.5–144°.

Anal. Calcd for $C_{17}H_{22}O_2S$: C, 70.31; H, 7.63; S, 11.04. Found: C, 70.14; H, 7.42; S, 10.90.

***In Situ* Generation of 1-Trimethylsilyl-1-(methylsulfinyl)-methyllithium. Reaction with Benzophenone.**—To a solution of 785 mg (10 mmol) of dimethyl sulfoxide (distilled from calcium hydride) in 30 ml of tetrahydrofuran was added 4.5 ml of 2.3 *M* *n*-butyllithium in *n*-hexane at 25°. After the addition was complete the resulting suspension was cooled to −15° and 0.7 ml (5.5 mmol) of trimethylchlorosilane was added to form a yellow solution. After 1 hr a solution of 910 mg (5 mmol) of benzophenone in 3 ml of tetrahydrofuran was added and the solution was stirred at −15° for 0.5 hr and then at 25° for 1.5 hr. Work-up in the usual way afforded 1.18 g of a thick yellow oil which was taken up in ether–dichloromethane and *n*-hexane was added until the hot solution was turbid. On cooling, 610 mg (50%) of **1-(methylsulfinyl)-2,2-diphenylethylene (12)**, mp 86–92°, was deposited. Recrystallization gave material of mp 98–100° (lit. mp 106°),[4d] the nmr spectrum of which was identical with that reported.

***In Situ* Generation of 1d. Reaction with Benzophenone.**—To a solution of 2.1 g (15 mmol) of methyl phenyl sulfoxide in 30 ml of purified tetrahydrofuran at −70° was added 16 mmol of *n*-butyllithium (6.83 ml of a 2.34 *M* solution in *n*-hexane). A yellow solution formed to which was added 0.96 ml (815 mg, 7.5 mmol) of trimethylchlorosilane and the solution was stirred for 50 min. Benzophenone (910 mg, 5 mmol) in 3 ml of tetrahydrofuran was added rapidly and after 15 min at −70° the cooling bath was removed and the now deep red solution was allowed to warm to room temperature. Hydrolysis with saturated aqueous ammonium chloride and extraction with dichloromethane gave 2.74 g of crude product which was chromatographed on 100 g of silica gel. Elution with 400 ml of ether gave 364 mg of a yellow liquid which was a complex mixture as estimated by nmr and was not further characterized. A further 100 ml of ether removed 567 mg of solid which on recrystallization from ether gave 246 mg (15%) of phenyl (2,2-diphenyl-2-hydroxy)ethyl sulfoxide (**7**), mp 128.5–131°, identified by comparison of its nmr spectrum with that of authentic material (see below). Recrystallization from dichloromethane–ether gave material of mp 122–123°; ir (KBr) 1450, 1200, 1180, 1060, 1025, 1000, 780, 760, 700 cm^{-1}; nmr ($CDCl_3$) δ 7.7–7.0 (m, 15, aromatic), 5.69 (s, 1, OH), and 3.58 ppm (s, 2, CH_2).

Anal. Calcd for $C_{20}H_{18}O_2S$: C, 74.50; H, 5.63; S, 9.94. Found: C, 74.42; H, 5.53; S, 10.06.

Concentration of the ether solution which remained after **7** had crystallized caused 146 mg (10%) of **6b** to be deposited, mp 100–104°.

Elution of the chromatographic column with 100 ml more of ether removed a further 360 mg (24%) of **6b** (identified by nmr) which on being washed with ether gave 280 mg of material, mp 111–112°.

Continued elution with 400 ml of 1:1 ethyl acetate–ether removed 71 mg of an oil, which was discarded. The solvent was changed to pure ethyl acetate (250 ml) to elute 462 mg (32%) of a white, crystalline solid, mp 85–89°, identified as **1-(*n*-butylsulfinyl)-2,2-diphenylethylene (13)**. Recrystallization from dichloromethane–ether gave the analytical sample: mp 94–95°; ir (KBr) 3070, 3050, 2970, 2940, 2880, 1500, 1480, 1450, 1410, 1340, 1100, 1080, 1035 (sh), 1015 (vs), 1000, 825, 805, 762, 730, 700 cm^{-1}; nmr ($CDCl_3$) δ 7.30 (10, aromatic), 6.72 (s, 1, vinyl), 2.7 [m, 2, $CH_2S(O)$], 2–1.1 (m, 4, CH_2CH_2), and 0.9 ppm (skewed t, 3, CH_3).

Anal. Calcd for $C_{18}H_{20}OS$: C, 76.01; H, 7.09; S, 11.27. Found: C, 75.90; H, 7.19; S, 11.08.

1,1-Diphenyl-2-(phenylsulfinyl)ethanol (7).—Methyl phenyl sulfoxide (1.05 g, 7.5 mmol) in 15 ml of tetrahydrofuran was metalated with phenyllithium (3.5 ml of a 2.3 *M* solution in 7:3 benzene–ether) at −70°. A solution of 1.365 g (7.5 mmol) of benzophenone in 3 ml of tetrahydrofuran was added. After 0.5 hr at −70° the solution was warmed to room temperature and worked up as usual to afford 2.40 g (100%) of **7** as a white, crystalline solid, mp 134–136°. Repeated recrystallization from methylene chloride–ether gave material of mp 127–128° (lit.[19] mp 152). The nmr spectrum was identical with that of the product formed in the preceding experiment.

1-(Phenylsulfinyl)methylcyclohexanol (8).—To a solution of (phenylsulfinyl)methyllithium prepared in a manner identical with that above was added 784 mg (8.0 mmol) of cyclohexanone. After recrystallization of the crude product from methylene chloride–ether, 1.63 g (91%) of **8** was obtained as white flakes, mp 97–99° (lit.[19] mp 98°).

Reaction of 1-Trimethylsilyl-1-(phenylsulfinyl)methyllithium with Ethyl Benzoate.—To a solution of **1d** prepared from 4.7 mmol of **4** in 25 ml of tetrahydrofuran (*tert*-butyllithium was the metalating agent) at −72° was added 705 mg (4.7 mmol) of ethyl benzoate. After 10 min at −72° the cooling bath was removed and the solution was allowed to stir for 3 hr and then refluxed for 30 min. Saturated ammonium chloride solution was added and the reaction mixture was extracted with dichloromethane. The organic extracts were dried ($MgSO_4$) and the solvent was evaporated to yield 1.14 g of a yellow oil which was chromatographed (preparative tlc) on silica gel (1:1 ethyl acetate–benzene). The major component of the mixture (435 mg, 76%) crystallized and was determined to be (phenylsulfinyl)acetophenone (**15**) by comparison of its nmr[20] and ir[20,21] spectra with those reported.

Because the melting point of repeatedly recrystallized product (70.5–71.5°) was at variance with that recorded in the literature (mp 76–77°,[21] 79–80°,[20] 81°[22]) it was submitted for analysis.

Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12. Found: C, 68.75; H, 4.92; S, 13.02.

1-Trimethylsilyl-1-(phenylsulfinyl)ethane (16).—To a solution of **1d** prepared from 2.35 mmol of **4** and *n*-butyllithium in 15 ml of tetrahydrofuran was added 0.16 ml (355 mg, 2.5 mmol) of methyl iodide. After 0.5 hr at −70° the solution was kept at −40° for 0.5 hr and then warmed to 25° and worked up in the usual manner to give 489 mg (92%) of **16** as an oil which crystallized on standing. The nmr of the crude product was identical with that of the analytical sample, mp 66–67.5°, obtained by preparative tlc (silica gel with methylene chloride–ether) and recrystallization from ether–cyclohexane: nmr ($CDCl_3$) δ 7.47 (s, 5, aromatic), 1.91 (q, 1, J = 7 Hz, SCHSi), 1.0 (d, 3, J = 7 Hz, CH_3C), and 0.25 ppm (s, 9, $SiMe_3$).

Anal. Calcd for $C_{11}H_{18}OSSi$: C, 58.36; H, 8.01; S, 14.16; Si, 12.39. Found: C, 58.48; H, 8.05; S, 14.00; Si, 12.18.

Rearrangement of 16.—A solution of **16** (57 mg, 0.25 mmol) in 10 ml of dry benzene was refluxed under nitrogen for 2 hr. Tlc analysis of the reaction mixture at this point indicated the absence of starting material, so the solution was evaporated to leave 38.7 mg (68%) of **17** as a colorless oil: ir (neat) 3090, 2970, 1600, 1480, 1450, 1250, 1110, 1030, 950, 750, and 700 cm^{-1}; nmr ($CDCl_3$) δ 7.5–7.2 (m, 5, aromatic), 5.25 (q, 1, J = 7 Hz, SCHO), 1.55 (d, 3, J = 7 Hz, CH_3CH), and 0.05 ppm (s, 9, $SiMe_3$); mass spectrum (70 eV) *m/e* (rel intensity) 226 (4), 117 (62), 75 (22), 73 (100).

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Anal. Calcd for $C_{11}H_{18}OSSi$: C, 58.36; H, 8.01; S, 14.16. Found: C, 58.52; H, 7.79; S, 14.31.

Registry No.—**1d**, 40110-24-5; **4**, 18789-72-5; *cis*-**6a**, 40110-65-4; *trans*-**6a**, 40110-66-5; **6b**, 40110-26-7; **6c**, 40110-27-8; *cis*-**6d**, 40110-67-6; *trans*-**6d**, 40110-68-7; *trans*-**6e**, 40110-69-8; *cis*-**6e**, 40110-70-1; *cis*-**6f**, 40110-71-2; *trans*-**6f**, 40110-72-3; **6g**, 40110-28-9; **6h**, 40110-29-0; **7**, 23975-23-7; **8**, 23975-27-1; **10**, 40110-32-5; **12**, 21147-11-5; **13**, 40110-34-7; **15**, 6099-23-6; **16**, 40110-36-9; **17**, 40110-37-0; benzaldehyde, 100-52-7; adamantanone, 700-58-3; cyclohexanone, 108-94-1; acrolein, 107-02-8; *trans*-cinnamaldehyde, 14371-10-9; cyclohexenone, 930-68-7; 1-trimethylsilyl-1-(methylsulfinyl)methyllithium, 40110-38-1; benzophenone, 119-61-9; dimethyl sulfoxide 67-68-5; trimethylchlorosilane, 75-77-4; methyl phenyl sulfoxide, 1193-82-4; ethyl benzoate, 93-89-0.

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Silane Reductions in Acidic Media. II. Reductions of Aryl Aldehydes and Ketones by Trialkylsilanes in Trifluoroacetic Acid. A Selective Method for Converting the Carbonyl Group to Methylene[1a,b]

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Trialkylsilanes in trifluoroacetic acid media selectively reduce the carbonyl group of arylcarbonyl compounds to methylene. Aryl alkyl ketones and diaryl ketones that can be synthesized by Friedel–Crafts acylation procedures are quantitatively reduced to the corresponding arenes. Benzaldehydes substituted with activating groups form the corresponding toluenes; however, substituted toluene formation is competitive with Friedel–Crafts alkylation. Specific γ-lactone formation occurs in the reduction of 3-benzoylpropanoic and *o*-benzoylbenzoic acids. The requirements and limitations of trialkylsilane reductions have been examined and procedures for the isolation of arene products determined.

The reduction of the carbonyl group of aldehydes and ketones to methylene has enjoyed wide application in organic syntheses. Of the reductive methods that have been employed, the Clemmensen[2] and Wolff–Kishner[3] reactions have exhibited the most general utility. Other methods, including catalytic hydrogenation,[4] reductions using Raney nickel in hydroxide media,[5] and trichlorosilane–trialkylamine[6] and metal hydride reductions,[7] have been successfully applied more specifically to aryl aldehydes and ketones.

Kursanov, Parnes, and coworkers have recently reported the reduction of the carbonyl group of benzophenone, Michler's ketone, acetophenone, and 2,4,6-trimethylbenzaldehyde to methylene using triethylsilane in trifluoroacetic acid media.[8] Because of the good yields reported for these silane reductions and the reported ability of silanes to undergo hydride transfer to relatively stable carbenium ions,[9,10] we expected that silane reductions of aldehydes and ketones would represent a convenient and synthetically useful method for transforming a carbonyl group to methylene. In this paper we report the application of trialkylsilanes to reductions of aryl aldehydes and ketones in acidic media.

Results

The yields of arylhydrocarbon products from trialkylsilane reductions of the corresponding carbonyl compounds are given in Table I. In general, 2 equiv of silane are required for the reduction of 1 equiv of carbonyl compound to the methylene product in trifluoroacetic acid (eq 1); silane products are the trialkylsilyl trifluoroacetate and hexaalkyldisiloxane in amounts that vary with the reaction conditions. Reductions were observed to occur readily at room temperature and for phenyl alkyl ketones and diaryl ketones generally required less than 15 min for complete reduction. Reductions of aliphatic aldehydes and ketones, such as octanal and cyclohexanone, did not give the corresponding methylene products.

$$\mathrm{ArCR} \overset{\mathrm{O}}{\parallel} + \mathrm{R'_3SiH} + \mathrm{CF_3CO_2H} \longrightarrow \mathrm{ArCH_2R} + \mathrm{R'_3SiO_2CCF_3} + \mathrm{R'_3SiOSiR'_3} \quad (1)$$
$$\mathrm{R} = \mathrm{H, alkyl, aryl}$$

Trifluoroacetic acid was chosen as the solvent for these reactions because of its acidity and good solvat-

(1) (a) Support for this work from the Research Corporation is gratefully acknowledged. (b) Part I: M. P. Doyle, D. J. DeBruyn, and D. A. Kooistra, *J. Amer. Chem. Soc.*, **94**, 3659 (1972). (c) National Science Foundation Undergraduate Research Participant, summer 1971.

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(9) D. N. Kursanov, Z. N. Parnes, V. A. Tsyryapkin, and R. V. Kudryavtsev, *Dokl. Akad. Nauk SSSR*, **202**, 874 (1972), and previous papers in this series.

(10) F. A. Carey and H. S. Tremper, *J. Org. Chem.*, **36**, 758 (1971), and previous papers in this series.

TABLE I

SILANE REDUCTIONS OF ARYLCARBONYL COMPOUNDS IN TRIFLUOROACETIC ACID MEDIA[a]

Registry no.	Carbonyl compound	Solvent	Equiv CF_3CO_2H[b]	Equiv R_3^1SiH[b,c]	Reaction time, hr[d]	Yield of $ArCH_2R$, %[e]
487-68-3	2,4,6-Trimethylbenzaldehyde	CF_3CO_2H	10.0	2.2	0.25	98
123-11-5	*p*-Anisaldehyde[f]	CF_3CO_2H	5.0	2.5[f]	0.50	76
		CF_3CO_2H[h]	5.0	6.0[g]	1.50	80
		CF_3CO_2H	5.0	6.0[g]	0.50	81
		CF_3CO_2H	5.0	6.0	0.75	83
104-87-0	*p*-Tolualdehyde	CF_3CO_2H	8.0	2.2	11	20
		CF_3CO_2H	8.0	2.2[g]	13	46
		CF_3CO_2H	5.0	2.5[g]	0.25	52
		CH_3CN (2.5 ml)–CF_3CO_2H[i,j]	5.0	6.0	170	50
		CH_3CN (2.5 ml)–CF_3CO_2H[h,i]	6.7	2.2	180	43
		CH_3NO_2 (2.5 ml)–CF_3CO_2H[i]	5.0	6.0	54	61
		CCl_4 (2.5 ml)–CF_3CO_2H[i]	5.0	2.2	100	50
		CCl_4 (2.5 ml)–CF_3CO_2H[i]	5.0	6.0	336	66
98-86-2	Acetophenone	CF_3CO_2H	10.0	2.2	0.25	100
		CF_3CO_2H	3.3	1.0	0.50	50[k]
		CF_3CO_2H	6.8	4.4[l]	44	91
93-55-0	Propiophenone	CF_3CO_2H	5.4	2.5	0.25	100
495-40-9	Butyrophenone	CF_3CO_2H	10.0	2.2	0.25	100
611-70-1	Isobutyrophenone	CF_3CO_2H	5.4	2.5	0.25	100
1009-14-9	Valerophenone	CF_3CO_2H	10.0	2.2	0.25	100
4433-30-1	Undecanophenone	CF_3CO_2H	10.0	2.2	0.25	100
3375-38-0	1,4-Dibenzoylbutane	CF_3CO_2H	9.0	4.4	19	100
99-91-2	*p*-Chloroacetophenone	CF_3CO_2H	6.7	2.2	200	100
779-90-8	1,3,5-Triacetylbenzene	CF_3CO_2H[m]	12.0	6.6	72	100
529-34-0	α-Tetralone	CF_3CO_2H	8.0	2.2	2.5	100
70-11-1	α-Bromoacetophenone	CF_3CO_2H	7.0	4.4	44	93[n]
1501-05-9	4-Benzoylbutanoic acid	CF_3CO_2H	6.5	2.2	48	100
		CF_3CO_2H	6.5	1.1	12	50[k]
4144-62-1	5-Benzoylpentanoic acid	CF_3CO_2H	7.0	2.4	5.5	100
		CF_3CO_2H	7.0	1.1	20	50[k]
3481-02-5	Phenyl cyclopropyl ketone	H_2O (0.3 ml)–CF_3CO_2H	9.5	2.6	7.0	48[o]
		CCl_4 (2.5 ml)–CF_3CO_2H	5.0	2.2	22	25[p]
		CF_3CO_2H	10.0	2.5	3.5	27[q]
5407-98-7	Phenyl cyclobutyl ketone	H_2O (0.3 ml)–CF_3CO_2H	9.9	2.2	6.0	25
		CCl_4 (2.5 ml)–CF_3CO_2H	5.0	5.0	7.5	26
119-61-9	Benzophenone	CF_3CO_2H	15.0	2.2	0.25	100
		CF_3CO_2H	15.0	1.0	0.25	50[k]
611-95-0	4-Benzoylbenzoic acid	CCl_4 (7.0 ml)–CF_3CO_2H	7.7	3.0	120	100
1144-74-7	4-Nitrobenzophenone	CF_3CO_2H	6.7	2.4	47	100

[a] Reductions were usually carried out at room temperature by adding triethylsilane to a trifluoroacetic acid solution containing the carbonyl compound (5.0 mmol). [b] With respect to carbonyl compound. [c] Unless noted otherwise, triethylsilane was used. [d] Time of analysis; does not necessarily reflect required reaction times. Reactions were continued until no further reduction by silane could be observed. [e] Yield based on pmr analysis of products prior to work-up. Reproducibility was ±2%. [f] Aldehyde in trifluoroacetic acid was added to silane. [g] Phenyldimethylsilane. [h] Reaction performed at 0°. [i] Aldehyde added to silane in acidic media. [j] Reaction run at 55°. [k] Only unreacted starting material (50%) remained. [l] Chlorodimethylsilane. [m] Reaction carried out at 65°. [n] Reaction run at 80°. [o] Aqueous trifluoroacetic acid was added to a stirred solution of triethylsilane and phenyl cyclopropyl ketone at 0°. Yield is based on the amount of reduced material; 25% of starting material remained after 7 hr reaction time. [p] Observed yield; 50% unreacted ketone is present. After 1 week 18% of unreacted ketone, 5% of phenylcyclopropylmethane, and 47% of 1-phenyl-2-butyl trifluoroacetate were observed. [q] 8% unreacted ketone remained.

ing properties. Other acids, including sulfuric acid and antimony pentafluoride, reacted with the trialkylsilane.[11] Aqueous acids were not used because of the insolubility of the silane and carbonyl compounds in these media. When the silane was rapidly added to a trifluoroacetic acid solution containing the carbonyl compound, a reaction occurred that was demonstrably exothermic. A nonhydroxylic solvent, such as carbon tetrachloride, acetonitrile, or nitromethane, was used in specific cases to moderate the reaction temperature during the addition of the silane or to facilitate the homogeneity of the solution. With the exception of the reaction between 4-benzoylbenzoic acid and triethylsilane in trifluoroacetic acid–nitromethane, all reaction solutions reported in Table I were homogeneous. During the reduction of 4-benzoylbenzoic acid an insoluble white solid formed; the use of carbon tetrachloride as a cosolvent eliminated this problem. The use of a cosolvent, however, noticeably increased the reaction time for complete reduction.

Under similar conditions, triethyl-, tri-*n*-propyl-, tri-*n*-butyl-, and tri-*n*-hexylsilane quantitatively reduced acetophenone to ethylbenzene without significant differences in reaction times. Chlorodimethylsilane, however, slowly reacted with trifluoroacetic acid and was observed to undergo a minor competing reaction to form a silyl ether of 1-phenylethanol. Trihexylsilane was only partially soluble in trifluoroacetic acid.

(11) The oxidation of triethylsilane in acidic media has been studied: H. H. Anderson, *J. Amer. Chem. Soc.*, **80**, 5083 (1958).

With the exception of reactions performed in trifluoroacetic acid–nonhydroxylic solvent mixtures and of reductions of *p*-chloroacetophenone, α-bromoacetophenone, 1,3,5-triacetylbenzene, and 4-nitrobenzophenone, trialkylsilane reductions of the carbonyl compounds listed in Table I were rapid. Aryl alkyl ketones and diaryl ketones were quantitatively converted to the corresponding methylene compound.

2,4,6-Trimethylbenzaldehyde was converted to isodurene in 98% yield; only 2% of the Friedel–Crafts alkylation product previously observed by Kursanov and coworkers under similar reaction conditions[12] was obtained. Friedel–Crafts alkylation became increasingly important in reductions of *p*-anisaldehyde and *p*-tolualdehyde by trialkylsilanes. Neither changing the reducing agent from triethylsilane to phenyldimethylsilane, increasing the amount of initially added silane threefold, nor running the reaction at 0° had a significant effect on the yield of *p*-methylanisole. However, the use of phenyldimethylsilane was preferred over triethylsilane for the reduction of *p*-tolualdehyde in trifluoroacetic acid, and the addition of a cosolvent, particularly nitromethane and carbon tetrachloride, led to a minimization of the competing Friedel–Crafts alkylation process. Here again, the reaction temperature had no significant effect on the ratio of the competing reactions, and a threefold increase in the silane concentration did not have the expected effect of eliminating the Friedel–Crafts alkylation reaction. Both vanillin and salicylaldehyde gave reaction products that could be explained by exclusive Friedel–Crafts alkylation; neither *o*-cresol nor 2-methoxy-4-methylphenol was observed.

The reduction of *p*-tolualdehyde by trialkylsilanes in trifluoroacetic acid media proceeded stepwise to initially yield the trifluoroacetate and symmetrical ether derivatives of *p*-toluyl alcohol, followed by the conversion of these products to *p*-xylene and Friedel–Crafts products (eq 2 and 3). The yields of these

$$p\text{-}CH_3C_6H_4CHO \xrightarrow[CF_3CO_2H]{R'_3SiH} p\text{-}CH_3C_6H_4CH_2O_2CCF_3 \ (\mathrm{I}) + (p\text{-}CH_3C_6H_4CH_2)_2O \ (\mathrm{II}) \quad (2)$$

$$\mathrm{I} + \mathrm{II} \xrightarrow[CF_3CO_2H]{R'_3SiH} p\text{-}CH_3C_6H_4CH_3 + \text{Friedel–Crafts products} \quad (3)$$

products with time for the reduction of *p*-tolualdehyde by triethylsilane in trifluoroacetic acid–carbon tetrachloride are presented in Table II. These data indicate that *p*-xylene is produced predominantly by reduction of *p*-toluyl trifluoroacetate and that the symmetrical ether is slowly converted to the trifluoroacetate.[13] Friedel–Crafts alkylation occurs only after all of the *p*-tolualdehyde has been reduced to *p*-toluyl alcohol derivatives and after approximately 25% of *p*-xylene has been produced. Similar results were observed for reductions of *p*-tolualdehyde in other trifluoroacetic acid media and for reductions of *p*-chloroacetophenone, 1,3,5-triacetylbenzene, and α-bromoacetophenone. For these compounds reduction

(12) D. N. Kursanov, Z. N. Parnes, N. M. Loim, and G. V. Bakalova, *Dokl. Akad. Nauk SSSR*, **179**, 1106 (1968).

(13) We were not able to determine the amount of *p*-xylene produced directly from the ether under these reaction conditions.

TABLE II

YIELDS OF PRODUCTS FROM THE REDUCTION OF *p*-TOLUALDEHYDE BY TRIETHYLSILANE IN TRIFLUOROACETIC ACID–CARBON TETRACHLORIDE[a]

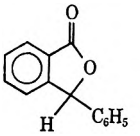
Time, hr[b]	Trifluoroacetate (I), %	Ether (II), %[c]	*p*-Xylene, %	Friedel–Crafts products, %
16	31	56	13	0
22	31	46	23	0
45	42	30	26	2
89	38	12	39	11
209	9	0	61	30
336	0	0	66	34

[a] *p*-Tolualdehyde (5.0 mmol) was added to triethylsilane (30.0 mmol) in a constantly stirred solution of trifluoroacetic acid (25.0 mmol) and carbon tetrachloride (2.5 ml) at 25°. Yields were obtained by pmr spectroscopy through reference to an internal standard. [b] No *p*-tolualdehyde was observed at 16 hr reaction time. [c] Per cent of *p*-tolualdehyde that yielded ether.

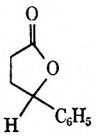
to the arene is much slower than reduction to the alcohol derivative. The relative yields of trifluoroacetate and ether varied with reaction conditions and with each carbonyl compound. Generally, ketones did not give appreciable yields of symmetrical ethers under these conditions.

No trifluoroacetates or symmetrical ethers were observed during the reductions of *p*-anisaldehyde and of aryl alkyl or diaryl ketones. When only 1 equiv of trialkylsilane was used in the reductions of acetophenone and benzophenone, only the corresponding methylene compound (50%) and ketone (50%) were obtained. Even with substituted benzophenones, *p*-nitrobenzophenone and *p*-benzoylbenzoic acid, that required long reaction times for complete reduction, no alcohol derivatives were observed. For these compounds reduction to the arene is faster than the initial reduction of the carbonyl group.

When *o*-benzoylbenzoic acid was treated with 2.2 equiv of triethylsilane in trifluoroacetic acid at room temperature, 3-phenylphthalide (III) was produced quantitatively. Further reduction to *o*-benzylbenzoic acid did not occur with longer reaction times. Similarly, 3-benzoylpropanoic acid gave 4-phenylbutyrolactone (IV) in 86% yield and 4-phenylbutyric



III

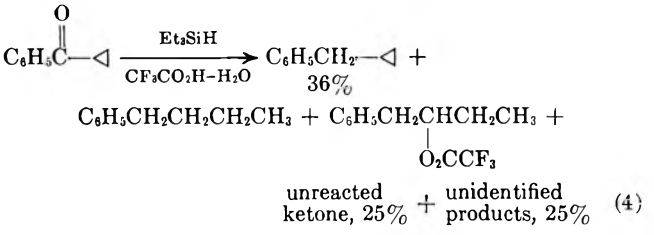


IV

acid in 14% yield when treated with 2.2 equiv of triethylsilane under similar reaction conditions; when only 1.4 equiv of triethylsilane was used, IV was produced quantitatively. An attempt was made to increase the yield of 4-phenylbutyric acid in the reduction of 3-benzoylpropanoic acid by using 8.0 equiv of triethylsilane; however, results identical with those for the reaction with 2.2 equiv of silane were obtained. Attempts were also made to convert the homologous 4-benzoylbutanoic and 5-benzoylpentanoic acids to the δ- and ε-lactones, respectively, by using only 1 equiv of triethylsilane. For these reactions, reported in Table I, only the methylene product and unreacted starting material were observed; no lactones were formed. Thus, even with substituted benzophenones and acetophenones, which were observed in earlier

examples to undergo rapid reduction to arylhydrocarbons, a highly specific intramolecular formation of γ-lactones successfully competes with silane reduction to methylene products; the formation of δ- and ε-lactone is not competitive with hydride transfer from triethylsilane.

Carbonyl compounds that yielded products that were sensitive to the acidity of the medium were also examined. Phenyl cyclopropyl ketone gave phenylcyclopropylmethane, 1-phenylbutane, and 1-phenyl-2-butyl trifluoroacetate when treated with triethylsilane in aqueous trifluoroacetic acid (eq 4). A number

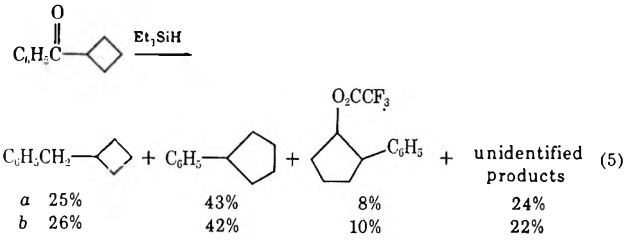


(4)

of minor reaction products, each formed in less than 5% yield, were also observed but not identified in this study. When the reduction of phenyl cyclopropyl ketone was performed in trifluoroacetic acid without water, 27% of phenylcyclopropylmethane and 43% of 1-phenyl-2-butyl trifluoroacetate were obtained. The use of carbon tetrachloride as a cosolvent did not increase the yield of phenylcyclopropylmethane. Under the reaction conditions employed phenyl cyclopropyl ketone is stable to trifluoroacetic acid, but phenylcyclopropylmethane reacts with trifluoroacetic acid to form 1-phenyl-2-butyl trifluoroacetate.

Carey and Tremper have reported that when cyclopropylphenylcarbinol was treated with trifluoroacetic acid in methylene chloride only *trans*-4-phenyl-3-butenyl trifluoroacetate was formed, and that when the same reaction was performed in the presence of triethylsilane at −15° only a trace amount of the trifluoroacetate and greater than 99% of phenylcyclopropylmethane were produced.[14] We attempted to reduce phenyl cyclopropyl ketone under these same conditions but found that no reduction had occurred, even after 70 hr. Under the reaction conditions reported in Table I neither 4-phenyl-3-butenyl trifluoroacetete nor products derived from trifluoroacetic acid addition to or silane reduction of this olefin were observed.

The reduction of phenyl cyclobutyl ketone by triethylsilane was significantly more rapid than the corresponding reduction of phenyl cyclopropyl ketone. Phenylcyclobutylmethane, phenylcyclopentane, and 2-phenylcyclopentyl trifluoroacetate were formed when phenyl cyclobutyl ketone was treated with triethylsilane in aqueous trifluoroacetic acid or in carbon tetrachloride–trifluoroacetic acid media (eq 5). Nearly identical results were observed despite the differences in the reaction media and the number of equivalents of silane used (see Table I). Neither 1-phenylpentane nor 1-phenyl-2-pentyl trifluoroacetate, the expected product from ring opening of phenylcyclobutylmethane in these reactions, were detected. Phenyl cyclobutyl ketone was stable under the reaction conditions.



(5)

a	25%	43%	8%	24%
b	26%	42%	10%	22%

[a] Yield in CF_3CO_2H–H_2O. [b] Yield in CF_3CO_2H–CCl_4.

Numerous attempts were made to reduce benzaldehyde to toluene. Under reaction conditions that were successful in reducing *p*-tolualdehyde to *p*-xylene and Friedel–Crafts products, only benzyl trifluoroacetate and dibenzyl ether were produced from benzaldehyde. The use of stronger acids than trifluoroacetic acid (H_2SO_4, HCl, FSO_3H, and FSO_3H–SbF_5 in acetonitrile), longer reaction times, or higher temperatures did not effect the production of toluene. Similarly, *p*-chlorobenzaldehyde, *p*-nitrobenzaldehyde, *p*-cyanoacetophenone, *p*-nitroacetophenone, 1- and 2-naphthaldehydes, and 9-anthraldehyde were reduced to their corresponding trifluoroacetates and symmetrical ethers, but not to the arylhydrocarbon products. Although initial reduction of the carbonyl group proceeded rapidly under the reaction conditions employed, further reduction of trifluoroacetate and ether products was dramatically dependent on substituent effects.

Silane reductions are remarkably selective for the carbonyl group. Other functional groups, which included carboxylate, cyano, and nitro, were not affected during reductions of the carbonyl group. Additionally, displacement of bromide did not occur during the reduction of α-bromoacetophenone.

With respect to physical properties trialkylsilanes and their oxidized products, trialkylsilanols and derivatives of trialkylsilanols, are analogous to their carbon counterparts.[15] In the absence of acid or base functional groups, similarities in polarity render separation of carbon products from silicon products by conventional means of extraction difficult at best. On a small scale, preparative glpc is easily accomplished. On a larger scale, however, alternate means of isolation that cleanly and efficiently separate silane products from carbon products must be employed.

The products from silane reductions of carbonyl compounds in trifluoroacetic acid were the silyl trifluoroacetate and disiloxane (eq 1). After extraction of the reaction mixture with aqueous base the silane products consisted of silanol and disiloxane. When the boiling point of the carbon product was higher than those of the silane products, direct distillation was possible even without basic extraction. However, for arenes with boiling points comparable to those of the silanol or trifluoroacetate, alternate methods, employing the conversion of the silanol to the higher boiling disiloxane, were used. Since trialkylsilanols are readily converted to hexaalkyldisiloxanes under

(14) F. A. Carey and H. S. Tremper, *J. Amer. Chem. Soc.*, **91**, 2967 (1969).

(15) (a) C. Eaborn, "Organosilicon Compounds," Butterworths, London, 1960; (b) L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill, New York, N. Y., 1965.

basic conditions,[16] simple distillation methods can be used to separate the reduced product from the unreacted trialkylsilane and the disiloxane. Representative examples of reductions that have employed these isolation methods are given in Table III. Generally,

TABLE III

ISOLATED YIELDS FROM SILANE REDUCTIONS OF ARYLCARBONYL COMPOUNDS IN TRIFLUOROACETIC ACID MEDIA[a]

Carbonyl compd (mmol)	R_3SiH (mmol)	Mmol CF_3CO_2H	Isolation method[b]	Isolated yield, %[c]
p-Benzoylbenzoic acid (6.6)	Et_3SiH (26)	68[d]	Ia	96
4-Benzoylbutanoic acid (16)	Et_3SiH (35)	101	Ia	59
5-Benzoylpentanoic acid (4.8)	Et_3SiH (12)	34	Ia	77
o-Benzoylbenzoic acid (10)	Et_3SiH (14)	121	Ib	74
3-Benzoylpropanoic acid (10)	Et_3SiH (14)	68	Ib	73
1,4-Dibenzoylbutane (5.0)	Et_3SiH (20.0)	34	Ic	72
1,4-Dibenzoylbutane (15)	Et_3SiH (66)	135	Ic	79
4-Nitrobenzophenone (5.0)	Et_3SiH (12)	34	Ic	96
Acetophenone (27)	n-Hex_3SiH (60)	135	IIa	65[e]
Acetophenone (20)	n-Hex_3SiH (50)	68	IIb	64[f]
Acetophenone (40)	n-Hex_3SiH (90)	155	IIc	55[f]
α-Tetralone (25)	Et_3SiH (55)	125	IIb	71[g]
α-Tetralone (25)	Et_3SiH (55)	75[h]	IIb	83[g]
1,3,5-Triacetylbenzene (15)	n-Pr_3SiH (90)	180	IIb	54[i]
1,3,5-Triacetylbenzene (15)	n-Pr_3SiH (90)	180	IIc	41[j]

[a] See footnote *a*, Table I. Reaction times were at least as long as those reported in Table I. [b] Full procedures are given in the Experimental Section: Ia, products isolated by crystallization or distillation following base extraction and reacidification of extract; Ib, lactone products isolated by crystallization or distillation following extraction; Ic, direct distillation of reaction mixture without extraction; IIa, reaction mixture neutralized with excess Na_2CO_3, KOH, or NaOH and product steam distilled; IIb, distillation from KOH following extraction; IIc, direct distillation of reaction mixture following neutralization with excess Na_2CO_3. [c] Recovery yield of arylhydrocarbon product after recrystallization or fractional distillation. [d] Cosolvent, carbon tetrachloride (7.5 ml), was used. [e] Contains 1 mol % silanol or disiloxane. [f] Less than 5 mol % silicon impurities. [g] After first distillation 25 mol % of hexaethyldisiloxane was present; a second distillation gave tetrahydronaphthalene with 4 mol % disiloxane. [h] Cosolvent, carbon tetrachloride (12.5 ml), was used. [i] Contains 8 mol % disiloxane. [j] Contains 75 mol % disiloxane.

the silane reducing agent which yielded a disiloxane having a boiling point sufficiently different from that of the arene provided the best results. Triethylsilane was suitable for carbonyl compounds whose reduced products had a boiling point greater than 300°, tri-*n*-hexylsilane was suitable for the isolation of arylhydrocarbons with boiling point less than 220°, and tri-*n*-propylsilane was found to be suitable for compounds in the intermediate boiling point range.

Discussion

Trialkylsilanes are remarkably selective reducing agents. With carbonyl compounds containing carboxylate, cyano, or nitro functional groups, among others, only the carbonyl group is reduced in trifluoroacetic acid media. However, silane reductions of the carbonyl group to methylene are specific for arylcarbonyl compounds and further limited by substituent effects. Only benzaldehydes substituted with activating groups are reduced to arylhydrocarbons, and substitution with one or more strongly activating groups, such as hydroxy, results in predominant Friedel–Crafts alkylation. Reductions of the carbonyl group of aryl ketones to methylene are not so limited, however, as can be seen by the summary given in Table IV.

TABLE IV

SILANE REDUCTIONS OF SUBSTITUTED BENZALDEHYDES, ACETOPHENONES, AND BENZOPHENONES IN TRIFLUOROACETIC ACID MEDIA

	Yield of $ArCH_2R$, %[a]		
Ar	R = H	R = CH_3	R = C_6H_5
p-$CH_3OC_6H_4$	83		
p-$CH_3C_6H_4$	66		
C_6H_5	0	100	100
p-ClC_6H_4	0	100	
p-$HO_2CC_6H_4$			100
p-NCC_6H_4		0	
p-$O_2NC_6H_4$	0	0	100

[a] All compounds investigated were reduced in their corresponding alcohol derivatives, trifluoroacetate and symmetrical ether.

The reduction of the carbonyl group to methylene by trialkylsilanes may be viewed as occurring in two steps: reduction of the carbonyl group to an alcohol or alcohol derivative (eq 6) followed by reduction of

$$R_2C{=}O + R'_3SiH + CF_3CO_2H \longrightarrow R_2CHOH + R'_3SiO_2CCF_3 \text{ or } R_2CHO_2CCF_3 \text{ and } (R_2CH)_2O \quad (6)$$

the intermediate alcohol or alcohol derivative (eq 7).

$$R_2CHOH + R'_3SiH + CF_3CO_2H \longrightarrow R_2CH_2 + R'_3SiO_2CCF_3 + H_2O \quad (7)$$

All compounds examined underwent reduction of the carbonyl group; however, of those compounds that were further reduced, only with *p*-tolualdehyde were we able to detect intermediate products.[17] The rate for eq 6 was not drastically affected by structural effects. However, the rate for eq 7 is primarily determined by structural effects and is the principal limiting factor in the use of silanes to convert the carbonyl group to methylene.

Carey and coworkers have studied the process given in eq 7 extensively and have shown that only those alcohols that form relatively stable carbenium ions are reduced to the corresponding alkanes.[10] The formation of arenes in silane reductions of the carbonyl group are similarly limited. Stronger acids than trifluoroacetic acid, which might be expected to provide higher concentrations of carbenium ions, react with trialkylsilanes.

Results from the reduction of phenyl cyclopropyl ketone are consistent with the formation and rapid reduction of phenylcyclopropylcarbinol or its deriva-

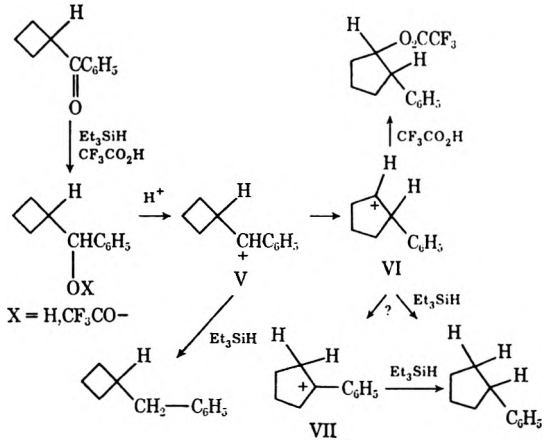
(16) D. N. Kursanov, A. N. Parnes, G. I. Bassova, N. M. Loim, and V. I. Zdanovich, *Tetrahedron*, **23**, 2235 (1967). In attempts to distill reaction products from powdered potassium hydroxide, conditions under which silanol products are converted to potassium silanolates,[15b] disiloxane products often codistilled with the arene products.

(17) However, when triethylsilane was slowly added to acetophenone in trifluoroacetic acid, approximately 2% of the symmetrical ether could be observed after 15 min.

tives. Although at least five minor products are produced in these reductions, the absence of products from ring opening of phenylcyclopropylcarbinol[14] suggests that this reaction is suppressed even at room temperature when phenyl cyclopropyl ketone is reduced by triethylsilane in trifluoroacetic acid media. Ring opening of phenylcyclopropylmethane, however, occurred under all reaction conditions used at a rate comparable to the rate of reduction. The behavior of cyclopropane hydrocarbons in the presence of trifluoroacetic acid and triethylsilane has been studied by Kursanov and coworkers;[18] ring opening occurred in all of the cases studied by these workers.

Triethylsilane was not effective in eliminating ring expansion of phenylcyclobutylcarbinol or its derivatives in trifluoroacetic acid. Only 25% of phenylcyclobutylmethane and more than 50% of ring-expanded products were obtained. These results, which were surprisingly insensitive to the different reaction conditions used, can be explained by the reaction sequence given in Scheme I. The formation of 2-

SCHEME I



phenylcyclopentyl trifluoroacetate suggests that ring expansion of V is not concurrent with a 1,2-hydride shift to form the more stable tertiary benzylic cation, VII. Although VI may react directly with triethylsilane an alternate process, involving either a 1,2-hydride shift or an elimination–addition sequence and followed by hydride transfer from triethylsilane, can also explain the observed formation of phenylcyclopentane. If triethylsilane does react directly with VI, however, the usefulness of silanes as hydride transfer reagents in studies of carbenium ion processes would be considerably expanded.

The selectivity, lack of competing reactions with aryl alkyl ketones and diaryl ketones, and short reaction times at room temperature make trialkylsilane reductions a useful method for the conversion of the carbonyl group to methylene. The Clemmensen reduction of these same compounds usually gives coupling products and requires significantly longer reaction times.[19] Although silane products cannot be removed by conventional extractions, simple distillation techniques are adaquate for the isolation of arene products in good yields. Those same compounds that can be formed by Friedel–Crafts acylation can be reduced by trialkylsilanes in trifluoroacetic acid media; the combination of these two methods represents a convenient procedure for the production of arenes by a net Friedel–Crafts alkylation without rearrangement.

(18) Z. N. Parnes, G. A. Khotimskayu, R. V. Kudryavtsev, M. Yu Lukina, and D. N. Kursanov, *Dokl. Akad. Nauk SSSR*, **184**, 615 (1969).

(19) H. L. Bradlow and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **69**, 1254 (1947); W. P. Duncan, J. E. Russell, E. J. Eisenbraun, G. W. Keen, P. W. Flanagan, and M. C. Hamming, *J. Org. Chem.*, **37**, 142 (1972).

Experimental Section

General.—Instrumentation has been previously described.[20] Mass spectra were obtained using a Finnigan Model 1015 gas chromatograph–mass spectrometer operated at 70 eV. Use was made of 5-ft columns of 10% Carbowax 20M, 20% SE-30, 10% SE-30 and a 6-ft column of OV-17, all on Chromosorb P. Triethylsilanol and hexaethyldisiloxane were prepared by conventional methods.[11,21] *o*-Benzoylbenzoic acid and 3-benzoylpropanoic acid were prepared by standard Friedel–Crafts acylation procedures from benzene and phthalic or succinic anhydride. Other carbonyl compounds and all silanes were commercially available and used without further purification. Melting points and boiling points were uncorrected.

General Reduction Procedure.—To a stirred solution of the carbonyl compound (usually 5.0 mmol) in trifluoroacetic acid (usually 20–75 mmol, 4–15 equiv) or in trifluoroacetic acid–cosolvent mixture at room temperature was added the trialkylsilane (usually 11 mmol, 2.2 equiv). With the exception of reactions in trifluoroacetic acid–nitromethane or aqueous acid, or those using tri-*n*-hexylsilane, all solutions were homogeneous. Rapid addition of trialkylsilane to the trifluoroacetic acid solution produced a noticeable exothermic reaction; dropwise addition of the silane or use of a cosolvent moderated the temperature increase. Reactions proceeded faster at higher temperatures; triethylsilane reacted slowly with trifluoroacetic acid and at 50–60° was stable for a period of days. The progress of each reaction was monitored by pmr spectroscopy. Products were identified from their chemical shifts and the multiplicity of their pmr absorptions. Yields were based on integrations of the individual and characteristic absorption signals of each compound through reference to the total phenyl absorption and/or an added internal standard. Integrations were maximized and averaged over several integrations of the same signal. Reproducibility was shown to be ±2% in duplicate runs.

The products from several reactions listed in Table I were further analyzed following work-up. Usually water or a saturated sodium bicarbonate solution was added to the trifluoroacetic acid reaction solution followed by ether, the ether layer was separated, and the aqueous layer was washed with ether. The combined ether solution was dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure. The products from the reduction of *p*-anisaldehyde by triethylsilane were subjected to glpc analysis; triethylsilanol and hexaethyldisiloxane were identified by comparison of glpc retention times to those of authentic samples and peak enhancement. *p*-Methylanisole was collected and identified by pmr spectroscopy. Isodurene was isolated after work-up by distillation of the reaction products from the reduction of 2,4,6-trimethylbenzaldehyde and identified by pmr spectroscopy through comparison to an authentic sample. Dibenzyl ether and benzyl trifluoroacetate were also identified after work-up by glpc comparison to authentic samples.

Friedel–Crafts alkylation products were inferred from the pmr spectra of some of the reaction mixtures. In reductions of *p*-tolualdehyde absorptions were observed at δ 3.7–3.9 which were similar to those found when *p*-methylbenzyl alcohol was treated with trifluoroacetic acid without added trialkylsilane. Similarly, absorptions in the same region, attributable to a methylene group adjacent to two aromatic rings, were observed in reductions of *p*-anisaldehyde, 2,4,6-trimethylbenzaldehyde, vanillin, and salicylaldehyde.

Reduction of 1,4-Dibenzoylbutane by Triethylsilane. Identification of Silane Products.—To a stirred solution of 1,4-dibenzoylbutane (4.00 g, 15.0 mmol) and triethylsilane (7.65 g, 66.0 mmol) was added 10.0 ml (135 mmol) of trifluoroacetic acid dropwise over a 1-hr period; during the addition of the last 5.0

(20) M. P. Doyle and W. Wierenga, *J. Amer. Chem. Soc.*, **94**, 3896 (1972).

(21) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **68**, 2282 (1946).

ml of acid, the reaction mixture was cooled in an ice bath. After 19 hr pmr analysis indicated complete reduction, and the reaction solution was directly distilled through a short-path distillation apparatus. Four fractions were collected: bp 25–52° (17 Torr), triethylsilyl trifluoroacetate (2.51 g, 11.6 mmol), and trifluoroacetic acid; bp 52–54° (17 Torr), triethylsilyl trifluoroacetate (3.17 g, 14.7 mmol); bp 120–160° (17 Torr), hexaethyldisiloxane (4.79 g, 19.5 mmol); and bp 107–109° (0.05 Torr), 1,6-diphenylhexane (2.80 g, 11.8 mmol, 78.5%). Hexaethyldisiloxane was identified by glpc comparison to an authentic sample. Triethylsilyl trifluoroacetate was isolated by glpc and characterized from its ir spectrum (carbonyl absorption at 1765 cm^{-1}) and its pmr spectrum; the pmr spectrum of the isolated product was identical with that of a sample prepared by treating triethylsilanol with trifluoroacetic acid. The pmr spectrum and boiling point (lit.[22] bp 206–208°) of 1,6-diphenylhexane were consistent with its structure. The total yield of recovered silane products was 99%.

Triethylsilane Reduction of Phenyl Cyclopropyl Ketone.—Reactions were performed according to the general procedure. The products after working were subjected to glpc analysis. In addition to triethylsilanol and hexaethyldisiloxane, nine peaks were observed using a 10% Carbowax 20M column. The major products, phenylcyclopropylmethane, 1-phenylbutane, 1-phenyl-2-butyl trifluoroacetate, and phenyl cyclopropyl ketone, were identified by retention times and peak enhancement using authentic samples. 1-Phenyl-2-butyl trifluoroacetate was prepared by the reaction of phenylcyclopropylmethane with trifluoroacetic acid. Yields were calculated by determining the peak areas of each compound relative to that of phenyl cyclopropyl ketone and using the relative response ratio of each product. Yields determined by glpc analysis were within 2% of those calculated by pmr analysis using an internal standard. Pmr analysis of the reaction products in the δ 3.8–7.0 region shows only a single quintet centered at δ 5.20, attributable to 1-phenyl-2-butyl trifluoroacetate.

Triethylsilane Reduction of Phenyl Cyclobutyl Ketone.—Reactions were performed according to the general procedure. The products after work-up were subjected to glpc analysis. In addition to hexaethyldisiloxane, five peaks were observed using a 10% Carbowax 20M column. The three major products were isolated by glpc. Phenylcyclopentane was identified from its pmr spectrum and by glpc retention time and peak enhancement using an authentic sample. Phenylcyclobutylmethane was identified from its pmr and mass spectra: pmr (CCl_4) δ 7.15 (s, 5 H), 2.67 (broadened singlet, 2 H), and 2.3–1.5 (multiplet, 7 H); mass spectrum *m/e* (relative intensity) 146 (11, parent ion), 118 (83), 117 (99), 114 (50), 91 (100). The structure of 2-phenylcyclopentyl trifluoroacetate was inferred from spectral data: ir (CCl_4) carbonyl absorption at 1780 and strong absorptions at 1160 and 1220 cm^{-1}; pmr (CCl_4) δ 7.25 (s, 5 H), 5.31 (multiplet, 1 H), 3.32 (multiplet, 1 H), 2.6–1.6 (multiplet, 6 H); mass spectrum[23] *m/e* (rel intensity) 145 (20, M − CF_3CO_2), 144 (62, M − CF_3CO_2H), 143 (36), 129 (51), 117 (44), 115 (31), 91 (100). Yields were determined by pmr analysis using an internal standard. Pmr analysis of the reaction products in the δ 3.9–7.0 region shows only the multiplet centered at δ 5.31, attributable to 2-phenylcyclopentyl trifluoroacetate.

Isolation of 6-Phenylhexanoic Acid. Method Ia.—Triethylsilane (1.35 g, 11.6 mmol) was added to 5-benzoylhexanoic acid (1.00 g, 4.85 mmol) in 2.5 ml of trifluoroacetic acid according to the general procedure. After 3 days at room temperature, a 5% solution of sodium hydroxide was added until the reaction mixture was basic to litmus. The aqueous layer was washed once with ether and acidified with hydrochloric acid. The acidic solution was washed twice with 30-ml portions of ether, the combined ether solution was dried over anhydrous sodium sulfate, and the ether was removed under reduced pressure. The resulting residue was distilled at 37 Torr to give 0.71 g (3.70 mmol, 77% yield) of 6-phenylhexanoic acid, bp 218–219° (lit.[24] bp 180–90° at 17 Torr).

Isolation of 4-Phenyl-4-Hydroxybutyric Acid γ-Lactone (IV). Method Ib.—3-Benzoylpropanoic acid (1.78 g, 10.0 mmol) was added to triethylsilane (1.62 g, 14.0 mmol) in 5.0 ml of trifluoroacetic acid. After 4 hr at room temperature the reaction solution was neutralized by adding a saturated solution of sodium bicarbonate. The resulting solution was washed three times with ether, the combined ether extracts were dried with anhydrous sodium sulfate, and the ether was removed under reduced pressure. The resulting residue was a two-phase liquid; the lower layer (1.69 g) consisted of IV (91%) and triethylsilanol. The lower layer was a viscous oil that after crystallization and washing with heptane gave 1.20 g (7.32 mmol, 73% yield) of IV, mp 34.0–35.0° (lit.[25] mp 36–37°).

Isolation of *p*-Nitrodiphenylmethane. Method Ic.—*p*-Nitrobenzophenone (1.14 g, 5.0 mmol) was added to triethylsilane (1.40 g, 12.0 mmol) followed by 2.5 ml of trifluoroacetic acid. After 47 hr at room temperature the reaction mixture was directly distilled under reduced pressure to give 1.03 g (4.8 mmol, 96% yield) of *p*-nitrodiphenylmethane, bp 114–115° (0.05 Torr) [lit.[26] bp 178–181° (4 Torr)].

Isolation of Ethylbenzene. Method II. A.—Acetophenone (3.26 g, 27.2 mmol) was added to tri-*n*-hexylsilane (17.00 g, 59.7 mmol) followed by 10 ml of trifluoroacetic acid. After 15 hr at room temperature 85% aqueous potassium hydroxide (10 g, 0.18 mol) was added to the reaction mixture and the resulting solution was steam distilled. The distillate was cooled and the organic layer was separated from the aqueous layer. The organic layer contained 1.86 g (17.6 mmol, 65% yield) of ethylbenzene that showed only a trace of contaminant by pmr analysis.

B.—The reaction mixture, following extraction to remove trifluoroacetic acid, was distilled from solid powdered potassium hydroxide. Ethylbenzene distillation required pot temperatures in excess of 200°. Although a significant amount of the arene was retained in the residue following distillation, a 64% yield of ethylbenzene was recovered.

C.—The reaction mixture was treated with excess sodium carbonate (0.10 mol) and the resulting solution distilled. Throughout the distillation foaming occurred, and water codistilled with ethylbenzene. The distillate was taken up in ether, dried over anhydrous sodium sulfate, and distilled to give a 55% yield of ethylbenzene that contained a small amount of silane impurity. Inspection of the pot residue from the initial distillation showed substantial amounts of ethylbenzene and silane products.

Registry No.—Trifluoroacetic acid, 76-05-1; triethylsilane, 617-86-7; triethylsilyl trifluoroacetate, 562-98-1; hexaethyldisiloxane, 994-49-0; 1,6-diphenylhexane, 1087-49-6; phenylcyclobutylmethane, 5244-88-2; 2-phenylcyclopentyl trifluoroacetate, 40127-82-0; 6-phenylhexanoic acid, 5581-75-9; 5-benzoylhexanoic acid, 40127-84-2; 4-phenyl-4-hydroxybutyric acid γ-lactone, 1008-76-0; 3-benzoylpropanoic acid, 2051-95-8; *p*-nitrophenylmethane, 1817-77-2; ethylbenzene, 100-41-4; tri-*n*-hexylsilane, 2929-52-4; *o*-benzoylbenzoic acid, 85-52-9.

(22) E. A. Evans and M. Whalley, *J. Chem. Soc.*, 3642 (1954).

(23) The parent ion was not observed; the first observed *m/e* value was at 145.

(24) J. V. Braun, *Ber.*, **44**, 2867 (1911).

(25) R. R. Russell and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **69**, 11 (1947).

(26) G. S. Kolosnikov, V. V. Korshak, and T. V. Smirnova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.*, 1123 (1958); *Chem. Abstr.*, **53**, 3135 (1959).

Stable Carbocations. CLIII.[1] Fluorinated Phenylcarbenium Ions and Benzoyl Cations

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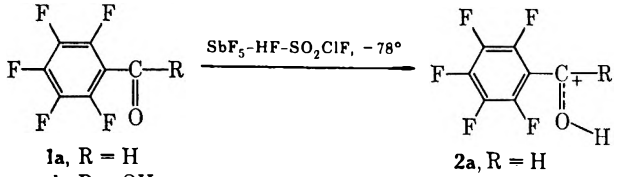
The preparation and nmr study of a series of fluorinated phenylcarbenium ions and benzoyl cations is described. Resonance stabilization (charge delocalization) of these ions is discussed on the basis of their fluorine nmr spectra.

Fluorinated phenylcarbenium ions were first prepared and studied by Olah and Comisarow.[2] Recently, Pozdnyakovich and Shteingarts reported the preparation and ^{19}F nmr of the $C_6F_5CF_2^+$ and $(C_6F_5)_2CF^+$ ions.[3] The unusual stability of these ions suggests that it is due to n–π conjugative stabilization *via* fluorine "back-donation."[4] In order to gain a better understanding of fluorinated carbocations and of the electronic structure of these ions, we have now undertaken the preparation and nmr study of a series of additional fluorinated phenylcarbenium ions and benzoyl cations.

Results and Discussion

Pentafluorophenylcarbenium Ions.—Protonation of pentafluorobenzaldehyde (**1a**) and -benzoic acid (**1b**) and



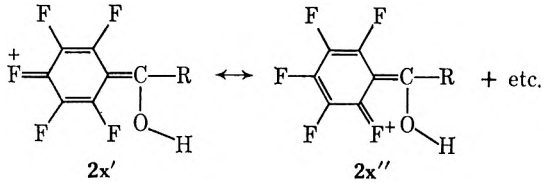
1a, R = H
b, R = OH
c, R = C_6F_5

2a, R = H
b, R = OH
c, R = C_6F_5

decafluorobenzophenone (**1c**) was achieved in SbF_5–HF–SO_2ClF solution at −78°. The nmr (^1H and ^{19}F) parameters of **1x** (**x** = **a**, **b**, and **c**) and their protonated derivatives **2x** (**x** = **a**, **b**, and **c**) are summarized in Table I. The nmr (^1H and ^{19}F) spectrum of ion **2a** is shown in Figure 1.

The ^{19}F nmr data of **1b** have been reported by Graham and Hogben.[5] The small differences in chemical shifts are primarily due to the use of an external capillary reference ($CFCl_3$) as well as the solvent (SO_2ClF) at low temperature (−30°) in the present work. The ^{19}F nmr spectra of the pentafluorophenyl group should be considered as an AA'KXX' type (as Graham and Hogben did in their study of a series of pentafluorophenyl derivatives[5]). It is, however, in the nmr spectra of the ions obtained at low temperature, difficult to obtain good enough resolution to allow detailed analysis. In case of ion **2c** the four meta fluorines of the two C_6F_5 groups display further only one multiplet at ϕ 155.6. Instead of a complete analysis, therefore, only a simple first-order interpretation of spectra was used. Fortunately, this does not affect our purpose to study the conjugative stabilization in these ions, which is primarily based on relative deshielding of fluorine shifts.

The ortho fluorine atoms of **1a**, **1b**, and **1c** are more deshielded than the corresponding para fluorine atom, presumably because the former experience a greater inductive withdrawing effect by the carbonyl group. On the other hand, the para fluorine atom of the protonated species **2x** is generally more deshielded than the ortho fluorine atoms. These data suggest that the degree of charge delocalization into the para position is greater than into the ortho positions. Consequently, resonance forms of para-quinoidal nature **2x'** are more important than ortho-quinoidal forms such as **2x''**.



2x' **2x''**

Furthermore, the differences in fluorine shift ($\Delta\phi$) between **1x** (**x** = **a**, **b**, and **c**) and **2x** (**x** = **a**, **b**, and **c**, respectively) show the trend $\Delta\phi_{para} > \Delta\phi_{ortho} > \Delta\phi_{meta}$ again indicating that charge delocalization into the para position is greater than into the ortho and meta positions. It is also interesting to note that the difference in fluorine shifts ($\Delta\phi_{para}$ and $\Delta\phi_{ortho}$ in particular) between **1a** and **2a** is larger than those between **1b** and **2b** and between **1c** and **2c**. These data suggest that, in the pentafluorophenylcarbenium ions **2x**, the order of stabilization by substituents is OH > C_6F_5 > H.

In accordance with the partial double bond character of $C_{Ar}{=}C_\alpha HOH$,[6] two different ortho fluorine shifts were observed in ion **2a**. The difference in the meta fluorine shifts must be small, since only a single multiplet at ϕ 156.2 was observed. The pmr spectrum of ion **2a** shows two doublets at δ 10.3 (J_{HH} = 8 Hz) and 14.4 (J_{HH} = 8 Hz), indicating that the OH proton is syn to the aldehydic proton. In ion **2c**, two readily distinguishable para-F shifts were found. It reveals that there are two different C_6F_5 rings; one is anti and the other syn to the OH group. However, only two ortho and one meta fluorine multiplet absorptions were observed, presumably owing to the small differences in fluorine shifts between each pair of ortho fluorine atoms and also between the four meta fluorine atoms. For ion **2c**, only three fluorine absorptions at ϕ 129.1 (triplet, J_{FF} = 16 Hz, *o*-F), 156.5 (doublet of doublets, J_{FF} = 16 and 20 Hz, *m*-F), and 127.8 (quintet, J_{FF} = 20 Hz, para) were observed, because of the rapid pro-

(1) Part CLII: G. A. Olah and Y. K. Mo, *J. Org. Chem.*, **38**, 2212 (1973).

(2) G. A. Olah and M. B. Comisarow, *J. Amer. Chem. Soc.*, **89**, 1027 (1967); **91**, 2955 (1969).

(3) Yu. V. Pozdnyakovich and F. D. Shteingarts, *Zh. Org. Khim.*, **6** (8), 1753 (1970).

(4) G. A. Olah, Y. K. Mo, and Y. Halpern, *J. Amer. Chem. Soc.*, **94**, 3551 (1972).

(5) (a) M. G. Hogben and W. A. G. Graham, *ibid.*, **91**, 283 (1969); (b) M. G. Hogben, K. S. Oliver, J. A. J. Thompson, and W. A. G. Graham, *ibid.*, **91**, 291 (1969).

(6) G. A. Olah, A. M. White, and D. H. O'Brien, *Chem. Rev.*, **70**, 561 (1970).

TABLE I

NMR (^{1}H AND ^{19}F) PARAMETERS OF PENTAFLUOROPHENYLCARBENIUM IONS AND THEIR PRECURSORS[a]

				R		
C_6F_5R	ϕ, ortho	ϕ, meta	ϕ, para	δ, CH	δ, OH	ϕ, CF
CHO (1a)	146.5 (m)	163.2 (m)	146.5 (m)	10.2 (s)		
$^+$CHOH (2a)	115.2 (m)	156.2 (m)	111.2 (m)	10.3 (d)	14.4 (d)	
	125.0 (m)			J_{HH} = 8 Hz	J_{HH} = 8 Hz	
COOH (1b)	141.7	163.8 (m)	152.2 (m)		11.6 (s)	
$^+$COOH$_2$ (2b)	129.1 (t)	156.5 (d d)	127.8 (q)		12.8 (s br)	
	J_{FF} = 16 Hz	J_{FF} = 16, 20 Hz	J_{FF} = 20 Hz			
COC_6F_5 (1c)	143.3 (m)	162.3 (m)	148.7 (t t) J_{FF} = 20, 6 Hz			
$^+$COHC$_6$F$_5$ (2c)	125.4 (m)	155.6 (m)	119.1 (m)		14.0 (s br)	
	130.2 (m)		123.1 (m)			
CHF_2 (4a)	145.3 (m)	163.1 (m)	151.6 (t) J_{FF} = 20 Hz	7.03 (t) J_{HF} = 53 Hz		115.2 (d t d) J_{FF} = 2, 16 Hz, J_{HF} = 52 Hz
$^+$CHF (3a)	97.2 (m)	151.4 (t)	106.1 (m)	9.93 (d)		−31.35 (m)
	71.8 (m)	J_{FF} = 21 Hz		J_{HF} = 59 Hz		
CF_2Cl (4b)	141.6 (m)	162.0 (m)	151.2 (t t) J_{FF} = 6, 20 Hz			47.5 (t) J_{FF} = 31 Hz
$^+CF_2$ (3b)	100.6 (m)	148.1 (m)	81.6 (m)			−32.6 (m)

[a] Proton and fluorine chemical shifts are referred to external capillary TMS and $CFCl_3$, respectively.

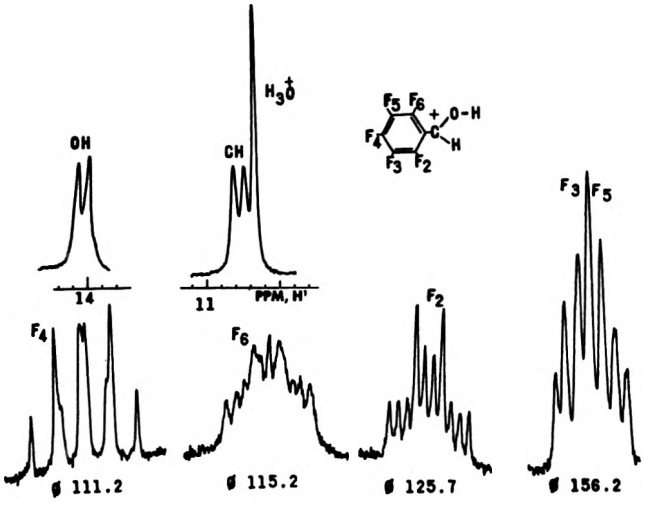


Figure 1.—^{1}H and ^{19}F nmr spectra of protonated pentafluorobenzaldehyde in SbF_5–HF–SO_2ClF solution at −78°.

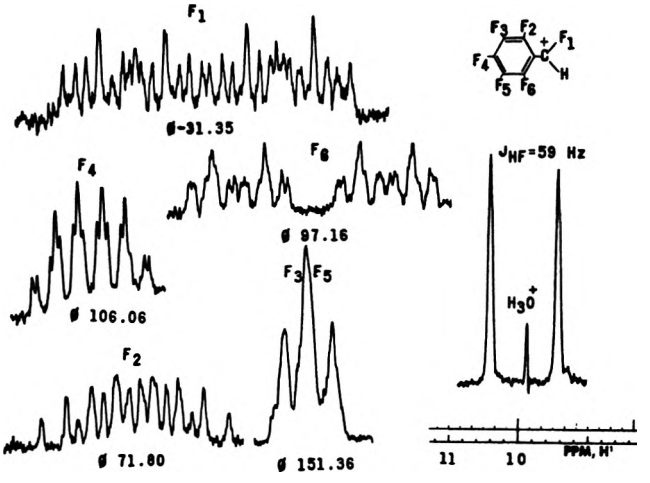
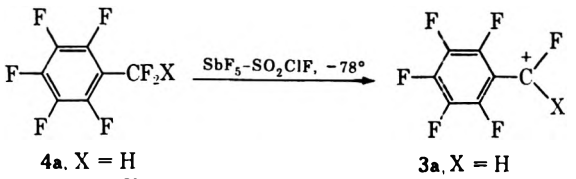


Figure 2.—Proton and fluorine nmr spectra of pentafluorophenylfluorocarbenium ion (3a).

ton exchange with the superacid. Indeed, the OH proton of 2b shows a broadened absorption at δ 12.8 in the pmr spectrum. Similar results were observed when benzoic acid was protonated in HF–SbF_5–SO_2-ClF solution at −78°.[7]

We also have prepared the pentafluorophenylfluorocarbenium ion ($C_6F_5C^+HF$, 3a) and for comparison reinvestigated the perfluorobenzyl cation ($C_6F_5C^+F_2$, 3b) by ionizing pentafluorobenzyl fluoride ($C_6F_5CHF_2$)



and heptafluorobenzyl chloride ($C_6F_5CF_2Cl$), respectively, in SbF_5–SO_2ClF solution. The nmr (^{1}H and ^{19}F) spectra of ions 3a and 3b are shown in Figures 2 and 3, respectively. The ^{19}F nmr spectrum of ion 3b is similar to that reported by Pozdnyakovich and Shteingarts[3] (prepared from octafluorotoluene and SbF_5) but was obtained with much better resolution. The pmr spectrum of ion 3a displays a doublet at δ 9.93 (J_{HF} = 59 Hz), indicating that ionization of $C_6F_5CHF_2$ has occurred.

The ^{19}F nmr spectrum of ion 3a displays a very deshielded symmetrical multiplet centered at ϕ −31.35 which could be assigned to the benzylic fluorine (F_1). Fluorine F_1 must be strongly coupled to one of the ortho fluorines, since it is symmetrically split into two multiplets by 128 Hz. By comparison with the studied *o*-fluorophenyldifluorocarbenium ion,[8] fluorine F_2 of ion 3a should be strongly coupled to F_1. Indeed, fluorine F_2 shows two sets of doublet of triplets at ϕ 97.16 (first-order analysis), again separated by 128 Hz. The other ortho fluorine (F_6) shows a multiplet at ϕ 71.80. It is also coupled to fluorine F_1, as well as

(7) G. A. Olah and P. W. Westerman, unpublished results.

(8) G. A. Olah and Y. K. Mo, *J. Org. Chem.*, 38, 2686 (1973).

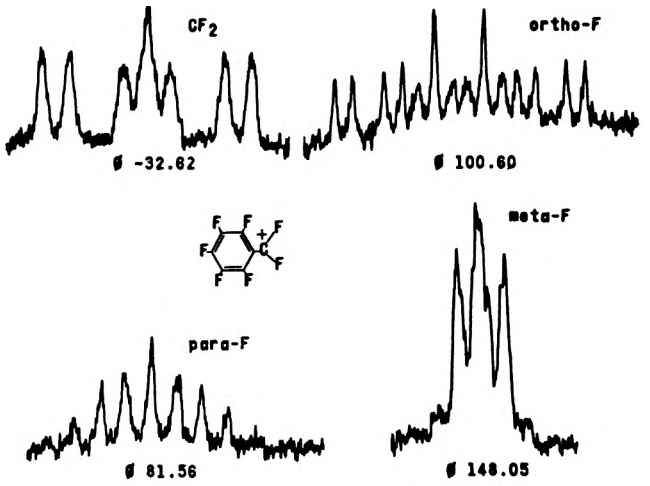
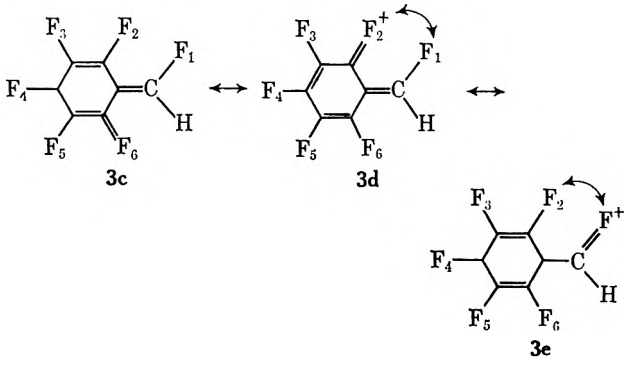


Figure 3.—Fluorine-19 nmr spectrum of perfluorobenzyl cation (3b).

the aromatic fluorine atoms (F_2, F_4, and F_5). One possible explanation why fluorine F_6 is being more deshielded than F_2 is that fluorine back-donation of F_6 (3c) is greater than that of F_2 (3d). This is because



the latter is affected by the obvious charge–charge replusion (3e). The para fluorine of ion 3a displays a sextet of multiplets at ϕ 106.06. The nonequivalent meta fluorines (F_3 and F_5) display a triplet of multiplets centered at ϕ 151.36.

Ion 3a is the first secondary arylfluorocarbenium ion ever prepared. Attempts to prepare the parent phenylfluorocarbenium ion, $C_6H_5C^+HF$, by ionizing $C_6H_5CHF_2$ with SbF_5–SO_2ClF solution at −78° were unsuccessful. Only polymeric materials and tar were observed in the reaction.

Owing to the symmetry of ion 3b, its ^{19}F nmr spectrum (Figure 3) is more simple than that of ion 3a. The benzylic fluorines (CF_2^+) display two sets of doublet of doublets at −32.62, indicating the long-range fluorine–fluorine coupling with the ortho fluorine (J_{FF} = 82 and 66 Hz) and para fluorine (J_{FF} = 21 Hz). The para fluorine is coupled to all the six fluorine atom in ion 3b, and thus displays a heptet at ϕ 81.56 (J_{FF} = 21 Hz). The ortho fluorines show a symmetrical multiplet centered at ϕ 100.06. They couple to all the fluorine atoms in ion 3b, but the one that is para to each of them. The meta fluorenes are coupled to both ortho and para fluorines and thus show a shielded triplet at ϕ 148.05.

Fluorinated Benzoyl Cations.—Tomalia[9] reported the pmr studies of a series of substituted benzoyl cations,

(9) D. A. Tomalia, *J. Org. Chem.*, **34**, 2583 (1969).

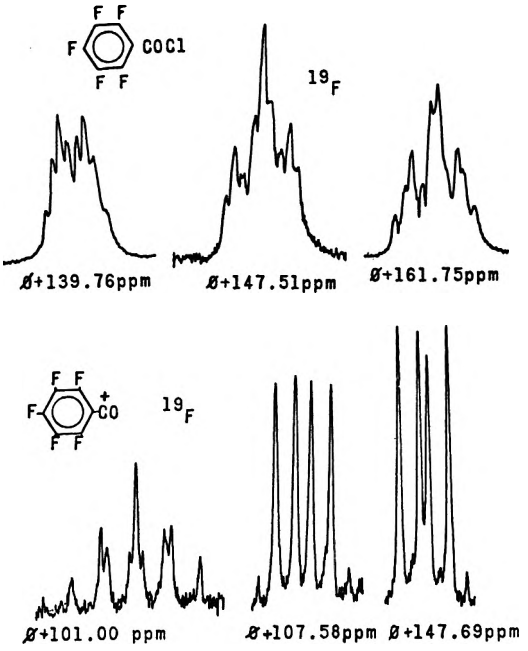
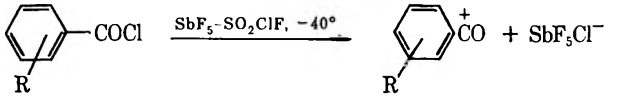


Figure 4.—^{19}F nmr spectrum of pentafluorobenzoyl chloride and pentafluorobenzyl cation.

including the *o*-, *m*-, and *p*-fluorobenzoyl cations. The ^{19}F nmr spectra of these ions were not yet reported. In our continuing studies of fluorocarbenium ion we undertook a study of these fluorinated benzoyl cations, as well as that of the pentafluorobenzoyl cation. The isomeric fluorobenzoyl cations and the pentafluorobenzoyl cation were prepared by ionizing the corresponding benzoyl chlorides with SbF_5–SO_2ClF solution



R = *o*-F, *m*-F, *p*-F, and F_5 R = *o*-F, *m*-F, *p*-F, and F_5

at −40°. Nmr data of these ions and their precursors are summarized in Table II. The pmr data of isomeric fluorobenzoyl cations are identical with those reported by Tomalia.[9] The ^{19}F nmr data of pentafluorobenzoyl chloride has been reported by Graham and Hogben.[5] The slight differences in chemical shifts are presumably due to the use of external capillary $CFCl_3$ as reference, as well as the use of a different solvent (SO_2ClF) at lower temperature (−30°). The ^{19}F nmr spectra of the pentafluorobenzoyl cation and its precursor are shown in Figure 4.

The ^{19}F nmr chemical shifts of these ions are interesting. The chemical shift differences ($\Delta\phi$) between the ions and their precursors are significant in the case of the *o*- ($\Delta\phi$ = 28.7 ppm) and the *p*-fluorobenzoyl ($\Delta\phi$ = 35.2 ppm) cation, but are smaller in the case of the *m*-fluorobenzoyl cation ($\Delta\phi$ = 10.6 ppm). These data indicate that contribution of significant resonance by

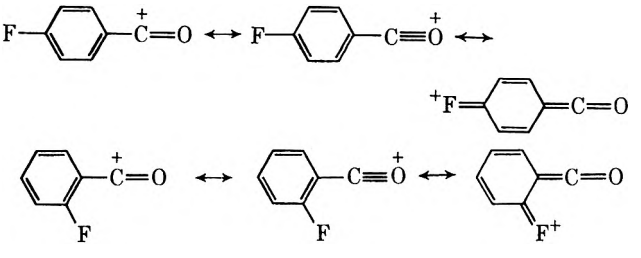


TABLE II

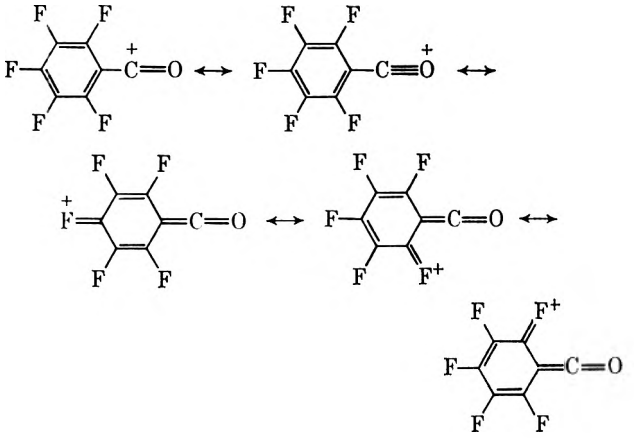
^{19}F AND ^{1}H NMR CHEMICAL SHIFTS OF FLUOROBENZOYL CHLORIDES AND CATIONS[b]

		Ortho		Meta		Para	
Registry no.	Chlorides and cations	δ, CH	φ, CF	δ, CH	φ, CF	δ, CH	φ, CF
393-52-2	*o*-Fluorobenzoyl chloride	+7.68 (m)	+111.31 (m)	+7.41[a] +7.30[a]		+8.20 (c, d) J_{HF} = 2 and 7 Hz	
39982-32-6	*o*-Fluorobenzoyl cation	+8.85[a]	+82.62 (m)	+8.15[a] +8.30[a]		+8.85[a]	
1711-07-5	*m*-Fluorobenzoyl chloride	+7.90[a] +7.50[a]		+7.40[a]	+112.19 (m)	+7.90[a]	
39981-34-5	*m*-Fluorobenzoyl cation	+8.70[a]		+8.70[a]	+101.59 (m)	+8.70[a]	
403-43-0	*p*-Fluorobenzoyl chloride	+8.25 (d d)		+7.26 (t)			+102.30 (m)
39981-36-7	*p*-Fluorobenzoyl cation	+9.22 J_{HF} = 4 and 8 Hz		+8.17 (t) J_{HF} = 9 Hz			+67.06 (m)
2251-50-5	Pentafluorobenzoyl chloride		+139.76 (m)		+161.75 (m)		+147.51 (t t) J_{FF} = 7 and 20 Hz
39981-37-8	Pentafluorobenzoyl cation		+107.58 (d d) J_{FF} = 26 and 14 Hz		+147.69 (d d) J_{FF} = 14 and 21 Hz		+101.00 (t t) J_{FF} = 21 and 26 Hz

[a] No attempt was made to determine the multiplicities since they are complicated patterns. [b] m, multiplet; d, doublet; and t, triplet.

fluorine back-donation occurs in the *o*- and *p*-fluorobenzoyl cations, but not in the case of *m*-fluorobenzoyl cation.

Similar results are obtained in the case of pentafluorobenzoyl cation.



The differences in fluorine shifts ($\Delta\phi$) are 46.5 ppm in the case of ortho, 32.2 ppm in the case of para, and only 14.1 ppm in the case of meta positions. The unusual stability of this ion can again be accounted for by resonance contributions of the ortho and para fluorine atoms.

Fluorine is the most electronegative element and should inductively destabilize carbocations. However, its n–π conjugative stabilization *via* back-donation of the nonbonded electron pairs in carbocations can now be considered as one of the most important factors related to their stability. The degree of fluorine back-donation is related to the fluorine chemical shifts of the fluorinated carbocations. The proton and ^{13}C nmr study of phenylcarbenium ions indicates that substantial charge is delocalized into the ortho and para positions.[10] Consequently, fluorine at these positions (*i.e.*, in phenylcarbenium ions) is capable of stabilizing the ions *via* fluorine back-donation. The present data further substantiate this concept by the study of fluorine chemical shifts in the studied series of fluorinated phenylcarbenium ions, and benzoyl cations.

Experimental Section

Materials.—All of the fluorinated benzoyl chlorides were commercially available (K & K Laboratories). Pentafluorobenzaldehyde, pentafluorobenzoic acid, and decafluorobenzophenone were obtained from Aldrich Chemical Co. α,α-Difluorotoluene was prepared from benzaldehyde and sulfur tetrafluoride.[11]

Antimony pentafluoride (Allied Chemical) was triply distilled before use.

Preparation of Ions and Their Nmr Studies.—Solution of the ions in SbF_5–SO_2ClF or SbF_5–HF–SO_2ClF solution were prepared as described previously.[2] ^{1}H and ^{19}F nmr spectra were obtained on a Varian A-56-60A nmr spectrometer equipped with a variable-temperature probe. Proton and fluorine shifts are referred to external capillary TMS and $CFCl_3$, respectively.

The nmr spectra of the precursors were obtained as 15–20% (w/w) solution in SO_2ClF at −30°.

Registry No.—**1a**, 653-37-2; **1b**, 602-94-8; **1c**, 853-39-4; **2a**, 39981-38-9; **2b**, 40082-97-1; **2c**, 39981-39-0; **3a**, 39981-40-3; **3b**, 29680-43-1; **4a**, 22006-44-6; **4b**, 40081-60-5.

Acknowledgment.—Support of our work by grants of the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

(10) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **91**, 5801 (1969).
(11) W. R. Hasek, W. C. Smith, and V. A. Engelhardtdt, *ibid.*, **82**, 543 (1960).

Stable Carbocations. CLIV.[1] Halogenated Phenyldifluorocarbenium Ions

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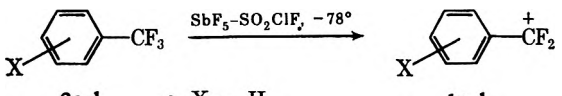
A series of ring halogenated phenyldifluorocarbenium ions was prepared and their structures were studied on the basis of their nmr (^{1}H and ^{19}F) spectra. The electronic structure and the degree of halogen back-donation in the ions are discussed, based on experimental data of their nmr spectra.

In 1969, Olah and Comisarow reported the first direct observation of alkyl(aryl)halocarbenium ions and haloarylcarbenium ions.[2] The degree of halogen back-donation and the relative stability of halocarbenium ions have been studied by Olah, Mo, and Halpern.[3] As an extension of this work, we have now prepared a series of ring halogenated phenyldifluorocarbenium ions in order to gain better understanding of their electronic structures, based on their nmr spectra, and to study the relationship of fluorine shifts with the degree of halogen back-donation and relative stability of these difluorocarbenium ions.

Results and Discussion

The series of ring halogenated phenyldifluorocarbenium ions (**1a–l**) were prepared by treating halogenated benzotrifluorides (**2a–l**) with SbF_5–SO_2ClF solution at −78°. The nmr (^{1}H and ^{19}F) chemical



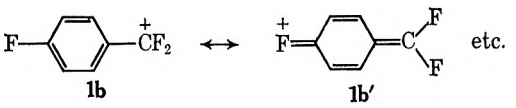
2a–l **1a–l**

a, X = H
b, X = *p*-F
c, X = *p*-Cl
d, X = *p*-Br
e, X = *p*-I
f, X = *o*-F
g, X = *o*-Cl
h, X = *o*-Br
i, X = *m*-F
j, X = *m*-Cl
k, X = *m*-Br
l, X = *p*-Cl and *m*-Br

shifts of ions **1x** (**x** = **a–l**) and their precursor halogenated benzotrifluorides **2x** are summarized in Table I. Representative nmr spectra are shown in Figures 1–4. The parent difluorocarbenium ion (**1a**) has been previously prepared and characterized by nmr spectroscopy.[2] The characteristic, highly deshielded fluorine shift of ion **1a** was considered particularly suitable to study the effect of halogen substitution in the phenyl ring. The stabilization of the ions, *via* halogen back-donation, should be reflected in the $^+CF_2$ fluorine shifts in ions **1b–l**.

In the ^{19}F nmr spectra of all ions **1x**, the $^+CF_2$ group shows a substantially deshielded fluorine shift in the range ϕ −6.45 to −21.0 (deshielded from $CFCl_3$). The CF_3 group of the precursors shows shielded fluorine absorptions ranging from ϕ 62.8 to 66.5. These data are good evidence that ionization of halobenzotrifluorides **2x** to halophenyldifluorocarbenium ions **1x** has occurred. In addition, the aromatic proton absorptions of **1x** are generally 1 ppm deshielded from their precursors.

The aromatic fluorine atoms in ions **1b**, **1f**, and **1i** show highly different chemical shifts at ϕ 40.41, 69.24, and 101.00, respectively. The highly deshielded para-fluorine of **1b** indicates substantial fluorine back-donation.[3]



1b **1b′**

Similar fluorine back-donation is also observed in ion **1f**, but is less significant. In the case of ion **1i**, such a resonance effect is not feasible and the slight deshielding of the meta fluorine atom (11.2 ppm) is due solely to the inductive effect of the $^+CF_2$ group.

In *p*-halophenyldifluorocarbenium ions, the fluorine absorption of the $^+CF_2$ group is deshielded in the order **1d** > **1c** > **1b** > **1e** (ϕ −8.64 < −8.61 < −6.77 < −6.45, respectively). If the inductive effect of the halogens would alone be operating in these ions (**1x**, **x** = **b, c, d,** and **e**), an opposite trend should be observed (**1b** > **1c** > **1d** > **1e**). The possible explanation of these discrepancies may be the greater halogen back-donation in **1b** than in other ions. Recently, we have reported the degree of halogen back-donation of alkylhalocarbenium ions[3] and found it to be in the order F > Cl > Br. Consequently, a similar resonance

effect can lead to charge delocalization which is more extensive for fluorine than for the other halogen atoms. Based on previous data, bromine back-donation was found to be insignificant.[3] Our present data showing the $^+CF_2$ group of **1d** to be more deshielded than that of **1e** suggests that inductive effects are predominantly operating in these ions (**1d** and **1e**).

In contrast, when halogen back-donation is not feasible, as in ions **1i**, **1j**, and **1k**, the $^+CF_2$ fluorine shifts show the opposite trend (ϕ −18.51, −17.90, and −14.70, respectively).

In the case of *o*-halophenyldifluorocarbenium ions (**1f**, **1g**, and **1h**), the two fluorine atoms of the $^+CF_2$ group are nonequivalent and show different chemical shifts (Table I). They also couple to each other with unusually large fluorine–fluorine coupling constants (*e.g.*, 250 Hz in **1g**). The nonequivalence of the two fluorine atoms in the $^+CF_2$ group of ions **1f**, **1g**, and **1h** rises from the partial double bond character of the C_{Ar}=C^+F_2 bond. Similar observations have been

(1) Part CLIII: G. A. Olah and Y. K. Mo, *J. Org. Chem.*, **38**, 2682 (1973).
(2) G. A. Olah and M. B. Comisarow, *J. Amer. Chem. Soc.*, **91**, 2955 (1969).
(3) G. A. Olah, Y. K. Mo, and Y. Halpern, *ibid.*, **94**, 3551 (1972).

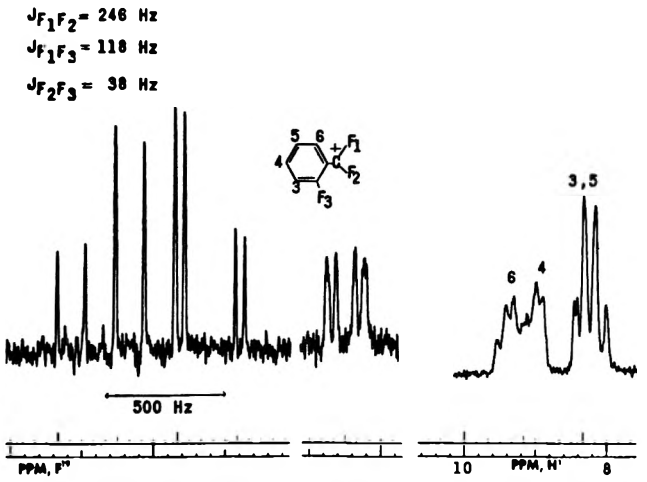


Figure 1.—Nmr (^{1}H and ^{19}F) spectra of ion 1f.

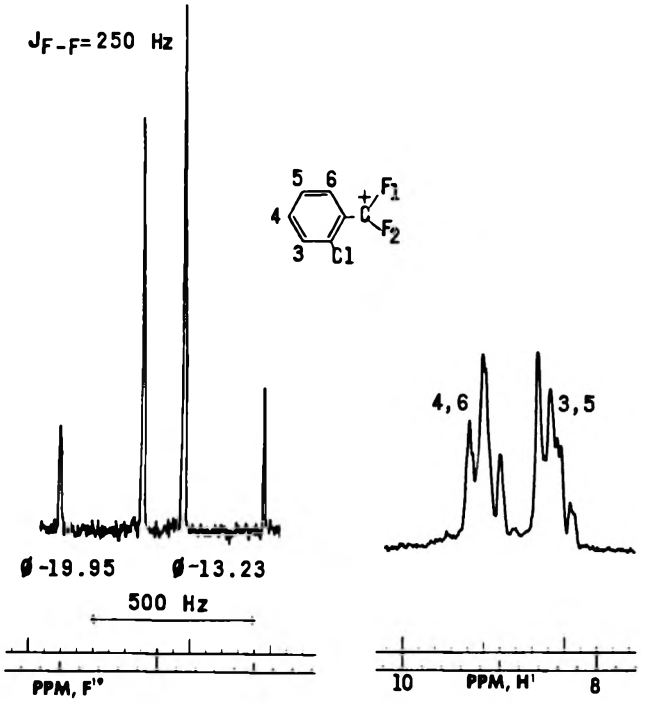
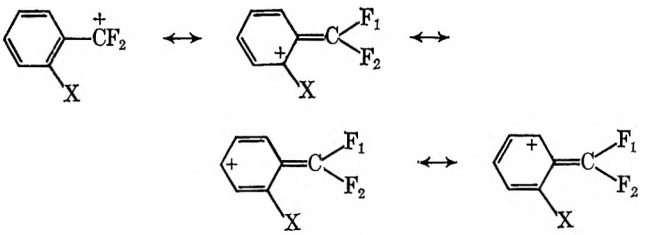


Figure 2.—Nmr (^{1}H and ^{19}F) spectra of ion 1g.



1f, X = F
g, X = Cl
h, X = Br

made in benzyl cations[4] and styryl cations.[5] Since F_2 is closer to the ortho halogen and should exercise a greater inductive deshielding effect, we thus assign the more deshielded fluorine absorption to F_2. Furthermore, F_2–F_3 spin–spin interaction of ion 1f (118 Hz) is

(4) J. M. Bollinger, M. B. Comisarow, C. A. Cupas, and G. A. Olah, *J. Amer. Chem. Soc.*, **89**, 5687 (1967).

(5) (a) G. A. Olah, R. D. Porter, and D. P. Kelly, *ibid.*, **93**, 464 (1971), (b) G. A. Olah, M. B. Comisarow, E. Namanworth, and B. Ramsey, *ibid.*; **89**, 5259 (1967).

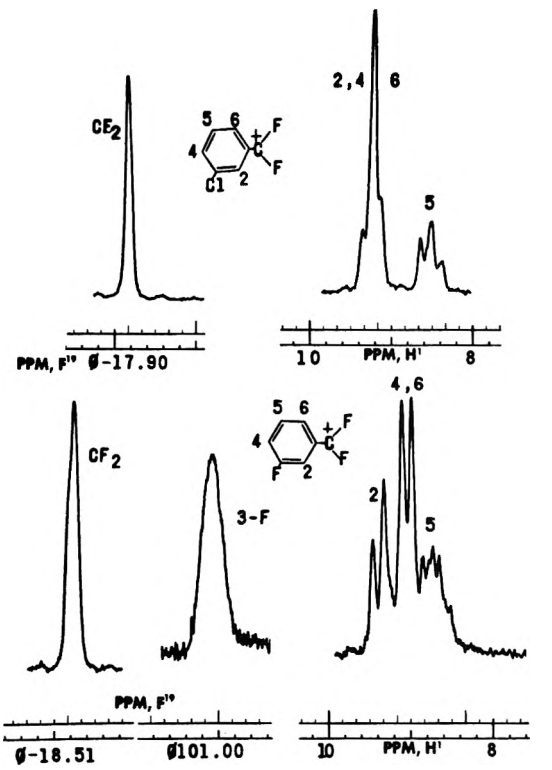


Figure 3.—Nmr (^{1}H and ^{19}F) spectra of ions 1j (upper) and 1i (lower).

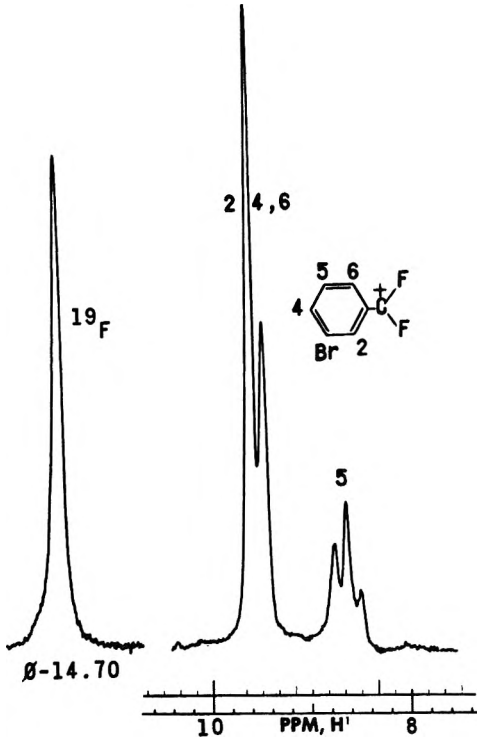


Figure 4.—Nmr (^{1}H and ^{19}F) spectra of ion 1k.

greater than that of F_1–F_3 (38 Hz) (see Figure 1). Our assignments can be based on analogy with the fluorine–fluorine coupling constants ($J_{F_aF_c}$ = 3.6 and $J_{F_bF_d}$ =

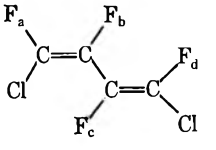


TABLE I

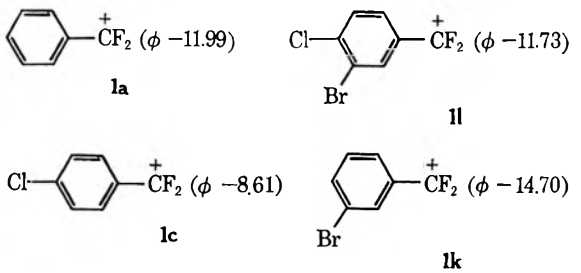
NMR (^{1}H AND ^{19}F) PARAMETERS OF ARYLDIFLUOROCARBENIUM IONS AND THEIR PRECURSORS[a,b]

	Precursor[c] $XC_6H_4CF_3$				Ion $XC_6H_4CF_2^+$			
X	ϕ, CF_3	Ortho	Meta	Para	ϕ, CF_2^+	Ortho	Meta	Para
H	63.63 (s)	7.5 (m)	7.5 (m)	7.5 (m)	−11.99 (q)	8.88 (d d)	8.04 (t d)	8.84 (t d)
					J = 1.0	J_{HH} = 9	J_{HH} = 9	J_{HH} = 9
						J_{FH} = 1		$J_{F\text{-}H}$ = 1
p-F	62.92 (s)	7.5 (m)	7.1 (m)	ϕ 108.52 (m)	−6.77 (d t)	9.00 (d d t)	8.96 (t)	ϕ 40.41 (m)
					J_{FF} = 19.8	J_{HH} = 10	J = 10	J_{FF} = 19.8
					$J_{F\text{-}o\text{-}H}$ = 1	J_{HF} = 4.6		$J_{F\text{-}o\text{-}H}$ = 4.6
						$J_{H\text{-}CF_2}$ = 1.1		$J_{F\text{-}m\text{-}H}$ = 8.4
p-Cl	63.49 (s)	7.6 (d)	7.4 (d)		−8.61 (t)	8.80 (d d)	8.06 (d)	
		J_{HH} = 9	J_{HH} = 9		$J_{F\text{-}o\text{-}H}$ = 1	$J_{F\text{-}o\text{-}H}$ = 1	J_{HH} = 10	
						J_{HH} = 10		
p-Br	63.54 (s)	7.8 (d)	7.5 (d)		−8.78 (d)	8.64 (d d)	8.23 (d)	
		J_{HH} = 10	J_{HH} = 10		$J_{F\text{-}o\text{-}H}$ = 1	$J_{F\text{-}o\text{-}H}$ = 1	J_{HH} = 10	
						J_{HH} = 10		
p-I	66.50 (s)	7.64 (d)	7.26 (d)		−6.45 (t)	8.78 (d)	8.61 (d)	
		J_{HH} = 8	J_{HH} = 8		$J_{F\text{-}o\text{-}H}$ = 1	J_{HH} = 10	J_{HH} = 10	
o-F	62.80 (d)	ϕ 116.13 (m)	7.3 (m)	7.3 (m)	−20.92	ϕ 69.24 (d d)	8.3 (m)	8.9 (m)
	J_{FF} = 11	7.5 (m)	7.5 (m)		J_{FF} = 246	$J_{F\text{-}o\text{-}F}$ = 118,		
					$J_{F\text{-}o\text{-}F}$ = 118	38		
					−13.47 (d d)			
					J_{FF} = 246			
					$J_{F\text{-}o\text{-}F}$ = 38			
o-Cl	63.83 (s)	7.7 (m)	7.7 (m)	7.7 (m)	−19.95 (d)	9.1 (m)	8.5 (m)	9.1 (m)
					J_{FF} = 250			
					−13.23 (d)			
					J_{FF} = 250			
o-Br	63.90 (s)	7.8 (m)	7.5 (m)	7.5 (m)	−17.94 (d)	9.35 (d)	8.4 (m)	8.7 (m)
					−12.13 (d)	J_{HH} = 8	8.7 (m)	
					J_{FF} = 252			
m-F	64.08 (s)	7.4 (m)	ϕ 112.15 (m)	7.4 (m)	−18.51 (s)	9.3 (m)	ϕ 101.0 (s)	9.0 (m)
			7.4 (m)			9.0 (m)	8.7 (m)	
m-Cl	64.00 (s)	7.6 (m)	7.6 (m)	7.6 (m)	−17.90 (s)	9.2 (m)	8.5 (m)	9.1 (m)
m-Br	64.00 (s)	7.9 (s)	7.7 (m)	7.7 (m)	−14.70 (s)	9.6 (m)	8.6 (m)	9.6 (m)
		7.7 (m)						
m-Br-*p*-Cl	64.00 (s)	8.04 (s)	7.70 (s)		−11.73 (s)	9.60 (s)	8.7 (d)	
		7.70 (s)				9.23 (d)	J_{HH} = 10	
						J_{HH} = 10		

[a] Proton and fluorine chemical shifts are referred to external capillary TMS and $CFCl_3$, respectively. Abbreviation used: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. [b] Coupling constants are in hertz. [c] In SO_2ClF solution at −30°.

14.5 Hz) in *cis,trans*-1,4-dichlorotetrafluorobuta-1,3-diene reported by Bladon, Sharp, and Winfield.[6]

It is of interest to compare the fluorine shifts of the $^+CF_2$ group in ions **1a**, **1c**, **1k**, and **1l**. The $^+CF_2$



fluorine shift of **1a** is more deshielded than that of **1c**, indicating partial charge delocalization onto the chlorine atom (*via* back-donation). However, the $^+CF_2$ fluorine shift of **1a** is shielded from that of **1k**, showing that mainly the inductive effect is operating in the latter. Similar $^+CF_2$ fluorine shifts are found in both ions **1a** and **1l** because the resonance effect of the chlorine atom cancels out the inductive effect of the bromine atom.

We consider our results of significance, since a more quantitative picture of halogen back-donation could be given in the series of halogenated phenyldifluorocarbenium ions. The present data are not only in good agreement with our previous studies[2,3] but also the general concept of halogen back-donation studied in considerable detail by other methods and considered of significance in both inorganic[7] and organic[8] systems.

Experimental Section

Materials.—All of the halobenzotrifluorides **2x** were commercially available (Columbia Organic Chemicals or PCR Inc.). Antimony pentafluoride (Allied Chemical) was triply distilled before use.

Preparation of Ions and Nmr Studies.—Solutions of the ions

(6) P. Bladon, D. W. A. Sharp, and J. M. Winfield, *Spectrochim. Acta*, **22**, 343 (1966).

(7) (a) H. S. Gutowsky and D. W. McCall, *J. Phys. Chem.*, **57**, 481 (1953); (b) T. P. Onak, H. Landesman, R. E. Williams, and I. Shapiro, paper presented to the Division of Inorganic Chemistry, 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959; (c) F. A. Cotton and G. Wilkinson "Advanced Inorganic Chemistry," Interscience, London, 1966, p 256.

(8) See references quoted in our preceding papers (ref 2–5). For a more comprehensive review see, for example, W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, p 18.

in SbF_5–SO_2ClF solution were prepared as described previously.[3] Nmr spectra were obtained on a Varian A-56-60A nmr spectrometer equipped with a variable-temperature probe. Proton and fluorine shifts are referred to external capillary TMS and $CFCl_3$, respectively.

Registry No.—**1a**, 24154-19-6; **1b**, 24154-20-9; **1c**, 24226-22-0; **1d**, 24154-21-0; **1e**, 39982-15-5; **1f**, 39982-16-6; **1g**, 39982-17-7; **1h**, 39982-18-8; **1i**, 39982-16-6; **1j**, 39982-20-2; **1k**, 39982-21-3; **1l**, 39982-22-4; **2a**, 98-08-8; **2b**, 402-44-8; **2c**, 98-56-6; **2d**, 402-43-7; **2e**, 455-13-0; **2f**, 392-85-8; **2g**, 98-15-7; **2h**, 392-83-6; **2i**, 401-80-9; **2j**, 88-16-4; **2k**, 401-78-5; **2l**, 454-78-4.

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Effect of pK on the Rate of Amine-Catalyzed Cleavage of Diacetone Alcohol

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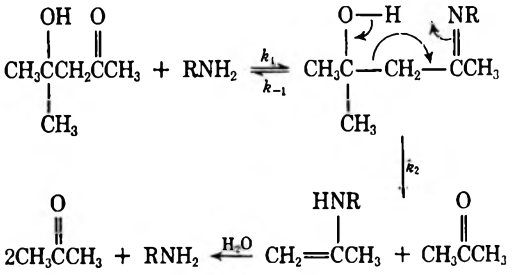
The primary amine catalyzed dealdolization of diacetone alcohol has been investigated with a series of amines whose pK's range from 5.7 to 10.9. Changing the pK of the amine from 10.9 to 5.7 has a small effect on the equilibrium constant for formation of the intermediate ketimine (fourfold decrease) and only a modest effect on the rate of cleavage of ketimine to products (25-fold decrease), indicating a relatively nonpolar transition state. The relevance of these results to the mechanism of aldolase is discussed.

A large class of enzymes, including many aldolases, appears to function *via* the formation of an imine intermediate from a carbonyl group of the substrate and a lysine residue of the enzyme.[1] The replacement of the carbonyl oxygen with the much more basic nitrogen of the enzyme allows facile protonation of the nitrogen and subsequent (or concurrent) acceptance of a pair of electrons from a leaving group to form an enamine. Hydrolysis of the enamine then leads to regeneration of the enzyme. It appears that catalysis by these enzymes is due in large part to a replacement of C=O by C=N.

In an effort to evaluate the contribution of this factor to the rate accelerations caused by these enzymes, much effort has been devoted to catalysis by simple primary amines. A convenient model system for the aldolase enzymes is the primary amine catalyzed dealdolization of diacetone alcohol (Scheme I). This reaction involves an analogous mechanism to that proposed for the enzymes.[2-4] For catalysis by *n*-propylamine (pK 10.9) we have shown that the formation of the intermediate ketimine is rapid and reversible followed by slow decomposition to products.[4] In addition we were able to evaluate the individual rate constants k_1, k_{-1}, and k_2. The rate constant for cleavage of imine to products (k_2) is of particular interest since a comparison of this rate to the rate of cleavage of the carbonyl compound itself gives a direct evaluation of the effect of replacing an oxygen by a nitrogen in this system.

SCHEME I



The choice of *n*-propylamine was due to its resemblance to the lysine side chain both in structure and pK. Although the pK of *n*-propylamine is similar to that normally observed for lysine residues of proteins (p$K \cong 10$), it is not clear that the active site lysine of aldolase has a "normal" pK. In fact, for the related enzyme acetoacetate decarboxylase, the pK of the active site amine group has been found to be about 6.[5] Although the pK of this group in aldolase has not been determined, it is reasonable to suppose that it may be perturbed in a similar manner.

We have now extended our previous work to include a series of primary amines with widely different pK's. Our objectives in this study were threefold: (1) to establish whether there is a change in rate-determining step with changing amine pK; (2) to obtain information concerning the polarity of the transition state for cleavage of the imine; and (3) to determine what, if any, advantage could accrue to an aldolase enzyme if it were to have a lowered active site pK.

Experimental Section

Materials.—Diacetone alcohol and *n*-propylamine were purified as previously described.[4] Ethanolamine was distilled prior to use. Glycine and glycinamide were reagent grade chemicals used without further purification. 2,2,2-Trifluoroethylamine was prepared by the method of Bissell and Finger.[6]

Kinetic Methods.—For all catalysts except trifluoroethylamine, kinetic measurements were carried out at 260 nm for dealodolization and 235 nm (240 nm for glycinamide) for formation of the imine as described previously.[4] For 2,2,2-trifluoroethylamine, rate constants for conversion of diacetone alcohol

(1) (a) B. L. Horecker, S. Pontremli, C. Ricci, and T. Cheng, *Proc. Nat. Acad. Sci. U. S.*, **47**, 1949 (1961); (b) E. Grazi, P. T. Rowley, T. Cheng, O. Tchol, and B. L. Horecker, *Biochem. Biophys. Res. Commun.*, **9**, 38 (1962); (c) for a general review of the mechanism of action of aldolases see D. E. Morse and B. L. Horecker, *Advan. Enzymol. Relat. Subj., Biochem.*, **31**, 125 (1968).

(2) (a) F. H. Westheimer and H. Cohen, *J. Amer. Chem. Soc.*, **60**, 90 (1938); (b) F. H. Westheimer and W. A. Jones, *ibid.*, **63**, 3283 (1941).

(3) R. W. Hay and K. R. Tate, *Aust. J. Chem.*, **19**, 1651 (1966).

(4) R. M. Pollack and S. Ritterstein, *J. Amer. Chem. Soc.*, **94**, 5064 (1972).

(5) (a) D. E. Schmidt, Jr. and F. H. Westheimer, *Biochemistry*, **10**, 1249 (1971); (b) F. C. Kokesh and F. H. Westheimer, *J. Amer. Chem. Soc.*, **93**, 7270 (1971).

(6) E. Bissell and M. Finger, *J. Org. Chem.*, **24**, 1256 (1959).

TABLE I

RATE OF CLEAVAGE OF DIACETONE ALCOHOL CATALYZED BY AMINES IN AQUEOUS SOLUTION

[Amine][a]	pH[b]	Ionic strength[c]	Temp, °C	k_{obsd}, sec^{-1} [d]
			Ethanolamine	
0.200	9.70	0.4	25.1	$3.17 \pm 0.04 \times 10^{-5}$
0.100	9.70	0.4	25.1	$1.58 \pm 0.05 \times 10^{-5}$
				$k = 1.58 \pm 0.07 \times 10^{-4}\ M^{-1}$ sec^{-1}
			Glycine	
0.200	9.78	0.4	25.1	$2.45 \pm 0.3 \times 10^{-5}$
0.100	9.78	0.4	25.1	1.12×10^{-5}
				$k = 1.17 \pm 0.06 \times 10^{-4}\ M^{-1}$ sec^{-1}
			Glycinamide	
0.472	8.23	1.0	25.0	$2.49 \pm 0.07 \times 10^{-5}$
0.330	8.22	1.0	25.0	$1.66 \pm 0.01 \times 10^{-5}$
0.188	8.21	1.0	25.0	$8.71 \pm 0.26 \times 10^{-6}$
				$k = 4.98 \pm 0.20 \times 10^{-5}\ M^{-1}$ sec^{-1}
			Propylamine	
0.471	11.04	1.0	53.4	$2.22 \pm 0.07 \times 10^{-3}$
0.314	11.04	1.0	53.4	$1.62 \pm 0.07 \times 10^{-3}$
0.157	11.04	1.0	53.4	$1.07 \pm 0.06 \times 10^{-3}$
				$k = 3.63 \pm 0.40 \times 10^{-3}\ M^{-1}$ sec^{-1}
			2,2,2-Trifluoroethylamine	
0.478	5.8	1.0	53.6	1.7×10^{-5}
0.239	5.8	1.0	53.6	8.7×10^{-6}
				$k = 3.56 \times 10^{-5}\ M^{-1}$ sec^{-1}

[a] Concentration of free amine. [b] At 23°. [c] Ionic strength was maintained with either KCl or NaCl. [d] Errors are average deviations for two runs.

into the ketimine were also measured at 235 nm. The overall rate of dealdolization, however, was monitored by nmr by observing the increase of a singlet at δ 2.1 owing to formation of acetone and the decrease of a singlet at δ 1.2 owing to diacetone alcohol. The nmr tubes were removed at appropriate time intervals from a constant-temperature bath, measurements were taken, and the tubes were returned to the bath. It was assumed that no time passed during the measurement since the temperature of measurement was about 20° lower than that of the bath and the tubes were only out of the bath for about 15 min. (For the fastest run, 15 min corresponds to less than 2% reaction at 53.6° and certainly less than 1% reaction at room temperature). These reactions were followed to greater than 90% completion and were strictly first order in diacetone alcohol.

Equilibrium constants for formation of the ketimine were measured at 235 nm for all amines except glycinamide. For glycinamide measurements were made at 240 nm because of a large background absorbance due to the amine at 235 nm. Control experiments with glycine and ethanolamine showed that the change in absorbance at 235 nm upon formation of the ketimine was identical with the absorbance change at 240 nm. Equilibrium constants were calculated as before, assuming an extinction coefficient of 192 for all imines.[4]

Results

The dealdolization of diacetone alcohol (4-hydroxy-4-methyl-2-pentanone) was followed spectrally by monitoring the appearance of acetone at 260 nm for all catalysts except 2,2,2-trifluoroethylamine. With this amine, the dealdolization reaction was complicated by the formation of a species absorbing at 243 nm, presumably mesityl oxide, and first-order kinetics could not be obtained spectrally. Since mesityl oxide has an extinction coefficient about 100 times greater than that of acetone at 260 nm, it is apparent that formation of a small amount of mesityl oxide is enough to preclude a uv method of analysis. (We estimate that about 1% mesityl oxide formed under our conditions.) Instead we chose to follow the reaction by nmr. Diacetone alcohol shows a spectrum consisting of three singlets at δ 2.6 (2 H), 2.1 (3 H), and 1.1 (6 H). All three peaks are easily observable in an aqueous solution of 2,2,2-trifluoroethylamine. Upon heating the solution, the peaks at δ 2.6 and 1.1 disappear with concurrent enhancement of the peak at δ 2.1. We attribute this enhancement to the formation of acetone, which also has a peak at δ 2.1. The reaction rate was followed by determining the per cent acetone in the medium at various time intervals. No products other than acetone were detected by nmr.

Each catalyst was studied in aqueous solution at 1:1 buffer ratios of amine:amine hydrochloride at two or more amine concentrations. All reactions were first order in amine concentration with a negligible contribution to the rate from hydroxide ion catalysis, except for propylamine. Rate constants were obtained at either 25° or 53.5° at constant ionic strength (either 0.4 or 1.0). Observed pseudo-first-order rate constants, along with calculated second-order rate constants, are given in Table I.

In addition to the change in absorbance due to the overall dealdolization at 260 nm, a much more rapid increase in absorbance may be observed at 235 or 240 nm. We have previously attributed this change to the formation of the imine intermediate from diacetone alcohol and the amine.[4] Other workers have also shown that imines absorb in this region of the spectrum.[7,8] Rate constants for imine formation were measured at 25° by following the increase in absorbance at either 235 or 240 nm. Equilibrium constants were calculated from the total change in absorbance due to this

(7) A. Williams and M. L. Bender, *J. Amer. Chem. Soc.*, **88**, 2508 (1966).

(8) (a) J. Hine, C. Y. Yeh, and F. C. Schmalsteig, *J. Org. Chem.*, **35**, 340 (1970); (b) J. Hine and C. Y. Yeh, *J. Amer. Chem. Soc.*, **89**, 2669 (1967).

reaction, with the assumption that there is no change in diacetone alcohol concentration. Measurements were all made at 0.2 *M* free amine in 1:1 buffers of amine:amine hydrochloride. Values of equilibrium constants for imine formation are known to be independent of both the concentration of amine and the pH.[4,7,8] On the other hand, rate constants for imine formation and hydrolysis do depend on pH,[9] so that any comparison of our observed rates for ketimine formation must be done with caution. Equilibrium constants were calculated using an assumed extinction coefficient of 192 for all imines. This value is that observed for the imine from acetone and *n*-butylamine in acetonitrile solution at 235 nm.[7] Although the absolute value of the extinction coefficient may be somewhat in error, it is reasonable to suppose that the extinction coefficient is independent of the p*K* of the amine precursor. Support for this assumption may be found in the work of Hine, *et al.*,[8] in which they found that for *N*-isobutylidenealkylamines neither the position of the absorption maximum nor the extinction coefficient is significantly altered for a wide variety of alkyl groups.

Observed values are given in Table II. There appears to be little variation of either rate or equilibrium

TABLE II

RATE AND EQUILIBRIUM CONSTANTS FOR THE FORMATION OF KETIMINE FROM DIACETONE ALCOHOL[a]

Amine	pH	k_{ket}^{obsd},[b] sec^{-1}	K, M^{-1} [b,c]
n-Propylamine[d]	10.9	$7.0 \pm 0.5 \times 10^{-2}$	0.15 ± 0.02
Glycine	9.78	$4.42 \pm 0.09 \times 10^{-2}$	0.048 ± 0.001
Ethanolamine	9.70	$4.25 \pm 0.17 \times 10^{-2}$	0.069 ± 0.014
Glycinamide	8.13	$6.25 \pm 0.20 \times 10^{-3}$	0.037 ± 0.001
2,2,2-Trifluoroethylamine	5.67	$2.03 \pm 0.29 \times 10^{-2}$	0.037 ± 0.004

[a] 25.0°, ionic strength 0.4. [b] Errors are standard deviations for four or more runs. [c] The equilibrium constant does not include a term in water concentration. [d] Values from ref 4 (μ 0.2).

constants with the basicity of the amine. Both are slightly higher for the more basic *n*-propylamine but the range is only a factor of 10 in rate and 4 in equilibrium constant.

Discussion

Nature of the Rate-Determining Step.—In order to compare rate constants for each of the catalysts, it is necessary to extrapolate the rates to common conditions. Overall rates were determined at 25° for ethanolamine, glycine, and glycinamide. In addition, we previously measured the rate for *n*-propylamine catalysis at 25°. In order to extrapolate the rate constant for 2,2,2-trifluoroethylamine to 25°, we use the fact that the second-order rate constant for catalysis by *n*-propylamine shows an increase in rate of 7.3-fold on going from 25.0 to 53.6°. Application of this correction factor to 2,2,2-trifluoroethylamine catalysis gives an extrapolated rate constant for 25°. Rate constants for each of the catalysts can now be compared under similar conditions.[10]

The individual rate constants for the dealdolization reactions can be readily calculated from the following steady-state equations, where k is the second-order rate constant for the overall dealdolization reaction, k_{ket}^{obsd} is the observed rate of ketimine formation, and k_1, k_{-1},

$$k = k_2K \quad (1)$$

$$K = k_1/(k_{-1} + k_2) \quad (2)$$

$$k_{ket}^{obsd} = k_1[\text{amine}] + k_{-1} + k_2 \quad (3)$$

and k_2 are the rate constants of Scheme I.[11] These values are given in Table III.

TABLE III

VALUES OF RATE CONSTANTS FOR AMINE-CATALYZED DEALDOLIZATION OF DIACETONE ALCOHOL IN WATER AT 25.0°

Amine	pK[a]	k_1, M^{-1} sec^{-1}	k_{-1}, sec^{-1}	k_2, sec^{-1}
n-Propylamine[b]	10.9	1.1×10^{-2}	6.7×10^{-2}	3.3×10^{-3}
Glycine	9.8	2.1×10^{-3}	4.2×10^{-2}	2.5×10^{-3}
Ethanolamine	9.7	2.9×10^{-3}	4.0×10^{-2}	2.3×10^{-3}
Glycinamide	8.1	2.3×10^{-4}	5.0×10^{-3}	1.3×10^{-3}
2,2,2-Trifluoroethylamine	5.7	7.5×10^{-4}	2.0×10^{-2}	1.4×10^{-4}[c]

[a] pH of 1:1 buffer at μ 0.4. [b] Reference 4, pK at μ 0.2. [c] Extrapolated value.

The relative rates of cleavage of ketimine to products (k_2) and reversal to reactants (k_{-1}) show that for all amines investigated the rate-determining step is cleavage of the ketimine (k_2) at the pH values investi-

$$\text{amine} + \text{diacetone alcohol} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{ketimine} \xrightarrow{k_2} \text{products}$$

gated. The ratio k_{-1}/k_2 varies from 4 for glycinamide to about 150 for trifluoroethylamine. It should be emphasized that, since k_{-1} is probably pH dependent,[9] the k_{-1}/k_2 ratios given here apply only to the pH values at which the measurements were made. k_2, however, is independent of pH,[4] which allows comparisons to be made of cleavage rates for all of the amine catalysts.

Polar effects have little effect on the equilibrium constant for ketimine formation. Over a range in basicity of greater than 10^5, K changes by only a factor of 4. The small variation in equilibrium constants may be compared with the work of Hine, *et al.*,[8] in which they found that for the formation of imines from isobutyraldehyde and primary amines, electron-withdrawing substituents on the amine decrease the equilibrium constant. A plot of log K *vs.* amine pK for their data was linear with a total change in the equilibrium constant of 18-fold in going from *n*-propylamine (pK 10.9) to 2,2,2-trifluoroethylamine (pK 5.7). Over this same range of pK we observe a similar trend but a somewhat lower sensitivity to polar effects (fourfold).

Polarity of the Transition State.—We have previously proposed that the amine-catalyzed dealdolization of diacetone alcohol involves a transition state with little or no charge separation.[4] This interpretation was based upon the small solvent effect observed on the cleavage step in going from water to 80% ethanol ($k_{H_2O}/k_{80\%\ ethanol} = 8$). One possible structure consistent with this result is a cyclic transition state involving a six-membered ring. On the basis of a low solvent isotope effect on the cleavage step ($k_{H_2O}/k_{D_2O} = 1.4$) we suggested that this structure would involve the hydrogen in a potential well while the carbon–carbon

(9) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 10.

(10) Although the ionic strength varied between catalysts, these effects have been shown to be negligible (R. M. Pollack, unpublished results).

(11) Implicit in the deviation of eq 3 is the assumption that $k_{-1} \gg k_1$.

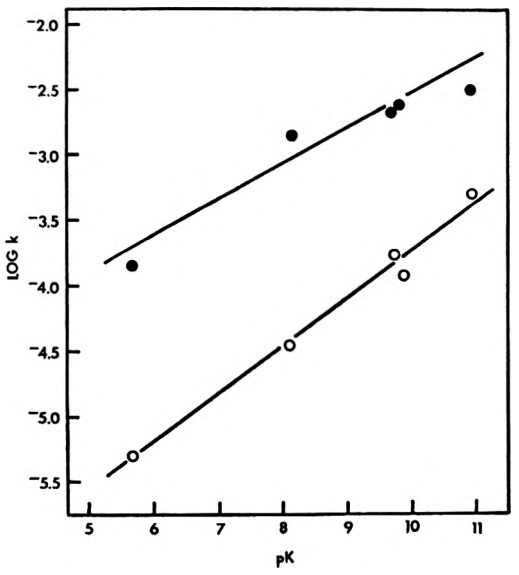
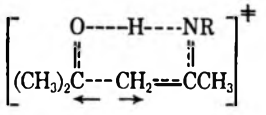


Figure 1.—Variation of the rate of amine-catalyzed cleavage of diacetone alcohol with amine pK at 25°. Closed circles are values for k_2 (cleavage of the imine intermediate). Open circles are overall rates of cleavage.

bond is undergoing cleavage. In other words, the asymmetric stretching vibration of the O–H–N system is a genuine vibration with a restoring force and zero-point energy. One could regard the hydrogen as acting to stabilize the transition state by forming a hydrogen bond.



The variation of the cleavage rate (k_2) with amine polarity allows an independent assessment of the extent of charge separation in the transition state. A plot of log k_2 *vs.* pK of the amine (Figure 1) gives a slope of 0.27 ± 0.04, indicating that this rate is about 25% as sensitive to polar effects as the equilibrium constant for protonation of the amine. This result suggests that about 25% of a full positive charge is generated on the nitrogen at the transition state. A partial negative charge, presumably on the hydroxyl oxygen, must also be formed to maintain electrical neutrality. A charge separation of this magnitude is consistent with a model in which the hydrogen acts to stabilize the transition state by formation of a hydrogen bond. Two other mechanisms which are also compatible with all the available data are (1) rate-determining proton transfer followed by rapid cleavage of the carbon–carbon bond, with the transition state occurring early along the reaction coordinate, and (2) preequilibrium proton transfer followed by rate-determining carbon–carbon bond cleavage, with a product-like transition state.

Relevance to the Aldolases.—Although the pK of the active site amine group of any of the aldolases has not as yet been determined, it is interesting to speculate on the effect that a lowered pK might have for these enzymes. It does not appear unreasonable to suppose that the active pK is perturbed in the aldolases. The cause of the perturbation in acetoacetate decarboxylase has been shown to be the presence of one or more positive charges at the active site,[5b] and one might expect the same type of interaction in the aldolases. In fructose diphosphate aldolase, at least, the substrate is negatively charged and is thought to be bound to the enzyme by electrostatic interaction with a positive charge (or charges).[12] The positive charge on the enzyme could perturb the pK of the active lysine residue of aldolase as it does in acetoacetate decarboxylase. Other evidence of similarity between the two types of enzymes also exists.[1c] In fact, Rutter has suggested that imine-forming aldolases may actually have evolved from the β-decarboxylases.[13]

The advantage to an enzyme of having a lowered pK is that at pH values near neutrality an amine of pK 11 will have about one part in 10^4 unprotonated, whereas a large fraction of an amine with a pK near 6 or 7 will be free. If the rate-determining step for enzymatic aldol cleavage is formation of the imine, a lowered pK is clearly favored since attack on the substrate carbonyl must occur through the free amine.[9] However, if the slow step is cleavage of the imine, as it is in our model system, then it is necessary to look at the effect of an altered pK on both steps of the reaction. Since the amount of free amine in solution at physiological pH's is much greater for a weakly basic amine and the equilibrium constants are only moderately sensitive to pK, a weakly basic amine will form a much larger (*ca.* 10^4) amount of reactive intermediate. However, a lowering of the amine pK by four units results in a diminished rate of cleavage by a factor of about 10 on the basis of the diacetone alcohol system. Consequently, a lowered pK value, while highly favoring imine formation, gives a more modest rate acceleration (*ca.* 10^3) to the overall reaction. It is noteworthy that the effect of changing amine pK at neutral pH is much greater on the equilibrium concentration of imine than on the rate of cleavage. Even though the decomposition step is retarded, the overall effect is still a rate acceleration.

Registry No.—Diacetone alcohol, 123-42-2; ethanolamine, 141-43-5; glycine, 56-40-6; glycinamide, 598-41-4; propylamine, 107-10-8; 2,2,2-trifluoroethylamine, 753-90-2.

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(12) See ref 1c, p 145 ff.
(13) W. J. Rutter, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **23**, 1248 (1964).

Radical Anions of o-Dicarbonylbenzenes and Phthalides

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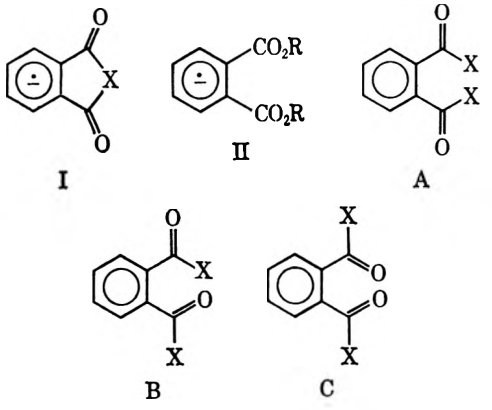
The esr spectra of radical anions of o-acylbenzoates (IV), alkyl o-acylbenzoates (V), phthalide, and 1-indanone are reported, and the spin distributions are discussed. Electrolytic reduction of alkyl o-acylbenzoates give V, and at higher potential mixtures of the 1,3 indandione obtained by Claisen condensation and IV. 3-Alkoxyphthalides give V, by an alkoxide-catalyzed cleavage. The hydrogens at C_3 of phthalide are rapidly replaced by deuterium in DMSO-d_6, as are those at C_2 of 1-indanone, but the C_3 hydrogens of 1-indanone do not exchange.

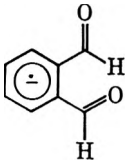
In an earlier esr study of the effect of carbonyl substitution on its spin delocalization properties, we reported esr spectra of several derivatives of phthalic anhydride radical anion (I), including the species with X = O, CR^-, and NR.[1] These substitutions resulted in rather small differences in spin density distribution. A symmetry node in the odd electron molecular orbital passes through the "X" position, resulting in very low spin density at X, minimizing the effect of substitution.

The effect of having ortho ester carbonyls was investigated with dimethyl and diethyl phthalate radical anions (II).[2] Although the carbonyl groups



I II A B C

are no longer held planar with the ring, and rotational isomerism about the carbonyl oxygen bonds should lead to three different isomers (A–C) for II, only a "symmetrical" spectrum, showing equal splittings at both alkoxy groups, and two sets of equivalent ring splittings, was observed.[2] Stone and Maki[3] showed several years ago that the lifetime of rotamer B of o-phthalaldehyde anion (IIIb) was long on the esr time scale,



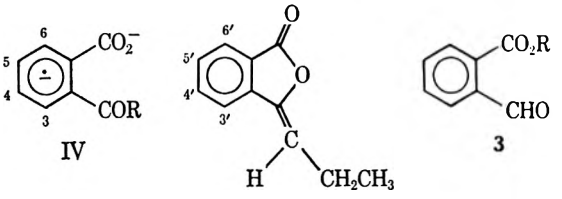
IIIb

and that only this rotamer was observable.[4] That different ring splittings ought to be observed for different rotamers of various types of carbonyl groups is indicated by the unsymmetrical spectra of benzaldehyde and acetophenone, and the different spectra observed for two ester carbonyl rotamers for fumeric ester anions.[5]

The work reported here was undertaken to investigate the effects of having two different types of carbonyls ortho to each other on the spin distribution in the radical anion.

Results

o-Acylbenzoate Anions.—Electrolytic reduction of o-acylbenzoic acids in DMSO containing 0.05 *M* tetrabutylammonium perchlorate (used throughout this study) inside the esr cavity gave esr spectra which we assign to the expected o-acylbenzoate dianion radicals IV on the basis of splitting constants. The same esr



IV 3

1, 4′-*tert*-butyl

2, 5′-*tert*-butyl

spectra were observed as the ultimate products of electrolytic reduction of esters and pseudoesters of o-acylbenzoic acids, and of alkylidine phthalides. This is consistent with our earlier observation of formation of the half ester dianion radicals from phthalates and fumarates.[2] The formyl splitting in IV (R = H) was assigned by deuteration, but the 4- and 5-*tert*-butyl compounds were used to assign the H_3 and H_5 ring splittings. Since phthalic anhydride is the most convenient starting material for these systems, specific ring deuteration would be inconvenient. We did not assign the small H_4 and H_6 splittings, which are very similar in magnitude. The *tert*-butylated radicals IV were generated from 4′- and 5′-*tert*-butylphthalide (**1** and **2**), prepared as a mixture by Perkin condensation of 4-*tert*-butylphthalic anhydride with butyroyl anhydride and sodium butyrate. In contrast to similar mixtures of ring *tert*-butylated o-acyl esters and pseudoesters, **1** and **2** proved to be conveniently separated by tlc. The largest ring splitting was shown to be $a(H_5)$ (para to the acyl substituent), and the next largest ring splitting was not at the 4′ position, as would be the case if both carbonyl groups were effective in spin de-

(1) S. F. Nelsen, *J. Amer. Chem. Soc.*, **89**, 5256, 5925 (1967); see also R. E. Sioda and W. S. Koski, *ibid.*, **89**, 475 (1967).

(2) S. F. Nelsen, *Tetrahedron Lett.*, 3395 (1967).

(3) E. W. Stone and A. H. Maki, *J. Chem. Phys.*, **38**, 199 (1963).

(4) We have repeated this work in DMSO using *intra muros* generation and did not have the problems of signal instability mentioned.[1] Although we were able to resolve the sixth splitting constant (splittings of 4.58, 3.67, 2.95, 2.19, 0.47, and 0.14 were observed), lines attributable to IIIa or IIIc were not observed.

(5) Reference 2. The suggestion of ref 2 that the two radicals observed for dialkyl maleates or fumerates are cis and trans forms about the C=C bond is clearly incorrect; the two species are present in too similar concentrations. Both must be trans, and ester carbonyl rotamers are observed.

TABLE I

ESR SPLITTINGS (GAUSS) FOR O-ACYLBENZOATE DIANION RADICALS (IV) AND RELATED COMPOUNDS

Registry no.	Compd reduced[a]	Radical observed	R	$a(H_4)$ and $a(H_6)$	$a(H_5)$	$a(H_3)$	a_R
40496-67-1	A, B, C	IV	H	0.96, 1.09	6.03	4.02	8.80 (1 H_α)
40496-68-2	A, C	4-*t*-Bu-IV	H	1.03	6.18	4.06	9.11 (1 H_α)
40496-69-3	C	IV	D	0.95, 1.05	6.15	3.90	1.31 (1 D_α)
40496-70-6	A, B, D	IV	CH_3	1.13, 1.25	6.41	4.04	7.52 (3 H_β)
40496-71-7	A, B, D	IV	CH_2CH_3	1.01, 1.13	6.49	3.80	6.33 (2 H_β)
							0.13 (3 H_γ)
40496-72-8	D	4-*t*-Bu-IV	$CH_2CH_2CH_3$	1.16	6.49	3.79	6.18 (2 H_β)
							0.31 (2 H_γ)
40496-73-9	D	5-*t*-Bu-IV	$CH_2CH_2CH_3$	1.13, 1.13		4.00	6.73 (2 H_β)[b]
40496-74-0	A, B, D	IV	$CH(CH_3)_2$	1.06, 1.06	6.52	3.98	1.30 (1 H_β)
							0.05 (6 H_γ)
40496-75-1	A, B	IV	OCH_3	~0.9	7.53	3.77	~0.9 (3 H)
40496-76-1	A, B	IV	OCH_2CH_3	0.74, 1.00	7.51	3.79	~0.74 (2 H)
		[PhCHO]·−[c]		0.75, 1.31	6.47	3.39, 4.69	8.51 (1 H_α)
		[$PhCOCH_3$]·−[c]		0.88, 1.07	6.60	3.71, 4.25	6.73 (3 H_β)

[a] A, benzoic acid; B, normal ester **3**; C, pseudoester **4**; D, alkylidine phthalide. [b] A splitting for many hydrogens of about 0.17 G for the *tert*-butyl group was observed. Presumably the γ splitting was about twice this. [c] Reference 6.

TABLE II

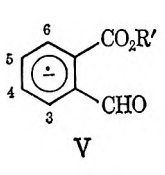
ESR SPLITTINGS OF ALKYL O-FORMYLBENZOATE ESTER RADICAL ANIONS (V)

Registry no.	Compd reduced[a]	Radical (R′)	$a(H_4)$ and $a(H_6)$	$a(H_6)$	$a(H_3)$	$a(H_\alpha)$	$a(R')$
40496-77-3	A, B, C	V (CH_3)	0.97 (2 H)	4.37	1.47	6.00	0.64 (3 H)
40496-78-4	A, B, D	V (CH_2CH_3)	0.97 (2 H)	4.26	1.45	5.72	0.56 (2 H)
40496-79-5	B	V-α-*d* (CH_2CH_3)	0.97 (2 H)	4.26	1.45	0.88 (1 D)	0.55 (2 H)
40496-80-8	C	V ($CH(CH_3)_2$)	0.96, 1.04	4.45	1.54	6.01	0.31 (1 H)
40496-81-9	B	4-*t*-Bu-V (CH_3)	0.93	4.13	1.55	5.90	0.60 (3 H)

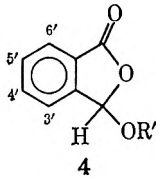
[a] A, Alkyl ester **3**; B, 3-alkoxyphthalide (pseudoester, **4**); C, 3-ethoxyphthalide plus alcohol; D, **3** (R′ = CH_3) plus ethanol.

localization. We therefore assign structure IV to these radicals. The protonated form, with one acid and one acyl substituent, would be expected to give a spectrum more closely related to those of the diester anions II. Splitting constants for IV, benzaldehyde,[6] and acetophenone[6] are summarized in Table I.

Alkyl *o*-Acylbenzoate Radical Anions.—Reduction of alkyl 2-formylbenzoates (**3**) gave well-resolved esr spectra, to which we assign structure V. We obtained identical spectra starting with the related 3-alkoxyphthalides (pseudoesters) (**4**). After reduction at high potentials, the spectra corresponding to V faded, and were replaced by IV. The splittings observed are summarized in Table II.



V



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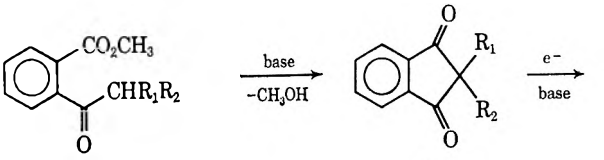
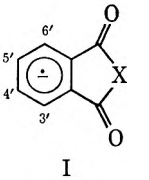
From the spectrum generated from **4-*3*-*d***, the formyl hydrogen splitting is the largest one, and that from 4-*tert*-butyl-**3** (R′ = CH_3) showed that the larger ring splitting was not that para to the ester group. The only reasonable assignment is that with $a(H_5) > a(H_3)$, which was used in Table II.

Reduction of Alkyl *o*-Acylbenzoates.—Reduction of methyl *o*-acylbenzoates **6** and **7** initially gave complex spectra which we were unable to analyze. The spectra were broadened, especially at the high-field end. Rotational isomerism, possibly with intermediate rotation rates, comparable to the splittings, leading to broadening, might be responsible for these complex spectra, but this point remains to be elucidated. Ester **8** did give an analyzable spectrum on reduction, and the observed splittings of 6.92, 5.27, 1.82, 1.39, and 0.13 (4 H) G seem compatible with the simple radical anion, [**8**]·−.



6, $R_1 = R_2 = H$
7, $R_1 = H$; $R_2 = CH_3$
8, $R_1 = R_2 = CH_3$

9



I

At higher potentials, the initial spectra from **6**–**8** faded and were replaced by the spectra of the related benzoate dianions IV and, in addition, a second radical. This second radical proved to be the related I radical, which had been previously observed from electrolytic reduction of the 1,3-diketohydrindans.[1] These radicals logically arise by base-catalyzed intramolecular Claisen condensation to **9**, followed by further reduction (and deprotonation, if possible). Isopropylidine phthalides **1** and **2** both gave 4′-*tert*-butyl-I (X = C-CH_2CH_3) under these conditions. The spectra of the I derivatives observed appear in Table III.

(6) N. Steinberger and G. K. Fraenkel, *J. Chem. Phys.*, **40**, 732 (1964).

Table III

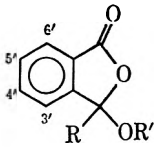
Esr Spectra of 1,3-Diketohydrindan Anion Derivatives (I)

Registry no.	Compd reduced	X	a(H4)	a(H3)	a(X)
40488-41-3	6	CH^-	2.50	0.16	0.77 (1 H)
40488-42-4	7	CCH_3^-	2.64	0.17	1.32 (3 H)
40488-43-5	1, 2	$CCH_2CH_3^-$(4′-t-butyl)	2.27 (1 H)	0.24	0.89 (2 H)
40496-82-0	8	$C(CH_3)_2$	2.62	0.10	0.10 (6 H)
40496-83-1	7[a]	$CHCH_3$	2.63	0.08	2.26 (1 H)

[a] See text.

Interestingly, reduction of **7** usually gave a fleeting, intermediate radical which was rapidly replaced by I (X = C^-CH_3), which had the splittings expected for I (X = $CHCH_3$), to which it is assigned in Table III. I (X = CMe_2) is an excellent model for the latter species. Although the outer lines in the nine-line patterns caused by the 3,6 hydrogens plus the two methyl groups of I [X = $C(CH_3)_2$] were little larger than noise, the observed intensity ratios make it clear that the splittings for both types of hydrogen were 0.1 G: observed (in per cent of central peak, from center to edge of multiplet), 100, 80.5, 39.2, 11.9, ?; calculated for six equivalent H, 100, 85, 30, 5, 0; calculated for eight equivalent H, 100, 80, 40, 11.4, 1.4. Thus both the ring splittings in the transient symmetrical radical from **7** fit well for the structure being I (X = $CHCH_3$), as assigned.

Radicals from the Reduction of 3-Alkoxyphthalides.—As mentioned previously, reduction of 3-alkoxyphthalides gave radical V, followed at higher potential by radical IV. We used this observation to prepare the formyl deuterated IV and V radicals, since phthalic anhydride is cheaply reduced to 3,3-dideuteriophthalide, and **12** can be prepared by bromination and

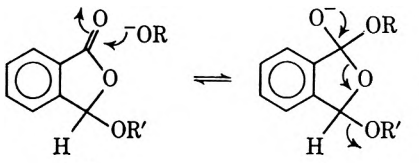


10, R = H; R′ = CH_2 13, 4′-t-Bu, R = H; R′ = CH_3

11, R = H; R′ = CH_2CH_3 14, R = CH_3; R′ = CH_3

12, R = D; R′ = CH_2CH_3

solvolysis (see Experimental Section). By adding excess alcohols to the mixture of electrolyte and alkoxyphthalide, the esr spectrum of the alcohol-exchanged o-formylbenzoate V was obtained (see Table II). The normal methyl ester exchanged rapidly with added ethanol during reduction, but the exchange reaction of isopropyl alcohol and methyl o-formylbenzoate was quite sluggish. When 3-methoxyphthalide (**10**) was electrolyzed in the presence of isopropyl alcohol, V [R′ = $CH(CH_3)_2$], the isopropyl alcohol-exchanged formylbenzoate anion, was the first radical to be observed. Under the same conditions, reducing methyl o-formylbenzoate remained unchanged, even after 1 hr of electrolysis. This requires that observing V (R′ = CH_3) upon reduction of **10** (R′ = CH_3) is not the result of an intramolecular rearrangement of [**10**]·$^-$, and strongly suggests to us that alkoxide-catalyzed cleavage of the 3-alkoxyphthalide is observed. Reduction of **14** gave the same broadened spectrum as reduction of the normal ester, but in this case we detected a prior species which we



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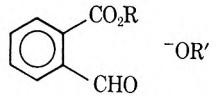
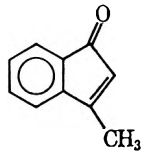


3

believe to be the pseudoester radical anion from the similarity of its splittings [7.62, 4.89, 1.11, 0.40 (4 H)] to those of phthalide anion radical.

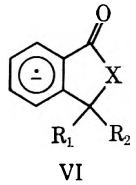
Another base-catalyzed reaction was unfortunately observed in our attempts to generate the radical anion of o-diacetylbenzene. The major radical produced had splittings of 7.93 (3 H), 1.92, 1.39, 1.88, 0.81, and 0.52 G, and can only correspond to the radical anion of 3-methylindenone (**15**), the dehydrated aldol product.



15

Its multitude of lines obscured the spectra of at least one other species present in low concentration sufficiently to preclude analysis.

Phthalide and 1-Indanone Radical Anions.—As models for the closed form of 3-alkoxyphthalides, and also for benzene rings conjugated to planar ester and ketone carbonyl groups, we determined the esr spectra of the radical anions of phthalide (VI, X = O) and



VI

1-indanone[7] (VI, X = CH_2). Our results appear in Table IV.

Since the 13.4-G splitting hydrogens of VI (X = CH_2; R = H) rapidly exchanged upon reduction in DMSO-d_6, these may be confidently assigned to the hydrogens at C_2. The C_3 hydrogens did not exchange even after 2 hr of continuous reduction; so there is a huge difference in exchange rate at the two positions. In contrast, the C_3 hydrogens of phthalide exchange

(7) G. A. Russell and G. R. Stevenson, *J. Amer. Chem. Soc.*, **93**, 2432 (1971).

TABLE IV
ESR SPLITTINGS OF PHTHALIDE AND 1-INDANONE RADICAL ANIONS

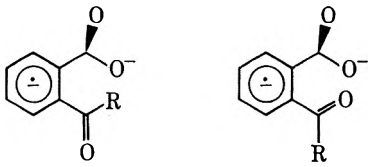
Registry no.	Radical	$a(H_3')$	$a(H_4')$	$a(H_5')$	$a(H_6')$	$a(H_3)$	Other
34507-52-3	VI (X = CH_2; R = H)	0.16	6.92	1.47	5.69	1.60	13.40 (2 H)
40496-85-3	VI (X = CD_2; R = H)	0.16	6.88	1.46	5.60	1.59	1.99 (2 D)
40496-86-4	VI (X = O; R = H)	0.31	7.79	1.37	5.66	6.25	
40496-87-5	VI (X = O; R = D)	0.31	7.79	1.39	5.69	0.95 (2 D)	
40488-44-6	4'-*t*-Bu-VI (X = O; R = H)	Obscured		1.62	~6.25	~6.25	(0.17-*t*-Bu)
40488-45-7	5'-*t*-Bu-VI (X = O; R = H)	0.15	7.73		5.91	6.77	
40488-46-8	VI (X = O; R_1 = H; R_2 = CH_3)	Unobsd	8.07	1.31	5.89	5.89 (1 H)	Unobsd

with solvent rapidly under our conditions, as was verified both by washing the label out of 3,3-dideuterio material by reducing in DMSO, and exchanging it into protio material, using DMSO-d_6.

Discussion

The splittings of Table I show that the carboxylate group is not effective at delocalizing spin; in fact, an ortho carboxylate actually forces spin onto the acyl group [comparing IV (R = H) with benzaldehyde ketyl, and IV (R = CH_3) with acetophenone ketyl]. Similar effects have been noted previously for nitro anions.[8] This suggests that one negative charge is essentially localized in the carboxylate group, which is twisted at a large angle to the ring, and has a minimal effect on the benzaldehyde-type π system. The splittings of the alkyl *o*-formylbenzoates of Table II show that substantially more spin density is present in the ester carbonyl of V than in the carboxylate carbonyl of IV. The a_3 splitting, meta to the ester carbonyl, is distinctly lower in V than in IV, and the methoxy splitting of V (R' = CH_3) is 70% as large as that of IV (R' = OCH_3), where the ester is the principal function stabilizing the aromatic anion radical. When the *o*-formyl group of V (R' = CH_3) is replaced by an *o*-isobutyryl group, [**8**]$\cdot^-$, significantly more spin density is present in the ring and less at the methoxy group. Apparently, two large acyl substituents are more twisted from the plane of the ring, and at least the ester accepts less spin density.

We only saw one isomer for the *o*-acylbenzoates of Table I, although we would expect to be able to see different splittings for ring carbonyl isomers, if they were both present in substantial amounts. This is perhaps not surprising for the *o*-formylbenzoates, for the oxygen anti isomer IVa is favored both on steric



IVa IVb

grounds and on the basis of charge repulsion (maximum separation of the negatively charged oxygens). That these factors are not the only important ones has been shown by Stone and Maki.[3] No explanation was offered for *o*-phthalaldehyde anion existing only as IIIb, whereas IIIa is the favored one considering steric and charge repulsion factors. The suggestion of Bauld and coworkers[9] that a carbonyl carbon remains positively charged, even in the radical anion, would reverse the electrostatic argument for III, and give a rationale for IIIb being the observed form. In the case of IV, which has a full negative charge on the carboxylate, IVa would remain the prediction. From the similarity of the ring splittings for IV (R = CH_3) and IV [R = $C(CH_3)_2$], it is difficult to support the contention that they have different configurations at the carbonyl group. The question of whether IVa or IVb (or an equilibrating mixture) is observed remains unanswered.

We were able to detect a minor species with very similar splittings to the major one in the wings of the V (R' = CH_2CH_3) spectrum reported in Table II. We suggest that this minor species is the other ester conformation, but do not know how to even guess which is which. The complex spectra mentioned for alkyl *o*-acylbenzoates seem certain to be caused by rotamers, perhaps interconverting ones.

The 3.9 ratio of $a(H_3)$ for the anion radicals from phthalide (VI, X = O) and indanone (VI, X = CH_2) seems surprising at first, considering the substantial similarity of the ring splittings. We suggest that the increased $a(H_3)$ for phthalide anion arises principally from the fact that the C_3–H_3 bond can hyperconjugate simultaneously with the π orbital at C_2' and that at oxygen. McLachlan calculations show that the coefficient signs at both atoms are the same, so that the proper "spin density" in an $a(H_3) = Q\rho$ McConnell equation should be $[c(2') + c(0)]^2$ where $c(i)$ is the coefficient at atom i.[10] Since the McLachlan spin density at oxygen is sensitive to the heteroatom parameters chosen, and no set of these parameters is generally suitable for many compounds, we have not attempted to devise sets which would fit our single observed splitting. It is worth mentioning that the $a(H_3)$ for 1-indanone appears anomalously low compared to $a(H_6')$, because the spin densities at $c(2')$ and $c(6')$ are the same except for an inductive effect. Since McLachlan calculations appear not to be very good in predicting such effects (one gets into the problem of making up parameters which are clearly not transferable from compound to compound), this statement may not be correct, but we wish to point out that the unusually large spin density at the C_2 hydrogens might have a cancelling effect on $a(H_3)$ in phthalide.

(8) P. Ludwig, T. Layoff, and R. N. Adams, *J. Amer. Chem. Soc.*, **86**, 4568 (1964).

(9) N. L. Bauld, R. Gordon, and J. Zoeller, Jr., *ibid.*, **89**, 3948 (1967).

(10) D. H. Wiffen, *Mol. Phys.*, **6**, 223 (1963).

Unfortunately, we do not have at our disposal a sophisticated enough scheme of calculating what is expected for the splittings of IV–VI as a function of geometry to give a quantitative interpretation of the observed splittings, but we believe that the data could prove valuable in testing future methods of calculating spin densities for heteroatomic systems.

The observation that the hydrogens at C_3 of phthalide exchange in seconds, whereas those of 1-indanone do not exchange in hours, is a striking one, and must mean that there is a huge difference in the acidity of the C_2 and C_3 hydrogens in 1-indanone.[11] Our result represents a substantial contrast to that of Dubois and Dodin,[11e] who observed competitive oxidation of the carbons α to the carbonyl and those α to the ring in *p*-alkylacetophenones using HMPA–*tert*-butoxide–air. They, then, observed vinylogous enolization at the para position competing with ordinary enolization.

Experimental Section

A Varian A-60A instrument was used for nmr spectra, a Varian E.3 or E.15 for esr spectra, and an AEI MS.9 for mass spectra. Vpc separations used a 5-ft 15% Cargowax 20M on Chromosorb W column in a Varian Aerograph A.90.P-3 (thermal conductivity detector) instrument.

Commerical samples of phthalaldehyde and *o*-acetylbenzoic acid were employed. The preparations of Kariyone and Shimizu[12] were used for the alkylides and phthalides used, and *o*-isobutyrylbenzoic acid. 3-Methylphthalide was prepared by zinc–hydrochloric acid reduction of *o*-acetylbenzoic acid,[13] and purified by vpc. *o*-Diacetylbenzene was prepared by chromic acid oxidation of commercial 1,4-dimethylnaphthalene,[14] and crystallized from pentane–CCl_4, mp 41–42° (lit.[14] mp 39–40°). Methyl *o*-acylbenzoates **6**, **7**, and **8** were prepared from the acids and diazomethane.[15] None of the corresponding 3-methoxyphthalides were detected by nmr.[15]

3-Methoxyphthalide (**10**) was prepared as a mixture with the normal ester when phthalaldehydic acid was refluxed both in methanolic HCl and in thionyl chloride, followed by removal of excess reagent and addition of alcohol at 0°. Refluxing the acid with methanol and concentrated sulfuric acid gave a mixture of **10** and methyl phthalaldehyde dimethyl acetal [nmr (CCl_4) δ aromatic multiplet (4 H), 5.98 (s, 1 H), 2.83 (s, 3 H), 3.26 (s, 6 H); mass spectrum consistent]. Pseudoester **10** was separated by tlc or vpc, mp 43–44° (lit.[15] mp 44°).

3-Ethoxyphthalide (**11**), uncontaminated by the normal ester, was prepared from 3-bromophthalide[16] by dissolving it in absolute ethanol and crystallizing the product from alcohol, mp 66–67° (lit.[16] mp 68°).

4′-*tert*-Butylphthalide was prepared as a mixture with the 5′ isomer by zinc–acetic acid reduction[17] of 4′-*tert*-butylphthalic anhydride.[18] We were unsuccessful at tlc separation (silica gel PF-254 plates), but the 4′ isomer was isolated by crystallization:[19] mp 70–72°; nmr ($CDCl_3$) δ 7.48, 7.63, 7.75, 7.90 (aromatic multiplets, 3 H total), 5.28 (s, 2 H), 1.37 (s, 9 H). The 5′ isomer was only separated in small amounts by vpc, and had the same nmr as the 4′ isomer except in the aromatic region.

4′-*tert*-Butyl-3-methoxyphthalide (**13**).—Bromination of 5.7 g of the phthalide with 6.2 g of bromine,[16] followed by distillation, gave the 3-bromophthalide [bp 131–137° (0.23 mm), contaminated with 5% phthalide by nmr], which was added to 1.6 g of sodium methoxide in 25 ml of methanol, and stirred for 12 hr. After solvent removal, dissolution in ether, washing with water, drying with sodium sulfate, and trituration of the residue with pentane, the solid product was recrystallized from heptane:[19] mp 100–101°; nmr ($CDCl_3$) aromatic multiplet (3 H), δ 6.32 (s, 1 H), 3.66 (s, 3 H), 1.37 (s, 9 H). The best proof of position of *tert*-butylation we have for compounds in this series is the esr spectrum of the *o*-formylbenzoate dianion, which clearly shows that the proton meta to the formyl substituent is the missing one.

Phthalide-*3,3-d*$_2$ was prepared in low yield (2 g) but high deuteration by treating 10 g of phthalic anhydride with 30 g of zinc dust, 16 ml of D_2O (99.8%), and 80 ml of acetic anhydride at 120° for 16 hr, and subliming the residue, mp 75–77°; no C_3 hydrogen was detected by nmr.

3-Ethoxyphthalide-*3-d*.—The 3 bromide was prepared from 2 g of dideuteriophthalide and 2.6 g of bromine,[16] bp 92–97° (0.4 mm), 1.6 g. The deuteriobromide was stirred with absolute ethanol and sodium carbonate for 14 hr and distilled, bp 87–95° (0.15 mm). Crystallization from CCl_4–pentene gave material melting at 63–64°; no C_3 hydrogen was detected by nmr.

4′- and 5′-*tert*-butyl-3-propylidinephthalides were prepared by heating 5 g of 4-*tert*-butylphthalic anhydride and 4 g of butyric anhydride at 155–160°, adding 2.5 g of sodium butyrate over a 30-min period, and, after 1 hr, raising the temperature to 175–180° for 5 hr.[20] After cooling, addition of 25 ml of water, extraction into carbon tetrachloride, and drying over sodium sulfate, the solvent and starting materials were distilled off. The residue was separated by tlc on PF-254 silica gel plates (CCl_4) to give the 5′ isomer[21] (**2**) as the fastest moving band, and the 4′ isomer[21] as the next band; both were oils. The nmr spectra of the two isomers were indistinguishable [δ 5.49 (t, 1 H), 2.45 (m, 2 H), 1.38 (s, 9 H), 1.15 (t, 3 H)] except in the aromatic region, where the 4′ isomer showed the least split aromatic proton at the higher field end of the aromatic multiplets, and the 5′ isomer had the least split proton at the lower field end, as might have been predicted. Once again the esr spectra of the benzoate dianion radicals confirm the positional assignments. The cis double bond isomers were observed as slower moving bands on the tlc plate, but were not of interest in this work.

Esr spectra were determined by *intra muros* generation, using the Varian flat electrolysis cell, half filled with mercury, and DMSO containing 0.05 *M* tetrabutylammonium perchlorate as supporting electrolyte. A Heath 0.25-V dc power supply was used to apply potential. Voltage was adjusted to give the best attainable esr spectra, but we did not control the potential, or measure E° values for our starting materials. Many of the radicals observed by us were products of complex base-catalyzed reactions, and frequently we used applied potentials beyond those for solvent breakdown.[22] Bases are obviously generated under these conditions. The splitting constants of Tables I–IV are estimated to be ±0.05 G for splittings under 2 G, and ±0.1 G for larger splittings.

Registry No.—Phthalide-*3,3-d*$_2$, 40496-88-6; phthalic anhydride, 85-44-9; 3-ethoxyphthalide-*3-d*, 40496-89-7; 3-bromophthalide-*3-d*, 40496-90-0; 4′-*tert*-butyl-3-propylidinephthalide, 40496-91-1; 5′-*tert*-butyl-3-propylidenephthalide, 40496-92-2; 4-*tert*-butylphthalic anhydride, 40496-93-3.

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(11) Previous workers have also not noted deuteration at C_3 of 1-indanone under a variety of conditions. For references in which nmr (a, b), mass spectra, and optical intensity of the 3-methyl compound (d) were used for detection, see (a) E. Lustig and E. P. Ragelis, *J. Org. Chem.*, **32**, 1398 (1967); (b) Y. Kawazre and M. Ohnishi, *Chem. Pharm. Bull.*, **14**, 1403 (1966); (c) M. I. Gorfinkel, M. A. Chirkovan, and M. F. Lhomme, *Chem. Abstr.*, **69**, 42257d (1968); (d) J. Almy and D. J. Cramm, *J. Amer. Chem. Soc.*, **91**, 4459 (1969); (e) J.-E. Dubois and C. Dodin, *ibid.*, **94**, 7520 (1972).

(12) T. Kariyone and S. Shimizo, *J. Pharm. Soc. Jap.*, **73**, 336 (1953).

(13) C. H. Wang, *et al.*, *J. Amer. Chem. Soc.*, **69**, 1909 (1947).

(14) R. Riemschneider and S. Foerster, *Monatsh. Chem.*, **93**, 616 (1962).

(15) (a) P. R. Jones and P. A. Desio, *J. Org. Chem.*, **30**, 4293 (1961); (b) D. S. Erleyod and J. W. Pots, *Chem. Ind. (London)*, **46**, 1915 (1964).

(16) R. L. Shriner and E. J. Wolf, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 737.

(17) J. H. Brewster, A. M. Fusco, L. E. Carvsino, and B. G. Corman, *J. Org. Chem.*, **28**, 498 (1963).

(18) B. Lawler and A. T. Peters, *J. Chem. Soc.*, 680 (1952).

(19) An acceptable C, H analysis was obtained for this compound.

(20) For the condensation with phthalic anhydride, see D. T. Mowry, E. L. Ringwald, and M. Rendly, *J. Amer. Chem. Soc.*, **71**, 120 (1949).

(21) High-resolution mass spectroscopy was used to establish the molecular formula as $C_{11}H_{10}O_3$.

(22) (a) I. M. Kolthoff and T. B. Reddy, *J. Electrochem. Soc.*, **108**, 980 (1961); (b) J. C. Jones and H. A. Fritsche, *J. Electroanal. Chem.*, **12**, 334 (1966).

Competition between Wagner–Meerwein Rearrangement and Intramolecular Electrophilic Substitution in the 3-Diphenylmethylene Isobornyl System

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Epimerization of 3-diphenylmethyleneisobornyl acetate (4), between 25 and 60° and in acid medium (HOAc–H_2SO_4), yields preferentially the endo isomer 4. Prolonged treatment, under the same reaction conditions, makes the reaction proceed through an irreversible electrophilic substitution toward the indene-type hydrocarbon 8. Structure of the latter is documented with spectroscopic data as well as with chemical proof by transformation into diketone 9, the stereochemistry of which is discussed. The acid-catalyzed dehydration of diphenylmethyleneisoborneol (2) depends upon the acid strength of the dehydrating agent and of the temperature. In the presence of PTSA and at 60°, only Wagner–Meerwein rearrangement, leading to hydrocarbons 12 and 13 in the 1:9 ratio, is observed. Around 130° and using potassium bisulfate as dehydrating agent, 2,6-hydrogen shift and Nametkin rearrangement occur together with the Wagner–Meerwein rearrangement; a 30:1:15:5 mixture of hydrocarbons 12, 13, 14, and 15 is then obtained. Above 130°, the dehydration leads to the indene-type structure 8.

The influence of an unsaturated substituent upon the solvolysis of bridged bicyclic compounds has received but little attention. Interaction between carbonium ions and olefinic double bonds, which stabilizes the charge by allylic isomerization, reduces considerably the usual rearrangements of the bridged system and induces selectively the attack of the ion from the less hindered side of the molecule. Thus, acetolysis of 3-*exo*-bromo-2-methylenenorbornane leads exclusively to a mixture of 3-*exo*-acetoxy-2-methylenenorbornane and 2-acetoxymethylnorbornene.[1] On the other hand, a 3-benzylidene substituent stabilizes the carbonium ion and limits, at room temperature, the acetolysis to only *cis,trans*-benzylidene and exo–endo isomerizations.[2] In these two examples, the nucleophilic attack at the level of carbon 3 takes place in the same way as in the absence of the conjugated double bond.

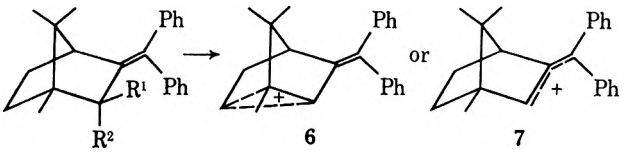
In order to extend the results obtained for *trans*-3-benzylideneisobornyl acetate,[2] the acetolysis of 3-diphenylmethyleneisoborneol (2) and derivatives has been investigated.

Results

3-Diphenylmethyleneisobornyl acetate (4) is prepared from the corresponding alcohol 2, obtained by $LiAlH_4$ reduction of 3-diphenylmethylenecamphor (1).[3] Acetolysis of compound 4, at room temperature and in the presence of traces of sulfuric acid, leads to an equilibrated mixture of 20% of 4 and 80% of its endo isomer 5, together with a hydrocarbon, the proportion of which increases with time and the structure of which will be discussed later. The same ratio (1:4) is reached when starting from pure compound 5. The high relative amount of the endo isomer is quite unusual. Thus, acetolysis of apoisobornyl, *exo*-camphenilyl, or β-fenchoisocamphoryl brosylates gives exclusively exo acetates.[4] Similarly, acetolysis of bornyl or isobornyl chloride yields only isobornyl acetate.[5]

Bicyclo[2.2.1]heptane derivatives are known to give, in acid medium, nonclassical ions by anchimeric assistance of the C_1–C_6 σ bond; as a result, molecules with exo leaving groups react faster than their endo epimers, and the attack of the ion by the nucleophile occurs from the exo side. On the other hand, a localized ion should give a mixture of endo and exo isomers, in which the former, being thermodynamically the more stable, should predominate.[6] These considerations exclude ion 6 (Scheme I) as the principal

SCHEME I



2, R^1 = OH; R^2 = H
3, R^1 = H; R^2 = OH
4, R^1 = OAc; R^2 = H
5, R^1 = H; R^2 = OAc

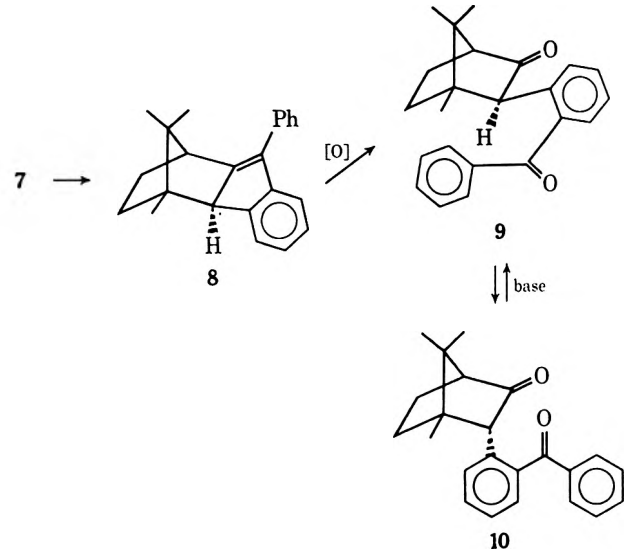
intermediate in the acetolysis of compound 4 and rather favor a "localized" ion as in the isomerization of isobornyl chloride into bornyl chloride induced by Lewis acids.[7] For compound 4 (or 5), stabilization of the charge by the conjugated diphenylmethylene group probably accounts for the absence, even at 60°, of the expected rearrangements of the bridged bicyclic system. Thus, the intermediate ion can be depicted as 7 (Scheme I). This result parallels the one obtained for *trans*-3-benzylideneisobornyl acetate,[2] although Wagner–Meerwein rearrangement was then observed when the reaction was carried out at 60°. As the difference in stability between endo and exo epimers is small,[8] the stereochemistry of the major reaction product reflects the steric effect of the 7-syn methyl and cis phenyl groups on the approach of the ion by the nucleophile, under a thermodynamic control of the reaction.

Structure of Hydrocarbon 8.—Isolated from the acid-catalyzed acetolysis of compound 4, this hydro-

(1) C. W. Jefford and W. Wojnarowski, *Helv. Chim. Acta*, **53**, 137 (1970).
(2) J. Kossanyi, B. Furth, and J.-P. Morizur, *Tetrahedron*, **26**, 395 (1970).
(3) A. Haller, *C. R. Acad. Sci.*, **113**, 22 (1891).
(4) A. Couter, E. C. Friedrich, N. J. Holmes, and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 378 (1965).
(5) J. Simonsen and L. N. Owen, "The Terpenoids," Vol. II, Cambridge University Press, New York, N. Y., 1949, p 315.
(6) P. v. R. Schleyer, M. M. Donaldson, and W. E. Watts, *J. Amer. Chem. Soc.*, **87**, 375 (1965).
(7) H. Meerwein and K. van Emster, *Ber.*, **53**, 1815 (1920).
(8) "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 115.

carbon accounts for 25% of the reaction mixture after 20 min at 60°, and is the only reaction product after 1.25 hr at 70°. The absence of Wagner–Meerwein rearrangement, or 2,6-hydrogen shift, at this temperature makes one presume that this hydrocarbon is formed directly from the allylic ion **7**. The phenylindene structure **8** (Scheme II) has been attributed to it from spectral evidences and chemical proofs.

SCHEME II

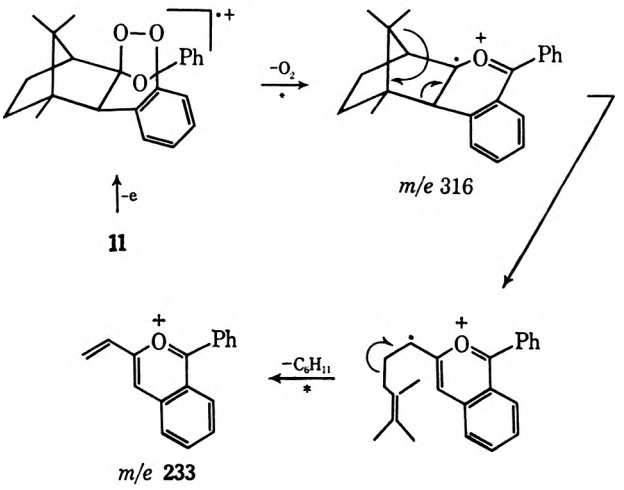


Its nmr spectra shows three methyl groups (at 0.26, 0.80, and 1.23 ppm) and no olefinic protons; the strongly shielded methyl group results from the anisotropy effect of one phenyl group[9] on the 7-syn methyl substituent; the presence of only nine aromatic protons also favors structure **8**. Other evidence arises from the uv absorption of the compound [238 nm (ε 20,000)] which can be compared to that[10] of 3-phenylindene itself [230 nm (ε 18,000)]. Mass spectrometric measurements give a molecular ion at *m/e* 300 which corresponds to $C_{23}H_{24}$. Chemical proofs of structure **8** comes from its oxidation to diketone **9** either using Jones reagent[11] or by ozonolysis according to the Pappas procedure[12] (Scheme II).

In the latter case, the intermediate ozonide **11**, which can be isolated, shows a mass spectrometric fragmentation (depicted in Scheme III) which favors the postulated structure: the molecular ion (*m/e* 348, $C_{23}H_{24}O_3$ from high-resolution mass measurement) expels successively one oxygen molecule (to yield ion *m/e* 316) and 83 mass units (C_6H_{11}) to form the stable pyrylium ion (*m/e* 233) which constitutes the base peak of the spectra (Scheme III). Ozonide **11** gives almost quantitatively diketone **9** when submitted to Jones reagent.

For compound **9**, the spectroscopic data [ir 1748 and 1668 cm^{-1}, uv 235 nm (ε 13,000)] as well as mass spectrometric results (molecular ion at *m/e* 332 corresponding to $C_{23}H_{24}O_2$ from high-resolution mass measurement) support the presence of two carbonyl groups, one of them being part of a benzophenone moiety.

SCHEME III



The nmr spectrum of diketone **9** exhibits three methyl groups (two overlapped at 0.92 ppm and one at 1.05 ppm), two methylene groups (m centered at 1.74 ppm), one tertiary hydrogen (broad signal at 2.20 ppm assigned to the bridgehead proton), one other tertiary proton (s at 4.43 ppm), and nine aromatic protons (m between 7.3 and 8.0 ppm). The exo configuration of the benzophenone moiety is deduced from the narrow signal (half-width *ca.* 2 Hz) of the singlet at 4.43 ppm, as can be expected for an uncoupled proton. In order to verify the given stereochemistry of the benzophenone moiety in diketone **9**, exo–endo epimerization has been carried out in basic medium. This leads to a 3:7 mixture (Scheme II) of compounds **9** and **10**, respectively, the latter showing in its nmr spectrum a small long-range coupling (half-width of 4 Hz) for the exo hydrogen atom linked to C-3. This result is consistent with a W-type coupling with the exo H-5 proton. Compared to the usual chemical shifts found for the exo–endo protons in bicyclo[2.2.1]-heptane systems, an unexpected shielding of the exo H-3 proton is observed: 4.30 ppm (in compound **10**) compared to 4.43 for the endo proton (in compound **9**). In spite of these reversed chemical shifts, which certainly are the result of different shielding caused by the benzophenone substituent, the observed long-range coupling is a more valuable argument for the postulated stereochemistry.

Ion **7** should be involved, also, in the acid-catalyzed dehydration of 3-diphenylmethyleneisoborneol (**2**). An earlier report[13] indicates that alcohol **2** yields a 1:3 mixture of 5-diphenylmethylene-2,3,3-trimethyltricyclo[2.2.1.$0^{2,6}$]heptane (**12**) and 7-diphenylmethylenecamphene (**13**) when heated for 0.5 hr at 160° in the presence of $KHSO_4$. The apparent discrepancy between this result and what one would have expected from the above-described acetolysis of **4** prompted us to reinvestigate the acid-catalyzed reaction of alcohol **2**.

Dehydration of 3-Diphenylmethyleneisoborneol (2).—Treatment of a benzene solution of alcohol **2** by *p*-toluenesulfonic acid at 60° yields a 1:9 mixture of hydrocarbons **12** and **13**, respectively (Scheme IV). These two compounds have been identified from their nmr spectra, which have already been discussed

(9) See, for instance, B. L. Shapiro, M. J. Gattuso, and G. R. Sullivan, *Tetrahedron Lett.*, 223 (1971), and references cited therein.

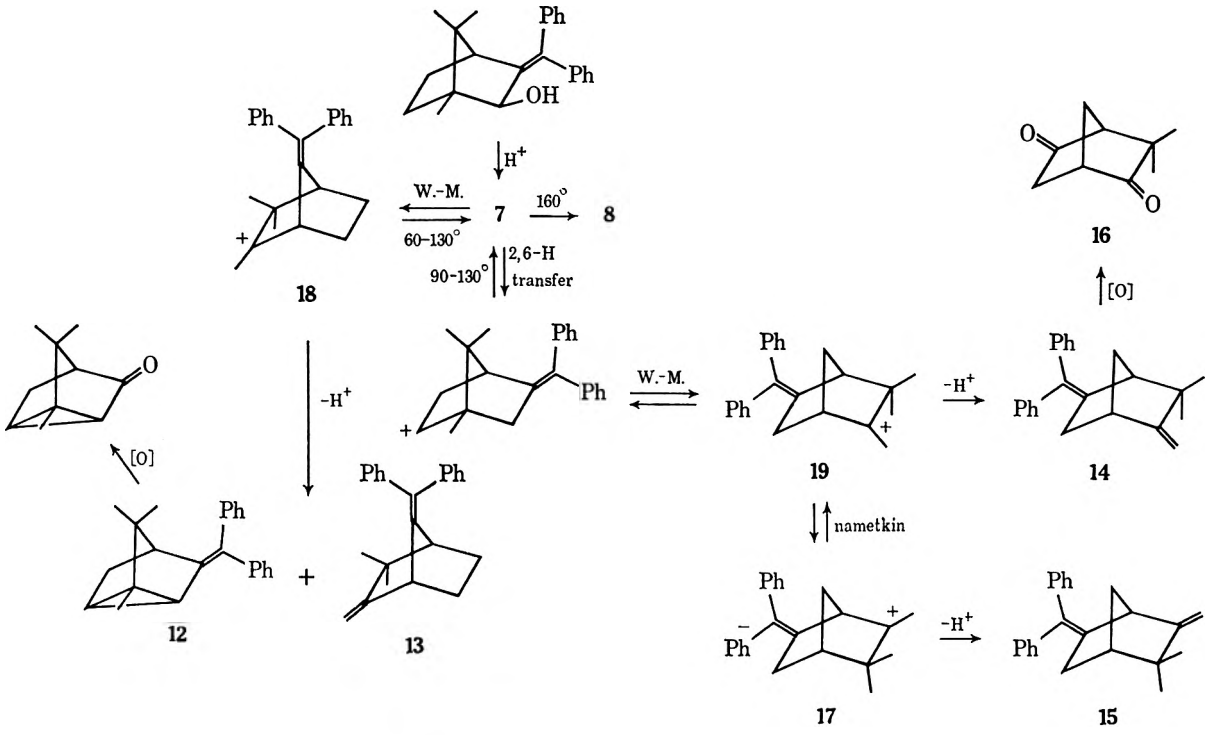
(10) L. Skattebøl and B. Boulette, *J. Org. Chem.*, **31**, 81 (1966).

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

(12) J. J. Pappas and W. P. Keaveney, *Tetrahedron Lett.*, 4273 (1966).

(13) D. C. Kleinfelter, R. W. Aaron, T. J. Gerteisen, J. M. Miller, and T. B. Bennett, *J. Org. Chem.*, **32**, 3521 (1967).

SCHEME IV



elsewhere.[13] Furthermore, ozonolysis of tricyclene **12** leads to the already known[14] 2,3,3-trimethyltricyclo-[2.2.1.$0^{2,6}$]heptanone (Scheme IV) and to benzophenone. On the other hand, hydrocarbon **13**, which contains two olefinic protons, partly isomerizes into tricyclene **12** when heated to around 300°; this verifies its camphenic structure.

Under more drastic conditions ($KHSO_4$, 160°), 3-diphenylmethyleneisoborneol (**2**) forms a single product, with yields as high as 80%, in all points identical with hydrocarbon **8**. The difference between this result and that of the literature[13] led us to determine the temperature above which hydrocarbon **8** is formed to the detriment of **12** and **13**. The critical value of 130° has been found. In the 90–130° temperature range, a mixture of four hydrocarbons, **12**, **13**, 5-diphenylmethylenecamphene (**14**), and 6-diphenylmethylenecamphene (**15**) is obtained (Scheme IV). At 130°, the relative proportions of the hydrocarbons are 30:1:15:5, respectively. Each of them leads to the same mixture of the four hydrocarbons when heated to around 130° in the presence of $KHSO_4$. Furthermore, pure samples of hydrocarbons **12**, **13**, **14**, or **15** lead to compound **8** when kept for 1 hr at 160° in the presence of $KHSO_4$. Thus, the equilibrium mixture in acid medium, obtained from these hydrocarbons, undergoes an irreversible displacement to hydrocarbon **8** under conditions of thermodynamic control.

Proof of structure of hydrocarbon **14** comes from its nmr spectra (two olefinic protons, one at 4.77 and the other at 4.55 ppm as indication of a camphenic skeleton) and, mainly, from the diketone formed by ozonolysis; this diketone is shown to be identical with 5-oxocamphenylone (**16**), obtained by oxidation of camphenylone following ref 15.

(14) S. S. Nametkin and S. S. Zabrodina, *C. R. Acad. Sci. USSR*, **36**, 142 (1942); *Chem. Abstr.*, **37**, 5712[8] (1943).

(15) J. Meinwald, J. Shelton, G. Buchanan, and A. Courtin, *J. Org. Chem.*, **33**, 99 (1968).

Hydrocarbon **15**, obtained in low yields, has been identified only from its spectroscopic data. High-resolution mass spectrometry gives the expected $C_{23}H_{24}$ formula for the molecular ion. The nmr spectrum displays two olefinic protons and one strongly deshielded aliphatic proton at 3.33 ppm. By comparison with the spectra of *cis*- and *trans*-6-benzylidenecamphene (obtained[2] from *trans*-benzylideneisoborneol), for which the H-1 bridgehead proton gives a signal at 3.28 and 3.67 ppm, respectively, the 6-diphenylmethylenecamphene structure **15** has been attributed to this compound.

Discussion

The absence of Wagner–Meerwein rearrangement during the acetolysis of compound **4** (or **5**) reflects the stability of the allylic ion **7** which, in the presence of a large excess of the nucleophile, proceeds either reversibly toward a mixture of acetates **4** and **5** or irreversibly toward hydrocarbon **8**. The preferred endo attack by the nucleophile, combined with the electrophilic substitution of the cis benzene ring by the carbonium ion from the exo side of the bicyclic system, emphasizes the stereoselectivity of the reaction.

In the absence of nucleophile, therefore, under dehydrating conditions, alcohol **2** gives three reactions depending upon the thermal conditions and the strength of the acid. In the presence of PTSA and at 60°, only Wagner–Meerwein rearrangement, leading to hydrocarbons **12** and **13**, is observed to the exclusion of 2,6-hydrogen transfer or Nametkin rearrangement (migration of the exo[16] methyl group); absence of the latter at the level of ion **18**, which forms hydrocarbon **13**, is verified from the high optical activity (+218°) of this compound. Nametkin rearrangement would have induced, then, racemization of product **13**.

(16) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 699 (1967), and references cited therein.

By use of $KHSO_4$ instead of PTSA and, mainly, of a higher temperature (100–130°), the energy, given to the system, becomes sufficient to induce a 2,6-hydrogen shift (ion **17**) to form hydrocarbon **14** by subsequent Wagner–Meerwein rearrangement. Nametkin rearrangement of ion **19** forms compound **15**.

It is noteworthy that, in the absence of nucleophile, no evolution toward the indene structure **8** is observed for a temperature lower than 130°, although this occurs even at room temperature in the presence of acetic acid. The energy of the transition state for electrophilic substitution on the benzene ring being high, in the absence of electron-withdrawing groups, the formation of the reaction intermediate must lower sufficiently the activation energy of the reaction and make it possible even at room temperature.

Over 130°, the single product **8** formed in the reaction under thermodynamic control, starting from any hydrocarbon **12** to **15** or from alcohol **2** (in the presence of only $KHSO_4$), reflects the irreversible displacement of the reaction toward intramolecular electrophilic substitution.

Such a reaction should occur, also, with 3-benzylideneisoborneol; for this reason, this compound has been submitted to acid-catalyzed ($KHSO_4$) dehydration at 160°. No product related to **8** has been found in this case but only the previously described[2] hydrocarbons. Introduction of an electron-donor group for stabilizing the allylic ion, using 3-*p*-methoxybenzylideneisoborneol, does not lead either to any indene-type compound when treated by $KHSO_4$ at 160°. Thus, the intramolecular electrophilic substitution is apparently limited to the diphenylmethylene substituent.

The nmr spectra of compounds **12** and **13** have already been described[13] and the ones obtained here are compatible with them. However, slight differences have been found for the position of their uv maximum absorption. A 1:3 mixture of **12** and **13** is reported[13] to have λ_{max}^{EtOH} 239 nm (log ϵ 4.14), while our results on pure samples give λ_{max}^{MeOH} 259 nm (log ϵ 4.20) for **12**, λ_{max}^{MeOH} 249 nm (log ϵ 4.26) for **13**, and λ_{max}^{MeOH} 239 nm (log ϵ 4.30) for the substituted indene **8**.

It should be noted, to conclude, that small variations in acid strength of the dehydrating agent or in temperature may induce the reaction to proceed toward different hydrocarbons.

Experimental Section

Physical Measurements.—Melting points, taken on a Leitz-Weltzlar apparatus, are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 141 instrument. Elemental analyses were performed at the University of Paris VI. Gas chromatographic analyses were carried out on a Varian Aerograph HiFi Model 1400 equipped with a 0.25 in. × 10 ft column containing 15% silicone GE XE-60 (nitrile gum) on 80–100 mesh Chromosorb W. Ir spectra (CCl_4 solution) were obtained using a Perkin-Elmer Model 257 apparatus. Uv spectra were determined in methanol solution on a SP 800 Unicam instrument. Nmr spectra were run on a Varian 60-Mc instrument with tetramethylsilane as internal standard. Mass spectra have been obtained at 70 eV, through the direct inlet system of a Hitachi RMU-6E device (ion source at 150°).

3-Diphenylmethylenecamphor (1), $[\alpha]^{25}D$ +230°, was prepared according to Haller.[3]

3-Diphenylmethyleneisoborneol (2), $[\alpha]^{25}D$ −173°.—A solution of **1** (3.16 g, 0.01 mol) in 100 ml of anhydrous ether was added to a cooled slurry of lithium aluminum hydride (120 mg) in 30 ml of anhydrous ether. The reaction mixture was stirred overnight at room temperature. The excess of $LiAlH_4$ was destroyed with 10% HCl (30 ml), and the ethereal layer was washed successively with saturated Na_2CO_3 solution and water, then dried (Na_2SO_4) and concentrated. The solid residue, when recrystallized twice from petroleum ether (bp 40–50°), gave 2.5 g (80%) of 3-diphenylmethyleneisoborneol (**2**): mp 87–88°; uv max 247 nm (ϵ 11,800); ir 3590, 3480, 1608, 1500, and 1067 cm^{-1}; nmr (CCl_4) δ 7.20 (m, 10, aromatic H), 4.19 (s, 1, CHOH), 2.53 (d, 1, J = 3.6 Hz, bridgehead H), 2.00–1.20 [complex m, 5, $(CH_2)_2$ and OH], 1.14 (s, 3), 0.87 (s, 3), and 0.82 (s, 3).

Anal. Calcd for $C_{23}H_{26}O$: C, 86.74; H, 8.23. Found: C, 86.33; H, 8.14.

The mother liquors contain a mixture of the endo and exo isomers.

3-Diphenylmethyleneborneol (3), $[\alpha]^{25}D$ +524°.—The endo epimer **3** was purified by thin layer chromatography (silica gel, benzene) of the above mixture after distillation of the solvent: mp 93–96°; uv max 251 nm (ϵ 13,000); ir 3630, 1606, 1503, and 1056 cm^{-1}; nmr (CCl_4) δ 7.21 (m, 10), 4.45 (s, 1), 2.38 (d, 1, J = 4.2 Hz), 2.30–1.10 (complex m, 5), 0.92 (s, 3), 0.88 (s, 6).

Anal. Found: C, 86.70; H, 8.21.

3-Diphenylmethyleneisobornyl Acetate (4), $[\alpha]^{25}D$ −265°.—A 15-g (0.0471 mol) portion of the exo alcohol **2** in anhydrous pyridine (50 ml) solution was added to a pyridine solution (100 ml) of 10.2 g (0.1 mol) of acetic anhydride. The mixture was maintained for 24 hr at 70°, then cooled and evaporated to dryness. The obtained crystals were recrystallized twice from ligroin to give 15.2 g (90%) of the exo acetate **4**: mp 168–169.5°; ir 1733, 1601, 1495, and 1405 cm^{-1}; nmr (CCl_4) δ 7.23 (m, 10), 5.56 (s, 1), 2.61 (d, 1, J = 3.0 Hz), 1.90–1.30 (m, 7, out of which a sharp signal appeared at 1.47 attributed to the acetate methyl group), 1.15 (s, 3), 1.00 (s, 3), and 0.95 (s, 3).

Anal. Calcd for $C_{25}H_{28}O_2$: C, 83.29; H, 7.83. Found: C, 83.44; H, 8.04.

3-Diphenylmethylenebornyl Acetate (5), $[\alpha]^{25}D$ +380°.—A 159-mg (5×10^{-4} mol) portion of the endo alcohol **3**, dissolved in 2 ml of anhydrous pyridine, was added to 0.1 g (10^{-3} mol) of acetic anhydride in 1 ml of pyridine. After it was heated for 24 hr at 70°, the reaction mixture was cooled and evaporated to dryness and the crude residue was recrystallized twice from ligroin to yield 150 mg (83%) of the endo acetate **5**: mp 152–154°; ir 1731, 1604, 1498, and 1041 cm^{-1}; nmr (CCl_4) δ 7.21 (s, 10), 5.86 (s, 1), 2.48 (d, 1, J = 3.8 Hz), 2.25–1.25 (m, 7, one intense signal at 1.51 ppm integrated for 3 H and was attributed to the acetate methyl group), 1.01 (s, 3), 0.88 (s, 3), and 0.85 (s, 3).

Anal. Calcd for $C_{25}H_{28}O_2$: C, 83.29; H, 7.83. Found: C, 83.37; H, 7.85.

Isomerization of 4. A.—A 500-mg portion of acetate **4**, dissolved in 20 ml of glacial acetic acid containing 20 mg of concentrated sulfuric acid, was stirred for 24 hr at room temperature. The solution was then poured into 30 ml of water and neutralized with a dilute solution of $NaHCO_3$. After extraction with CCl_4, the organic layer was dried over anhydrous Na_2SO_4. The mixture of endo and exo epimers (4:1) was analyzed by nmr. The two isomers did not separate from each other by tlc nor by glc. Four recrystallizations in ligroin gave pure endo acetate **5** identical with the above-described compound.

B.—In another run, $LiAlH_4$ reduction of the crude reaction mixture gave pure alcohols **2** and **3** after preparative tlc (silica gel, benzene).

C.—Acetate **4** (100 mg) in 4 ml of acetic acid containing 12 mg of concentrated sulfuric acid, was heated for 20 min at 60°. After treatment, the crude reaction products were analyzed by nmr: 60% endo acetate **5**, 15% exo acetate **4**, and 25% hydrocarbon **8** (the determination of the relative proportion of compound **8** was based on the signal of the methyl group shielded to 0.26 ppm). Absence of hydrocarbons **12**–**15** was verified by glc (XE 60 on Chromosorb W, 195°) and by tlc (silica gel impregnated with 10% $AgNO_3$, ligroin). Composition of the reaction mixture as a function of time and temperature is shown in Table I.

Characterization of Hydrocarbon 8, $[\alpha]^{25}D$ −17°6.—The crude oily mixture, obtained after treatment of the acetolysis product (1.25 hr, 70°) of 2.0 g of acetate **4**, was filtered over neutral alumina using petroleum ether (bp 40–45°) as eluent. Distillation of the solvent under vacuum gave 1.58 g (95%) of

TABLE I

Reaction time	1 hr[a]	4 hr[a]	8 hr[a]	16 hr[a]	24 hr[a]	20 min[b]	75 min[c]
4, %	64	26	19	18	17.5	15	
5, %	36	74	76	72	70.5	60	
8, %		1	5	10	12	25	100

[a] 25°. [b] 60°. [c] 70°.

hydrocarbon **8** exhibiting one single glc peak: bp 135–140° (0.05 mm); uv max 238 nm (ε 20,000); nmr (CCl_4) δ 7.30 (complex m, 9, aromatic H), 3.18 (s, $W_{1/2}$ = 2 Hz, 1, CH, tertiary endo), 2.55 (broad signal, $W_{1/2}$ = 7 Hz, 1, bridgehead H), 2.10–1.60 (complex m, 4, $-CH_2CH_2-$), 1.23 (s, 3), 0.80 (s, 3), and, 0.26 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 300 (67), 285 (17), 257 (29), 231 (40), 217 (69), 202 (39), 83 (100), and 55 (50).

Anal. Calcd for $C_{23}H_{24}$: C, 91.95; H, 8.05. Found: C, 91.73; H, 8.00.

Oxidation of Hydrocarbon 8. Diketone 9, $[\alpha]^{25}D$ +45°3. A.—Jones reagent[11] was added in excess to a solution of hydrocarbon **8** (400 mg, 1.33 mmol) in acetone (20 ml). The mixture was concentrated *in vacuo* and water (25 ml) was added. After three extractions with ether, the mixed organic extract was washed successively with saturated Na_2CO_3 solution and water, then dried (Na_2SO_4) and concentrated to give 420 mg (95%) of an oil which crystallized on standing. Recrystallization from ether–petroleum ether gave pure diketone **9**: mp 138–139°; uv max 253 nm (ε 13,000); ir 1748, 1668, 1600, 1576, 1485, and 1450 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 332 (40), 317 (14), 304 (44), 286 (11), 271 (6), 194 (42), 165 (20), 105 (100), and 77 (35).

B.—The procedure of Pappas[12] was used with the following modification. A solution of hydrocarbon **8** (400 mg, 1.33 mmol) in 25 ml of a MeOH–$CHCl_3$–Me_2S mixture (6:3:1) cooled at −78° was treated with 1 equiv of ozone and concentrated. The tlc (SiO_2, benzene) examination of the crude product showed two spots. The ir, nmr, melting point, and tlc behavior of the more polar material (120 mg, 27%) was identical with that of the previously described diketone **9**. The less polar compound (200 mg, 43%) proved to be due to the corresponding ozonide **11**: $[\alpha]^{25}D$ +44°1; ir 1606, 1580, 1208, 1135, 1055, and 1020 cm^{-1}; nmr δ 7.6–6.6 (m, 9), 2.95 (s, 1), 2.15 (s, 1), 1.70 (s, 4), 1.35 (s, 3), and 0.95 (s, 6); mass spectrum (70 eV) *m/e* (rel intensity) 348 (7), 320 (3), 316 (17), 233 (100), 211 (12), 194 (25).

Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.44; H, 7.06.

Oxidation of **11** (200 mg) by Jones reagent yielded 175 mg (89%) of diketone **9**.

Epimerization of Diketone 9.—A solution of 33 mg (0.1 mmol) of diketone **9** in a mixture of pyridine (0.5 ml) and water (0.1 ml) was heated for 2 hr at 95°. After removal of the solvents, 5 ml of ether was added. The ethereal solution, washed first with dilute HCl and then with water, was dried (Na_2SO_4) and concentrated. The crude oily residue was found to be a 3:7 mixture of the two epimers **9** and **10** by direct nmr measurement.

Dehydration of Alcohol 2 by PTSA.—A 3.18-g (10^{-2} mol) portion of exo alcohol **2** in 35 ml of benzene containing 50 mg of PTSA was heated for 40 min at 60°. After cooling, the solution was washed successively with a saturated solution of $NaHCO_3$ and water. Direct glc (195°) analysis of the organic layer indicated a 1:9 mixture of hydrocarbons **12** and **13**, respectively. Distillation of the solvent, followed by filtration over neutral alumina (eluent ligroin), gave 2.51 g (83%) of the two hydrocarbons as a mixture. Column chromatography (10% $AgNO_3$ impregnated Florisil) gave first compound **12** (175 mg, elution with petroleum ether), then product **13** (1.46 g, elution with a 95:5 petroleum ether–benzene solution).

5-Diphenylmethylene-2,3,3-trimethyltricyclo[2.2.1.$0^{2,6}$]heptane (12), $[\alpha]^{25}D$ +24°, had mp 65–66°; uv max 259 nm (ε 16,000); ir 1660, 1603, 1495, 1447, 1283, 1132, 1074, 1038, and 863 cm^{-1}; nmr (CCl_4) δ 7.15 (s, 5), 7.11 (s, 5), 2.06 (broad s, 1), 1.95–1.28 (m, 4), 1.10 (s, 3), 0.97 (s, 3), 0.85 (s, 3).

Anal. Calcd for $C_{23}H_{24}$: C, 91.95; H, 8.05. Found: C, 91.73; H, 8.00.

2,3,3-Trimethyltricyclo [2.2.1.$0^{2,6}$]heptan-5-one, $[\alpha]^{25}D$ −67°5.—A 300-mg (1 mmol) portion of hydrocarbon **12** in a mixture of methanol (30 ml) and chloroform (10 ml) was treated with 1 equiv of ozone at −50°. Decomposition of the reaction mixture with 1.5 ml of methanol containing 0.5 g of INa and 0.4 ml of AcOH was followed by concentration *in vacuo*. The residue, dissolved in 50 ml of ether, was washed out successively with sodium thiosulfate and sodium bicarbonate aqueous solutions, then with water. Separation of trimethyltricyclanone and benzophenone, carried out by preparative glc (30% SE-30 on Chromosorb W, 10 ft, 180°) after concentration, gave 90 mg (50%) of benzophenone and 33 mg (21%) of the expected trimethyltricyclanone: mp 108–109° (sublimation at around 72°); ir 1755 cm^{-1}; uv max (MeOH) 208.5 nm (ε 5400), 271.5 (72), and 276 (67); mol wt, 150 (mass spectrum) (lit.[14] mp 111–112°).

7-Diphenylmethylenecamphene (13), $[\alpha]^{25}D$ +218°, had mp 60–62°; uv max 248 nm (ε 18,300); ir 1657, 1596, 1488, 1458, 1443, 1200, 1106, 1074, 1030, and 883 cm^{-1}; nmr (CCl_4) δ 7.16 (s, 10), 4.81 (s, 1), 4.60 (s, 1), 3.20 (broad s, 1), 2.33 (broad s, 1), 2.16–1.24 (m, 4), 1.11 (s, 3), and 1.02 (s, 3).

Anal. Calcd for $C_{23}H_{24}$: C, 91.95; H, 8.05. Found: C, 91.67; H, 8.27.

Dehydration ($KHSO_4$) of Alcohol 2 at 160°.—A mixture of 3-diphenylmethyleneisoborneol (**2**) (4 g, 12.6 mmol) and $KHSO_4$ (5 g) was heated at 160° for 15 min; water was added to the cooled mixture and the contents of the reaction vessel were washed out with ether. The ethereal solution was washed successively with saturated sodium carbonate solution and water, then dried (Na_2SO_4) and concentrated. The crude yellow oil, on column chromatography with alumina using petroleum ether (bp 40–50°) as eluent, gave 3.09 g (82%) of hydrocarbon **8**, exhibiting one single glc peak and identical with the above-described compound.

Dehydration ($KHSO_4$) of Alcohol 2 at 130°.—A 3.18-g (10 mmol) portion of alcohol **2** mixed with 4 g of $KHSO_4$ was heated for 20 min at 130°. After cooling, the reaction mixture was extracted with ether; the ethereal fraction was washed with a saturated aqueous solution of $NaHCO_3$, then with water. Glc analysis of the crude reaction mixture exhibited four peaks corresponding to hydrocarbons **12**, **13**, **14**, and **15** (relative ratios 30:1:15:5, respectively). Evaporation of the solvent followed with filtration over 20 g of neutral alumina (benzene as eluent) yielded 2 g (66%) of the mixture of the four compounds. Column chromatography (10% $AgNO_3$ impregnated Florisil) gave successively hydrocarbons **12** (elution with petroleum ether, bp 45–55°), **13** (elution with 95:5 petroleum ether–benzene solution), and a mixture of **14** and **15** (elution with 85:15 petroleum ether–benzene solution). The latter compounds were separated from each other by preparative glc (30% QF 1 over Chromosorb W, 10 ft, 210°).

5-Diphenylmethylenecamphene (14), $[\alpha]^{25}D$ +166°, had mp 54–58°; uv max 249.5 nm (ε 14,500); ir 1668, 1600, 1496, 1460, 1443, 1192, 1134, 1104, 1090, 1073, 1034, 1012, and 882 cm^{-1}; nmr (CCl_4) δ 7.13 (m, 10), 4.77 (s, 1), 4.55 (s, 1), 2.78 (broad s, 1), 2.21 (d, 1, J = 3, 6 Hz), 1.95–1.23 (m, 4), 1.05 (s, 3), and 0.95 (s, 3); mol wt, 300 (mass spectrum).

5-Oxocamphenylone (16), $[\alpha]^{25}D$ −60°.—A 300-mg (1 mmol) portion of hydrocarbon **14** was treated, as described for the ozonolysis of compound **12**, to give 97 mg (54%) of benzophenone and 41 mg (26%) of 5-oxocamphenylone (**16**): mp 68–70°; ir 1760, 1718, 1150, 960, and 950 cm^{-1}; uv max 292 nm (ε 63); nmr (CCl_4) δ 2.90 (m, 1), 2.53 (unresolved q, 1), 2.30–1.95 (m, 4), 1.12 (s, 3), and 1.00 (s, 3); mol wt, 152 (mass spectrum). (lit. racemic[17] mp 56°; optically active[18] mp 74°, $[\alpha]^{40}D$ −90°).

6-Diphenylmethylenecamphene (15), $[\alpha]^{25}D$ +9°4, had mp 78–81°; uv max 252.5 nm (ε 11,600); ir (CCl_4) 1655, 1603, 1495, 1447, 1200, 1168, 1112, 1102, 1075, 1033, 1017, 1003, and 883 cm^{-1}; nmr (CCl_4) δ 7.16 (m, 10), 4.76 (s, 1), 4.62 (s, 1), 3.33 (broad s, 1), 2.36 (m, 1), 2.13–1.26 (m, 4), 1.07 (s, 6); mol wt, 300 ($C_{23}H_{24}$) (mass spectrum).

Registry No.—**1**, 40428-02-2; **2**, 40428-03-3; **3**, 40488-47-9; **4**, 40488-48-0; **5**, 40488-49-1; **8**, 40488-50-4; **9**, 40488-51-5; **11**, 40488-52-6; **12**, 40488-53-7; **13**, 40488-54-8; **14**, 40488-55-9; **15**, 40488-56-0; **16**, 40488-57-1; 2,3,3-trimethyltricylo[2.2.1.$0^{2,6}$]heptan-5-one, 28070-35-1.

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The Hydrolysis of Methyl Methylarylphosphinates in Perchloric Acid Solution

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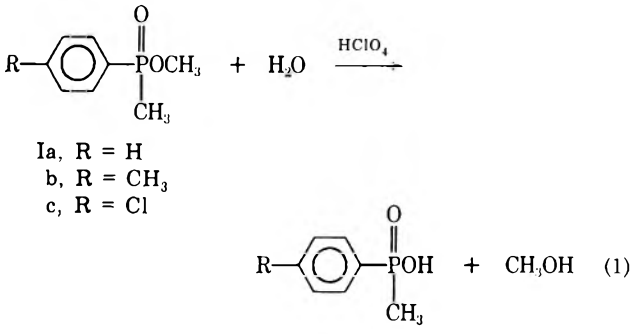
Rates of hydrolysis of methyl methylphenylphosphinate (Ia) and its *p*-CH_3 (Ib) and *p*-Cl (Ic) derivatives have been determined at several perchloric acid concentrations and at three temperatures. Ia and Ib show rate maxima at *ca.* 6–7 *M* $HClO_4$, but no rate maximum was observed for Ic. The apparent pK_{SH^+} value of Ia in perchloric acid is estimated to be −3.27 by nmr methods. Equilibrium protonation of these substrates is best correlated with the H_A function. Rate maxima for Ia and Ib appear at the position of substrate protonation. However, the transition states for hydrolysis of Ia and Ib as well as Ic are likely not to be significantly different from the transition states of organophosphorus esters which display rate maxima not corresponding to substrate protonation.

In recent years the kinetics of the hydrolysis of alkyl and aryl esters of phosphoric acid in mineral acid solutions have been reported.[1-11] Aryl esters containing electron-withdrawing substituents show rate maxima in moderately concentrated acidic media, where substantial substrate protonation has been shown not to occur at the position of maximum rate. This is in contrast to most aryl phosphate esters containing hydrogen or an electron-donating substituent, where no significant acid maximum obtains. Unbranched alkyl phosphates such as methyl phosphate show a smooth increase in rate with acid concentration, and are thought to proceed *via* an A2 mechanism.[6] A recent review has been presented.[11] *p*-Nitrophenyl diphenylphosphinate[12] and phenyl methylphosphonic acid[13] also show rate maxima in acid solution which cannot be due to substrate protonation. The latter compound is unique in that an electron-withdrawing substituent is not present in the aryl leaving group.

As part of our interest in the nucleophilic reactivity of organophosphorus substrates, we have investigated the hydrolysis of methyl methylphenylphosphinate (Ia)



(1)

and its *p*-methyl (Ib) and *p*-chloro (Ic) derivatives in moderately concentrated perchloric acid solutions at several temperatures (eq 1).

Results and Discussion

Stoichiometry.—Substrates Ia, Ib, and Ic were prepared by standard synthetic procedures (see Experimental Section). The most extensive study was carried out on the parent compound, Ia. The reaction of Ia in concentrated perchloric acid solutions gave methylphenylphosphinic acid in nearly quantitative yield (95% by isolation). Thus the stoichiometry is in accord with eq 1. No evidence for other reaction products was found. For Ib and Ic, the change in ultraviolet absorption was that expected for analogous stoichiometry.

Kinetics.—The kinetics of hydrolysis in aqueous perchloric acid solutions were followed by the change in the ultraviolet absorption of aliquots quenched in acetate buffer. The differences in extinction coefficients of reactant esters and product acids were small, but the extinction coefficients of the neutralized acids (methylphenylphosphinate anions) differed significantly from those of the esters. This difference allowed a convenient spectrophotometric analysis. All kinetic data gave linear first-order plots, usually to better than two half-lives. The rate law is given in eq 2, where sub-

$$\frac{-\mathrm{d[substrate]}}{dt} = k_\psi[\mathrm{substrate}] \qquad (2)$$

strate represents phosphorus ester and k_ψ the pseudo-first-order rate constant, which is dependent on perchloric acid concentration. Rates of hydrolysis of each substrate were determined at three temperatures over a range of perchloric acid concentrations. Data for Ia, Ib, and Ic are given in Table I.

The dependence of rate on perchloric acid concentration at *ca.* 95° is shown in Figure 1 for the three substrates. For Ia and Ib, the value of k_ψ first increases and then decreases with increasing acid concentration. A rate maximum is observed at *ca.* 6–7 *M* $HClO_4$. However, *the data for Ic do not show a rate maximum*, but rather a monotonic dependence of rate on acid concentration. For Ia and Ib, data at other temperatures show maxima much like those in Figure 1, but for Ic the data at other temperatures do not extend to concentrations above 6 *M* where a maximum might occur.

For Ia, it is evident (Table I and Figure 1) that, up to 5.5 *M* $HClO_4$ at 95.1°, the data conform to the rate law

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TABLE I

HYDROLYSIS OF METHYL METHYLPHENYLPHOSPHINATES $CH_3(XC_6H_4)P(=O)OCH_3$ IN AQUEOUS $HClO_4$

Temp, °C	$[HClO_4]$, M[a]	10^4k[b]	Log k − log $([SH^+]/[S]_{st})$[c]	$-H_0$ + log $[HClO_4]$[d]	Log k + H_A[e]	a_{H_2O}[d]
			X = H[f]			
67.2	1.03	0.086				
	3.08	0.270				
	4.11	0.390				
	5.59	0.556				
	7.09	0.585				
	9.13	0.468				
95.1	0.52	0.63			−5.12	0.980
	1.03	1.21	−2.00	0.34	−5.24	0.957
	2.08	2.49	−2.23	0.57	−5.48	0.897
	3.08	3.74	−2.49	0.88	−5.82	0.820
	4.11	5.30	−2.68	1.21	−5.94	0.715
	5.08	6.44	−2.92	1.63	−6.19	0.587
	5.59	7.20	−3.02	1.88	−6.30	0.518
	6.12	7.51	−3.17	2.18	−6.47	0.450
	6.61	7.40	−3.34	2.43	−6.67	0.382
	7.09	7.56	−3.50	2.70	−6.87	0.316
	8.11	7.30	−3.79	3.40	−7.30	0.194
	9.13	6.10	−4.03	4.31	−7.74	0.110
	10.13	4.58	−4.30	5.26	−8.21	
107.6	1.01	3.19				
	3.04	9.48				
	5.56	18.8				
	7.09	20.6				
	9.13	16.0				
			X = p-CH_3[g]			
67.2	1.01	0.154				
	3.04	0.257				
	5.56	0.447				
	7.09	0.504				
	9.13	0.435				
95.1	1.01	1.36	−2.17	0.31	−5.17	0.960
	3.04	3.18	−2.61	0.86	−5.79	0.824
	5.56	6.05	−3.03	1.86	−6.37	0.524
	7.09	6.55	−3.43	2.70	−6.93	0.316
	9.13	5.25	−3.97	4.31	−7.81	0.110
107.6	3.04	11.5				
	5.56	18.1				
	7.09	23.4				
	9.13	16.4				
			X = p-Cl[h]			
67.4	1.01	0.057				
	2.99	0.157				
	5.52	0.288				
94.4	1.01	1.07	−2.01	0.31	−5.27	0.960
	2.99	2.20	−2.48	0.85	−5.94	0.828
	5.52	4.83	−2.82	1.84	−6.46	0.528
	7.03	6.10	−3.15	2.66	−6.93	0.325
	9.03	8.01	−3.54	4.19	−7.58	0.117
107.9	1.01	3.97				
	2.99	7.74				
	5.52	16.2				

[a] As measured by titration with standard base. [b] Pseudo-first-order rate constants, in sec^{-1}. [c] $[S]_{st} = [SH^+] + [S]$. [d] H_0 and a_{H_2O} values were obtained by interpolation from reported data; see, *e.g.*, C. J. O'Connor, *J. Chem. Educ.*, 46, 686 (1969). [e] H_A values, at 25.0°, in aqueous $HClO_4$ were obtained from ref 19. [f] [Ia] = 2.00×10^{-3} M. [g] [Ib] = 2.00×10^{-3} M. [h] [Ic] = 4.00×10^{-3} M.

given in eq 3. Further inspection shows that Ia and

$$\frac{-d[\text{substrate}]}{dt} = k_2[\text{substrate}][H^+] \quad (3)$$

Ib obey eq 3, at the three temperatures studied, up to near the observed rate maxima. Substrate Ic obeys eq 3 under all conditions examined.

Activation parameters for the hydrolysis of Ia–c, each at several perchloric acid concentrations, are given in Table II. For each substrate the values of the activation energies and entropies are almost independent of acid concentration. Ic has a slightly more positive energy of activation and less negative entropy of activation than do Ia and Ib. The values for Ia and Ib are similar to the reported activation parameters for the acid-catalyzed hydrolyses of aryl phosphates,[4,8-11] phosphinates,[12] and phosphonates,[13] which display rate maxima.

pK_{SH^+} Measurements.—In an attempt to determine the equilibrium ionization constants for the con-

TABLE II

ACTIVATION PARAMETERS FOR THE ACID-CATALYZED HYDROLYSIS OF Ia–c

Substrate	$[HClO_4]$, M	E_a, kcal mol^{-1}	$\Delta S^{\pm}$, cal mol^{-1} deg^{-1} × 4
Ia	1.03	23.3	−20
	3.08	22.1	−21
	5.59	22.6	−19
	9.13	22.9	−18
Ib	3.04	24.2	−16
	7.09	22.4	−19
	9.13	22.9	−18
Ic	1.01	27.0	−10
	2.99	25.0	−14
	5.52	25.6	−11

jugate acids of Ia and Ib, their ultraviolet spectra in concentrated $HClO_4$ were determined. However, for both Ia and Ib a gradual absorbance change was observed with increasing acid concentration, making accurate pK_{SH^+} measurements difficult. It is known that the change in absorption values of esters upon protonation can be ascribed to both solvent effects and protonation.[14]

Further, the observation of variable chemical shifts for the two different methyl groups supports the interpretation,[15,16] indicating a high degree of solvation of the phosphoryl group. Toward protonation, the phosphoryl function acts in fashion similar to the carbonyl function in amides[17] and the sulfonyl function in sulfoxides.[18] These three classes of oxygenated compounds obey the H_A function better than the H_0 function.[16]

The pK_{SH^+} value of Ia in perchloric acid was estimated by the nuclear magnetic resonance method.[12,18,19] Nmr measurements were made on solutions of Ia in 0.6–11.7 M $HClO_4$. Chemical shifts (ν) of the methyl group directly bonded to phosphorus[15] were measured (at 25°) relative to $(CH_3)_3NH^+$, the internal standard.[16,18,19] Data are given in Table III. Plotting these data in the form

$$\{\log([SH^+]/[S]) + H_0\} \text{ vs. } \{H_0 + \log [HClO_4]\}$$

according to the usage of Bunnett and Olsen,[20] a straight line is obtained (plot not shown), with a slope (ϕ_e value) of 0.51 ± 0.04 and an intercept of −2.76 ± 0.15 which represents the pK_{SH^+} of Ia at infinite dilution in water.[20] Since the ϕ_e value is near to that observed for amides, the H_A function[21] seems appropriate to our type of substrate. Plotting values of log $([SH^+]/[S])$ vs. $-H_A$ yields a straight line with a slope of 1.01 ± 0.06 and an intercept of −3.27 ± 0.20; this is the apparent pK_{SH^+} value (*i.e.*, H_A value at half-protonation) of substrate Ia in perchloric acid. Apparent pK_{SH^+} values for Ia–c in sulfuric acid, as determined by the H_A function, from the nmr spectra of the methyl groups bound to phosphorus are −3.11, −2.94, and −3.17,[16] respectively. Therefore the apparent pK_{SH^+} values of Ia in sulfuric and perchloric acids are the same within the limits of error. We conclude that Ia–c behave as "moderately basic substrates." Also the three values vary in order of the expected electronic effect of substituent on the phenyl group.

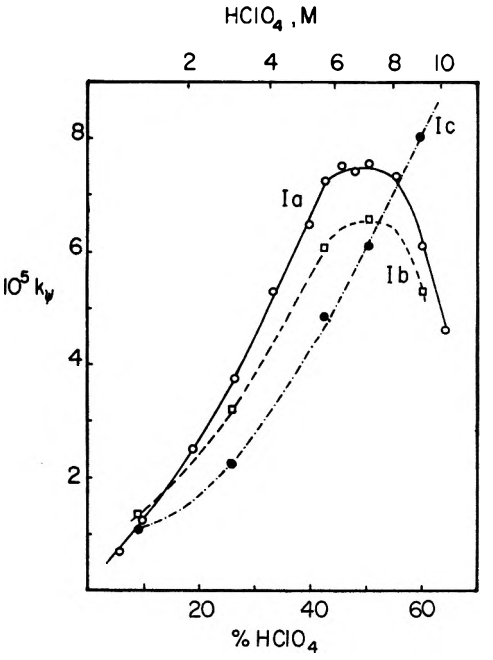

Figure 1.—Plot of $k \times 10^5$ (in sec^{-1}) against perchloric acid concentration (at top) and against per cent perchloric acid (at bottom) for the hydrolysis of Ia (○) and Ib (□) at 95.1°, and of Ic (●) at 94.4°.

TABLE III

DEPENDENCE OF CHEMICAL SHIFTS OF *p*-CH_3 GROUP AND OF PROTONATION RATIOS ON AQUEOUS $HClO_4$ CONCENTRATION FOR METHYL METHYLPHENYLPHOSPHINATE (TEMPERATURE 25.0°)

$[HClO_4]$, M[a]	H_2[b]	$[SH^+]/[S]$[c]	$-H_A$	Log $([SH^+]/[S]) + H_0$	$-\{H_0 + \log [HClO_4]\}$
0.64	98.8 ($\Delta\nu_S$)				
2.04	98.7$_5$	0.0016	0.86	−3.67	0.56
2.44	98.4	0.0127	1.03	−2.96	0.68
3.04	98.3	0.0160	1.30	−3.14	0.87
4.03	98.1$_5$	0.0209	1.62	−3.49	1.19
6.00	94.3$_5$	0.163	2.32	−3.68	2.12
8.13	87.3	0.567	3.12	−4.58	3.42
8.87	79.6	1.524	3.41	−4.77	4.01
10.09	72.6$_5$	4.628	3.85	−5.42$_5$	5.10
11.70	67.1	158	4.50	−5.62	6.75
	67 ($\Delta\nu_{SH^+}$)[d]				

[a] As determined by titration. [b] As measured from $(CH_3)_3NH^+$ internal standard. [c] $[SH^+]/[S] = (\Delta\nu_S - \Delta\nu)/(\Delta\nu - \Delta\nu_{SH^+})$. [d] Estimated value.

Treatment of Kinetic Data.—Having established that all of the three organophosphorus compounds examined should behave as moderately basic substrates in the range of $HClO_4$ concentrations employed in the kinetic runs, rate data in Table I can be handled

(14) E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.*, **82**, 5660 (1960).

(15) A previous investigation[16] has shown that pK_{SH^+} determinations by nmr, using methyl and methoxy resonances, yield values that can differ by as much as 0.4 pK unit.

(16) R. Curci, A. Levi, V. Lucchini, and G. Scorrano, *J. Chem. Soc., Perkin Trans. 2*, accepted for publication.

(17) (a) K. Yates, J. B. Stevens, and A. R. Katritsky, *Can. J. Chem.*, **42**, 1957 (1964); (b) K. Yates, *Accounts Chem. Res.*, **4**, 136 (1971).

(18) D. Landini, G. Moden, G. Scorrano, and F. Taddei, *J. Amer. Chem. Soc.*, **91**, 6703 (1969).

(19) P. Haake, R. D. Cook, and G. Hurst, *ibid.*, **89**, 2650 (1967).

(20) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899, 1917 (1966).

(21) (a) H_A values at 25.0° were obtained by interpolation from the data of H. Wai, Ph.D. Thesis, Toronto University; *cf.* ref 21b. (b) Acidity function values in perchloric acid were obtained from the data of K. Yates and H. Wai, *J. Amer. Chem. Soc.*, **86**, 5408 (1964). Correlations of percentage composition of perchloric acid solutions with molarity are from the data of C. J. O'Connor, *J. Chem. Educ.*, **46**, 686 (1969). All values are at 25°.

accordingly,[20] by making plots of $\{\log k_\psi - \log([SH^+]/[S])\}$ *vs.* $\{-(H_0 + \log [HClO_4])\}$. For compounds Ib and Ic, the log $([SH^+]/[S])$ values at various $HClO_4$ concentrations were calculated on the basis of the apparent pK'_{SH^+} values in H_2SO_4. Inspection of Figure 2 reveals that satisfactory straight lines are obtained; these give ϕ (slope) values of 0.49 ± 0.02 (r = 0.99), 0.44 ± 0.04 (r = 0.99), and 0.38 ± 0.05 (r = 0.98) for Ia, Ib, and Ic, respectively. Bunnett and Olsen[20] have pointed out that ϕ values from 0.22 to 0.56 are characteristic for reactions in which water is involved as nucleophile in the rate-determining step. Plots of $\{\log k_\psi + H_A\}$ *vs.* log a_{H_2O} (see Table II and Figure 3) show a clear deviation from linearity at relatively low $HClO_4$ concentrations; however, they are all similar in shape for the three phosphinic esters considered, and this despite the monotonic, no-maximum rate increase of Ic with $HClO_4$ concentration (Figure 3). Furthermore, discarding log $k_\psi + H_A$ values at aqueous $HClO_4$ concentrations below 20%, good straight lines (correlation coefficient ≥ 0.99) can be drawn through the remaining points, and slopes (r values)[17b] of 2.26 ± 0.04, 2.27 ± 0.17, and 1.90 ± 0.20 can be estimated for Ia, Ib, and Ic, respectively. These values are fairly similar and indicate a strong positive water activity dependence, which is analogous for all of the three phosphorus compounds. Again, no indication of the occurrence of a change in the mechanism of hydrolysis on passing from Ia and Ib to Ic is found.

Mechanistic Implications.—In substrates Ia–c, $H_2{}^{18}O$ tracer studies have not been performed and the positions of bond cleavage, either P–O or alkyl C–O, have not been determined. The fact that substrates Ia and Ib display rate maxima in moderately concentrated perchloric acid solutions can be taken as evidence for P–O fission. The hydrolysis data of Ia and Ib are similar to that of other substrates which show rate maxima; in the latter cases exclusively P–O bond fission has been demonstrated. In addition Haake and coworkers[12,22] have observed that hydroxide attacks phosphinate esters only at the phosphorus center. One might expect P–O cleavage also to occur for acid-catalyzed hydrolyses. All of the evidence indicates attack at phosphorus, but a labeling experiment to confirm this assignment would be worthwhile.

The acid-catalyzed hydrolyses of aryl phosphates containing electron-withdrawing substituents on the leaving group show rate maxima at acid concentrations not corresponding to complete substrate protonation.[11] *p*-Nitrophenyl diphenylphosphinate[12] and phenyl methylphosphonic acid[13] show similar rate maxima. All of these reactions show characteristic features; *e.g.*, large negative entropies of activation are exhibited. Protonation and strong hydration are thought to be important in the transition state. The high degree of solvation in the transition state is evidence for mechanisms which require slow proton transfer in the rate-determining step.[10,11]

Rate maxima are observed for two (specifically Ia and Ib) of the three substrates studied here. Also the activation parameters for these two differ from those for the third (see Table II) by more than deviations due to experimental error. In part this could result from position of substrate protonation. However, we feel that the observed differences only represent slight variations in mechanistic behavior and that the mechanisms for all three hydrolyses are fundamentally similar. Also the associative character of these reactions is believed to be similar to that for many other strong-acid hydrolyses of phosphorus compounds. Another bit of evidence that the three behave in similar manner is the ultraviolet spectra. Although the spectra were not useful in our system as a means of obtaining good pK_{SH^+} values,[23] the similar spectral changes for Ia–c indicate similar interactions with the acid media.

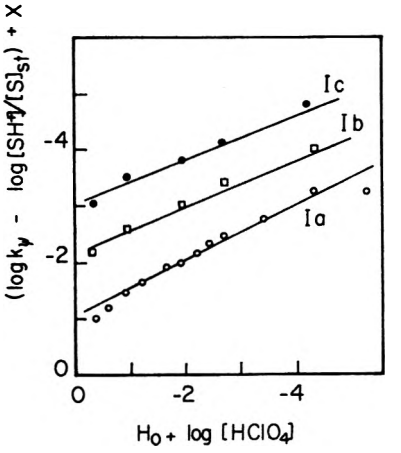

Figure 2.—Typical ϕ plots for hydrolysis of methyl methylphenylphosphinates in aqueous perchloric acid; vertical displacement values x = 1 for Ia, x = 0 for Ib, and x = −1 for Ic.

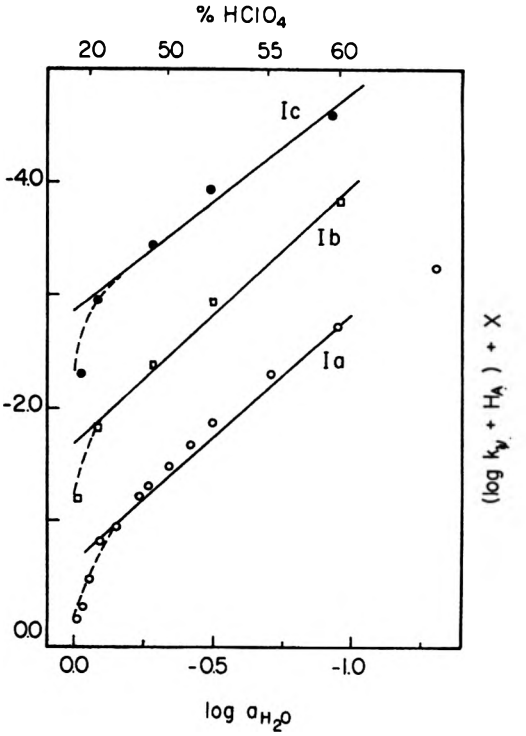

Figure 3.—Typical r plots for hydrolysis of methyl methylphenylphosphinates in aqueous perchloric acid; vertical displacement values x = 5 for Ia, x = 4 for Ib, and x = 3 for Ic.

(22) P. Haake, R. D. Cook, W. Schwarz, and D. R. McCoy, *Tetrahedron Lett.*, 525 (1968).

(23) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000 (1957), and references cited therein.

Points of Interest.—The ϕ values (Bunnett and Olsen) for the protonation of amides in sulfuric acid are between 0.42 and 0.55.[20] Values for Ia–c in sulfuric acid lie between 0.50 and 0.65.[16] For Ia in perchloric acid ϕ = 0.51. Clearly for these substrates the hydration requirements of SH^+ relative to S are high.[20]

Treatment of the hydrolysis data of Ia–c by the Bunnett and Olsen method (Figure 2) for "moderately basic substrates" yields for the rate-determining step ϕ values (0.49, 0.44, 0.38) which are characteristic of reactions for which water is involved in this step.

Experimental Section

Materials and Substrates.—The general procedure used in the synthesis of methyl methylarylphosphinates was according to the method of Arbuzov and Rozimov.[24] Arylphosphonous dichlorides were allowed to react with methanol in ether in the presence of *N,N*-dimethylaniline, producing dimethyl arylphosphonites $ArP(OCH_3)_2$. These compounds were rearranged in the presence of methyl iodide to the desired esters. A modification of the Arbuzov–Rozimov procedure[25] was employed owing to the rapidity and exothermicity of the reaction. Thus roughly equal portions of dimethyl arylphosphonite esters were added to 25 50-ml flasks. Two drops of reagent grade methyl iodide were added to each of the flasks; the flasks became hot and were cooled in water. The contents of the flasks were combined and each flask was rinsed with ether, the rinsings being added to the product.

Some specifics of the preparation and properties of each substrate are as follows. Methyl methylphenylphosphinate (Ia) had bp 133–134° (10 mm), $n^{25}D$ 1.5270 [lit.[25] bp 142° (14 mm), $n^{25.8}D$ 1.5260]. *Anal.* Calcd for $C_8H_{11}PO_2$: C, 56.47; H, 6.52; P, 18.21. Found: C, 56.20; H, 6.75; N, 18.07.

For methyl methyl-*p*-methylphenylphosphinate (Ib), *p*-methylphenylphosphonous dichloride was not available and was synthesized from *p*-bromotoluene by the method of Weil, Prijs, and Erlenmeyer.[26] From the dichloride the substrate was obtained by the modified Arbuzov–Rozimov procedure, bp 148–149° (11 mm), $n^{25}D$ 1.5190 [lit.[27] bp 151–152° (13 mm), $n^{15}D$ 1.5280]. *Anal.* Calcd for $C_9H_{13}PO_2$: C, 58.69; H, 7.12; P, 16.82. Found: C, 58.47; H, 7.31; P, 15.94.

For methyl methyl-*p*-chlorophenylphosphinate (Ic), *p*-chlorophenylphosphonous dichloride was synthesized[26] and the substrate was prepared in the usual manner, bp 156–157° (10 mm), $n^{25}D$ 1.5347 [lit.[28] bp 144° (5 mm), nD 1.5363]. *Anal.* Calcd for $C_8H_{10}PClO_2$: C, 46.97; H, 4.93; P, 15.14; Cl, 17.33. Found: C, 46.60; H, 5.00; P, 15.18; Cl, 16.82.

Purities of substrates were also confirmed by infrared spectra and gas chromatographic measurements. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Nmr absorbances are reported.[16]

Methylphenylphosphinic acid (MPA) was prepared by the hydrolysis of 51.6 g (0.303 mol) of Ia in 1000 ml of refluxing concentrated hydrochloric acid for 36 hr. On cooling the reaction mixture, white needles deposited from solution and were collected on a filter. The volume of the filtrate was reduced on a steam bath and more acid precipitated; 45 g of product (95%) was obtained, mp 133–133.5° (lit.[29] mp 133–134°).

For substrate syntheses the following reagents were obtained: phenylphosphonous dichloride (Technical Grade, Victor Chemical Works), methanol (reagent grade, Mallinckrodt), *N,N*-dimethylaniline (practical grade, Matheson Coleman and Bell), *p*-bromotoluene and *p*-bromochlorobenzene (White Label, Eastman Kodak), and phosphorus trichloride (reagent grade, Mallinckrodt). All other organic and inorganic reagents were of analytical or reagent grade and were used without further purification.

Equipment.—Nmr spectra were determined on a Bruker Model HFX-10 spectrometer. Infrared spectra were recorded using a Perkin-Elmer Model 137 Infracord. Ultraviolet spectra were obtained with Beckman Models DU and DK spectrometers. Gas chromatographic measurements were made on a Perkin-Elmer vapor fractometer, Model 154. Temperatures of the thermostats were checked with NBS thermometers calibrated to ±0.1°.

Spectra.—The ultraviolet spectra of Ia and MPA were determined in various aqueous systems. These spectra were similar in 6 *M* perchloric acid solutions but different in 1 *M* acetic acid–sodium acetate buffers, presumably owing to the ionization of the acid to its anionic form. Extinction coefficients were measured for Ia and MPA in a 1 *M* acetate buffer. Corrections for absorption of the buffer were made. For each compound a linear Beers Law relationship was observed. The following absorption maxima and extinction coefficients were determined: Ia, 270.6 nm (ϵ 616), 264.2 (750), and 258 (560); MPA, 270.6 nm (ϵ 217), 269.5 (300), 263 (387), 257.5 (315), and 252 (216). Compounds Ib and Ic in 1 *M* acetate buffer showed similar spectral changes on hydrolysis. For Ib maxima were at 272 nm (sharpest peak), 266, 260.5 (strongest peak), and 254.5 and for Ic at 275 nm (sharpest peak), 267 (strongest peak), and 257 . No extinction coefficients were determined.

pK_a Measurements. Nmr.—Perchloric acid solutions were prepared by dilution and titrated with standard NaOH solutions. H_0 and H_A values are from reported data.[21] Nmr spectra at 25° were recorded on a Bruker HFX-10 90-MHz instrument with trimethylamine as the internal standard.[16] Temperature was measured by a methanol standard.

For all pK_{SH^+} determinations, solutions in acid were prepared immediately prior to spectral measurement.

Kinetics.—Perchloric acid was added to substrate to form 100 ml of a 0.02 *M* master solution for Ia and Ib and 0.04 *M* for Ic. Aliquots (5 ml) of the solution were pipetted into 15-ml Pyrex vials. The vials were cooled in Dry Ice–CH_2Cl_2 and sealed. They were then placed in a thermostat, removed at various times, and stored at −20° until analyzed. The analysis procedure was as follows. A sample vial was opened and the contents were transferred to a 100-ml volumetric flask. The vial was rinsed with 1 *M* acetate buffer and this was added to the flask, which was then diluted to the mark with buffer. pH values of the resultant solutions were between 4.03 and 4.66 depending on initial $HClO_4$ concentration. The rate of hydrolysis was followed by monitoring the decrease in optical density at 270.6 nm for Ia, 272 for Ib, and 275 for Ic. All optical ddnsity measurements were corrected for buffer absorption. Experiments followed good first-order kinetics. Infinity measurements were taken at ten half-lives and their reliability was checked by the method of Guggenheim.[30,31]

Registry No.—Ia, 6389-79-3; Ib, 39013-59-7; Ic, 13114-08-4.

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Synthesis and Nucleophilic Properties of 4-Aryl-5-triphenylphosphonium-1,2,3-triazole Ylides or 4-Aryl-1,2,3-triazol-5-yltriphenylphosphoranes[1]

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The title heterocyclic compounds have been prepared by the addition of sodium azide to arylethynyltriphenylphosphonium halides in dimethylformamide. In hot basic aqueous solution these ylides hydrolyze to give 4-aryltriazole anion and triphenylphosphine oxide. More notably, the ylides are nucleophilic: displacements of halide from ethyl iodide, benzoyl chloride, ethyl chloroacetate, ethyl β-chloropropionate, 2,4-dinitrobromobenzene, and mercuric chloride and Michael additions to ethyl propiolate have been realized. In all of these examples, the point of attack is exclusively at the 2-nitrogen of the ylide. CNDO calculations on the hypothetical unsubstituted 1,2,3-triazol-4-ylphosphorane indicate a charge density in the molecule which is consistent with a mesoionic or ylide structure.

In exploring the scope of a recently developed approach to the synthesis of *H*-1,2,3-triazoles,[2] we discovered a new family of heterocyclic ylides (**2**). In general, the synthesis involves the addition of azide ion to acetylenes activated by electron-withdrawing groups.[2] Knowing that ethynylphosphonium compounds (**1**) are suitably activated and that nucleophiles add readily to them,[3,4] we carried out process 1 and

$$\underset{\mathbf{1}}{ArC{\equiv}CP(C_6H_5)_3{}^+X^-} + Na^+N_3^- \xrightarrow{DMF} \underset{\mathbf{2a},\ Y=H;\ \mathbf{b},\ Y=p\text{-}Cl}{\text{triazolyl-ylide}} + Na^+X^- \quad (1)$$

obtained the *H*-1,2,3-triazolyltriphenylphosphoranes (**2**). These ylides or phosphoranes show a pattern of reactivity, particularly as nucleophiles, which often differs markedly from that of typical ylides.[5]

Compounds of type **2** differ from the usual phosphoranes in the same general way that triphenylphosphonium and dimethylsulfonium cyclopentadienylides (**3**, **4**) differ from their respective simpler ylides:

3a (ylide) **3a′** (ylene) **4**

they do not undergo the Wittig reaction with carbonyl compounds, they react as nucleophiles rather than as dienes, and they are relatively stable.[5,6] The common structural feature of **2**–**4** is, of course, the delocalization of negative charge (aromaticity) in the five-membered ring. In fact, Yoshida, *et al.*, concluded that the ylide of **3** or **4** is the appropriate (*ca.* 88%) representation in the ground state, while the ylene is more suitable for the excited states.[6b] In this work we describe the first chemistry of **2**, which is quite different from the rather unexceptional properties reported for a number of other heterocyclic systems bearing various phosphorus substituents.[7]

Synthesis of Triazolyl Ylides.—The heterocyclic ylides, 4-aryl-5-triphenylphosphonium-1,2,3-triazoles (**2**), have been prepared by the addition of azide ion to arylethynyltriphenylphosphonium salts in dimethylformamide (DMF). This addition is, in principle, straightforward and similar to some 20 or so other activated additions.[2] A limiting factor would be the availablity of **1**, were it not that the conversions of eq 2

$$ArC{\equiv}CH \xrightarrow[X=Br,\ Cl]{OH^-,OX^-} ArC{\equiv}CX \xrightarrow[\text{ether, }25^\circ]{(C_6H_5)_3P} \underset{\mathbf{1}}{ArC{\equiv}CP(C_6H_5)_3{}^+X^-} \quad (2)$$

are on record. Admittedly, many acetylenes still have to be prepared in a fairly tedious set of steps,[8] some haloalkynes are still difficult to prepare,[8] our knowledge of ethynylphosphonium salts is still limited,[3] and as yet we have no information on the conversion of alkylethynyl or ethynylphosphonium salts to ylides. However, it does now seem possible to proceed from the stage of the arylhaloalkyne to several ylides (eq 1 and 2) by a one-vessel ("pot") reaction.

By analogy with process 1, we hoped that azide ion would also add to ynamines. Our preliminary results with ethynyltriethylammonium bromide were inconclusive, however.

Reactions of Triazolyl Ylides.—Like many phosphonium salts, the triazolyl ylides (**2**) are soluble in dipolar aprotic solvents such as DMF and alcohol. They are relatively stable, surviving 1 day of heating at reflux in ethanol–water solution; above the melting point, **2a** decomposes at *ca.* 260° while **2b** decomposes at *ca.* 280–300°. In aqueous *basic* solution, the ylides are easily hydrolyzed to afford quantitatively the *H*-1,2,3-triazole and triphenylphosphine oxide (eq 3).

It was of obvious interest to investigate **2** either as a Wittig reagent or as a diene. Heating **2** with benzalde-

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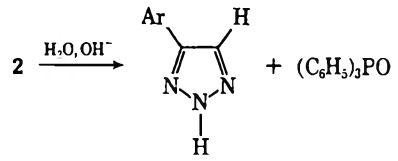
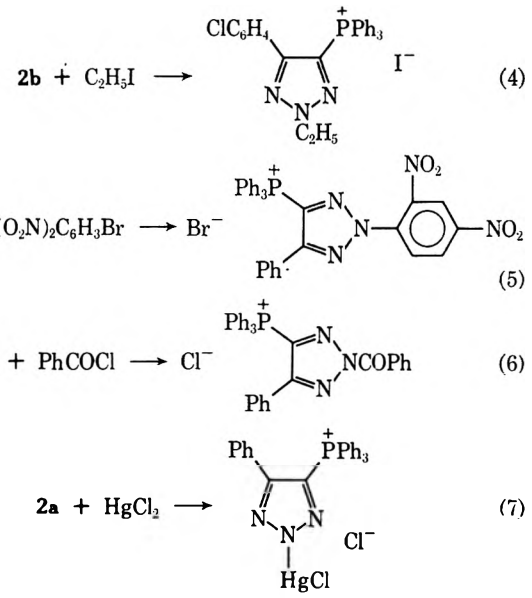


(3)

hyde in dimethyl sulfoxide (DMSO) for 48 hr at reflux did not yield the Wittig product. Likewise, treatment of 2 with dienophiles did not give Diels–Alder products but gave Michael adducts (see below).

Triazolyl ylides turn out to be excellent nucleophiles. Heating them with organic halides in chloroform produces stable phosphonium salts (eq 4–7).



(4)

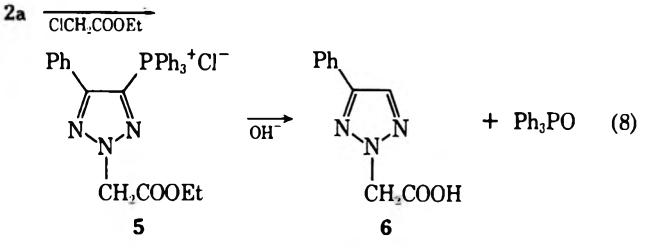
(5)

(6)

(7)

These reactions are analogous to alkylations or acylations of typical phosphoranes, although products of the latter tend to be relatively unstable.[6]

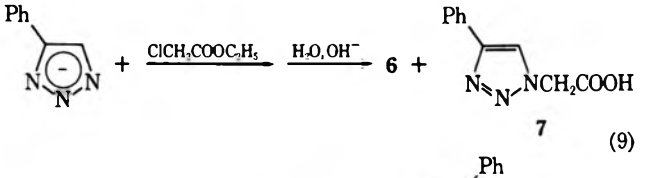
In 2 there are *five* potential sites for attack on the organic halide. This is a general problem in the triazole series which is also treated in a separate paper.[9] To establish that the central nitrogen was the *exclusive* point of attack in 2, we synthesized the possible products in a number of cases. The displacement in eq 8 yields one (**5**) of three plausible products which



(8)

gives 4-phenyltriazol-2-ylacetic acid (**6**) on hydrolysis. This differs from the reaction of 4-phenyltriazole anion with ethyl chloroacetate, in which esters leading to **6** and **7** are produced (eq 9).[9] Both of the isomeric acids (**7**, **8**) were prepared by the alternate route of eq 10. Since the structures of **7** and **8** are predetermined by their mode of synthesis as either 1 or 3 substituted, the remaining isomer (**6**) must be 2 substituted.

(9) Y. Tanaka and S. I. Miller, *Tetrahedron*, in press.



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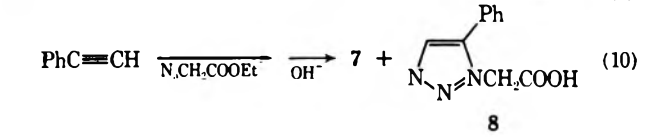
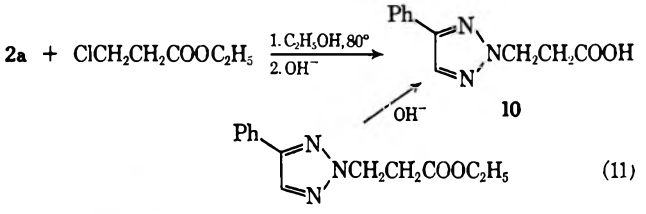


(10)

Our general approach of preparing the plausible products by independent routes is also illustrated by the following series of reactions (eq 11–15), among



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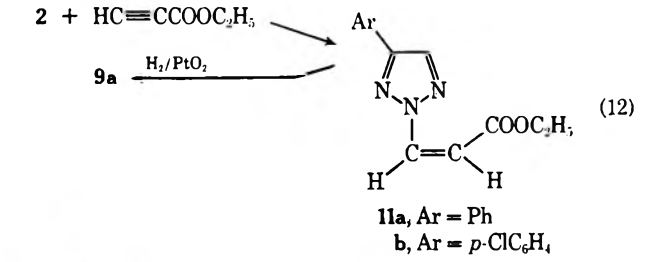
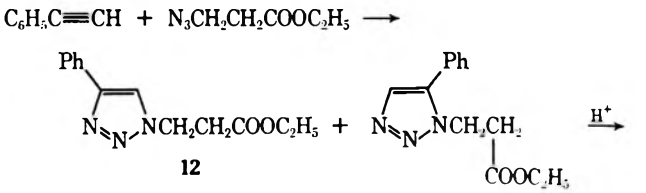
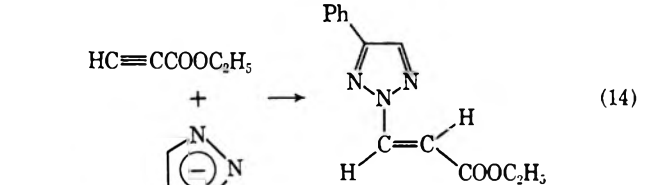


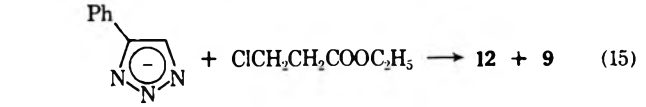
(12)



(13)



(14)



(15)

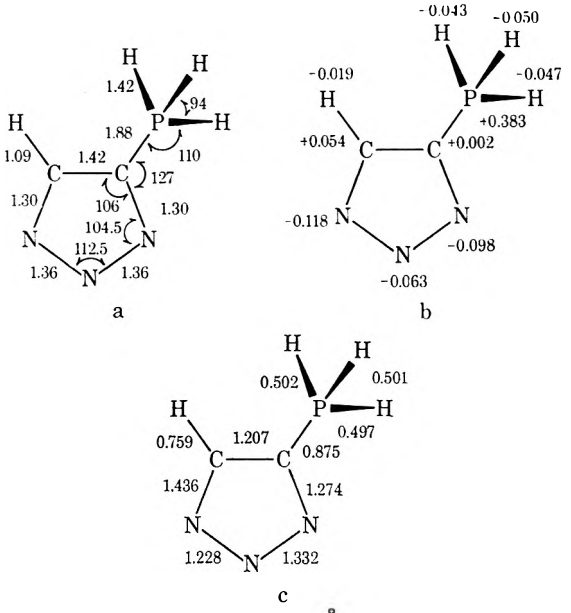
which the details on eq 13–15 are given in ref 9. Differerences among the propionic esters (**9**, **12**, **13**) would have sufficed to establish the orientation in the displacement process (eq 11), but it was somewhat easier to separate, purify, and identify the acids (**10**, **14**, **15**). Again, the displacement of eq 11 or the Michael addition (eq 12) involve the 2-nitrogen of the ylide. This was established by the sequence outlined in eq 11–15, showing that the final acid product (**9**) was both identical with that of eq 12 and different from the isomeric propionic acids (**14**, **15**).

Incidentally, other workers have shown that the nmr chemical shift of the 5-hydrogen of the triazole may be helpful as an indicator of structure, even with two of the three isomers in hand.[10] When a 4-phenyl is present, we find that $-CH_2COOH$ on 1-, 2-, or 3-nitrogen leads to δ 8.41, 8.16, and 7.81 ppm, respectively, and $-CH_2CH_2COOH$ on 1-, 2-, or 3-nitrogen gives δ 8.31, 8.04, and 7.83 ppm, respectively. The values of δ 8.46 and 7.81 ppm for $-CH_2COOC_2H_5$ on the 1- and 3-nitrogen presumably bracket δ for the 2-substituted compound. Although these data are for acetone-*d* and the chemical shifts will generally be solvent sensitive,[10b,c] their trends could be invaluable in differentiating isomeric triazoles.

Discussion

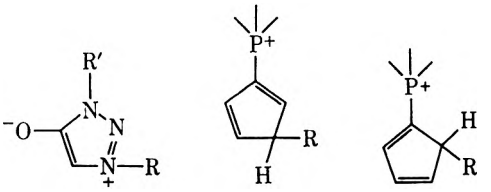
In an attempt to gain some understanding of the properties of *H*-1,2,3-triazoles and their anions, we carried out CNDO calculations on model systems.[9] This CNDO approach has been described[11] and a computer program is available.[12] Our model, given in Chart I, includes our assumed geometry and the calculated atomic charge densities and relative bond energies. Note that our model for the triazolyl ylide or phosphorane is consistent with the ylide representation. That is, there is polarization in the molecule with a net negative charge in the ring (mostly on nitrogen) and a net positive charge outside the ring (mostly on phosphorus). This charge distribution in the ylide is consistent with the nucleophilicity at nitrogen and the susceptibility to basic hydrolysis at phosphorus.

CHART I
CNDO CALCULATION OF
4-PHOSPHONIUM-1,2,3-TRIAZOLYL YLIDE[a]



[a] a, geometry, bond distances, Å, and angles in degrees; b, atomic charge densities; c, relative bond energies.

Comparisons of **2** with several other species are interesting. Compound **3** is one of the more stable compounds in the ylide series. It is not hydrolyzed with aqueous base and does not react with aldehydes or ketones as in the Wittig reaction. Electrophilic attacks on **3**, however, such as diazotization, bromination, Vilsmeier reaction, and Michael anti addition, do occur.[5,6c,d] Likewise, dimethylsulfonium cyclopentadienylide (**4**) reacts with similar electrophiles.[6a] These are properties we have found or can reasonably expect for **2**. By contrast mesoionic triazoles with the opposite arrangement of charges, positive charge inside and negative charge outside the ring, *e.g.*, **17**,[13] react as electrophiles and as Diels–Alder dienes.



The directiospecificity of electrophilic attacks on **2**, **3**, and **4** is puzzling. Our tentative conclusions for normal 1,2,3-triazoles are that electronic effects are relatively unimportant in unsubstituted triazoles and that steric effects appear in 4-substituted triazoles.[9] Anions of the former attack at all three nitrogens,[10a] whereas the latter favor the 1 and 2 positions.[9] In **2** we found attachment only to the middle nitrogen, that is, remote from $\geqslant P^+$, while in **3** and **4** it has been reported that bond formation is always vicinal to $\geqslant P^+$ or $>S^+$.[6] One can suppose that there is a buttressing effect in **2**: the 4-aryl and 5-PPh_3^+ substituents spring apart just enough to partially block the adjacent 1 and 3 positions so that only the middle nitrogen is open for electrophilic attack.

With regard to "explaining" or "predicting" orientation of electrophilic attacks in the species **2**–**4**, the simple quantum methods are still ineffective.[9] In our model for **2** (Chart I), the charge densities (au) on the three nitrogens are, 3-N, −0.118; 1-N, −0.098; and 2-N, −0.063. Of the three nitrogens, the middle one has the lowest electron density, which is not in accord with this being the most nucleophilic site.

With regard to **3**, Yoshida, *et al.*, examined HMO π electron densities and found the order for the 1, 2, and 3 positions to be −1.193, −1.165, and −1.178, respectively.[6b] Because these densities were inconsistent with the observed exclusiveness of 2 attack, Yoshida proposed a one-electron transfer process (16).[6c] Note that electron transfer between reactants is followed by combination of the radical pair. Recently, an addition reaction of **3** was formulated according to an ion pair and Elcb sequence (17).[14] Since we know of no precedent for, or real justification of, scheme 16, we are inclined to be skeptical of it.

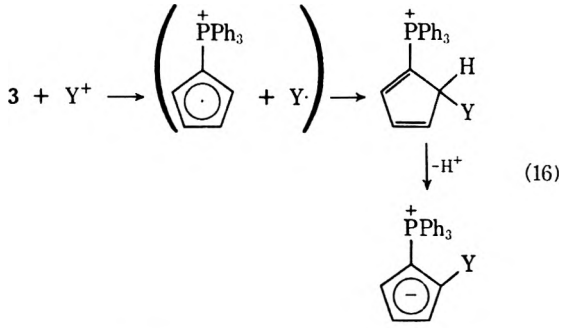
(10) (a) H. Gold, *Justus Liebigs Ann. Chem.*, **688**, 205 (1965); (b) G. Alonso, M. T. Garcia-López, G. Garcia-Muñoz, R. Madroñero, and M. Rico, *J. Heterocycl. Chem.*, **7**, 1269 (1970); (c) G. Garcia-Muñoz, R. Madroñero, M. Rico, and M. C. Saldaña, *ibid.*, **6**, 921 (1969).

(11) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, N. Y., 1970.

(12) Quantum Chemistry Program Exchange, Program 141, P. A. Dobosh, Indiana University, Bloomington, Ind. This program has been modified: A. L. Companion, *Theor. Chim. Acta*, **25**, 268 (1972); *J. Mol. Struct.*, **14**, 117 (1972).

(13) (a) M. Begtrup, *Acta Chem. Scand.*, **26**, 1243 (1972); (b) K. T. Potts and S. Husain, *J. Org. Chem.*, **37**, 2049 (1972), and previous papers.

(14) C. W. Rigby, E. Lord, M. P. Naan, and C. D. Hall, *J. Chem. Soc. B*, 1192 (1971).



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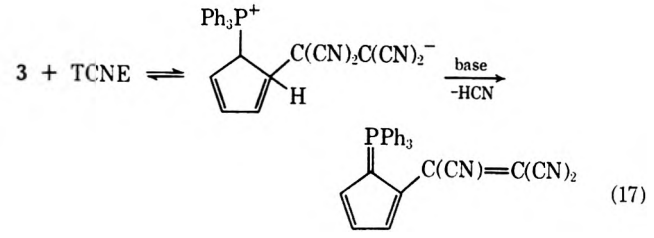

(17)

One can attempt to rationalize the specificities by paying attention to the transition states, or at least to the first intermediates (**18**, **19**) which may be regarded as models for them. Because of the extended rather than branched conjugation, it would seem that, on electronic grounds, **19** would be preferred over **18**, thus explaining the dominance of 2 attack on **3** and **4**. This electronic effect at the 2 position appears to overcome a steric effect which should favor 3 substitutions in **3** and **4**. The validity of this "explanation" could perhaps be decided by further work on the unsubstituted triazolyl ylide.

Experimental Section

All melting points were uncorrected. Infrared spectra were taken on a Beckman IR-8 spectrometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60 instrument using tetramethylsilane as an internal standard. Microanalyses were made by M-H-W Laboratories, Garden City, Mich.

4-Phenyl-5-triphenylphosphonium-1,2,3-triazolyl Ylide (2a).—Phenylethynyltriphenylphosphonium bromide was prepared in 72% yield by Dickstein's procedure given below for the para chloro salt.[3] It had mp 207–209° (lit.[3] mp 206°). To a stirred suspension of sodium azide (1.42 g, 2.8 mmol) in DMF (80 ml), phenylethynyltriphenylphosphonium bromide (9.2 g, 20.8 mmol) in DMF (70 ml) was gradually added at 60° for 30 min. It was kept at 60° for another 2.5 hr. Evaporation of the solvent under reduced pressure gave a white solid, which was taken up in chloroform. After removal of sodium bromide by filtration, the filtrate was evaporated to dryness. The white residue was washed with ether–methylene chloride (1:1) and recrystallized from ether–methylene chloride (2:3) (7.95 g, 93%): mp 240–241°; nmr ($CDCl_3$) δ 7.6 (m, 20 H); ir ($CHCl_3$) 2988, 1485, 1441, 1337, 1110 cm^{-1}; no NH peak.

Anal. Calcd for $C_{26}H_{20}N_3P$: C, 77.02; H, 4.97. Found: C, 76.78; H, 4.74.

***p*-Chlorophenylethynyltriphenylphosphonium Bromide.**—A solution of *p*-chlorophenylbromoethyne[8a] (2.45 g, 11.4 mmol) and triphenylphosphine (2.98 g, 11.4 mmol) in ether (90 ml) was put aside for 6 days. The precipitate was filtered off, washed with ether, and dried thoroughly *in vacuo* (2 mm) (5.04 g, 93%): mp 188–190°; nmr ($CDCl_3$) δ 8.1–7.4 (m, 19 H); ir ($CHCl_3$) 2195, 1590, 1489, 1442, 1113 cm^{-1}.

Anal. Calcd for $C_{26}H_{19}BrClP$: C, 64.02; H, 3.93. Found: C, 64.27; H, 3.85.

4-(*p*-Chlorophenyl)-5-triphenylphosphonium-1,2,3-triazolyl Ylide (2b).—Although both freshly prepared or aged samples of arylethynyltriphenylphosphonium salts may be used to prepare the ylide, the immediate consumption of these salts is recommended because of their hygroscopic character. *p*-Chlorophenylchloroethyne[8a] (3.61 g, 21.1 mmol) and triphenylphosphine (5.55 g, 21.1 mmol) were left for 5 days in ether at *ca.* 25°. The salt was filtered and its solution in DMF (70 ml) was added dropwise with stirring to a suspension of sodium azide (1.25 g, 19.3 mmol) in DMF (80 ml) at 60° over 20 min and then kept at 60° for 2 hr more. The work-up of compound **2b** was used to obtain a white solid (7.30 g, 86%): mp 278–280° dec; nmr ($CDCl_3$) δ 3.1–2.1 (m, 19 H); ir ($CHCl_3$) 2988, 1487, 1444, 1330, 1112 cm^{-1}. This triazole (4.24 g, 94%) was also prepared from *p*-chlorophenylethynyltriphenylphosphonium bromide (4.89 g, 10.2 mmol) and sodium azide (0.665 g, 10.2 mmol), as described above, mp 276–279° dec.

Anal. Calcd: C, 70.99; H, 4.35. Found: C, 70.88; H, 4.43.

Hydrolyses of 4-Aryl-5-phenyltriphenylphosphonium-1,2,3-triazolyl Ylides (2).—A solution of **2a** (0.350 g, 0.865 mmol), sodium hydroxide (0.100 g, 2.5 mmol), ethanol (5 ml), and water (10 ml) was heated at reflux for 2 hr, cooled, and extracted twice with chloroform. The organic extract gave the phosphine oxide, mp 152–153°, from ether–methylene chloride–hexane (2:1:1) (0.207 g, 86%). The aqueous portion was acidified with hydrochloric acid to give a white precipitate, which was recrystallized from water. The product, 4-phenyl-1,2,3-triazole, was identical with the product we made from phenylacetylene and trimethylsilyl azide[2] and had mp 147–148°. In an analogous experiment, **2b** (0.450 g, 1.01 mmol) gave triphenylphosphine oxide (0.290 g, 89%) and 4-*p*-chlorophenyl 1,2,3-triazole (0.101 g, 72%), mp 162–162.5°. The triazole was identified by comparison with an authentic sample we prepared from *p*-chlorophenylacetylene and trimethylsilyl azide.[2]

When **2b** was heated at reflux in aqueous ethanol or in 10% acetic acid for 1 day, hydrolysis did not take place.

2-Ethyl-4-*p*-chlorophenyl-5-triphenylphosphonium-1,2,3-triazole Iodide.—A solution of **2b** (0.418 g, 0.947 mmol) and iodoethane (0.155 g, 0.994 mmol) in chloroform (10 ml) was refluxed for 10 hr. Evaporation of the solvent deposited a white solid (0.402 g, 71%) which was recrystallized from methylene chloride–ether (1:1): mp 219–222°; nmr ($CDCl_3$) δ 1.73 (t, J = 7.2 Hz, 3 H), 4.71 (q, J = 7.2 Hz, 2 H), 8.1–7.1 (m, 20 H); ir (KBr) 1604, 1586, 1485, 1442, 1112 cm^{-1}.

Anal. Calcd for $C_{28}H_{24}ClIN_3P$: C, 56.44; H, 4.06. Found: C, 56.14; H, 3.96.

2-Benzoyl-4-phenyl-5-triphenylphosphonium-1,2,3-triazole Chloride.—A solution of **2a** (0.490 g, 1.31 mmol) and benzoyl chloride (0.193 g, 1.38 mmol) in chloroform (10 ml) was refluxed for 20 hr. A white solid which gradually precipitated was filtered off. The filtrate was evaporated to give a residue which was combined with the precipitate obtained above and then recrystallized from methylene chloride–ether (3:1): yield 0.635 g (94%); mp 299–305° dec; nmr ($CDCl_3$) δ 2.9–1.7; ir (Nujol) 2200–2400 (broad), 1544, 1184, 1111, 980 cm^{-1}.

Anal. Calcd for $C_{33}H_{25}ClN_3OP$: C, 72.59; H, 4.62. Found: C, 72.76; H, 4.55.

2-*o*,*p*-Dinitrophenyl-4-phenyl-5-triphenylphosphonium-1,2,3-triazole Bromide.—A solution of **2a** (0.439 g, 1.08 mmol) and 2,4-dinitrobromobenzene (0.268 g, 1.08 mmol) in chloroform (10 ml) was heated at reflux for 22 hr. Removal of the solvent gave a yellow solid, which was washed with ether (3 × 5 ml). After drying under vacuum, it was recrystallized from methylene chloride–benzene (1:4) to give yellow crystals (0.470 g, 67%): mp 95–96°; ir (Nujol) 1604, 1540, 1111, 980 cm^{-1}.

Anal. Calcd for $C_{32}H_{23}BrN_5O_4P$: C, 58.91; H, 355. Found: C, 58.79; H, 3.68.

2-Chloromercuric 4-Phenyl-5-triphenylphosphonium-1,2,3-triazole Chloride.—Compound **2a** (0.106 g, 0.261 mmol) in methanol (2 ml) was mixed with mercuric chloride (0.065 g, 0.240 mmol) in methanol (1 ml). The mixture was kept at 20° for 2 hr, while a white solid deposited gradually. The solid was filtered off and well washed with methanol (113 mg, 70%), mp 231–234°, ir (Nujol) 1112 cm^{-1}.

Anal. Calcd for $C_{26}H_{20}Cl_2HgN_3P$: C, 46.13; H, 2.98. Found: C, 45.76; H, 3.03.

4-Phenyl-1,2,3-triazol-2-ylacetic Acid (6).—A solution of 4-phenyl-5-triphenylphosphonium-1,2,3-triazolyl ylide (0.518 g, 1.28 mmol) and ethyl chloroacetate (0.173 g, 1.40 mmol) in chloroform (5 ml) was refluxed for 20 hr and then evaporated. The nmr spectrum of the first product, a phosphonium salt, had δ 5.66 ($-C_2N_3CH_2COO-$). This hygroscopic residue was treated with 10 ml of 5% sodium hydroxide in methanol–water (1:4),

heated at reflux for 3 hr, and evaporated under vacuum. The remaining aqueous solution was extracted with ether (10 ml) from which triphenylphosphine oxide (0.250 g, 70%) was eventually obtained. The aqueous layer was acidified to give a white solid which was crystallized from benzene (0.160 g, 79%): mp 199–200°; nmr (acetone) δ 5.37 (s, 2 H), 6.90 (broad, 1 H), 7.45 (m, 3 H), 7.90 (m, 2 H), 8.16 (s, 1 H).

Anal. Calcd for $C_{10}H_9O_2N_3$: C, 59.11; H, 4.46. Found: C, 58.78; H, 4.67.

We also traced this reaction by nmr. A solution of 4-phenyl-5-triphenylphosphonium-1,2,3-triazolyl ylide (0.06 g, 0.15 mmol) and ethyl chloroacetate (0.024 g, 0.20 mmol) in chloroform-*d* (0.800 ml) was heated at 60° and the nmr spectrum of the solution was checked after 1 and 2 days. After 2 days this solution was worked up as described above and again the product was checked by nmr; only **6** was observed.

Ethyl *cis*-(4-Phenyl-1,2,3-triazol-2-yl)acrylate (11a).—A solution of 4 phenyl-5-triphenylphosphonium-1,2,3-triazolyl ylide (0.798 g, 1.97 mmol) and ethyl propiolate (0.196 g, 2.0 mmol) in ethanol (10 ml) was heated at reflux. After 2 hr, water (0.1 ml) was added, and the solution was refluxed for another 20 hr and then evaporated. The oily residue was taken up in ether and washed with water, dried, and chromatographed on silica gel with ether. A white solid (0.35 g, 73%) was obtained: mp 54–56°; nmr (CCl_4) δ 7.87 (s, 1 H), 7.75 (m, 2 H), 7.35 (m, 3 H), 7.17 (d, J = 10.1 Hz, 1 H), 5.64 (d, J = 10.1 Hz, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 1.25 (t, J = 7.1 Hz, 3 H); ir (CCl_4) 2980, 1734, 1666, 1613, 1481, 1462, 1422, 1200, 1092, 1033, 982 cm^{-1}. The assignment of the cis rather than the trans structure to this ester was made on the basis of nmr (J_{HH} = 10.1 Hz) and ir (1637 cm^{-1}) and by analogies to similar additions.[9] The other isomer was assigned the trans structure in the same way.

Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39. Found: C, 63.99; H, 5.46.

Ethyl β-(4-Phenyl-1,2,3-triazol-2-yl)propionate (9a).—To a suspension of platinum oxide (0.04 g) in ethyl acetate (5 ml) was added 0.125 g (0.51 mmol) of **11a**. The hydrogenation was carried out with a pressure of hydrogen of 3–4 atm for 1 hr; the solution was then treated with ethanol (10 ml) and water (2 ml) and filtered to remove the catalyst. The filtrate was extracted with dichloromethane and washed with water. Removal of the solvent yielded the ester **9a** (0.110 g, 89%): nmr (CCl_4) δ 7.73 (s, 1 H), 7.65 (m, 2 H), 7.30 (m, 3 H), 4.67 (t, J = 7.1 Hz, 2 H), 4.09 (q, J = 7.1 Hz, 2 H), 2.95 (t, J = 7.1 Hz, 2 H), 1.20 (t, J = 7.1 Hz, 3 H); ir (CCl_4) 1738, 1192, 1095, 1026, 982 cm^{-1}. This nmr spectrum is similar to the one obtained on the same compound prepared by eq 15.[9]

β-(4-Phenyl-1,2,3-triazol-2-yl)propionic Acid (10).—A solution of 4-phenyl-5-phenylphosphonium-1,2,3-triazolyl ylide (0.620 g, 1.43 mmol) and ethyl 3-chloropropionate (0.220 g, 1.61 mmol) in ethanol (10 ml) was heated at reflux for 2 days and then evaporated. The residue was dissolved in aqueous sodium hydroxide and heated at *ca.* 100° for 15 min. On cooling, the solution, which deposited triphenylphosphine oxide (0.380 g, 93%), was filtered. The filtrate was washed twice with ether and then acidified with 10% hydrochloric acid to give a white solid. This acid was recrystallized from water–methanol (4:1) to give **10**: yield 0.190 g (58%); mp 145–146°; nmr (acetone) δ 8.04 (s, 1 H), 7.90 (m, 2 H), 7.42 (m, 3 H), 4.74 (t, J = 7.1 Hz, 2 H), 3.09 (t, J = 7.1 Hz, 2 H); ir (Nujol) 3120, 1730, 1408, 1214, 1181, 1100, 983 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.11. Found: C, 61.24; H, 5.04.

In an alternate synthesis of **10**, **9a** (0.058 g) was heated in aqueous sodium hydroxide (5 ml) and neutralized with 10% hydrochloric acid. The white solid (100% yield) had mp 143–144°; the nmr spectra (acetone) was identical with that obtained above.

β-(4-Phenyl-1,2,3-triazol-1-yl)propionic Acid (14) and β-(5-Phenyl-1,2,3-triazol-1-yl)propionic Acid (15).—Ethyl β-azidopropionate was prepared by heating ethyl β-chloropropionate (13.5 g, 0.092 mol) and sodium azide (7.5 g, 0.115 mol) in 1:1 water–ethanol (20 ml) for 24 hr. Work-up and distillation gave ethyl β-azidopropionate (1.95 g, 15%): bp 47–48° (0.8 mm) [lit.[15] bp 62° (5 mm)]; nmr (CCl_4) δ 4.15 (q, J = 7.2 Hz, 2 H), 3.54 (t, J = 6.7 Hz, 2 H), 2.51 (t, J = 6.7 Hz, 2 H), 1.25 (t, J = 7.2 Hz, 3 H); ir (film) 2980, 1733, 1480, 1185, 1030 cm^{-1}.

A solution of phenylacetylene (1.40 g, 13.9 mmol) and azide ester (1.79 g, 12.5 mmol) in toluene (9 ml) was heated at reflux for 3 days and evaporated. The liquid residue consisted of roughly equal amounts of **14** and **15** according to its nmr spectrum: δ (CCl_4) 8.11 (1,4 isomer) and 7.58 (1,5 isomer). An attempted separation of the isomers by chromatography on silica gel failed. The mixture was then hydrolyzed in aqueous sodium hydroxide at *ca.* 100° for 10 min and worked up. Repeated recrystallization from water–methanol (v/v 1:1) yielded **14** in the first fractions: mp 177–179°; nmr (acetone) δ 8.31 (s, 1 H), 7.85 (m, 2 H), 7.34 (m, 3 H), 4.72 (t, J = 7.0 Hz, 2 H), 3.06 (t, J = 7.0 Hz, 2 H); ir (Nujol) 1695, 1223, 1080, 980, 914, 842 cm^{-1}. The later fractions yielded **15**: mp 120–121°; nmr (acetone) δ 7.73 (s, 1 H), 7.56 (s, 5 H), 4.46 (t, J = 7.0 Hz, 2 H), 3.04 (t, J = 7.0 Hz, 2 H); ir (Nujol) 1710, 1408, 1223, 1151, 1121, 983, 944, 845 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.11. Found for **14**: C, 61.07; H, 5.08; Found for **15**: C, 60.98; H, 5.15.

Ethyl *cis*-(4-*p*-Chlorophenyl)-1,2,3-triazol-2-ylacrylate (11b).—A solution of 4-(*p*-chlorophenyl)-5-triphenylphosphonium-1,2,3-triazolyl ylide (0.600 g, 1.36 mmol) and ethyl propiolate (0.140 g, 1.43 mmol) in ethanol (20 ml) was heated at reflux for 10 hr. Water (0.1 ml) was added, and the solution was refluxed for 10 hr and evaporated. The oily residue was taken up in ether (8 ml), and hexane (1 ml) was added. A precipitate appeared which was filtered off; the filtrate was chromatographed on alumina with ether. The first eluate included **11b**, which separated on removal of ether (0.195 g, 52%): nmr (CCl_4) δ 1.26 (t, J = 7.2 Hz, 3 H), 4.25 (q, J = 7.2 Hz, 2 H), 5.71 (d, J = 9.9 Hz, 1 H), 7.11 (d, J = 9.9 Hz, 1 H), 7.85–7.25 (m, 4 H), 7.90 (s, 1 H); ir (film) 1729, 1664, 982 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}ClN_3O_2$: C, 56.22; H, 4.36. Found: C, 55.96; H, 4.37.

The next eluate gave triphenylphosphine oxide (0.26 g, 69%).

The possibility of syn *vs.* anti addition was investigated briefly. A solution of *p*-chlorophenyltriphenylphosphonium triazoyl ylide (0.035 g, 0.08 mmol), ethyl propiolate (9 μl), and a drop of water in dimethylacetamide (0.40 ml) was charged into an nmr tube and kept at −25° for 5 days. The nmr spectrum indicated 70% of the cis product (anti addition) and 30% of the trans product (syn addition): δ of $-CH{=}CHCO_2C_2H_5$ 5.60 (trans, J = 14.0 Hz), 5.13 (cis, J = 9.8 Hz).

Reaction of Ethynyltriethylammonium Bromide with Sodium Azide.—Ethynylammonium bromide was prepared in 37% yield, as described by Tanaka.[16] Several attempted additions of sodium azide to this ynamine in DMF (1 hr at *ca.* 25°), THF (1 hr at reflux), or triethylamine (1 hr at reflux) were attempted. Although reactions occurred, the products could not be isolated.

Registry No.—**1** (Ar = Ph; X = Br), 34387-64-9; **1** (Ar = *p*-ClC_6H_4; X = Br), 40139-22-8; **2a** ylide form, 40330-41-4; **2a** ylene form, 40139-23-9; **2b** ylide form, 40110-56-3; **2b** ylene form, 40139-42-2; **6**, 40139-43-3; **9a**, 40139-44-4; **10**, 40139-45-5; **11a**, 40132-84-1; *trans*-**11a**, 40132-85-2; **11b**, 40132-86-3; *trans*-**11b**, 40132-87-4; **14**, 40139-46-6; **15**, 40139-47-7; *p*-chlorophenylchloroethyne, 33491-02-0; triphenylphosphine, 603-35-0; 4-phenyl-1,2,3-triazole, 15965-35-2; 4-*p*-chlorophenyl-1,2,-3-triazole, 34108-73-1; 2-ethyl-4-*p*-chlorophenyl-5-triphenylphosphonium-1,2,3-triazole iodide, 40139-51-3; iodoethane, 75-03-6; 2-benzoyl-4-phenyl-5-triphenylphosphonium-1,2,3-triazole chloride, 40139-52-4; benzoyl chloride, 98-88-4; 2-*o*,*p*-dinitrophenyl-4-phenyl-5-triphenylphosphonium-1,2,3-triazole chloride, 40139-53-5; 2,4-dinitrobromobenzene, 584-48-5; 2-chloromercuric 4-phenyl-5-triphenylphosphonium-1,2,3-triazole chloride, 40139-54-6; mercuric chloride, 7487-94-7; ethyl chloroacetate, 105-39-5; ethyl propiolate, 623-47-2; ethyl 3-chloropropionate, 623-71-2; ethyl β-azidopropionate, 40139-55-7; sodium azide, 12136-89-9.

Acknowledgment.—We wish to thank Professor A. L. Companion for assistance with the CNDO calculations.

(15) M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **93**, 609 (1908).

(16) R. Tanaka and S. I. Miller, *J. Org. Chem.*, **36**, 3856 (1971).

Notes

Improved Syntheses of 12-Substituted 5β-Cholanes[1]

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The rearrangement of 12-substituted derivatives of various steroidal classes has been investigated[2] for both its synthetic possibilities and mechanistic interest. A study of the rearrangement reactions involving 12α-mesyloxy (**1**), 12β-mesyloxy (**2**), and 12-oxotosylhydrazone (**3**) derivatives of cholane[3] has been carried out,[4] the cholane system being chosen in order that the rearrangement process *per se* could be studied free of complications from other functional groups. To ensure adequate supplies of compounds **1**, **2**, and **3** for the study, practical methods for their preparation were sought.

12α-Cholanol (**4**), the key intermediate to the other compounds of the group, had been obtained as a side product in a previous research[5] which involved an attempt to selectively tosylate 3α,12α,24-cholanetriol (**5**). A direct preparation of **4** is available by $LiAlH_4$ reduction of the 24-mesylate[6] (**6**) of 12α,24-cholanediol (**7**). However the only currently feasible routes[5,7] to **7**, and in fact to any 12-hydroxycholane derivative, originate with the readily available deoxycholic acid as starting material; so a satisfactory overall method for obtaining **4** was already manifest in the reaction[5] which first yielded **4**. In that reaction **4** must have been formed from the triol **5** *via* an intermediary 3α,24-ditosylate derivative **8**, so that our first efforts were directed toward finding suitable conditions for obtaining **8** in reasonable yield. An obstacle to the satisfactory preparation of **8** was recognized in reviewing earlier tosylations[8] of 24-cholanols; invariably the desired tosylate would be contaminated with the chloro analog. The chloro compound was shown to be formed by a replacement of the tosyloxy group in a facile reaction by chloride ion of pyridinium chloride, which is formed as the tosylation proceeds.

An obvious way of minimizing this side reaction was to decrease the contact time between the sulfonate and pyridinium chloride. After careful experimentation, a satisfactory procedure, depending on precise temperature control, the use of a high ratio of mesyl chloride[9] to alcohol, and quick work-up, was found whereby the desired triol dimesylate[10] **9** can be obtained in crystalline form and good yield. Reduction of **9** with lithium aluminum hydride to **4** proceeded smoothly;[11] the overall yield of **4** from methyl deoxycholate[12] was 61%.

With the alcohol **4** available, direct mesylation to **1** is the method of choice, but **1** has been prepared also by selective reduction of the 12,24-diol dimesylate **11**. The $LiAlH_4$ reduction[13] was easily controlled to stop at the desired stage.

Oxidation of **4** to 12-oxocholane **15** by K_2CrO_4 in acetic acid proceeds smoothly when carried to completion, but incomplete oxidations are misleading, as crystalline products are obtained which consist of mixed (1:1) crystals of alcohol and ketone.

Raney nickel reduction[14a] of **15** (without additional base[14b]) gave 81% of the 12β isomer, a method representing an improvement over previous procedures.[15] The 12-ol epimers also form a 1:1 molecular compound.

The 12β-mesylate **2** is formed readily from the alcohol **16** but isolation and crystallization were achieved only after much careful experimentation. The compound is markedly unstable in an erratic manner. Our efforts to ascertain the precise conditions which cause decomposition of **2** were unsuccessful. Characterization of the compound is by ir and nmr spectroscopy. In experiments reported in the rearrangement study[4] the ir spectrum of a solution of **2** in anhydrous collidine was found to be unchanged after 4 hr at room temperature; decomposition was observed at higher temperatures.

(1) (a) Excerpted in part from the Ph.D. dissertation of R. C. E., University of Tennessee Medical Units, 1973. (b) The major portion of this work was reported at the 19th Southeastern Regional Meeting of the American Chemical Society, Nov 1967. (c) This work was supported in part by NIH Grants USPHS CA-05011 and FR-05423.

(2) See ref 6, 11, 13, and 26 cited in ref 4 of this paper.

(3) All cholane derivatives mentioned in this paper are 5β compounds; the designation "5β" will be omitted in referring to them.

(4) R. C. Ebersole and F. C. Chang, *J. Org. Chem.*, **38**, 2579 (1973).

(5) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **81**, 2835 (1959).

(6) F. C. Chang, *J. Pharm. Sci.*, **53**, 1014 (1964).

(7) G. V. Rao and C. C. Price, *J. Org. Chem.*, **27**, 205 (1962).

(8) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **80**, 2726 (1958).

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 662.

(10) In an early experiment in which the reaction mixture was allowed to stand for a longer period of time, 24-chloro-3α,12α-cholanediol 3-mesylate **10**, formed from **9** by the chloride replacement reaction, was isolated as a crystalline product (see Experimental Section).

(11) After this procedure was worked out and used as a standard preparation of **4**, a publication [S. Ahmed, M. Alauddin, B. Caddy, M. Martin-Smith, W. T. L. Sidwell, and T. R. Watson, *Aust. J. Chem.*, **24**, 521 (1971)] appeared which included a synthesis of **4** by essentially the same process. However, the dimesylate intermediate **9** was not isolated, and failure to do so might be caused by contamination of the product by the chloro analog **10**, as the reaction was of 16-hr duration and only 2.15 equiv of mesyl chloride was used.

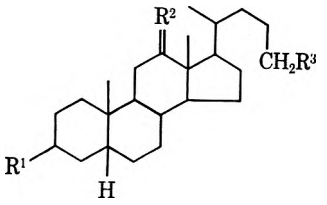
(12) The triol **5** can be prepared from deoxycholic acid, but in our experience the methyl ester is much more conveniently reduced[5] because of a more favorable solubility in the solvents used for $LiAlH_4$ reduction.

(13) Similar preferential $LiAlH_4$ reduction of 3α,24-cholanediol dimesylate **12** gave 3α-cholanol mesylate **13**, in contrast to the difficulty encountered[6] in attempting to selectively mesylate the 3α,24-diol **14**. The 24-carbomethoxy group is also reduced by $LiAlH_4$ in preference to either the 3α- or 12α-mesyloxy group when both (mesyloxy and carbomethoxy) are substituents in cholane. (Unpublished results from this laboratory.)

(14) (a) M. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **26**, 2097 (1943); (b) F. C. Chang, N. F. Wood, and W. G. Holton, *J. Org. Chem.*, **30**, 1718 (1965).

(15) (a) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970); J. W. Huffman and J. T. Charles, *J. Amer. Chem. Soc.*, **90**, 6486 (1968); M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, p 269; (b) J. W. Huffman, D. M. Alabran, J. W. Bethea, and A. C. Ruggles, *J. Org. Chem.*, **29**, 2963 (1964).

The 12β-acetate **17** was prepared by conventional room-temperature treatment of the β-ol with acetic anhydride, but the 12α-acetate **18** from **4** required more vigorous acetylating conditions.



Compd	R¹	R²	R³
1	H	H, α-OMs	H
2	H	H, β-OMs	H
3	H	NNHTs	H
4	H	H, α-OH	H
5	OH	H, α-OH	OH
6	H	H, α-OH	OMs
7	H	H, α-OH	OH
8	OTs	H, α-OH	OTs
9	OMs	H, α-OH	OMs
10	OMs	H, α-OH	Cl
11	H	H, α-OMs	OMs
12	OMs	H, H	OMs
13	OMs	H, H	H
14	OH	H, H	OH
15	H	O	H
16	H	H, β-OH	H
17	H	H, β-OAc	H
18	H	H, α-OAc	H

Experimental Section[16]

3α,12α,24-Cholanetriol 3,24-dimesylate (9) was prepared by adding a solution of methanesulfonyl chloride (76.1 ml dissolved in 300 ml of freshly distilled pyridine and cooled to 0°) to a solution of 3α,12α,24-cholanetriol[5,17] (76.1 g of triol **5** dried by azeotropic distillation of a benzene solution, dissolved in 740 ml of pyridine and maintained at 0°). The reaction mixture, after 5 min in the ice bath, was allowed to stand at room temperature for an additional 3.5 min, then stirred into ice chips. The total product was promptly extracted into ether. The ethereal solution was washed successively with ice-cold dilute HCl, dilute $NaHCO_3$, and water, then decolorized with Norit and dried over calcium sulfate. Evaporation of the ether gave a viscous oil (99.1 g) which crystallized from a mixture of benzene (560 ml) and petroleum ether (bp 63–70°) (300 ml added under reflux) in the form of fine needles (75 g, 72%): mp 128.5–129.0°; $[\alpha]_D$ +44.3° (*c* 2.07); ir ($CHCl_3$) 2.78, 9.70 (12α-OH), 7.38, 8.53 ($-SO_2-$), 10.86, 11.45 μ (mesylate[6]); nmr τ 9.35 (s, 3, C-18 Me), 9.07 (s, 3, C-19 Me), 6.98 (s, 6, $-OSO_2Me$), 6.02 (m, 1, -CHOH), 5.78 (t, 2, $-CH_2OMs$), 5.33 (br s, 1, CHOMs).

Anal. Calcd for $C_{26}H_{46}O_7S_2$: C, 58.39; H, 8.67. Found: C, 58.25; H, 8.73.

24-Chloro-3α,12α-cholanediol 3-Mesylate (10).—In a similar reaction (as the above) which was allowed to stand for 8 hr after addition of the mesyl chloride, after similar processing and rapid column chromatography on a Florisil column, the ether-eluted fractions afforded a residual oil which crystallized in isopropyl ether to give **10** as needles: mp 124.0–127.0°; ir (KBr) 2.73, 9.65 (12α-OH), 7.38, 8.53 ($-SO_2-$), 10.57, 11.40, 11.72 μ (mesylate); nmr τ 9.30 (s, 3, C-18 Me), 9.07 (s, 3, C-19 Me), 7.0 (s, 3, $-OSO_2Me$), 6.47 (t, 2, $-CH_2Cl$), 5.97 (m, 1, -CHOH); 5.32 (br s, 1, -CHOMs).

Cnal. Calcd for $C_{25}H_{43}O_4SCl$: C, 63.19; H, 9.12. Found: *A*, 63.23; H, 8.99.

12α-Cholanol[5] (4) was prepared by $LiAlH_4$ (a stirred suspension of 39.4 g of powdered hydride in 640 ml of anhydrous tetrahydrofuran) reduction of **9** (70.0 g dissolved in 400 ml of tetrahydrofuran added dropwise). After 24 hr under reflux, the reaction was processed by addition of aqueous sodium sulfate until formation of a white precipitate was completed. Filtration and evaporation of the organic layer left 44.0 g (97%) of crystalline product. Crystallization from methyl Cellosolve gave colorless, prismatic needles: mp 103.5–104.0°; $[\alpha]_D$ +45.8° (c 5.00) (lit.[5] mp 100.9–103.3°; $[\alpha]_D$ +41.0°); nmr τ 9.32 (s, 3, C-18 Me), 9.08 (s, 3, C-19 Me), 6.00 (m, 1, -CHOH-).

12-Oxocholane[15b] (15) was prepared by oxidation of **4** (20.0 g) in a stirred suspension of K_2CrO_4 (16.0 g) in acetic acid (600 ml) and water (18 ml). After 24 hr at 23°, the reaction mixture was added to ice chips and the precipitated solid (18.4 g) was washed with water and collected. Recrystallization from methanol gave rectangular plates of **15** (16.9 g), mp 112.0–115.0° (lit. mp 116–117°).

12β-Cholanol[15b] (16).—12-Oxocholane (2.00 g) in methanol (250 ml) was hydrogenated in the presence of W-2 Raney nickel (an equal quantity air dried weighed 12 g) at a pressure of 3 atm in a Parr apparatus. After 30 hr, the catalyst was removed by filtration, and the concentrated filtrate was taken up in benzene (200 ml). Evaporation of the benzene gave a colorless oil (1.95 g). Glc analysis indicated that the oil was composed of 81% 12β- and 17% 12α-cholanol. Crystallization from acetone produced 1.12 g of dense rhombic crystals (by glc, 96% pure). Further recrystallization produced a sample, homogeneous by glc and tlc: mp 93.0–94.0°; $[\alpha]_D$ +31.3° (c 4.98) (lit.[15b] mp 92–93°, $[\alpha]_D$ +45°); ir (CS_2) 2.73 (OH), 7.29, 9.80, 9.90 μ (CO); nmr τ 9.32 (s, 3, C-18 Me), 9.07 (s, 3, C-19 Me), 6.62 (m, CHOH).

Anal. Calcd for $C_{24}H_{42}O$: C, 83.16; H, 12.22. Found: C, 82.81; H, 12.28.

Further concentration of the mother liquor induced formation of long, prismatic crystals. Tlc showed that these crystals were composed of the 12α- and 12β-ols in equal proportion.

12α-Cholanol Mesylate[6] (1). A.—12α-Cholanol **4** was mesylated as previously reported[6] to give **1**.

B.—Two grams of 12α,24-cholanediol dimesylate[6] (**11**), dissolved in 50 ml of ether and 5 ml of tetrahydrofuran, was added dropwise to a stirred suspension of 390 mg of $LiAlH_4$ in 80 ml of ether. Stirring was continued for 4 hr, and after overnight standing the mixture was processed as for the preparation of **9** (above), resulting in a residual oil, which on crystallization in methanol yielded **1** (0.77 g, 47%) as thin rectangular plates, mp 99.5–100.0°, identical with the product of part A according to melting point, ir, and nmr comparisons.

12β-Cholanol mesylate[2b] (2) was prepared by adding 12β-cholanol (0.100 g) to a pyridine (2 ml) solution of methanesulfonyl chloride (0.05 ml) chilled to 4°. After 14 hr at 4°, the reaction mixture was poured on 250 ml of ice chips and then covered with cold water. After standing for 2 hr, the semicrystalline material was filtered and washed free of pyridine with cold water. The air-dried material was dissolved in ether, and the solvent was removed under a stream of nitrogen. The residual oil was dissolved in ethanol for crystallization, which yielded colorless, slender needles (0.05 g): mp 56.0–56.5°; $[\alpha]_D$ +27.2° (*c* 2.68); ir (CS_2) 7.33, 7.47, 8.50 ($-SO_2-$), 10.86, 11.04, 11.16, 11.30 μ (-OMs); nmr (CCl_4) τ 9.23 (s, 3, C-18 Me), 9.03 (broad singlet, *ca.* 6, C-19 Me plus contributions from C-21 and C-24), 7.12 (s, 3, $-OSO_2CH_3$), 5.57 (t, 1, J = 7 Hz, CHOMs).

12α-Acetoxycholane[18] (18) was obtained by *p*-toluenesulfonic acid (0.03 g) catalyzed acetylation of 12α-cholanol (1.00 g) with acetic anhydride (0.66 ml) in acetic acid (10 ml). After 24 hr at room temperature, conventional work-up yielded a yellowish oil (1.00 g). Crystallization from an acetone–ethanol mixture produced dense cubes: mp 75.0–75.5°; $[\alpha]_D$ + 71.3° (c 5.06); ir (CS_2) 5.73 (acetate C=O), 8.03, 9.73, 9.82 (acetate CO–), 7.27, 10.30 μ; nmr τ 9.27, 9.10 (s, 6, 2 Me), 7.93 (s, 3, $-OOCCH_3$), 4.90 (t, 1, J = 3 Hz, CHOAc).

Anal. Calcd for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41. Found: C, 79.88; H, 11.33.

12β-Acetoxycholane[18] (17) was prepared from **15** in the usual way with acetic anhydride–pyridine. The acetate crystallized

(16) See Experimental Section of ref 4 for general experimental information.

(17) G. B. Spero, *J. Amer. Chem. Soc.*, **70**, 1907 (1948).

(18) These acetates were mentioned in ref 15b but were neither crystallized nor characterized.

from an ethanol–acetone mixture: mp 74.0–74.5°; $[\alpha]_D$ +16.5° (*c* 5.07); ir (CS_2) 5.75 (C=O), 8.05, 9.78, 9.73 μ (acetate CO–); nmr τ 9.23, 9.08 (s, 6, 2 Me), 7.98 (s, 3, $-OOCCH_3$), 5.33 (m, 1, CHOAc).

Anal. Calcd for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41. Found: C, 80.03; H, 11.25.

Registry No.—**1**, 1251-13-4; **2**, 40429-72-9; **4**, 35649-45-7; **5**, 2603-77-2; **9**, 40429-41-2; **10**, 40429-42-3; **11**, 1259-02-5; **15**, 5916-16-5; **16**, 40429-45-6; **17**, 40429-46-7; **18**, 19684-29-8; methanesulfonyl chloride, 124-63-0; acetic anhydride, 108-24-7.

Synthesis of 3,4,5,10,11,12-Cyclotetradecahexaene-1,8-dione, a Monocyclic Dicumulenedione[1]

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We have recently described the synthesis of 12- and 14-membered monocyclic diallenes containing carbonyl groups,[2] and we have explored this method as a means of preparing monocyclic dicumulenes. We now report the synthesis of 3,4,5,10,11,12-cyclotetradecahexaene-1,8-dione (**6**), and the attempted preparation of 3,4,5,6,11,12,13,14-cyclohexadecaoctaene-1,9-dione (**8b**).

The racemic diallene (**1**), prepared by the previously described method,[2] was treated in pentane at 0° with excess bromoform and potassium *tert*-butoxide. Two isomeric bis(dibromocarbene) adducts were obtained, **2a** (mp 117–118°) and **2b** (mp 95–97° dec). The spectra of **2a** and **2b** (Table I) both showed signals in the olefinic and cyclopropyl regions, but no signals in the allenic region (τ 4.5–5.5), and thus addition to both allene groups of **1** must have occurred. Furthermore, the nmr spectrum of **2a** showed only one type of methoxyl proton, which suggests that **2a** most probably has the symmetric structure shown.[3] By contrast, the nmr spectrum of **2b** showed two methoxyl signals, and the spectrum can be accommodated by a number of isomeric structures.

The *meso*-diallene **3**,[2] under the same conditions, gave two further bis(dibromocarbene) adducts, **4a** (mp 79–80° dec) and **4b** (mp 77–78° dec). The nmr spectra (Table I) showed that both allenic groups in **3** had reacted. The spectrum of **4b** had three types of methoxyl signals, suggesting the asymmetric structure shown,[4] whereas that of **4a** showed two methoxyl signals and consequently provided less structural information.

(1) For a preliminary communication of part of this work, see P. J. Garratt, K. C. Nicolaou, and F. Sondheimer, *Chem. Commun.*, 1018 (1971).

(2) P. J. Garratt, K. C. Nicolaou, and F. Sondheimer, *J. Amer. Chem. Soc.*, **95**, 4582 (1973).

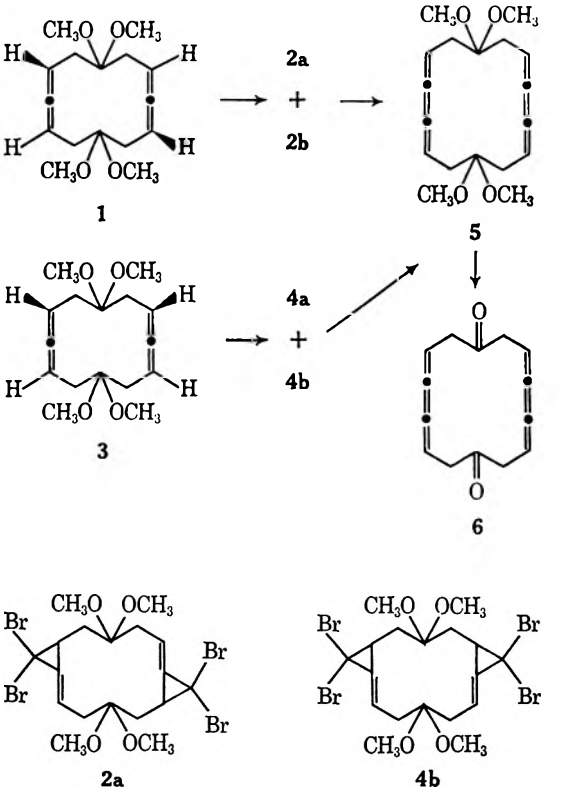
(3) The cyclopropyl rings in **2a** might be both on the same side of the 12-membered ring or on opposite sides. For either structure, the spectrum is still deceptively simple, since two methoxyl groups in different environments must have fortuitously coincidental chemical shifts. However, the environment of the methoxyl groups in the alternative isomers are even less similar.

(4) The two cyclopropyl rings would have to be on the same side of the 12-membered ring, and the spectrum is again deceptively simple.

TABLE I

NMR SPECTRA (100 MHz, CCl_4) OF **2a**, **2b**, **4a**, AND **4b** AS τ VALUES RELATIVE TO TMS

2a	3.74	(m, 2 H, olefin)
	6.72	(s, 12 H, OCH_3)
	7.32	(d, J = 8 Hz, 4 H, allylic CH_2)
	7.65	(d, J = 14 Hz, 2 H, CH_2)
	7.86	(d, J = 12 Hz, 2 H, CH_2)
	8.64	(dd, J = 12, 14 Hz, 2 H, cyclopropyl)
2b	3.66	(m, 2 H, olefin)
	6.66	(s, {12H, OCH_3})
	6.73	(s, {12H, OCH_3})
	7.26–8.00	(m, 8 H, allylic CH_2 + CH_2)
	8.32	(dd, J = 7, 14 Hz, 2 H, cyclopropyl)
4a	3.64	(m, J = 2, 8, 8 Hz, 2 H, olefin)
	6.70	(s, 6 H, OCH_3)
	6.77	(s, 6 H, OCH_3)
	7.32	(d, J = 8 Hz, 4 H, allylic CH_2)
	7.56	(d, J = 14 Hz, 2 H, CH_2)
	7.88	(dd, J = 2, 10 Hz, 2 H, CH_2)
	8.67	(dd, J = 10, 14 Hz, 2 H, cyclopropyl)
4b	3.63	(m, J = 2, 8 Hz, 2 H, olefin)
	6.64	(s, 3 H, OCH_3)
	6.74	(s, {9H, OCH_3})
	6.78	(s, {9H, OCH_3})
	7.30–7.70	(m, 4 H, allylic CH_2 + CH_2)
	8.38	(dd, J = 8, 16 Hz, 2 H, cyclopropyl)



When a mixture of the racemic **1** and *meso*-**3** diallenes were treated with bromoform and potassium *tert*-butoxide, a mixture of the four bis adducts was obtained. These could be separated by chromatography and this is the best method for the preparation of these compounds.

Reaction of either **2a** or **4a**, or a mixture of all four isomers, with methyllithium in ether at −10° gave a solution of the dicumulene **5**, which was stable under these conditions for several days. Removal of the ether below 0° gave **5** as a crystalline compound, which

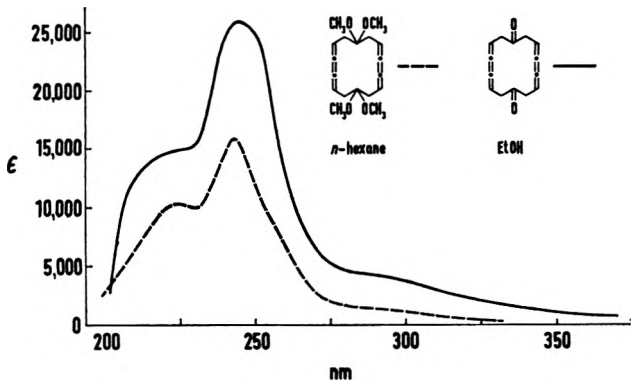


Figure 1.—Electronic spectra of 5 (in *n*-hexane) and 6 (in ethanol).

rapidly decomposed at higher temperatures, forming material insoluble in ether. The structure assigned to 5 is based on its spectral properties and ready hydrogenation (with concomitant hydrolysis) to 1,8-cyclotetradecanedione.[5] The nmr spectrum of 5 at 0° in CCl_4 showed signals at τ 4.85 (m, 4 H, cumulene), 6.82 (s, 12 H, methoxyl), and 7.52 (m, 8 H, methylene). The nmr spectrum was found to be temperature dependent, but irreversible changes occurred above 20°. The electronic spectrum [$\lambda_{max}^{n\text{-hexane}}$ 224 nm (ϵ 10,300), 243 (15,900), 290 sh (1350)][6] was consistent with the presence of the butatriene chromophore (Figure 1).[7]

Hydrolysis of the diketal 5 gave 3,4,5,10,11,12-cyclotetradecahexaene-1,8-dione (6) in 75% yield as a crystalline solid, mp ~130° dec. The monocyclic nature of 6 was confirmed by hydrogenation to 1,8-cyclotetradecanedione. The nmr spectrum ($CDCl_3$) of 6 showed signals at τ 4.40 (t, J = 6 Hz, 4 H) and 6.60 (d, J = 6 Hz, 8 H), attributable to the cumulene and methylene protons, respectively. The ir spectrum (KBr) had a band at 1701 cm^{-1} (C=O), but no appreciable absorption in the cumulene region (2000 cm^{-1}) and the electronic spectrum [λ_{max}^{EtOH} 223 nm (ϵ 15,000), 244 (26,000), 290 sh (4250), Figure 1] was consistent with the assigned structure.

The dione 6 is considerably more stable than the diketal 5 and could be stored at room temperature either in solution or the crystalline state. In the preparation of 5 from the tetrabromide precursors, no evidence for any other product was obtained. The simplicity of the nmr spectra of 5 and 6 suggests that in these compounds both of the cumulene groups have the same stereochemistry. Reasonably strain-free models of both the cis,cis and the trans,trans cumulenes can be made (see Figure 2), and the actual stereochemistry of these compounds is unknown. The temperature dependence of the nmr spectrum of 5 shows that it has a flexible conformation, but insufficient data are presently available to establish the barriers operating in this process.

The further ring expansion of the diketal 5 to 8 was examined. Reaction of a solution of 5 in pentane with excess bromoform and potassium *tert*-butoxide at −10° gave the bis(dibromocarbene) adduct 7,

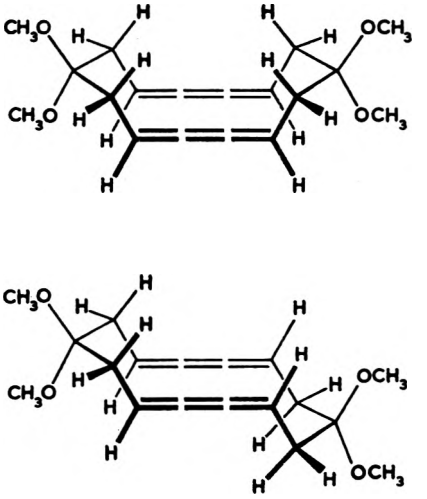
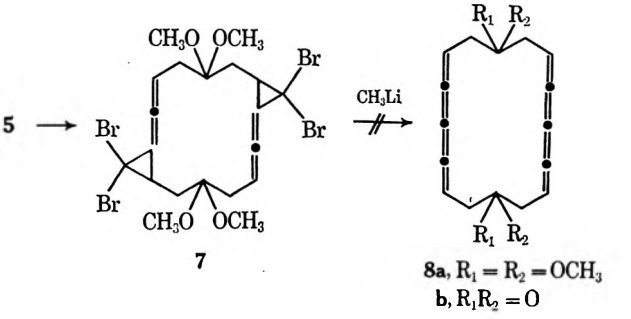


Figure 2.—The alternative cis,cis (above) and trans,trans (below) configurations of 5.

mp ~140° dec. The gross structure of 7 follows from the analytical and mass spectral data. The nmr spectrum showed a 1:1 ratio of the olefinic to cyclopropyl hydrogens, indicating that addition had occurred to the terminal and not to the central double bonds of 5. The spectrum also showed only a single methoxyl resonance, and these data are best accommodated by the symmetric structure 7. The poor yield of 7, together



with its low stability at room temperature, precluded an extensive study of its reaction with methyllithium. However, this reaction was found to give a very unstable product, for which no structural evidence could be adduced.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were recorded on either a Unicam SP 200 or a Perkin-Elmer 247 spectrophotometer, and only strong and medium bands are reported. Nmr spectra were recorded on a Varian HA-100 spectrometer as solutions in $CDCl_3$, unless stated otherwise, with TMS as internal standard and are reported in τ units. Mass spectra were recorded on either an AEI MS9 or MS12 spectrometer and were taken at 70 eV.

Silica for preparative thick layer chromatography (ptlc) was Merck Kieselgel GF_{254}, and that for column chromatography was Hopkins and Williams silica gel (MFC). Bromoform was dried ($CaCl_2$) and freshly distilled over P_2O_5 under N_2. Methyllithium in ether was obtained commerically from Alfa Inorganics. Solvents were May and Baker "R" grade and were purified and dried by standard methods.

Reaction of a Mixture of Racemic (1) and *meso*-5,5,11,11-Tetramethoxy-1,2,7,8-cyclodecatetraene (3) with Excess Bromoform and Potassium *tert*-Butoxide.—The diallenes 1 and 3 (350 mg, 1.25 mmol) and bromoform (3.20 g, 12.6 mmol) were dissolved in dry pentane (20 ml). The solution was cooled to 0° under N_2 and stirred and potassium *tert*-butoxide (sublimed, 1.40

(5) A. T. Blomquist and R. D. Spencer, *J. Amer. Chem. Soc.*, **70**, 30 (1948); F. Sondheimer and Y. Gaoni, *ibid.*, **81**, 6301 (1959).

(6) These are minimal absorption values based on complete conversion of the bis(dibromocarbene) adducts.

(7) For example, see W. J. Ball, S. R. Landor, and N. Punja, *J. Chem. Soc. C*, 194 (1967).

g, 12.5 mmol) was added in portions over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for a further 2 hr. Ether (100 ml) was added, the mixture filtered, and the residue washed with ether (100 ml). The combined ethereal layers were dried; the solvent was removed by evaporation and the residue chromatographed by ptlc on silica, eluting with pentane–ether (85:15). The four adducts in order of decreasing R_f value were as follows.

(i) Isomer **2b**: 50 mg (6.5%); mp 95–97° dec; mass spectrum *m/e* 596, 594, 592 (1), 590, 588 (1:4:6:4:1, $M^+ - CH_4O$), 565, 563, 561 (3), 559, 557 (1:4:6:4:1, $M^+ - C_2H_7O_2$), 547, 545, 543 (2.5), 541 (1:3:3:1, $M^+ - Br$), 515, 513, 511 (1.5), 509 (1:3:3:1, $M^+ - CH_4OBr$), 483, 481, 479 (3), 477 (1:3:3:1, $M^+ - C_2H_8O_2Br$), 401, 399 (3), 397 (1:2:1, $M^+ - C_2H_9O_2Br_2$), 95 (100); ir (KBr) 2960, 2840, 1750, 1454, 1439, 1300, 1282, 1256, 1233, 1222, 1194, 1135, 1121, 1055, 1044, 921, 748, and 719 cm^{-1}; nmr, see discussion. *Anal.* Calcd for $C_{18}H_{24}O_4Br_4$: C, 34.61; H, 3.84. Found: C, 34.95; H, 4.10.

(ii) Isomer **4b**: 80 mg (10.5%); mp 77–78°; mass spectrum *m/e* 596, 594, 592 (0.3), 590, 588 (1:4:6:4:1, $M^+ - CH_4O$), 565, 563, 561 (1.5), 559, 557 (1:4:6:4:1, $M^+ - C_2H_7O_2$), 547, 545, 543 (1), 541 (1:3:3:1, $M^+ - Br$), 515, 513, 511 (1), 509 (1:3:3:1, $M^+ - CH_4OBr$), 95 (100); ir (KBr) 2940, 1740, 1452, 1440, 1362, 1304, 1289, 1234, 1190, 1137, 1128, 1103, 1073, 1060, 1054, 1038, 1035, 1020, 914, 892, 859, 780, 725, 718, and 708 cm^{-1}; nmr, see discussion. *Anal.* Calcd for $C_{18}H_{24}O_4Br_4$: C, 34.61; H, 3.84. Found: C, 34.76; H, 3.94.

(iii) Isomer **2a**: 130 mg (16.5%); mp 117–118° dec; mass spectrum *m/e* 596, 594, 592 (0.1), 590, 588 (1:4:6:4:1, $M^+ - CH_4O$) 565, 563, 561 (0.4), 559, 557 (1:4:6:4:1, $M^+ - C_2H_7O_2$), 547, 545, 543 (0.4), 541 (1:3:3:1, $M^+ - Br$), 483, 481, 479 (0.7), 477 (1:3:3:1, $M^+ - C_2H_8O_2Br$), 469, 467, 465 (0.8), 463 (1:3:3:1, $M^+ - C_3H_8O_2Br$), 95 (100); ir (KBr), 2960, 1305, 1280, 1228, 1193, 1126, 1101, 1065, 1050, 987, 750, 715, and 695 cm^{-1}; nmr, see discussion. *Anal.* Calcd for $C_{18}H_{24}O_4Br_4$: C, 34.61; H, 3.84; Br, 51.28. Found: C, 34.44; H, 3.89; Br, 51.26.

(iv) Isomers **3a**: 250 mg (32%); mp 79–80° dec; mass spectrum *m/e* 565, 563, 561 (0.2), 559, 557 (1:4:6:4:1, $M^+ - C_2H_7O_2$), 547, 545, 543 (0.3), 541 (1:3:3:1, $M^+ - Br$), 483, 481, 479 (0.01), 477 (1:3:3:1, $M^+ - C_2H_7O_2Br$), 95 (100); ir (KBr) 2955, 1745, 1438, 1303, 1275, 1224, 1194, 1128, 1073, 1055, 1040, 985, 935, 775, 719, and 708 cm^{-1}; nmr, see discussion. *Anal.* Calcd for $C_{18}H_{24}O_4Br_4$: C, 34.61; H, 3.84; Br, 51.28. Found: C, 34.43; H, 4.00; Br, 50.78.

Reactions of the pure racemic diallene **1** (56 mg, 0.2 mmol) under the same conditions gave a mixture of the isomers **2a** (56.6 mg, 45%) and **2b** (22.5 mg, 18%), whereas reaction of the pure *meso*-diallene **3** (56 mg, 0.2 mol) gave a mixture of the isomer **4a** (62 mg, 50%) and **4b** (19 mg, 15%).

6,6,13,13-Tetramethoxycyclotetradeca-1,2,3,8,9,10-hexaene (5).—The mixture of bis(dibromocarbene) adducts **2a**, **2b**, **4a**, **4b** (100 mg, 0.15 mmol) was suspended in dry, degassed ether (5 ml) and the mixture cooled to −80° under N_2. Methyllithium (0.5 ml, 1 *M*, 0.5 mmol) was added to the magnetically stirred suspension, which was then allowed to warm to −10° and stirred for a further 30 min. Water (1 ml, distilled, degassed) was added, and the ether layer was rapidly separated and washed with water (0.5 ml, distilled, degassed). The solution was dried ($MgSO_4$) at 0° and filtered through neutral alumina (2 × 5 cm column) into a dry, N_2-filled flask at −10°. The solvent was removed by a stream of N_2 below 0° to give 6,6,13,13-tetramethoxy-1,2,3,8,9,10-cyclotetradecahexaene (**5**): mass spectrum *m/e* 304 (M^+, 63), 273 ($M^+ - CH_3O$, 38), 257 ($M^+ - C_2H_7O$, 19), 241 ($M^+ - C_2H_7O_2$, 13), 182 (35), 125 (31), 111 (44), 109 (40), 105 (63), 97 (63), 85 (60), 83 (53), 57 (100); ir (CCl_4) 2940, 2830, 1470, 1455, 1440, 1344, 1335, 1250, 1120, 1060, 875, and 703 cm^{-1}; nmr, see discussion; electronic spectrum, see discussion and Figure 1.

Reaction of either **2a** or **4a** under the same conditions gave a product identical in all observed respects with **5**.

Hydrogenation of **5**.—The dicumulene **5** (obtained from **2a**, 200 mg, 0.32 mmol) was dissolved in ethyl acetate (10 ml) at 0°, palladium on charcoal (100%; 15 mg) was added, and the mixture was stirred at 0° for 3.5 hr under a H_2 atmosphere. The catalyst was removed by filtration; the filtrate evaporated under reduced pressure to give a crystalline residue. Recrystallization from pentane gave 1,8-cyclotetradecanedione (55 mg, 76% based on **2a**), identical in all observed respects with an authentic sample.[5]

3,4,5,10,11,12-Cyclotetradecahexaene-1,8-dione (6).—The diketal **5** (obtained from **2a**, 200 mg, 0.32 mmol) was dissolved in ether (50 ml) and shaken with sulfuric acid (80%, 5 ml) at 0° for 1 min. The ether layer was separated, washed quickly with water (2 × 5 ml), and filtered through silica (2 × 5-cm column). Cooling the filtrate gave 3,4,5,10,11,12-cyclotetradecahexaene-1,8-dione (**6**): mp ~130° dec (51 mg, 75% yield based on **2a**); mass spectrum *m/e* M^+ 212.0827; calcd for $C_{14}H_{12}O_2$, 212.0837; 212 (M^+, 50), 184 ($M^+ - CO$, 52), 183 (34), 170 (16), 169 (23), 157 (19), 156 (79), 155 (99), 142 (41), 141 (100), 134 (65), 132 (60), 78 (47); ir (KBr) 1701, 1433, 1404, 1335, 1215, 1113, 930, and 714 cm^{-1}; nmr, see discussion; electronic spectrum, see discussion and Figure 1.

Reaction of 5 with Excess Bromoform and Potassium *tert*-Butoxide.—The dicumulene **5** (obtained from **2a**, 208 mg, 0.33 mmol) was dissolved in dry pentane (75 ml) and the solution cooled to −10° under N_2 with stirring. Bromoform (843 mg, 3.3 mmol) was added, and then potassium *tert*-butoxide (sublimed, 373 mg, 3.3 mmol) was slowly added over 30 min. The reaction mixture was then allowed to warm to 0° and was stirred for a further 1 hr. Ether (50 ml) was added, the mixture filtered, and the residue washed with ether (50 ml). The combined ethereal layers were evaporated, and trituration of the residue with methanol gave 8,8,16,16-tetrabromo-5,5,13,13-tetramethoxytricyclo[13.1.0.0^{7,9}]hexadeca-1,2,9,10-tetraene (**7**): mp 140° dec (22 mg, 10%); mass spectrum *m/e* 621, 619, 617, 615, 613 (1:4:6:4:1, $M^+ - CH_3O$), 589, 587, 585, 583, 581 (1:4:6:4:1, $M^+ - C_2H_7O_2$), 508, 506, 504, 502 (1:3:3:1, $M^+ - C_2H_7O_2Br$), 427, 425, 423 (1:3:1, $M^+ - C_2H_7O_2Br_2$); ir (CCl_4) 2970, 2700, 1460, 1440, 1308, 1280, 1257, 1198, 1129, 1080, 1060, and 878 cm^{-1}; nmr (60 MHz, CCl_4) 3.73 (m, 2 H, allene), 672 (s, 12 H, OCH_3), 7.2–8.1 (m, 8 H, CH_2), 8.3–8.8 (m, 2 H, cyclopropyl); electronic spectrum (EtOH), 237 nm.

Reaction of **7** (32.5 mg, 0.05 mmol) with methyllithium (0.2 ml, 1 *M*, 0.2 mmol) gave an unstable product which rapidly polymerized.

Registry No.—**1**, 29900-90-1; **2**, 40169-06-0; **3**, 29900-91-2; **4**, 40169-08-2; **5**, 34059-86-4; **6**, 34059-87-5; **7**, 40169-11-7; bromoform, 75-25-2; potassium *tert*-butoxide, 865-47-4; methyllithium, 917-54-4.

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cis,trans-5,6,7,8-Diepoxy-8-carboxamido-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridine

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The pyridine ring opening of 8-nitro- and 8-cyanotetrazolo[1,5-*a*]pyridines (**1a** and **1b**) in sodium hydroxide solution was described recently.[1] As part of this study we required 8-carboxamidotetrazolo[1,5-*a*]-pyridine (**1c**). The preparation of this compound was attempted by treatment of the nitrile **1b** with an ethanolic solution of potassium hydroxide and hydrogen peroxide.[2] However, the highly crystalline product **2**, mp 240° dec, obtained in high yield, exhibited none of

(1) B. Stanovnik and M. Tišlér, *Chimia*, **25**, 272 (1971).
(2) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **26**, 651 (1961).

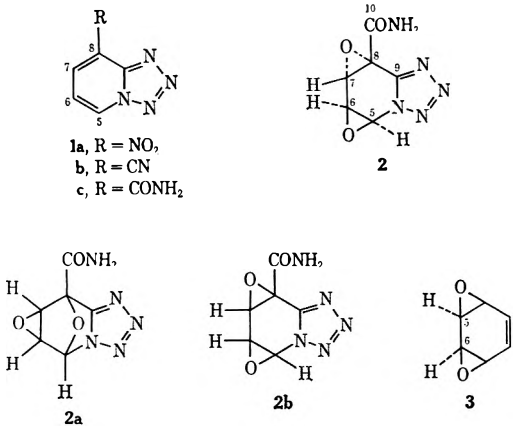

Figure 1.

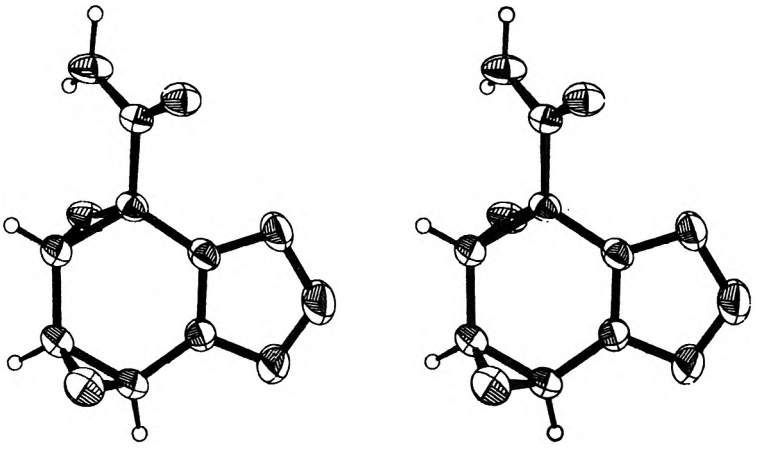

Figure 2.—Stereoview of one of the two independent molecules. The conformations of the two independent molecules are nearly identical.

the physical properties expected for the carboxamide **1c**. An inspection of the spectral data indicated that the product was the unusual heterocycle *cis,trans*-5,6,7,8-diepoxy-8-carboxamido-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridine. This structural assignment was confirmed by an X-ray crystallographic analysis.

The high-resolution mass spectrum indicated a molecular ion at *m/e* 195.0388, in agreement with the molecular formula $C_6H_5N_5O_3$, which was also confirmed by microanalysis. Since the product did not react with potassium iodide in acidic solution, the two additional oxygens in the molecule were not part of a hydroperoxide function. The absence of any uv absorption suggested that oxygenation has affected the pyridine ring system, while the infrared spectrum (Nujol) indicated the formation of a carboxamido group, 3356 (NH_2) and 1681 cm^{-1} (CO). The 100-MHz nmr spectrum (DMSO-d_6) exhibited, in addition to the signals for carboxamido protons (δ 7.84 and 7.94, br s), the signals for three vicinal protons, two of them coupled to the third proton, δ 4.50 (C_6 H, dd, $J_{5,6}$ = 3.5, $J_{6,7}$ = 2.0 Hz), 4.62 (C_7 H, d, $J_{6,7}$ = 2.0 Hz), and 6.20 (C_5 H, d, $J_{5,6}$ = 3.5 Hz). These spectral data led to the consideration of two structures, **2a** and **2b**, for the crystalline product **2** (Figure 1).

To differentiate between these two structures, the ^{13}C spectrum was examined. The proton noise decoupled natural abundance ^{13}C nmr spectrum in dimethyl sulfoxide solution exhibited six singlets, three of which became doublets in the off-resonance decoupled spectrum (Table I). This spectrum is only in accord with the structure **2b**, since it indicates that all four C_5–C_8 carbons are integral parts of epoxide rings.[3] The signals for the α carbons of tetrahydrofurans are usually at lower field at 65–75 ppm.[4] The small coupling constant between C_6 H and C_7 H of **2**, J = 2 Hz, suggests the anti arrangement of the epoxide oxygens. The coupling constant of the corresponding hydrogens in *syn*-benzene dioxide (**3**) was shown to be 2.83 Hz.[5]

The diepoxide structure (2b) and the trans stereochemistry of the product **2** were confirmed by an X-ray crystallographic analysis. Crystals of **2** are monoclinic, space group $P2_1/c$, with lattice constants a = 9.706 (2), b = 12.799 (s), c = 13.008 (2) Å, β = 107.58 (3)°. The unusually high density, d_{obsd} = 1.67 g cm^{-3} (flotation in $CCl_4/CHBr_2CHBr_2$) agrees with d_{calcd} = 1.682 g cm^{-3} for Z = 8. The intensity data were measured on a four-circle diffractometer (Cu Kα radiation, pulse height discrimination) from a crystal approximately 0.08 × 0.11 × 0.45 mm in size. The structure was solved by the multiple solution method.[6] The hydrogen atoms were located from a difference Fourier calculated after preliminary refinement of the structure. The final refinement was carried out by full matrix least squares with anisotropic thermal parameter for all atoms except the hydrogens which had individual isotropic temperature factors. The final discrepancy index is R = 4.0%.[7]

In the crystal there are two crystallographically independent molecules. The conformation of one of these molecules is shown in Figure 2. The double-bond system in the tetrazole ring is partially delocalized. The bond lengths in the ring are, N(1)–N(2), 1.372 (4); N(2)–N(3), 1.290 (4); N(3)–N(4), 1.342 (3); N(4)–C(9), 1.338 (3); C(9)–N(1), 1.310 (3) Å (average values for the two independent molecules).

TABLE I[a]

Carbon	^{13}C shift δ_C, ppm	Off resonance
	59.0	Doublet
C_5–C_7	58.5	Doublet
	51.8	Doublet
C-8	50.8	Singlet
C-9	148.7	Singlet
C-10	163.8	Singlet

[a] The spectrum was obtained on a Bruker HFX-90 spectrometer in the F. T. mode at 22.63 MHz. Chemical shifts are measured relative to internal TMS.

(3) D. B. Borders, Ping Shu, and J. E. Lancaster, *J. Amer. Chem. Soc.*, **94**, 2540 (1972).

(4) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra," Wiley, New York, N. Y., 1972, Spectra 73, 123, 125.

(5) H. J. Altenbach and E. Vogel, *Angew. Chem., Int. Ed. Engl.*, **11**, 937 (1972).

(6) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).

(7) Listings of coordinates, thermal parameters, and structure factors for **2** 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. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2717.

Experimental Section

cis,trans-5,6,7,8-Diepoxy-8-carboxamido-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridine (2).—To a solution of 1.45 g (0.01 mol) of 8-cyanotetrazolo[1,5-*a*]pyridine (**1b**) in 30 ml of ethanol was added 3 ml of 30% hydrogen peroxide and 3.5 ml of 3 *N* potassium hydroxide, and the reaction mixture was stirred at room temperature for 3 hr. After cooling in an ice–water bath the precipitated crystalline **2** was collected by filtration and washed well with ice-cold water. After recrystallization from water–methanol the product melted at 240° with decomposition.

Anal. Calcd for $C_3H_5N_5O_3$ (195.04): C, 36.93; H, 2.58; N, 35.89. Found: C, 36.81; H, 2.39; N, 36.14.

Registry No.—**1b**, 40306-97-6; **2**, 40306-98-7; hydrogen peroxide, 7722-84-1; potassium hydroxide, 1310-58-3.

o-Iodosophenylphosphoric Acid[1]

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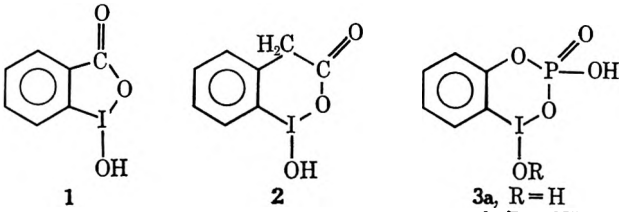
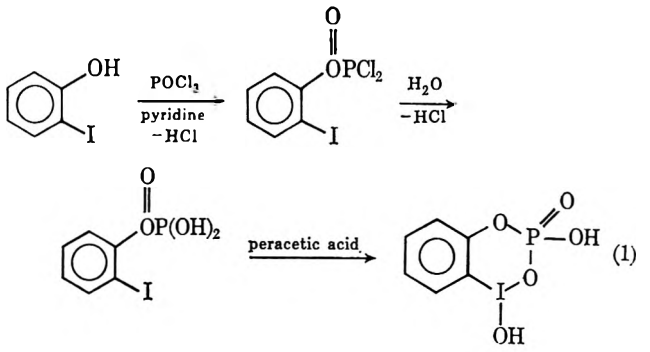
Received February 20, 1973

Heterocyclic compounds whose rings contain polyvalent iodine include the five-membered "*o*-iodosobenzoic acid" **1**,[2] several 3-butyl-2-phenylbenziodolium and tetraphenyliodolium salts,[3] and several benziodazoles[4] and benzdiiodoxoles.[5] The compound "*o*-iodosophenylacetic acid" is believed to have the six-membered cyclic structure **2**.[6] The present note describes the synthesis and properties of "*o*-iodosophenylphosphoric acid" and its methyl ester, to which we have assigned the six-membered cyclic structures **3a** and **3b**.



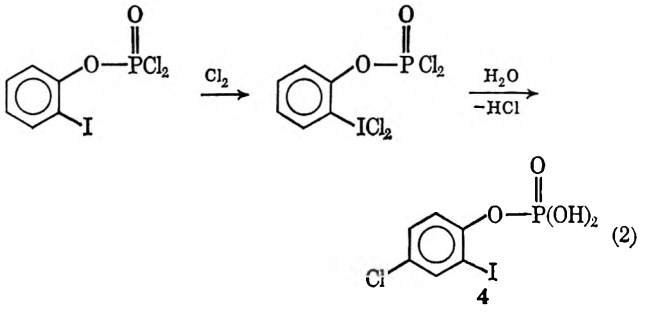
1 **2** **3a**, R = H; **b**, R = CH_3

Compounds **3** and **3a** were synthesized from *o*-iodophenol by the route shown in eq 1.



(1)

Hydrolysis of the iodosodichloride (eq 2) gave 4-chloro-2-iodophenylphosphoric acid (**4**) instead of the desired *o*-iodosophenylphosphoric acid.



(2)

4

The phosphoric acid (**4**) gives mass spectral peaks at M^+ and $M^+ - I$ as chlorine doublets. It also has a characteristic 1,2,4-substituted benzene infrared absorption pattern. In the pmr spectrum the proton ortho to iodine appears as a multiplet centered at τ 2.20, downfield from the other aromatic protons.

o-Iodosophenylphosphoric acid (**3a**) has a very broad hydrogen-bonded OH absorption in the ir with maxima at 3130 and 1643 cm^{-1}, a P=O stretch at 1236 cm^{-1}, and two peaks at 713 and 710 cm^{-1} assigned to the I–O bond.[7] The pmr spectrum in DMSO-d_6 shows a D_2O-exchangeable broad singlet at τ 1.60 for the hydroxyl protons. The proton ortho to the polyvalent iodine atom appears as a doublet at τ 2.06 (with further splitting evident).

Recrystallization of **3a** from anhydrous methanol gave the methyl derivative **3b**. The ir spectrum of **3b** has a very broad hydrogen-bonded OH absorption with maxima at 2284, 2162, and 1674 cm^{-1} similar to the spectrum of **3a**, a P=O stretch at 1230 cm^{-1}, and weak absorptions at 2945, 2923, and 2822 cm^{-1} characteristic of the methyl group. A sharp peak at 713 cm^{-1} is assigned to the I–O bond. The pmr spectrum of **3b** in DMSO-d_6 has a poorly resolved aromatic region, a singlet at τ 6.00 for the methyl group, and a singlet at τ 6.76 attributed to methanol formed by reaction with adventitious water. Upon addition of D_2O the resolution improved, giving a spectrum essentially identical with that of an equimolar mixture of **3a** and methanol in the presence of D_2O.

The equivalent weights of **3a** and **3b** were determined by iodometry, titration with base to a Methyl Red end point, and by potentiometric titration. The molecular weights were obtained by vapor phase osmometry to exclude alternative polymeric structures.

The potentiometric titration curves of **3a** and **3b** are essentially identical due to the instantaneous hydrolysis of **3b** to **3a**. The first end point (pK_{a_1} = 2.84) is sharp. The second (pK_{a_2} = 7.86), corresponding to the ionization of the weakly acidic I–OH proton, is characteristically broad. For comparison, the pK_a of **1** is 7.35[8] and the first and second pK_a's of phosphoric acid are 2.12 and 7.21.

Structure Assignments.—Structures **3a** and **3b** can be

(1) This research was supported by PHS Grant No. AM 10498 from the National Institute of Arthritis and Metabolic Diseases.

(2) C. Willgerodt, *Chem. Ber.*, **26**, 357 (1893).

(3) F. M. Beringer, P. Gavis, G. Avitabile, and H. Jaffe, *J. Org. Chem.*, **37**, 879 (1972).

(4) W. Wolf and L. Steinberg, *Chem. Commun.*, 449 (1965).

(5) W. Wolf, E. Chalekson, and D. Kobata, *J. Org. Chem.*, **32**, 3239 (1967).

(6) J. E. Leffler, L. K. Dyall, and P. W. Inward, *J. Amer. Chem. Soc.*, **85**, 3443 (1963).

(7) G. P. Baker, F. G. Mann, N. Sheppard, and A. J. Tetlow, *J. Chem. Soc.*, 3721 (1965).

(8) W. Wolf, J. C. J. Chen and L. L. J. Hsu, *J. Pharm. Sci.*, **55**, 68 (1966).

assigned to *o*-isodosophenylphosphoric acid and its methyl ester on the basis of pmr data. The position of the signal from the hydrogen ortho to iodine in **3a** (τ 2.06) is consistent with a covalent rather than an ionic structure such as $-I^+-O^-$ or $-I^+-OH$. The proton ortho to positively charged iodine in 3-butyl-2-phenylbenziodolium chloride, for example, gives a signal much further downfield at τ 1.05.[3]

A phosphate ester structure for the methyl derivative appears to be eliminated because of the absence of any phosphorus splitting (J_{POCH_3} = 7 to 15 Hz).[9] Crystals of both compounds have been subjected to X-ray diffraction,[10] but, because of complexities introduced by twinning, confirmation of the suggested structures is not yet available. The cyclic structure of **1**, however, has been confirmed by X-ray diffraction.[11]

Experimental Section

***o*-Iodophenoxyphosphorus Oxychloride.**—A solution of 82.30 g (0.374 mol) of *o*-iodophenol in 300 ml of dry hexane was added dropwise over a period of 35 min to a solution of 59.80 g (0.390 mol) of phosphorus oxychloride and 30.85 g (0.390 mol) of dry pyridine in 250 ml of dry hexane. The resulting suspension was refluxed for 1 hr and filtered through a fine sintered-glass funnel. The cloudy filtrate was concentrated under vacuum and distilled through a short column at reduced pressure giving 87 g (69%) of *o*-iodophenoxyphosphorus oxychloride as a pale yellow viscous liquid: bp 117° (0.025 mm); ir (neat) 3087, 3065, 3009, 1574, 1467, 1441, 1308 (P=O), 1264, 1201, 1121, 1050, 1039, 957, 770 (1,2 substitution), 709, and 650 cm^{-1}; nmr (neat) τ 2.08–3.20 (m, Ar H); mass spectrum *m/e* 340 (M^+ for ^{37}Cl), 338 (M^+ for ^{37}Cl and ^{35}Cl), 336 (M^+ for ^{35}Cl), 213 ($M^+ - I$ for ^{37}Cl), 211 ($M^+ - I$ for ^{37}Cl and ^{35}Cl), 209 ($M^+ - I$ for ^{35}Cl), 191, 139 ($M^+ - I - 2Cl$), 128, 127 (I^+), 92 ($C_6H_4O^+$), 76 ($C_6H_4^+$), 75, 74, 64, and 63 (PO_2^+).

Anal. Calcd for $C_6H_4ICl_2PO_2$: C, 21.39; H; 1.20; P, 9.19. Found: C, 21.77; H, 1.13; P, 9.20.

***o*-Iodophenylphosphoric Acid.**—To a flask containing 35.0 g (0.104 mol) of *o*-iodophenoxyphosphorus oxychloride was added 200 ml of distilled water. The reactants were vigorously stirred for 30 min during which an exothermic reaction suddenly ensued and a solution resulted. The solution was cooled to room temperature and extracted seven times with ether. The extracts were washed with water, dried ($MgSO_4$), evaporated, and pumped at high vacuum to give crude *o*-iodophenylphosphoric acid as a hygroscopic semisolid.

***o*-Iodosophenylphosphoric Acid (3a).**—The crude *o*-iodophenylphosphoric acid was taken up in acetone and transferred to a small flask. After removal of the solvent, the flask was thoroughly chilled in an ice–water bath and 38 g (0.250 mol) of 34.4% peracetic acid added dropwise over a period of 45 min. After addition, the frozen reaction mixture was gradually melted and warmed up to room temperature over a period of 100 min, during which it was occasionally shaken and then magnetically stirred after enough solid had melted. The resulting white suspension was poured into acetone, vigorously stirred, filtered, washed with acetone, and dried to give 23 g (70%) of crude *o*-iodosophenylphosphoric acid (**3a**). Recrystallization from 1270 ml of distilled water[12] maintained at 75–78° gave 7.0 g (22%) of pure **3a** as fine white needles: mp 123–124° dec to red oil (tube in at 120° and heated at 1–2°/min); ir (Nujol and hexachlorobutadiene) 3130 (br, OH), 3082, 1643 (br, OH), 1465, 1459, 1448, 1272, 1236 (P=O), 1140, 1122, 1031, 972, 950, 910, 869, 781 (1,2 substitution), 761, 713, and 710 cm^{-1}; nmr (DMSO-d_6) τ 1.60 (br s, 2, hydroxyl protons, exchangeable with D_2O), 2.06 (d with further splitting evident, 1, proton ortho to iodine), 2.24–2.89 (m, 3, other aromatic H).

Anal. Calcd for $C_6H_6IPO_5$: C, 22.81; H, 1.91; P, 9.80. Found: C, 22.64; H, 1.61; P, 9.74.

Equivalent weights: calcd 158; found 160 (iodometric), 159.2 (Methyl Red end point), 160.2 (potentiometric). Osmometric mol wt 314.

Disilver Salt of *o*-Iodophenylphosphoric Acid.—To a solution of the crude acid in water was added excess aqueous silver nitrate. The resulting voluminous white precipitate was filtered, washed with water, and dried to give disilver *o*-iodophenylphosphate as a white powder: mp *ca.* 170–230° dec; ir 3051, 1581, 1469, 1462, 1439, 1377, 1274, 1252, 1102, 1042, 1020, 980, 910, 853, 760, 750, 732, and 643 cm^{-1}.

Anal. Calcd for $C_6H_4Ag_2IO_4P$: C, 14.03; H, 0.78; P, 6.03. Found: C, 14.14; H, 0.52; P, 6.09.

Methyl *o*-Iodosophenylphosphoric Acid (3b).—Recrystallization of 3.00 g (0.00910 mol) of crude *o*-iodosophenylphosphoric acid (**3b**) from 425 ml of anhydrous methanol gave 1.60 g (53%, two crops) of methyl *o*-iodosophenylphosphoric acid (**3b**) as white fluffy needles: mp 122–123° dec to red oil (tube in at 122° and heated at *ca.* 1–2°/min); ir (Nujol and Fluorolube) 3070, 2944 (CH_3), 2923 (CH_3), 2822 (CH_3), 2284 (OH), 2162 (OH), 1674 (br, OH), 1581, 1461, 1448, 1439, 1263, 1232 (P=O), 1135, 1043, 1031, 1022, 978, 952, 909, 873, 781 (1,2 substitution), 759, 713, and 652 cm^{-1}.

The nmr spectrum in DMSO-d_6 exhibits a poorly resolved aromatic region consisting of a doublet at τ 2.06 (proton ortho to iodine) and a multiplet at τ 2.3–2.8 all superimposed on a broad hydroxyl absorption. There is also a sharp singlet at τ 6.00 for the iodosyl methyl, and a sharp singlet at τ 6.76 for methanol formed by hydrolysis of **3b** to **3a** by small amounts of water present in the DMSO-d_6. The intensity of these methyl singlets varies from sample to sample because of the different amounts of water present. On adding D_2O, **3b** is completely hydrolyzed, the resolution in the aromatic region improved, and the hydroxyl absorption is shifted. The resulting spectrum is identical with that of a mixture of **3a** and CH_3OD.

Anal. Calcd for $C_7H_8IPO_5$: C, 25.48; H, 2.44; P, 9.39. Found: C, 25.50; H, 2.38; P, 9.53.

Equivalent weights: calcd 165; found 168.5 (iodometric), 166.0 (Methyl Red), 168.3 (potentiometric). Osmometric mol wt 355.

***o*-Iodosodichloridephenoxyphosphorus Oxychloride.**—A stirred solution of 12.00 g (.0356 mol) of *o*-iodophenoxyphosphorus oxychloride in 27 ml of dry $CHCl_3$ was chilled in an ice–salt bath and treated with dry chlorine for 3 hr after which the precipitate was filtered, washed with hexane, and dried on the filter to give 11.0 g (76%) of *o*-iodosodichloridephenoxyphosphorus oxychloride as a yellow solid: mp 67–70° dec (gas evolution, with prior softening); ir (Nujol) 3073, 3055, 3008, 1583, 1562, 1469, 1448, 1433, 1304 (P=O), 1274, 1215, 1159, 1141, 1121, 1050, 1041, 1011, 978, 952, 889, 773 (1,2 substitution), 756, 700, and 645 cm^{-1}.

Reaction of *o*-Iodosodichloridephenoxyphosphorus Oxychloride and Water.—A suspension of 10.00 g (0.00245 mol) of *o*-iodosodichloridephenoxyphosphorus oxychloride in 12.5 ml of distilled water was vigorously stirred in the dark for 1 hr. The resulting light orange solution was extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated to give 8.20 g of a semisolid. Recrystallization from solvent–nonsolvent mixtures, such as $CHCl_3$–hexane or acetone–benzene, gave a low yield of colorless crystals of 4-chloro-2-iodophenylphosphoric acid (**4**): mp 162–164° dec to dark oil (tube in at 150° and heated at *ca.* 1–2°/min); ir (KBr) 3074, 2740 (br, OH), 1569, 1464, 1373, 1256, 1231, 1200, 1068, 1040, 1002, 945, 872 (1,2,4 substitution), 821 (1,2,4 substitution), 798, 710, 669, and 639 cm^{-1}; nmr (acetone-d_6) τ −0.94 (br s, OH, partially exchanged with acetone-d_6), 2.00–2.40 (m, 1, proton ortho to iodine), 2.40–3.25 (m, 2, other aromatic H); mass spectrum *m/e* 336 (M^+ for ^{37}Cl), 334 (M^+ for ^{35}Cl), 256 ($M^+ - PO_3H$ for ^{37}Cl), 254 ($M^+ - PO_3H$ for ^{35}Cl), 209 ($M^+ - I$ for ^{37}Cl), 208, 207 ($M^+ - I$) for ^{35}Cl), 143, 128, 127 (I^+), 99, 81, and 63.

Anal. Calcd for $C_6H_5O_4PClI$: C, 21.55; H, 1.51; P, 9.26. Found: C, 21.68; H, 1.26; P, 9.27.

Addition of silver nitrate solution to a solution of **4** in water gave a voluminous white precipitate of what was probably the disilver salt of **4**. Filtering, washing with water, and drying gave a somewhat hygroscopic white solid: mp 203–260° dec; ir (KBr) 3280 (br, H_2O), 1688, 1579, 1465, 1375, 1265, 1248, 1155, 1130, 1038, 990, 895, 875, 840, 765, 710, and 660 cm^{-1}.

(9) G. Mavel, "Progress in Nmr Spectroscopy," Vol. 1, J. W. Emsley, F. Feevy, and L. H. Sulcliffe, Eds., Pergamon Press, Elmsford, N. Y., 1966, p 251.

(10) R. McEwen and R. Gitany, private communication.

(11) E. Schefter and W. Wolf, *J. Pharm. Sci.*, **54**, 104 (1965).

(12) The material can also be crystallized from 50% aqueous THF.

Registry No.—**3a**, 40329-00-8; **3b**, 40329-01-9; **4**, 40329-02-0; **4** disilver salt, 40329-03-1; *o*-iodophenoxyphosphorus oxychloride, 40329-04-2; *o*-iodophenol, 533-58-4; phosphorus oxychloride, 10025-87-3; *o*-iodophenylphosphoric acid 40329-05-3; disilver salt of *o*-iodophenylphosphoric acid, 40329-06-4; silver nitrate, 7761-88-8; *o*-iodosodichloridephenoxyphosphorous oxychloride, 40329-07-5; chlorine, 7782-50-5.

Thermal Decomposition of a β-Ketophosphonic Acid[1]

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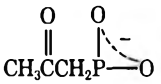
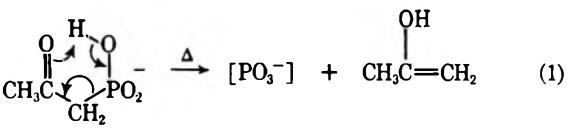
Received January 22, 1973

The decarboxylation of β-ketocarboxylic acids is a well-known reaction of synthetic[2] and mechanistic[3] interest. The reaction has received considerable kinetic study[4] and studies on its solvent dependence suggest that the reaction proceeds *via* an internally hydrogen-bonded transition state.[5] It has been proposed that β-ketosulfonamides, generated *in situ* by oxidation of 3-hydroxysulfoamides, decompose in an analogous fashion, although the intermediate keto compound has not been isolated.[6] A decomposition reaction of β-ketophosphonic acids by a similar route would be expected to lead to the initial production of the postulated (but never observed) species, monomeric metaphosphate,[7] and residual ketone. In neutral aqueous solution at room temperature, spontaneous decomposition of protonated β-ketophosphonic acids is not observed,[8] whereas protonated β-ketocarboxylic acids are readily decarboxylated.[4] We have examined the thermal lability of the monosodium salt of acetonylphosphonic acid (**1**) and of its methyl ester (**2**) in



1, R = H
2, R = CH_3

order to determine if conversion to metaphosphate and ketone (eq 1) can be brought about if more extreme conditions than those required for the analogous decarboxylation reaction are employed.



(1)

Experimental Section

The dimethyl ester of acetonylphosphonate can be conveniently prepared by published procedures.[8,9,10] Dimethyl acetonylphosphonate was converted to the monosodium salt of methyl acetonylphosphonate (**2**) by refluxing in acetone with a twofold excess of sodium iodide. The white precipitate was isolated by filtration and was recrystallized from ethanol to which ether was added, needles, mp 181–182°. *Anal.* Calcd for $C_4H_8O_4PNa$: C, 27.60; H, 4.63; P, 17.79. Found: C, 27.62; H, 4.64; P, 17.95. The sodium salt of acetonylphosphonic acid (**1**) was prepared as reported from the monomethyl ester.[8]

Studies of the thermal decomposition of these compounds were performed utilizing a bulb-to-bulb distillation apparatus under high vacuum, in order to permit the quantitative isolation of products. Acetonylphosphonic acid monosodium salt (0.30 g) was placed in one arm of the apparatus and, after pressure was below 0.1 Torr, heat was applied with an oil bath; the other arm of the apparatus was cooled in liquid nitrogen. Decomposition of the compound occurs at its melting point (146°) and heating to 150° was required to affect complete conversion. The material in the liquid nitrogen cooled arm was readily identified by its physical properties as being acetone; the isolated yield of acetone was 0.11 g (90%). The residue in the heated arm (0.18 g) was a high-melting white powder whose infrared spectrum was identical with that reported by Corbridge and Lowe[11] for $(NaPO_3)_n$, polymetaphosphate glass. Heating the sodium salt of the monomethyl ester of acetonylphosphonate to 185° (above its melting point) did not lead to the salt's decomposition.

Discussion

The reaction proposed in eq 1 (or its intermolecular counterpart) appears to be operative under the conditions studied (150°, no solvent) for **1**. The monomethyl ester of the phosphonate **2** is stable under conditions which lead to the immediate decomposition of the parent salt. Therefore, the availability of the proton of the phosphonic acid appears to be a requirement for the decomposition reaction; methyl transfer does not occur. This conforms with (but does not necessarily require) the mechanism in eq 1. The fact that the polymer of metaphosphate (rather than the elusive monomer or a lower oligomer[12]) is isolated is presumably a result of the reactive monomeric anion being produced under the conditions of high temperature necessary for the decomposition.

The thermal decomposition reaction of β-ketophosphonates is potentially of synthetic utility where the stability of the phosphonate relative to a carboxylate may be of value in an acetoacetic ester type synthesis.[13] The enolate of the phosphonate diester is a well-studied species[9] which should be readily alkylated.[13a] Ketones containing an α-halo substituent can be converted to β-ketophosphonate compounds by the Arbusov or related reactions[14] involving addition of a

(1) Support of this work by the Research Corporation is gratefully acknowledged.

(2) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold, New York, N. Y., 1961, pp 446–448.

(3) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 116–120.

(4) K. J. Pedersen, *J. Amer. Chem. Soc.*, **51**, 2098 (1929), and references cited therein.

(5) F. H. Westheimer and W. A. Jones, *ibid.*, **63**, 3283 (1941).

(6) E. J. Corey and T. Durst, *ibid.*, **88**, 5656 (1966).

(7) W. W. Butcher and F. H. Westheimer, [*J. Amer. Chem. Soc.*, **77**, 2420 (1955)] invoked this species to explain the peculiar pH dependence of the rate of hydrolysis of methyl phosphate, noting that Todd proposed in a lecture in 1954 that metaphosphate was an intermediate in phosphorylation reactions. The current status and applications of the metaphosphate hypothesis have recently been summarized by D. G. Gorenstein [*J. Amer. Chem. Soc.*, **94**, 2523 (1972)].

(8) R. Kluger and P. Wasserstein, *ibid.*, **95**, 1071 (1973).

(9) F. A. Cotton and R. A. Schunn, *ibid.*, **85**, 2394 (1963).

(10) H. I. Jacobson, M. J. Griffith, S. Preis, and E. V. Jensen, *ibid.*, **79**, 2608 (1957).

(11) D. E. C. Corbridge and E. J. Lowe, *J. Chem. Soc.*, 493 (1954).

(12) E. Thilo, *Angew. Chem., Int. Ed. Engl.*, **4**, 1061 (1965).

(13) C. R. Hauser and B. E. Hudson, Jr., *Org. React.*, **1**, 266 (1942).

(13a) NOTE ADDED IN PROOF.—P. A. Grieco and C. S. Pogonowski [*J. Amer. Chem. Soc.*, **95**, 3071 (1973)] have recently developed methods for alkylation of the 4 position of dimethyl acetonylphosphonate.

(14) G. M. Kosolapoff, *Org. React.*, **6**, 273 (1951).

phosphite to a "positive carbon atom" adjacent to the carbonyl function. Carboxylation reactions generally require proceeding *via* the α-keto carbanion. The differences in polarity of precursor species to the phosphonate and carboxylate, respectively, should be of utility for specific synthetic strategies.

Registry No.—1, 40463-76-1; 2, 40463-77-2; dimethyl acetonylphosphonate, 4202-14-6; sodium iodide, 7681-82-5.

Induced Decomposition of Di-*tert*-butyl Peroxide Using Chlorotris(triphenylphosphine)rhodium(I)/Hydrogen

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Heterogeneous hydrogenation of peroxides using various metal systems is well known.[1] The fact that nearly quantitative yields of alcohols are obtained without apparent secondary radical reactions such as β scission suggest either concerted cis addition of hydrogen or a very rapid sequential reaction which does not allow the escape of free alkoxy radicals. We now wish to report the induced decomposition of di-*tert*-butyl peroxide in a chlorotris(triphenylphosphine)rhodium(I)/hydrogen homogeneous system.

Hydrogenation of di-*tert*-butyl peroxide using chlorotris(triphenylphosphine)rhodium(I) in benzene solution yielded *tert*-butyl alcohol and acetone. The reaction is first order in catalyst, first order in peroxide (Figure 1), zero order in hydrogen pressure, and inversely proportional to added triphenylphosphine above a 1:1 weight ratio based on catalyst. It can be seen in Table I that only simple phosphine–rhodium (or ruthenium) halide systems are effective. Uncatalyzed reactions under identical conditions (but no catalyst or catalyst but no hydrogen) show only trace (1–3%) peroxide decomposition. Introduction of either radical-stabilizing solvents or effective hydrogen-transfer agents resulted in increased selectivity to *tert*-butyl alcohol (Table II).

TABLE I
EFFECT OF VARIOUS CATALYST SYSTEMS ON SELECTIVITY TO *tert*-BUTYL ALCOHOL[a]

Registry no.	Catalyst[b]	% reacted di-*tert*-butyl peroxide (conversion)	Yield *tert*-butyl alcohol based on reacted peroxide[c] (selectivity)
14694-95-2	L_3RhCl	29	58
14973-89-8	L_3RhBr	53	59
18284-36-1	L_4RhH	2	
13938-94-8	$L_2(CO)RhCl$	1	
20097-11-4	$L_2(NO)RhCl_2$	1	
15529-49-4	L_3RuCl_2	23	61

[a] Data for 0.043 mmol of catalyst, 20 mg of Ph_3P, 5.4 mmol of di-*tert*-butyl peroxide, 30 ml of benzene, 600 psig of hydrogen, 120°, and 1 hr reaction time. [b] L = triphenylphosphine. [c] Remainder was converted to acetone.

TABLE II
EFFECT OF VARIOUS ADDITIVES ON SELECTIVITY TO *tert*-BUTYL ALCOHOL[a]

Additive	g	% reacted di-*tert*-butyl peroxide (conversion)	Yield *tert*-butyl alcohol based on reacted peroxide[b] (selectivity)
Tetralin	1.0	80	94
Phenol	1.0	9	100
m-Cresol	0.5	85	99
Ionol[c]	0.5	57	86

[a] Data for 0.043 mmol of $(Ph_3P)_3RhCl$, 20 mg of Ph_3P, 5.4 mmol of di-*tert*-butyl peroxide, 30 ml of benzene, 600 psig of hydrogen, 120°, and 1 hr reaction time. [b] Remainder converted to acetone. [c] 2,6-Di-*tert*-butyl-4-methylphenol.

Of the additives tested, *m*-cresol appeared to be the best from the standpoint of reaction rate and selectivity. Quantitative measurements indicate that *m*-cresol was not destroyed in the reaction.

A mechanism which involves no induced decomposition and only simple abstraction of rhodium hydrogen seems unlikely because (1) the rate of peroxide decomposition is rapid relative to identical metal-free systems and (2) the rate of disappearance of peroxide is proportional to catalyst concentration, while the selectivity to *tert*-butyl alcohol is independent of catalyst

$$(CH_3)_3COOC(CH_3)_3 \xrightarrow{\Delta} 2(CH_3)_3CO\cdot \quad (1)$$

$$(CH_3)_3CO\cdot \xrightarrow{MH} (CH_3)_3COH \quad (2)$$

$$(CH_3)_3CO\cdot \longrightarrow CH_3COCH_3 + CH_3\cdot \quad (3)$$

$$HRh\ (complex) + (CH_3)_3COOC(CH_3)_3 \longrightarrow (CH_3)_3COH + (CH_3)_3CO\cdot + Rh\ (complex) \quad (4)$$

concentration. We suggest that a rhodium–hydrogen complex leads to the induced decomposition of peroxide resulting in the formation of free radicals. It should be noted that not all of the rhodium complexes in Table I induce peroxide decomposition. This might be explained by analogy to olefin hydrogenation activity in which these complexes exhibit diverse activity.[2] The inverse dependence on triphenylphosphine might be explained by loss of a triphenylphosphine moiety in the course of reaction; the facility with which the various complexes in Table I could lose a triphenylphosphine moiety is in general agreement with the observed induced decompositions.[2] Indeed, induced decomposition of nonmetallic systems is well known. Induced decomposition of di-*tert*-butyl peroxide has been reported by workers at Shell[3] in explaining increased decomposition rates of neat di-*tert*-butyl peroxide and by

(1) For discussion and references see P. N. Rylander, "Catalytic Hydrogenation over Platinium Metals," Academic Press, New York, N. Y., 1967, p 489.

(2) H. D. Kaesz and R. B. Saillant, *Chem. Rev.*, **72**, 263 (1972), and references cited therein.

(3) E. R. Bell, F. F. Rust, and W. E. Vaughan, *J. Amer. Chem. Soc.*, **72**, 337 (1950).

Huyser, Bredeweg, and Van Scoy[4,5] in explaining increased decomposition rates of di-*tert*-butyl peroxide in primary and secondary alcohols and amines.

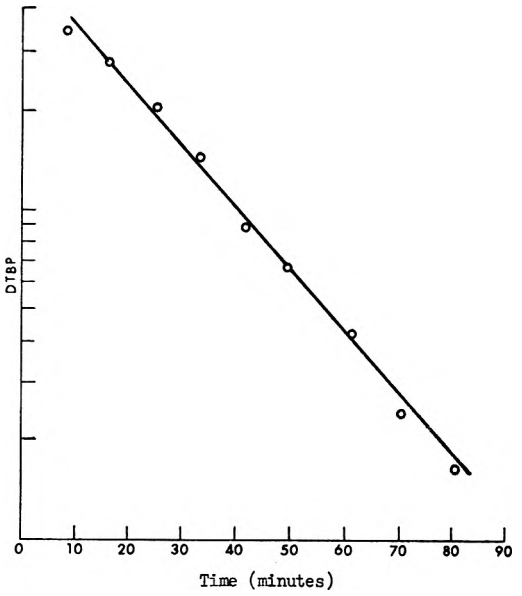

Figure 1.—First-order plot for the decomposition of di-*tert*-butyl peroxide (DTBP) in benzene with 0.043 mmol of L_2RhCl, 600 psig H_2, 20 mg of Ph_3P, 120°.

Experimental Section

Materials.—Except for the metal systems, commercial materials were used in this work: benzene, triphenylphosphine, tetralin, phenol, *m*-cresol, and Ionol. The following metal complexes were prepared as previously described: $(Ph_3P)_3RhCl$,[6,7] $(Ph_3P)_3RhBr$,[7] $(Ph_3P)_2CORhCl$,[7] $(Ph_3P)_4RhH$,[8] and $(Ph_3P)_3RuCl_2$.[9]

Decomposition of Di-*tert*-butyl Peroxide.—A solution of 0.79 g (5.4 mmol) of di-*tert*-butyl peroxide, 0.020 g (0.076 mmol) of Ph_3P, and 30 ml of benzene was charged in a nitrogen atmosphere to an 80-ml Inconel magnetically stirred autoclave (total free space including system, 126 ml). A pressure of 600 psig hydrogen was charged to the vessel. The temperature (120°) was maintained ±1% by a thermostatically controlled heating mantle. In experiments using metal catalysts, 0.043 mmol of catalyst was also added to the reaction solution. In experiments in which $(Ph_3P)_3RhCl$ concentrations were varied, 0.021, 0.06, and 0.09 mmol of catalyst were employed. The reaction mixture was analyzed by standard glc techniques for di-*tert*-butyl peroxide, *tert*-butyl alcohol, and acetone.

Decomposition of Di-*tert*-butyl Peroxide with Additives.—The above procedure and amounts of reactants were used and 0.5- or 1.0-g amounts of tetralin, phenol, *m*-cresol, or Ionol were also added. Glc analysis showed no loss of *m*-cresol in *m*-cresol experiments.

Registry No. —*tert*-Butyl alcohol, 75-65-0; *tert*-butyl peroxide, 110-05-4.

Acknowledgment.—The authors are grateful to Dr. L. H. Gale and Dr. H. V. Holler for helpful discussions.

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(6) K. C. Dewhirst, U. S. Patent 3,489,786 (1970), to Shell Oil Co.

(7) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc.*, 1711 (1966).

(8) K. C. Dewhirst, W. Keim, and C. A. Reilly, *Inorg. Chem.*, **7**, 546 (1968).

(9) T. A. Stephenson and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **28**, 1945 (1966).

The Acid-Catalyzed Addition of Acetic Acid to 2-Arylbornenes and 2-Arylapobornenes

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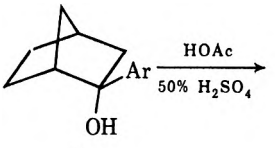
Ample results from product studies involving arylnorbornyl cationic intermediates have shown that the thermodynamically controlled product is often derived from a rearranged cation. An example that illustrates the above is the rearrangement observed in the interaction of 2-*exo*-aryl-2-*endo*-norbornanols (**1**) and 2-arylnorbornenes (**2**) with acetic acid in the presence of sulfuric acid to yield 1-aryl-*exo*-2-norbornyl acetates (**3**).[1]



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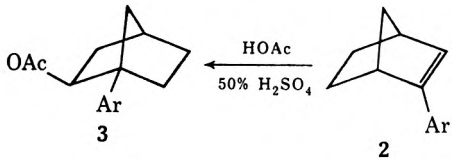

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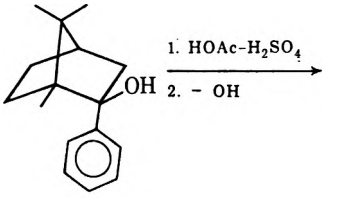
One of the more intriguing results of this type is the reported rearrangement of 2-*endo*-phenyl-2-*exo*-borneol (**4**) and 1-phenylcamphene (**5**) to produce 4-phenylisoborneol (**6**).[2] Obviously a gross structural reorganization has taken place, although the final product is again derived from a secondary norbornyl cation.



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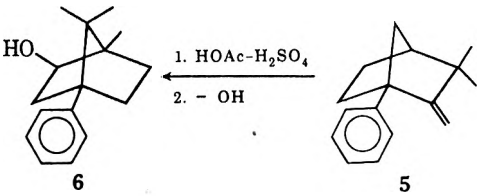


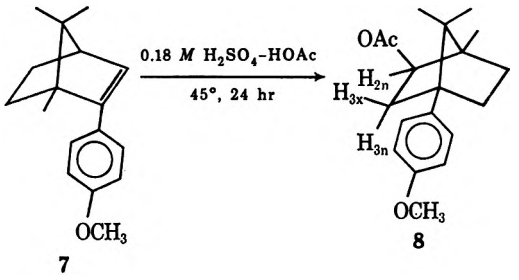
6 5

These earlier observations can be readily confirmed by utilizing nmr structural assignments. Thus, the treatment of 2-*p*-anisylbornene (**7**) with acetic acid and sulfuric acid under rigorous conditions produced almost exclusively 4-*p*-anisyl-2-*exo*-bornyl acetate (**8**).

When the reaction was carried out with the same reagent at 25° for 0.5 hr, the only product isolated was

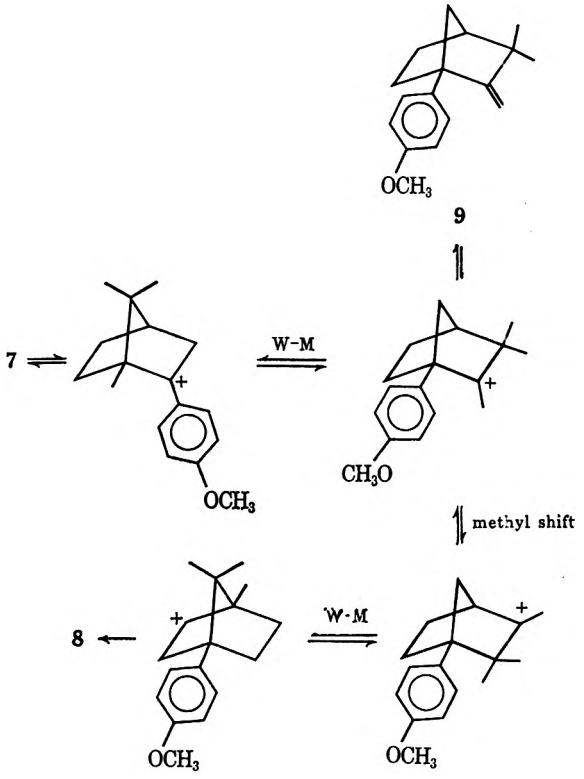
(1) For an excellent review on these and related rearrangements involving arylnorbornyl cations, see D. C. Kleinfelter, Ph.D. Thesis, Princeton University, 1960.

(2) (a) J. Bredt, *J. Prakt. Chem.*, **98**, 96 (1918); (b) S. Nametkin, A. Kitschkin, and D. Kurssanoff, *ibid.*, **124**, 144 (1930); (c) S. Leduc, *C. R. Acad. Sci.*, **180**, 1502 (1925).



7 8

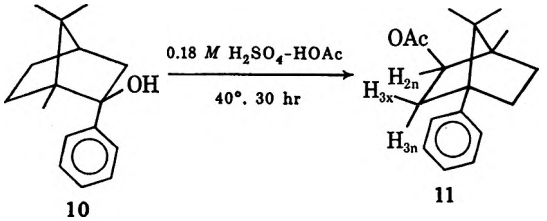
1-*p*-anisylcamphene (**9**). The intermediate **9** was slowly converted to **8** under the milder reaction conditions. A rearrangement scheme consistent with the formation of **8** and **9** is one involving a 3,2-methyl



shift.[3] An analogous scheme accounts for many aspects of the formolysis of the 2-*p*-anisylcamphenilols.[4]

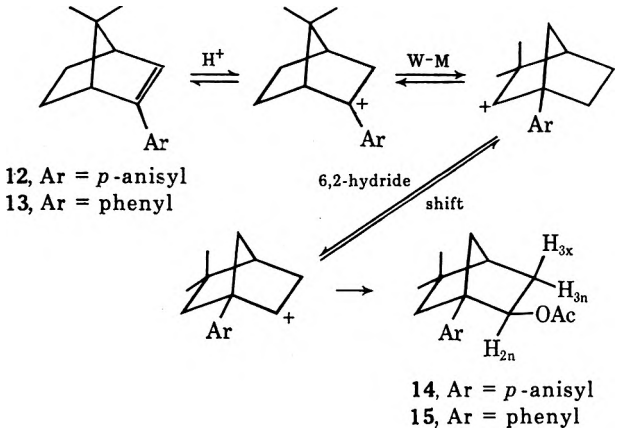
It is interesting to note that again rearrangements occur until a secondary norbornyl cation can be trapped, and acetates derived from the capture of a benzylic or tertiary norbornyl cation are apparently very labile and are not observed.

When the alcohol *endo*-2-phenyl-*exo*-2-bornanol (**10**) was treated directly with the acetic acid reagent the final product was again 4-phenyl-*exo*-2-bornyl acetate (**11**). When this acetolysis was carried out in acetic acid-d_1 and sulfuric acid-d_2, extensive deuterium incorporation occurred in the methyl groups as well as at C-3. Dideuteration at C-3 was evidenced by the complete collapse of the multiplet for H_{2n} and offers support for the structural assignment. The deuterium incorporation into the methyl groups occurred to approximately 67% and is consistent with a methyl shift and equilibration with the camphene intermediate. It was not possible to distinguish precisely the deuterium fraction in each of the methyls, although there appeared to be deuterium in all three methyls in spite of the known preference for exo methyl shifts.[3,5,6]



10 11

The complications associated with the arylbornene to arylcamphene rearrangement can be avoided in the 2-arylapobornene systems **12** and **13** where the bridgehead methyl is lacking. Treatment of the olefins **12** and **13** under similar thermodynamically controlled conditions again produced a rearranged secondary acetate whose structure is assigned to the 1-aryl-5,5-dimethyl-*exo*-2-norbornyl acetates **14** and **15**, respectively. A Wagner–Meerwein rearrangement followed by a 6,2-hydride shift can account for the formation of **14** and **15**.



14, Ar = *p*-anisyl
15, Ar = phenyl

The final acetates **14** and **15** are not derived from the first formed secondary carbonium ion intermediate but instead from a more accessible secondary norbornyl cation (not flanked by geminal dimethyls). This β-methyl steric effect has been noted previously by Berson[7] in his thorough study of hydride shifts in methylnorbornyl cations.[5,7] Also, no products could be detected in this instance that would be derived from a methyl shift as observed in the bornene systems. The nmr parameters for the bornene and apobornene systems are listed in Table I. Deuterium incorporation observed in the addition of acetic acid-d_1 and sulfuric

TABLE I

NMR SPECTRA[a] OF ACETATES 8, 11, 14, AND 15

Compd	Chemical shift,[b] ppm, for H_{2n}	Observed splittings, Hz[c] $J_{2n,3n}$	$J_{2n,3x}$
8	4.75 (dd)	8.0	3.5
11	4.75 (dd)	8.0	4.0
14	4.88 (dd)	8.0	3.5
15	4.94 (dd)	7.0	3.5

[a] Correct integration obtained for structure as listed. [b] In δ units, TMS internal reference, $CDCl_3$ solvent, at 60 MHz. [c] Long-range interaction less than 1 Hz.

(3) For examples of methyl shifts in closely related systems, see D. L. Adams and W. R. Vaughan, *J. Org. Chem.*, **37**, 3906 (1972), and references cited therein.

(4) P. B. Bartlett, E. R. Webster, C. E. Dills, and H. G. Richey, Jr., *Justus Liebigs Ann. Chem.*, **623**, 217 (1959).

(5) J. A. Berson, R. G. Bergman, J. H. Hammons, A. W. McRowe, A. Remanic, and D. Houston, *J. Amer. Chem. Soc.*, **87**, 3246 (1965).

(6) However, for an example of an endo 3,2-methyl shift, see S. Rengaraju and K. D. Berlin, *Tetrahedron*, **27**, 2399 (1971).

(7) J. A. Berson, A. W. McRowe, and R. G. Bergman, *J. Amer. Chem. Soc.*, **89**, 2573 (1967).

acid-d_2 to **12** and **13** is again consistent with the structural assignments.

Apparently in the apobornene systems the normal rate of solvent capture is inhibited by the β-methyl steric effect and the 6,2-hydride shift becomes more than competitive.[8] This steric inhibition of solvation has recently been noted by Kleinfelter and Watsky in studies involving the 3-*exo*-phenyl-2-norbornyl cation intermediates.[9] In fact, they suggest that a 3-*exo*-phenyl group blocks the approach to a 2-norbornyl cation intermediate more effectively than a 7-*syn*-phenyl group does. Furthermore, they have observed in their studies of the 3-phenyl-2-norbornyl cation system,[9,10] that in unbuffered acetic acid (thermodynamically controlled conditions) products derived from the 1-phenyl-2-norbornyl cation are formed in substantial quantities, in agreement with the present study.

In summary, it appears that, under equilibration conditions, the initially formed tertiary and benzylic norbornyl cation derived from arylbornenes or arylapobornenes will also rearrange to yield products resulting from the capture of a secondary cation. The results with the arylapobornene system suggest that, when more than one interconvertible secondary site is available, acetates will be derived from the more accessible one.

Experimental Section

Analytical.—Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60D spectrometer where the internal standard was tetramethylsilane. Galbraith Laboratories, Inc., Knoxville, Tenn., performed all the microanalyses. The melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

Reagents.—Acetic acid-d_1 (99.5%) and sulfuric acid-d_1 (99%) were obtained from Bio-Rad Laboratories. Apocamphor was synthesized according to the procedure developed by Brown, Kawakami, and Misumi.[11]

Synthesis of the Aryl Olefins 7, 12, and 13.—The aryl olefins were made by the Grignard reaction of the appropriate ketone and arylmagnesium halide to yield the corresponding aryl alcohol. These alcohols were directly dehydrated by stirring a few minutes with boron trifluoride etherate at room temperature. An attempted dehydration of **10** produced considerable phenylcamphene, as has been noted elsewhere.[12]

2-*p*-Anisylbornene (**7**) was recrystallized from cyclohexane to yield (almost quantitatively) pure **7**: mp 62–63°; nmr δ 5.85 (d, 1 H, $J_{3,4}$ = 3.0 Hz, vinyl H at C-3), bridgehead proton at H_4 centered at 2.44.

Anal. Calcd for $C_{17}H_{22}O$: C, 84.21; H, 9.15. Found: C, 84.37; H, 9.30.

2-*p*-Anisylapobornene (**12**) was purified by distillation, 45° (0.2 mm). This material subsequently solidified and was recrystallized from cyclohexane to yield 87% **12**: mp 44–45°; nmr δ 6.02 (d, 1 H, $J_{3,4}$ = 3.5 Hz, vinyl H at C-3), bridgehead protons at 2.60 and 2.30.

Anal. Calcd for $C_{16}H_{20}O$: C, 84.02; H, 8.83. Found: C, 84.03; H, 8.80.

2-Phenylapobornene (**13**) was likewise made from apocamphor and purified by distillation at 70° (0.1 mm) in a yield of 89%. An nmr spectrum exhibited the vinyl proton at C-3 at δ 6.08 with J = 3.0 Hz. The bridgehead hydrogens occur at δ 2.58 and 2.28. Difficulty was experienced in obtaining an acceptable microanalysis for **13** even though it appeared to be homogeneous by ir, nmr, tlc, and vpc techniques. In this instance, we purified and characterized the corresponding alcohol, *endo*-2-phenyl-*exo*-2-apobornanol. The alcohol distilled at 115° (0.2 mm).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.42; H, 9.63. Found: C, 83.30; H, 9.66.

4-Phenyl-2-*exo*-bornyl Acetate (11).—*endo*-2-Phenyl-*exo*-2-bornanol (**10**), 3.02 g (13.0 mmol), was dissolved in 50 ml of 0.18 *M* sulfuric acid in acetic acid and warmed to 40° for 30 hr. An nmr spectrum showed *ca.* 95% conversion to the title acetate in the recovered product (isolated as below). The product was recrystallized from cyclohexane, mp 84–85°.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.89. Found: C, 79.32; H, 8.97.

Acid-Catalyzed Addition of Acetic Acid to the Aryl Olefins 7, 12, and 13.—The procedure used is described for the formation of 4-*p*-anisyl-*exo*-2-bornyl acetate (**8**). 2-*p*-Anisylbornene (**7**), 3.50 g (1.5 mmol), was dissolved in 50 ml of 0.18 *M* sulfuric acid in acetic acid and warmed to 40° for 24 hr. Work-up consisted of an ether extraction where the extracts were washed with a 10% sodium bicarbonate solution. The ether extracts were dried (magnesium sulfate) and the solvent was removed under vacuum. An nmr spectrum on the crude product indicated *ca.* 95% conversion to the title acetate (**8**). The acetate was distilled, 75° (0.2 mm).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 75.46; H, 8.67. Found: C, 75.39; H, 8.59.

The conversion of **12** to 1-*p*-anisyl-5,5-dimethyl-*exo*-2-norbornyl acetate (**14**) was accomplished at 40° in 24 hr. An nmr spectrum showed the crude product to be *ca.* 85% **14** with the remainder being an unidentified but presumably polymeric type material. The acetate was purified by thick layer chromatography using silica gel G and a 2:1 chloroform to carbon tetrachloride mixture as the eluent. The acetate **14** was then distilled at 70° (0.1 mm).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.18; H, 8.49.

The formation of 1-phenyl-5,5-dimethyl-*exo*-2-norbornyl acetate (**15**) was accomplished as above with the crude product being close to 95% **15**. Purification was by distillation at 70° (0.1 mm).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.51. Found: C, 79.04; H, 8.51.

Registry No.—**7**, 31059-45-7; **8**, 40635-57-2; **10**, 40548-30-9; **11**, 40548-31-0; **12**, 40548-32-1; **13**, 40548-33-2; **14**, 40548-34-3; **15**, 40548-35-4; camphor, 76-22-2; apocamphor, 514-15-8; *endo*-2-phenyl-*exo*-2-apobornanol, 40548-36-5; acetic acid, 64-19-7.

Acknowledgment.—We are indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

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(9) M. B. Watsky, Ph.D. Dissertation, University of Tennessee, 1970.
(10) D. C. Kleinfelter, E. S. Trent, J. E. Mallory, and T. E. Dye, *J. Amer. Chem. Soc.*, **88**, 5350 (1966); *J. Org. Chem.*, **32**, 1734 (1967).
(11) H. C. Brown, J. H. Kawakami, and S. Misumi, *J. Org. Chem.*, **35**, 1360 (1970).
(12) J. M. Coxon, M. P. Hartshorn, and A. J. Lewis, *Aust. J. Chem.*, **24**, 1017 (1971).

Thermal Rearrangements of Bicyclo[3.1.0]hex-2-ene. Conversion of 3-Deuteriobicyclo[3.1.0]hex-2-ene to 1,3- and 1,4-Cyclohexadiene-d_1

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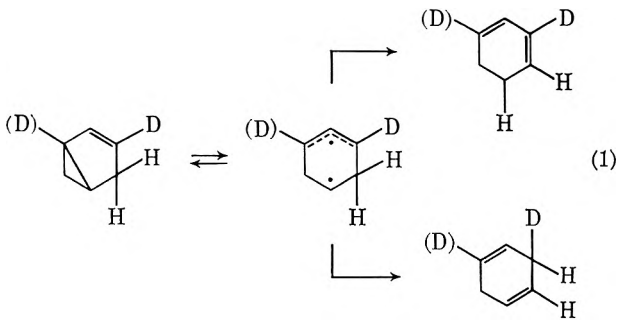
Detailed investigations[1] of the automerization of bicyclo[3.1.0]hex-2-ene have included studies of the reactivity at temperatures where nondegenerate pro-

(1) R. S. Cooke and U. H. Andrews, unpublished results.

cesses are important. Current controversy[2-8] over the mechanism of the isomerization of bicyclo[2.1.0]-pent-2-ene to cyclopentadiene prompts a report concerning the rearrangement of bicyclo[3.1.0]hex-2-ene to 1,3- and 1,4-cyclohexadiene.

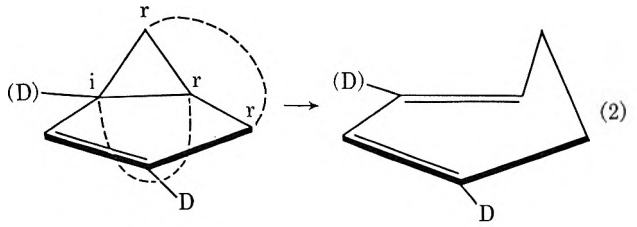
The transformation of bicyclo[3.1.0]hex-2-ene to 1,3- and 1,4-cyclohexadiene has been discussed[9] in terms of a mechanism involving a biradical intermediate arising from cleavage of the internal cyclopropane bond. The simplest representation of this process in which an intermediate possessing C_{2v} symmetry undergoes rate-determining 1,2 hydrogen migration is shown below (eq 1). It has been noted[9] that



(1)

1,3-cyclohexadiene might also arise upon 1,4 hydrogen migration.

An alternative mechanism effecting these transformations is an orbital symmetry allowed $_{\sigma}2_s + _{\sigma}2_a$ process not requiring hydrogen migration (eq 2 and 3).



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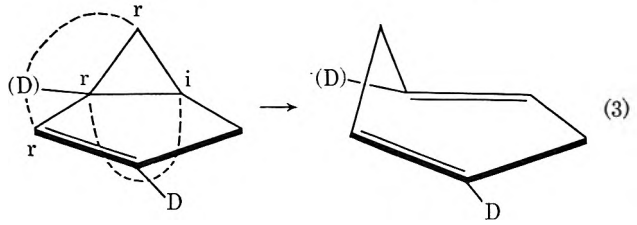

(3)

The relative importance of the $_{\sigma}2_s + _{\sigma}2_a$ and biradical mechanisms may be estimated by examination of the deuterium distribution in the cyclohexadienes-d_1 formed in the pyrolysis of 3-deuteriobicyclo[3.1.0]hex-2-ene. Since deuterium is scrambled in the bicyclic material much faster than isomerization occurs,[10] one may consider rearrangement of a species with one-half deuterium atom in the C_1 and C_3 positions.

In a typical experiment, 0.180 ml of 3-deuteriobicyclo[3.1.0]hex-2-ene, with 0.874 ± 0.006 deuterium atoms at the C_3 position and none elsewhere, was pyrolyzed in a well-seasoned plug-flow reactor at a nominal temperature of 432 ± 1°. Nitrogen was used as the carrier gas and the nominal residence time was 15.2 ± 0.5 sec. Recovered material contained bicyclo-[3.1.0]hex-2-ene-d_1 (0.358 ± 0.002), 1,4-cyclohexadiene-d_1 (0.162 ± 0.002), 1,3-cyclohexadiene-d_1 (0.381 ± 0.002), and benzene (0.100 ± 0.003). The products were separated and the pmr spectra were examined. A summary of the values of the allylic hydrogen/olefinic hydrogen ratio in 1,4-cyclohexadiene-d_1 expected for each mechanism and those found experimentally is shown in Table I.

TABLE I

PREDICTED AND EXPERIMENTAL ALLYLIC HYDROGEN/OLEFINIC HYDROGEN RATIOS IN 1,4-CYCLOHEXADIENE-d_1

Biradical mechanism 1,2 H	1.00[a]
$_{\sigma}2_s + _{\sigma}2_a$ mechanism	1.28
Experimental	0.992 ± 0.023
	0.985 ± 0.030

[a] The predicted ratio will probably be slightly less than that listed owing to the unknown primary deuterium isotope effect on the rate of conversion of this compound to benzene. See ref 9; S. W. Benson and R. Shaw, *Trans. Faraday Soc.*, **63**, 985 (1967); I. Fleming and E. Wildsmith, *J. Chem. Soc. D*, 223 (1970).

At 100 MHz the signals due to the two types of olefinic hydrogens in 1,3-cyclohexadiene are not resolved. Treatment of the recovered 1,3-cyclohexadiene-d_1 with maleic anhydride gave the expected Diels–Alder adduct.[11] Examination of the pmr spectrum permitted determination of the deuterium distribution at each position in 1,3-cyclohexadiene-d_1. These results are shown in Table II. Examination of

TABLE II

PREDICTED AND EXPERIMENTAL HYDROGEN RATIOS IN BICYCLO[2.2.2]OCT-2-ENE-5,6-DICARBOXYLIC ANHYDRIDE-d_1

	Olefinic	Methine	Methylene
Biradical 1,4 H	1.00	2.560	2.280
1,2 H	1.00	2.280	2.560
$_{\sigma}2_s + _{\sigma}2_a$	1.00	2.280	2.560
Statistical distribution	1.00	2.123	2.000
Experimental	1.00	2.118 ± 0.038	2.002 ± 0.036
	1.00	2.157 ± 0.036	2.003 ± 0.035

the dmr spectrum of the adduct verified that deuterium was statistically distributed in the recovered 1,3-cyclohexadiene-d_1.

Only a minor amount of the conversion of bicyclo-[3.1.0]hex-2-ene to 1,4-cyclohexadiene could result from operation of the $_{\sigma}2_s + _{\sigma}2_a$ mechanism. The major pathway probably involves a biradical intermediate which suffers rate-determining 1,2-hydrogen shift. However, orbital symmetry allowed mechanisms which involve synchronous cleavage of the cyclopropane ring and hydrogen migration are also consistent with the present results. The most reasonable of these find analogy in the conversion of *cis*-1-methyl-

(2) J. I. Brauman and D. M. Golden, *J. Amer. Chem. Soc.*, **90**, 1920 (1968).

(3) D. M. Golden and J. I. Brauman, *Trans. Faraday Soc.*, **65**, 464 (1969).

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(8) M. C. Flowers and H. M. Frey, *J. Amer. Chem. Soc.*, **94**, 8636 (1972).

(9) R. J. Ellis and H. M. Frey, *J. Chem. Soc. A*, 553 (1966).

(10) Identical results are obtained when 3-deuteriobicyclo[3.1.0]hex-2-ene or preequilibrated material where deuterium is distributed equally in the C_1 and C_3 positions is employed in the isomerizations.

(11) G. S. Hammond and J. Warkentin, *J. Amer. Chem. Soc.*, **83**, 2554 (1961).

2-vinylcyclopropane to *cis*-hexa-1,4-diene.[12,13] Owing to a rapid scrambling process in the product, no mechanistic statements may be made concerning the formation of 1,3-cyclohexadiene. The mechanism of the scrambling pathway presumably involves sequential [1,5]-sigmatropic shifts.[14-24]

Experimental Section

Preparation of 3-Deuteriobicyclo[3.1.0]hex-2-ene.—Cyclopenten-3-ol was prepared from cyclopentadiene using a slight modification of the procedure described by Allred, Sonnenberg, and Winstein.[25] Bicyclo[3.1.0]hexan-3-ol was prepared using a modification of the procedure of Winstein and Sonnenberg[26] employing the zinc–copper couple described by LeGoff.[27] The oxidation procedure of Corey and Dawson[28] was used to prepare bicyclo[3.1.0]hexan-3-one. The overall sequence was performed in 8.8% average yield.

A 4.023-g (41.9 mmol) sample[29] of bicyclo[3.1.0]hexan-3-one was reduced with 0.885 g (21.1 mmol) of lithium aluminum deuteride according to the procedure of Winstein and Sonnenberg.[26,30] Following work-up, the ether solution of 3-deuteriobicyclo[3.1.0]hexan-3-ol was concentrated to 30 ml by distillation employing a 15-cm Vigreux column.

A 250-ml three-necked flask was charged with 1.34 g (55.9 mmol) of sodium hydride and 50 ml of dry ether. The flask was fitted with a stirring bar, addition funnel, serum cap, and reflux condenser topped with a gas inlet–outlet system. The stirred slurry was heated to reflux under a nitrogen atmosphere for the entire course of the reaction. The solution of alcohol from above was added dropwise over 35 min. After 3 hr, 3.47 g (45.7 mmol) of carbon disulfide was added slowly by syringe. After an additional 3 hr, 9.25 g (65.0 mmol) of methyl iodide was added slowly by syringe. After an additional 11 hr, water was carefully added and the reaction mixture was washed with four 20-ml portions of water. The ether layer was dried over magnesium sulfate, filtered, and concentrated under vacuum. Bulb-to-bulb distillation at 0.005 mm gave 7.175 g of methyl 3-(3-deuteriobicyclo[3.1.0]hexyl)xanthate[31] as a clear yellow oil.

A 15-ml flask fitted with a short-path still was charged with the xanthate mixture. The material was heated in an oil bath at 186–190°. The pyrolysate was redistilled to give 2.077 g of 3-deuteriobicyclo[3.1.0]hex-2-ene boiling in the range 72–74°. The overall sequence from bicyclo[3.1.0]hexan-3-one was performed in 61.9% yield.

Final purification was achieved by preparative glpc on a 3.0 m × 4.5 mm 21% β,β′-oxydipropionitrile on Chromosorb P column at 50°. The material was compared with an authentic sample of bicyclo[3.1.0]hex-2-ene prepared by the method of Schnieder and Crawford.[32] Examination of the pmr spectrum[33] revealed 0.126 ± 0.006 residual protons at the C_3 position when the signal at δ 5.40 was compared with the signal at δ 5.96 due to the proton at the C_2 position. Examination of the dmr spectrum of 3-deuteriobicyclo[3.1.0]hex-2-ene in tetramethylsilane solution revealed a single resonance 1.88 ppm upfield from deuteriochloroform.

Preparation of Bicyclo[2.2.2]oct-2-ene-5,6-dicarboxylic Anhydride-d_1.—In a typical experiment, the method of Hammond and Warketin[13] was followed to prepare the adduct from 0.0730 g (0.744 mmol) of maleic anhydride and 0.0383 g (0.472 mmol) of 1,3-cyclohexadiene-d_1. Three recrystallizations from equal volumes of benzene and petroleum ether (bp 60–90°) gave 0.0278 g of adduct with a melting range of 142–146°. The pmr spectrum was examined, and the signals due to the olefinic, methine, and methylene protons were determined from the resonances centered at δ 6.24, 3.09, and 1.42, respectively. The dmr spectrum of a sample in benzene revealed three signals in the uncorrected ratio olefinic:methine:methylene of 1.00: 0.94 ± 0.02:2.11 ± 0.09.

Pyrolysis of 3-Deuteriobicyclo[3.1.0]hex-2-ene.—The 50-ml reaction zone of the pyrolysis apparatus was a 10-cm section of 30-mm Pyrex tubing butted to inlet and outlet tubes of 11-mm Pyrex tubing. A 7-mm Pyrex tube serving as a concentric thermocouple well ran the entire length of the apparatus, permitting measurement of temperature throughout the reactor zone and minimizing dead space in the inlet and outlet tubes. The pyrolysis apparatus was centered in a 30 cm × 33 mm tube furnace so that temperature was constant to ±1° across the reaction zone. Temperature was controlled with a Variac and measured using a chromel–alumel thermocouple. Dry nitrogen was employed as the carrier gas and the flow rate was regulated by means of a needle valve. The flow rate was measured with a soap bubble flow meter at room temperature and corrected to the temperature of the reaction zone.

The pyrolysis tube was washed with 15% ammonium hydroxide and air dried. Conditioning was achieved by pyrolysis of numerous samples of bicyclo[3.1.0]hex-2-ene under the conditions of the experiment. In a typical experiment, a sequence of nine 0.020-ml samples of 3-deuteriobicyclo[3.1.0]hex-2-ene were introduced into the system through a serum cap. The pyrolysate was condensed in a trap cooled in liquid nitrogen and transferred to storage ampoules using standard vacuum line techniques. In all cases, the recovery of material was close to quantitative.

The pyrolysate was analyzed by glpc on a 9.1 m × 2.0 mm 25% β,β′-oxydipropionitrile on a Chromosorb W column at 55°. Separation of the four components was achieved by preparative glpc on a 3.0 m × 4.5 mm 21% β,β′-oxydipropionitrile on Chromosorb P column at 50°. The pmr spectrum of 1,4-cyclohexadiene-d_1 was examined and the signals due to the olefinic and allylic protons were determined from the resonances centered at δ 5.72 and 2.68, respectively. In 1,3-cyclohexadiene-d_1, these resonances were centered at δ 5.88 and 2.18, respectively.

Registry No.—3-Deuteriobicyclo[3.1.0]hex-2-ene, 40387-26-6; lithium aluminum deuteride, 14128-54-2; bicyclo[3.1.0]hexan-3-one, 1755-04-0; 3-deuteriobicyclo[3.1.0]hexan-3-ol, 40387-28-8; methyl 3-(3-deuteriobicyclo[3.1.0]hexyl)xanthate, 40387-29-9; bicyclo[2.2.2]oct-2-ene-5,6-dicarboxylic anhydride-d_1, 40386-99-0; 1,4-cyclohexadiene-d_1, 40531-27-9; 1,3-cyclohexadiene-d_1, 40387-00-6.

Acknowledgment.—The authors thank the Research Corporation and the Merck Company for their generous support. Gregory D. Lyon provided much appreciated technical assistance.

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Synthesis of Murrayacine

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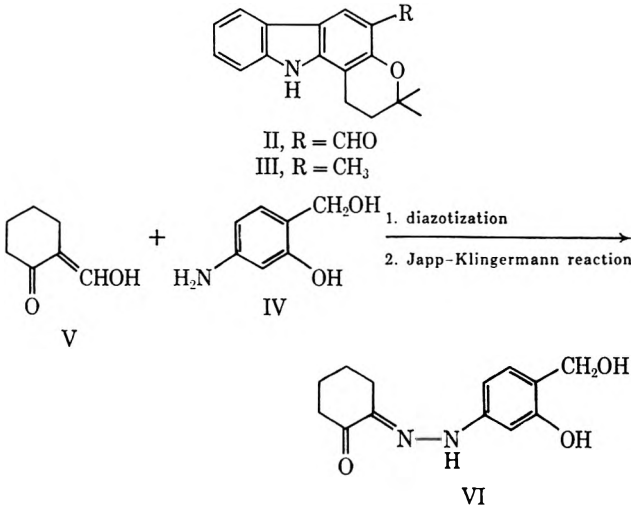
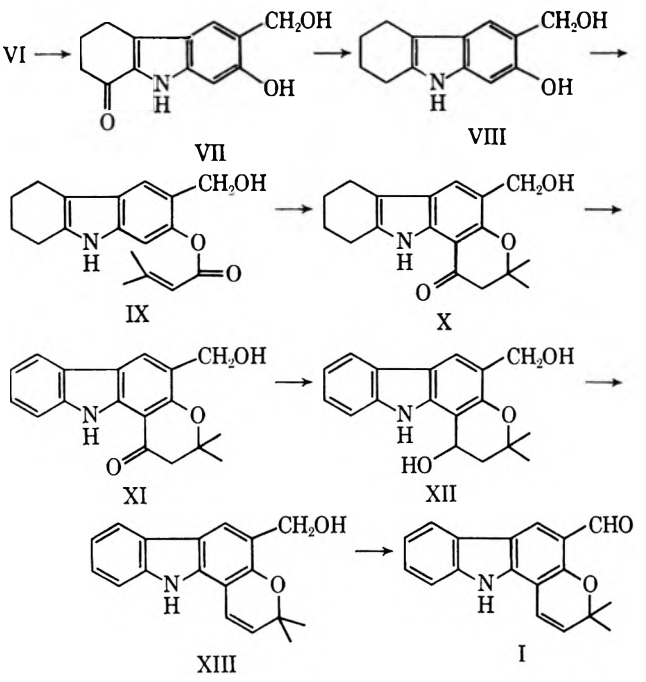
In previous communications[1,2] the structure of murrayacine (I), mp 244–245°, a carbazole alkaloid from the stem bark of *Murraya koenigii* Spreng, was reported. The structure was based on the identity of the reduction product of dihydromurrayacine (II) with dihydrogirinimbine (III). We now report the synthesis of I which confirms the structure.

The synthesis has been accomplished by preparation of a carbazole fragment with a potential aldehyde group and the incorporation of a 2,2-dimethyl-Δ^3-pyran ring into the phenolic substrate, following the method of Chakraborty, *et al.*[3]

4-Hydroxymethyl-3-hydroxyaniline (IV), mp 110°, on treatment with formylcyclohexanone (V) under Japp–Klingemann condition,[4] furnished cyclohexane-1,2-dione 4-hydroxymethyl-3-hydroxyphenylhydrazone (VI), mp 99–100°. The compound VI, on indolization with a mixture of glacial acetic acid and hydrochloric acid, furnished the indole-2-hydroxy-3-hydroxymethyl-8-oxo-5,6,7,8-tetrahydrocarbazole (VII), mp 113–115°. Wolff–Kishner reduction of the keto alcohol VII furnished 2-hydroxy-3-hydroxymethyl-5,6,7,8-tetrahydrocarbazole (VIII). The tetrahydrocarbazole VIII was acetylated with 2,2-dimethylacroylyl chloride at 5° in the presence of pyridine when the *O*-acyl compound IX, mp 147–150°, was obtained (ν_{max}^{Nujol} 1740 cm^{-1}). The phenol ester IX on Fries migration and subsequent treatment with hydrochloric acid furnished the chromanone X, mp 125°. The chromanone X was dehydrogenated with palladized charcoal when the indolochromanone XI, mp 160–162°, was obtained. The chromanone derivative was reduced with sodium borohydride when the alcohol XII, mp 114–115°, was obtained. Dehydrotosylation of the tosyl derivative XII in the presence of collidine furnished chromenoindole XIII, mp 199–200°, which had the characteristic uv spectrum [$\lambda_{max}^{ethanol}$ 226 mμ (log ε 4.60), 282.5 (4.57), 302 (4.58)] of a pyranocarbazole like girinimbine.





Oxidation of the chromenoindole XIII with active MnO_2[4] furnished murrayacine, which was identical with natural murrayacine in all respects (uv, ir, tlc, mixture melting point).

Experimental Section

All melting points are uncorrected. Petroleum ether had the boiling point 60–80° unless otherwise mentioned. For chromatography (tlc and column) silica gel supplied by Gouri Chemical, Calcutta, and alumina of M/s Sarabhai Merck, India, were used.

4-Hydroxymethyl-3-hydroxyaniline (IV).—The methyl ester of *p*-aminosalicyclic acid[3] (5 g) in THF (100 ml) was shaken with $LiAlH_4$ (1 g) for 4 hr. After decomposition of $LiAlH_4$ in the usual way and on removal of the solvent from the reaction mixture, a brown gum was obtained. This was dissolved in benzene and chromatographed over silica gel. The benzene–chloroform (1:1) eluent was collected, which furnished IV: mp 110°; yield 3 g; ν_{max}^{Nujol} 3440 (primary alcohol), 3360 (–NH–), 3260 (chelated –OH), 1620, 1600, 1500 cm^{-1} (aromatic).

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.00; H, 6.4; N, 10.41.

Cyclohexane-1,2-dione 4-Hydroxymethyl-3-hydroxyphenylhydrazone (VI).—A diazotized solution of IV (2 g) was gradually added over a period of 45 min to a solution of formylcyclohexanone (3 g) in methanol (35 ml) in the presence of an aqueous solution of sodium acetate (5 g in 10 ml), when a precipitate was obtained. The precipitate was washed acid free and on crystallization from petroleum ether–benzene furnished the hydrazone VI: mp 99–100°; yield 2 g; $\lambda_{max}^{ethanol}$ 380 mμ (log ε 4.46), 332 (2.89), 250 (4.44).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.80; H, 6.51; N, 11.25.

2-Hydroxy-3-hydroxymethyl-8-oxo-5,6,7,8-tetrahydrocarbazole (VII).—Phenylhydrazone (VI, 6.2 g) was boiled in a mixture of acetic acid and concentrated HCl (4 ml) for 2–3 min. The reaction mixture was poured into crushed ice and a solid was obtained after usual work-up. The crude product was dissolved in benzene and chromatographed on silica gel (20 g). The residue of the eluent which was crystallized from petroleum ether–benzene furnished the oxo compound VII: mp 113–115°; yield 1.5 g; $\lambda_{max}^{ethanol}$ 280 mμ (log ε 4.16), 230 (4.40); ν_{max}^{Nujol} 3520 (OH), 3410 (–NH–), 3300 (chelated –OH), 1700 (–CO–), 1610, 1515, 1460 cm^{-1} (aromatic).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.48; H, 5.64; N, 6.01.

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2-Hydroxy-3-hydroxymethyl-5,6,7,8-tetrahydrocarbazole (VIII).—Compound VII (1.2 g) dissolved in ethylene glycol (20 ml) was heated with hydrazine hydrate (99–100%, 1 g) and KOH (0.9 g) at 190° for 1 hr and under reflux for 3 hr. After chromatography of the reaction product on silica gel an oil was obtained which could not be crystallized. It responded to ferric reaction.

2-(2,2-dimethylacryloyloxy)-3-hydroxymethyl-5,6,7,8-tetrahydrocarbazole (IX).—Compound VIII in pyridine (5 ml) was treated with 2,2-dimethylacroylyl chloride (3 ml) at 5° and kept for 24 hr. The reaction product was poured into crushed ice containing dilute HCl. A solid product was obtained, which on crystallization from alcohol furnished IX, mp 147–150°. It was negative to ferric reaction, yield 1.3 g, ν_{max}^{Nujol} 1740 cm^{-1} (>C=O).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.01; H, 7.08; N, 4.60.

2,3,6,7,8,9-Hexahydro-5-hydroxymethyl-3,3-dimethyl-1-oxopyrano[3,2-*a*]carbazole (X).—Compound IX and powdered anhydrous $AlCl_3$ (2.5 g) were dissolved in freshly distilled nitrobenzene (25 ml) at 0–5° and kept at room temperature for 3 days. Then the product was poured into crushed ice (100 g) containing dilute HCl (25 ml) and extracted with ether. On removal of solvent from the extract a solid (0.7 g) was obtained which was crystallized from alcohol: mp 125°; $\lambda_{max}^{ethanol}$ 226 mμ (log ε 4.54), 282 (4.09), 290 (4.21).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.01; H, 7.08; N, 4.62.

2,3-Dihydro-5-hydroxymethyl-3,3-dimethyl-1-oxopyrano[3,2-*a*]carbazole (XI).—Chromanone (X, 600 mg) was dehydrogenated with Pd/C (10%, 50 mg) at 200° for 5 hr in a sealed tube in the presence of *p*-cymene. The mixture was cooled and filtered. Removal of *p*-cymene furnished a gum which was crystallized from benzene–chloroform and afforded 400 mg of XI: mp 160–162°; $\lambda_{max}^{ethanol}$ 228 mμ (log ε 4.65), 283 (4.08), 290 (4.23); ν_{max}^{Nujol} 3520 (primary alcohol), 3400 (–NH–), 1650 (>C=O), 1600, 1540, 1450 cm^{-1} (aromatic CH).

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.18; H, 5.82; N, 4.70.

2,3-Dihydro-1-hydroxy-5-hydroxymethyl-3,3-dimethyl-1*H*-pyrano[3,2-*a*]carbazole (XII).—Compound XI (300 mg) was dissolved in dry methanol (15 ml), and sodium borohydride (50 mg) was added. The solution was kept at room temperature for 20 hr. After the usual work-up a solid was obtained which on crystallization from benzene–petroleum ether yielded 200 mg of XII, mp 114–115°. The tosylate of XII, which was obtained by the usual technique, melted at 135–137°, $\lambda_{max}^{ethanol}$ 238 mμ (log ε 4.56), 288 (4.3), 330 (3.64).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.69; H, 6.40; N, 4.8.

5-Hydroxymethyl-3,3-dimethyl-3*H*-pyrano[3,2-*a*]carbazole (XIII).—The tosyl derivative of XII (80 mg) in collidine (3 ml) was boiled for 6 hr and then poured into crushed ice containing HCl (5 ml). A solid was obtained, which was filtered, washed, and recrystallized from alcohol, yielding 50 mg of XIII: mp 199–200°; $\lambda_{max}^{ethanol}$ 226 mμ (log ε 4.60), 282 (4.57), 302 (4.58); ν_{max}^{Nujol} 3251 (–NH–), 1675 (>C=O), 1640, 1601 (unsaturation and aromatic residue), 895, 740 cm^{-1} (substituted benzene derivative).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 11.46. Found: C, 77.35; H, 6.1; N, 11.5.

Synthetic Murrayacine (I).[5]—Compound XIII (30 mg) was dissolved in CCl_4 (5 ml) and stirred with active MnO_2 (200 mg) for 4 hr. After completion of the reaction the solution was filtered and the solvent was evaporated. The residue was dissolved in benzene and chromatographed on a silica gel column. The benzene–chloroform eluent furnished a solid which melted at 242–244° and was identical with natural murrayacine (uv, ir, mixture melting point).

Registry No.—I, 27300-29-4; IV, 40463-78-3; VI, 40463-79-4; VII, 40463-80-7; VIII, 40463-81-8; IX, 40463-82-9; X, 40463-83-0; XI, 40463-84-1; XII, 40463-85-2; XII tosylate, 40463-86-3; XIII, 27300-31-8; methyl ester of *p*-aminosalicylic acid, 4136-97-4; formylcyclohexanone, 823-45-0; dimethylacryloyl chloride, 3350-78-5.

(5) Since our work was completed, Kapil, *et al.*, reported a different synthesis of murrayacine at IUPAC Symposium on the Chemistry of Natural Products, Feb 1972, confirming the above structure.

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A Novel Synthesis of 2-Oxo-1,2,3,4-tetrahydrocarbazoles

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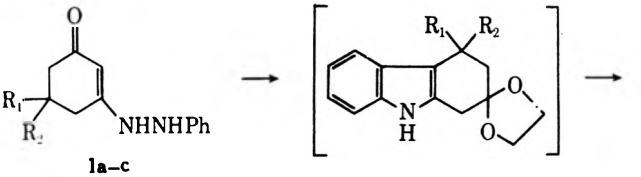
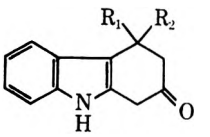
The synthesis of 2-ketotetrahydrocarbazole **2a** *via* a complex multistep sequence has been reported.[2] Based upon our need of this compound for a synthesis under investigation, we sought an alternate route for the preparation of **2a**. We were intrigued by the possibility that we might be able to alter the expected[3] direction of Fisher indole cyclization for 1,3-cyclohexanedione monophenylhydrazone **1a** to obtain **2a** directly. We wish to report that cyclization *via* the ethylene ketal does indeed give the desired 2-ketotetrahydrocarbazole as the only isolable cyclized product.

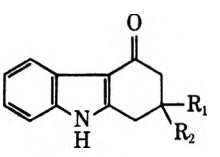
Reaction of hydrazone **1a** with *p*-toluenesulfonic acid in refluxing toluene gave, as expected,[3] the 4-oxo derivative **3a**. However, when the reaction was carried out in a mixture of ethylene glycol and toluene and the crude ketal hydrolyzed with aqueous sulfuric acid, the desired 2-keto derivative **2a** was obtained in 54% yield. In order to test the generality of the method, the two methylated phenylhydrazones **1b** and **1c** were subjected to this cyclization. The monomethyl derivative **1b** was smoothly converted to **2b** in 34% yield. Reaction of the dimethyl derivative **1c** with sulfuric acid–ethylene glycol–toluene, however, resulted in a complex mixture from which **2c** and **3c** were isolated in



1a–c



2a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = Me$
c, $R_1 = R_2 = Me$



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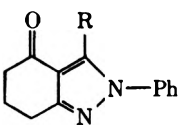


4a, R = H
b, R = Me

(1) (a) Alfred P. Sloan Foundation Fellow; (b) NDEA Title IV Fellow, 1971–1973.

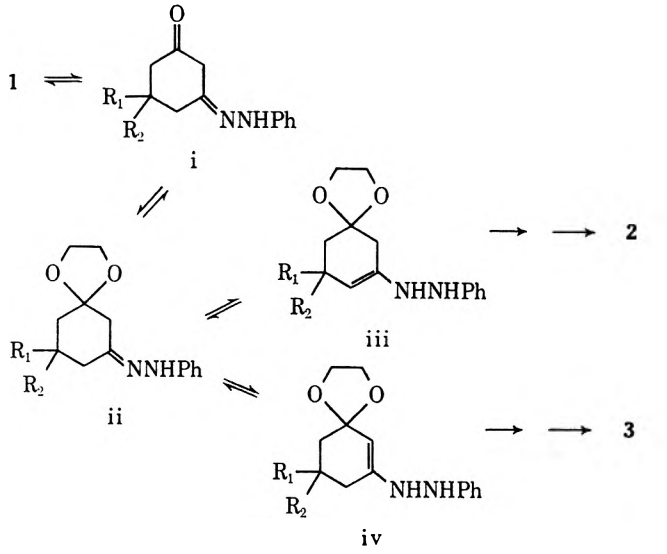
(2) H. J. Teuber and D. Cornelius, *Justus Liebigs Ann. Chem.*, **671**, 126 (1964).

(3) Cyclization of **1a** in aqueous sulfuric acid is reported to give the 4-keto derivative **3a**: G. R. Clemo and D. G. I. Felton, *J. Chem. Soc.*, 700 (1951).

6 and 5% yields, respectively. Cyclization of **1c** in the absence of glycol gave the expected 4-keto derivative in 38% yield.

We account for these results by assuming that rapid acid-catalyzed conversion of **1** to tautomer i is followed by ketalization to ii (vinylogous amides are generally resistant to ketalization under these conditions). Tautomerization of ii → iii should be more favorable then ii → iv for **1a** and **1b** on steric grounds, thus leading to **2a** and **2b** as the favored products. In the case of **1c**, however, tautomerization of ii to either iii or iv is energetically unfavorable, and thus both **2c** and **3c** are obtained in very low yield.

A brief examination of other ketalizing reagents revealed a different path for reaction of hydrazone **1b** with ortho esters. Thus, reaction of **1a** with triethyl orthoformate and *p*-toluenesulfonic acid (toluene, reflux) followed by hydrolysis of the diethyl ketal gave the tetrahydroindazole **4a**; similarly, triethyl orthoacetate led to the methyl analog **4b**. The assigned orientation of the carbonyl group in **4** adjacent to the pyrazole ring is based on the infrared carbonyl frequency at 1660 cm^{-1} and the ultraviolet absorption at



258 nm characteristic of 4-acyl-1-phenylpyrazoles.[4] The difference in orientation between the ortho ester and the ethylene glycol products suggests that the acylation of the vinylogous amide (either directly or *via* the adduct on the hydrazone nitrogen) by the ortho ester proceeds more rapidly than ketalization.

Experimental Section

2-Oxo-1,2,3,4-tetrahydrocarbazole (2a).—Cyclohexane-1,3-dione monophenylhydrazone[5] (10.10 g, 50 mmol) and *p*-toluenesulfonic acid (11.40 g, 60 mmol) were dissolved in 500 ml of toluene and 25 ml of ethylene glycol. The resulting mixture was refluxed with a Dean–Stark trap for 24 hr. The toluene solution was decanted from the reaction flask, washed with three 30-ml portions of saturated $NaHCO_3$ solution, dried ($MgSO_4$), and freed of solvent *in vacuo* to give 10.51 g of crude ketal. The ketal was dissolved in 165 ml of methanol containing 44 ml of 10% aqueous sulfuric acid and was stirred at room temperature for 6.5 hr. Water (100 ml) was added to the solution, and the resulting mixture was extracted with three 100-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 9.13 g of crude ketone. This material was purified by elution through a Florisil column (1 × 14 in.), the desired product being eluted in the first 100 ml of 1,2-dichloroethane. The resulting product (7.73 g) was crystallized from ethyl acetate–cyclohexane to give 7.24 g (78%) of **2a**, mp 125–129.5°. Two recrystallizations from ethyl acetate–cyclohexane afforded 4.99 g (54%) of **2a**: mp 131–133° (lit.[2] mp 131–133°); ir (Nujol) 3410, 1715 cm^{-1}; nmr ($CDCl_3$) δ 2.75 (m, 2 H), 3.10 (m, 2 H), 3.55 (s, 2 H), 7.30 (m, 4 H), 7.80 (s, 1 H).

4-Methyl-2-oxo-1,2,3,4-tetrahydrocarbazole (2b) was prepared by the procedure described for **2a** and purified by dry-column chromatography (1 × 22 in. alumina column, chloroform, R_f 0.28). The product, an oil, was obtained in 34% yield: ir (near) 3420, 1715, 1620, 1595 cm^{-1}; nmr ($CDCl_3$) δ 7.88 (s, 1 H), 7.30 (m, 4 H), 3.55 (s, 2 H), 2.68 (m, 3 H), 1.34 (d, 3 H); mass spectrum *m/e* 199 (molecular ion).

The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethanol, mp 221–223°.

Anal. Calcd for $C_{19}H_{17}N_5O_4$: C, 60.14; H, 4.53; N, 18.46. Found: C, 60.23; H, 4.61; N, 18.29.

Attempted Cyclization of 1c.—A mixture of 4.60 g (20 mmol) of phenyl hydrazone **1c**, 2.12 g (21 mmol) of concentrated sulfuric acid, 10 ml of ethylene glycol, and 250 ml of toluene was refluxed with a Dean–Stark trap for 24 hr. The hot toluene solution was decanted from the reaction vessel, and the residue was washed with 30 ml of hot chloroform. The toluene and chloroform solutions were combined, washed with three 40-ml portions of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The crude product (1.27 g) was chromatographed on a 1.5 × 20 in. silica gel dry column, using chloroform to elute. The band having R_f ~0.2 was removed and the crude ketone **3c** obtained was further purified by preparative tlc (silica gel, 1:4 ethyl acetate–benzene, R_f 0.17) and recrystallization (CH_2Cl_2–CCl_4) to give 190 mg (5%) of **3c**: mp 200–201.5°; ir (KBr) 3250, 1615 cm^{-1}; nmr ($CDCl_3$) δ 1.13 (s, 6), 2.42 (s, 2), 2.80 (s, 2), 7.12 (m, 3), 8.2 (s, 1), 9.08 (s, 1); mass spectrum *m/e* 213 (molecular ion).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.82; H, 7.10; N, 6,57. Found: C, 78.68; H, 6.83; N, 6.33.

The dry column band having R_f ~0.35 was removed to give 440 mg of crude ethylenedioxy ketal. This ketal was dissolved in a mixture of tetrahydrofuran (20 ml) and 10% aqueous sulfuric acid (20 ml) and was stirred for 6 hr at room temperature. The resulting solution was extracted with three 30-ml portions of chloroform. The combined extracts were washed with 20 ml of saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated to give 355 mg of product. Purification by preparative tlc (silica gel, 1:4 ethyl acetate–benzene, R_f 0.36) afforded 260 mg (6%) of **2c** as an oil: ir (neat) 3400, 1705 cm^{-1}; nmr ($CDCl_3$) δ 1.48 (s, 6 H), 2.58 (s, 2 H), 3.52 (s, 2 H), 7.12 (m, 3 H), 7.68 (m, 1 H), 8.08 (s, 1 H); mass spectrum *m/e* 213 (molecular ion).

3-Methyl-2-phenyl-4-oxo-4,5,6,7-tetrahydro(2*H*)indazole (4b).—A solution of 1.14 g (6 mmol) of *p*-toluenesulfonic acid was dissolved in 100 ml of toluene and distilled until 20 ml of toluene and water had been collected. Cyclohexane-1,3-dione monophenylhydrazone (1.01 g, 5 mmol) and triethyl orthoacetate (5 ml) were then added, and the resulting solution was refluxed for 29 hr. The cooled solution was washed with three 30-ml portions of saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo* to give 1.85 g of crude diethyl ketal. This ketal was hydrolyzed by stirring with THF (20 ml) and 10% H_2SO_4 (20 ml) for 44 hr at room temperature. The mixture was then extracted with three 25-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to give 1.28 g of crude product. Purification by preparative tlc (silica gel, 1:4 ethyl acetate–benzene, R_f 0.2) and recrystallization from petroleum ether (bp 30–60°) afforded 325 mg (29%) of **4b**: mp 98–99°; ir (KBr) 1660, 1590, 1555 cm^{-1}; nmr ($CDCl_3$) δ 2.30 (m, 2 H), 2.68 (m, 2 H), 2.75 (s, 3 H), 3.00 (t, 2 H), 7.65 (s, 5 H).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.30; H, 6.25; N, 12.38. Found: C, 74.26; H, 6.30; N, 12.31.

Registry No.—**1a**, 26593-16-8; **1b**, 39554-99-9; **1c**, 26593-17-9; **2a**, 40429-00-3; **2b**, 40429-01-4; **2b** 2,4-dinitrophenylhydrazone, 40429-02-5; **2c**, 40429-03-6: **3c**, 40429-04-7; **4b**, 23894-51-1.

(4) For example, Sadtler reports the infrared and ultraviolet maxima for methyl 5-methyl-1-phenyl-4-pyrazolyl ketone as 1660 cm^{-1} and 252 nm, respectively.

(5) J. B. Hester, *Chem. Abstr.*, **72**, 90425f (1970).

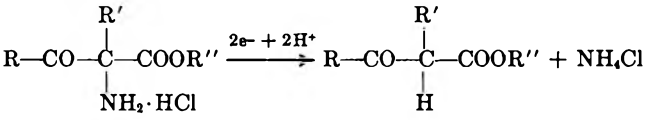
See Editorial, *J. Org. Chem.*, 37, No. 19, 4A (1972).

A Novel Electrolytic Deamination. Synthesis of β-Keto Esters[1]

Summary: An electrolytic deamination of the α-acylamino acid esters afforded the corresponding β-keto esters in good yields.

Sir: In the course of electrochemical studies of amino acids, we have reported the electrolytic cleavage of the N–S bond of *N*-tosyl amino acids and peptides,[2] the C–S bond of *S*-benzylcysteine,[3] and the C–S bond of *S*-methylmethionine.[4]

In this communication, an electrolytic reductive cleavage of the C–N bond of α-acylamino acid derivatives is described. We have carried out the electrolysis of α-acylamino acid esters[5] to produce the corresponding β-hydroxy amino acid esters. However, the yield of the resulting amino acids was too low for a practical preparation, but the β-keto esters due to the deamination were obtained in good yields. The electrolytic reduction proceeds *via* a two-electron change resulting in C–NH_2 bond cleavage according to the following scheme.



The electrolysis was carried out as follows. For example, α-benzoylglycine ethyl ester hydrochloride (1 g, 4.1 mmol) dissolved in a mixture of 50% aqueous methanol (20 ml) and concentrated hydrochloric acid (0.5 ml) was placed in a cathodic compartment using a mercury pool electrode (15 cm^2). The anodic compartment consisted of 50% aqueous methanol, a few drops of concentrated hydrochloric acid, and a platinum electrode. The anode and cathode compartments were separated by a pottery membrane. A dc voltage of about 10 V was applied until a current of 0.45 A flowed. The current was held constant, and the electrolysis was continued for 31 min at 7° with stirring (the current density being 0.03 A/cm^2 at the cathode). Reaction was complete with 87% current efficiency. The cathodic mixture was evaporated *in vacuo*, and the resulting products were extracted with chloroform. The chloroform solution was washed with water, dried, and evaporated under reduced pressure. Ethyl benzoylacetate was obtained by the vacuum distillation, yield 0.75 g (90%). The compound obtained was homogeneous by glc criterion and was identified by ir and nmr spectra, in which the amino group disappeared, and with an authentic specimen. On the other hand, the aqueous solution separated from the keto ester was neutralized with sodium bicarbonate solution and extracted with ethyl acetate. To the dried ethyl acetate solution was added HCl–ether to precipitate the amino acid ester hydrochloride. The resulting β-hydroxyphenylalanine ethyl ester hydrochloride was obtained in 9% yield and agreed with an authentic specimen.

In the same process, various β-keto esters which are of interest and useful as intermediates were easily obtained from the corresponding α-acylamino acid esters. These results are summarized in Table I.

Table I

Formation of β-Keto Esters by Electrolytic Deamination

R	R′	R″	Current density, A/cm^2	Yield, %	Current efficiency, %
Ph	H	Et	0.03	90	87
Ph	Et	Me	0.03	80	80
3,4-Methylenedioxyphenyl	Me	Me	0.02	82	80
$PhCH_2$	H	Et	0.03	85	60
CH_3	H	Et	0.03	35	25
$CH_3CH_2CH_2$	H	Et	0.03	40	40

Aromatic β-keto esters were generally obtained in high yields. In aliphatic compounds, however, the yield of the β-keto esters was low, and the β-hydroxyamino acid esters were afforded in considerable yields (*ca.* 50%).

Although the same process as described above was carried out using other electrodes, the yield was unsatisfactory. With zinc and nickel cathodes, methyl benzoylacetate was obtained from α-benzoylglycine methyl ester hydrochloride in 40 and 25% yields respectively.

The deamination occurred also in the case of α-amino ketones.[5] For example, acetophenone was obtained from phenacylamine hydrochloride by reduction with a mercury cathode in 75% yield.

Thus, the deamination proceeds easily under mild conditions, and this method is a new synthetic methode for β-keto esters. The study is currently in progress and will be reported elsewhere in the near future.

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(1) Synthesis of Amino Acids and Related Compounds. 5. Part 4: K. Matsumoto, M. Suzuki, and M. Miyoshi, *J. Org. Chem.*, **38**, 2094 (1973).

(2) K. Okumura, T. Iwasaki, M. Matsuoka, and K. Matsumoto, *Chem. Ind. (London)*, 929 (1971); T. Iwasaki, K. Matsumoto, M. Matsuoka, T. Takahashi, and K. Okumura, *Bull. Chem. Soc. Jap.*, **46**, 852 (1973).

(3) T. Iwasaki, K. Matsumoto, M. Matsuoka, and M. Miyoshi, *Bull. Inst. Chem. Res. Kyoto Univ.*, **50**, 220 (1972).

(4) T. Iwasaki, M. Miyoshi, M. Matsuoka, and K. Matsumoto, manuscript in preparation.

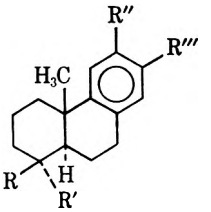
(5) M. Suzuki, T. Iwasaki, K. Matsumoto, and K. Okumura, *Syn. Commun.*, **2**, 237 (1972).

Reductive Backbone Rearrangements in Diterpene Acids[1]

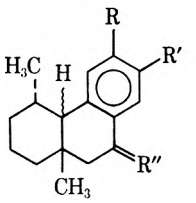
Summary: Reaction of dehydroabietic acid and podocarpic acid methyl ether derivatives with phosphoryl chloride affords 18-nor-5,10-freidoabietatrienes and podocarpatrienes, the result of decarboxylation, rearrangement, and reduction.

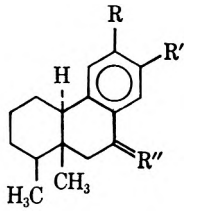
Sir: It was recently reported that reaction of either 12-methoxypodocarpa-8,11,13-trien-19-oic acid (**1**), abieta-8,11,13-trien-18-oic acid (**2**), or the corresponding acid chlorides and esters with phosphoryl chloride or polyphosphoric acid gave as major reaction products octahydrophenanthrenes **3** and **4**, respectively, plus derived naphthalenes and phenanthrenes.[2] These structural assignments were based on the coincidence of melting points of the dimethylphenanthrene and its picrate derived from **3** with those of 4,10-dimethylphenanthrene[3] and its picrate, combined with the observation that this phenanthrene had ". . . . an nmr spectrum identical to those (that) recorded for 4,10-dimethylphenanthrene."[2] However, the chemical shifts of the aromatic methyl signals for 4,10-dimethylphenanthrene are reported as δ 2.72 and 3.14,[3] while those of the dimethylphenanthrene described in ref 2 are δ 2.80 and δ 3.02. Consideration of the chemical shift data reported for other dimethylphenanthrenes,[3] and the course of carbonium ion rearrangements in a similar system,[4] indicates that more plausible structures for these reaction products are those of an 18- or 19-nor-5,10-freido-12-methoxypodocarpa-8,11,13-triene (**5**), derived from acid **1**, and the corresponding abietatriene (**6**), derived from acid **2**.

Repetition of the reactions of acids **1** and **2** with phosphoryl chloride gave the products described by Baguley, *et al.*,[2] and abieta-8,11,13-trien-19-oic acid (**7**)[5] under these conditions afforded the same hydrocarbon as its 4 epimer (**2**). The methoxyoctahydrophenanthrane derived from acid **1** (*i.e.*, **3** or **5**) was oxidized with chromic acid to the oily ketone:[6,7] nmr ($CHCl_3$) δ 0.92 (s, 3 H), 0.92 (d, J = 5 Hz, 3 H), 2.08 (d, J = 17 Hz, 1 H), 2.58 (m, $w_{1/2}$ 14 Hz, 1 H), 2.90 (d, J = 17 Hz, 1 H), 3.55 (s, 3 H), 6.48 (m, 2 H), 7.55 (d, J = 8 Hz, 1 H); ir 5.99 μ; uv $\lambda_{max}^{CH_3OH}$ 281 nm (log ϵ 4.17); M^+ (70 eV) 258. The presence of the benzylic proton as a broad multiplet is characteristic of an axial proton coupled to two adjacent protons,[8] and is consistent with structure **8**, but not with structure **9** in which this proton would appear as a doublet. It is assumed that the angular methyl group will migrate stereospecifically and the small coupling constant (5 Hz) for the secondary methyl indicates that this group is



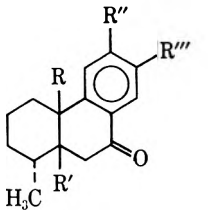
1, R = CO_2H; R′ = CH_3; R″ = OCH_3; R‴ = H
2, R = CH_3; R′ = CO_2H; R″ = H; R‴ = $(CH_3)_2CH$
7, R = CO_2H; R′ = CH_3; R″ = H; R‴ = $(CH_3)_2CH$



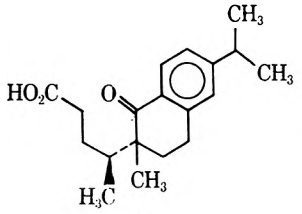


3, R = OCH_3; R′ = H; R″ = H_2
4, R = H; R′ = $(CH_3)_2CH$; R″ = H_2
9, R = OCH_3; R′ = H; R″ = O

5, R = OCH_3; R′ = H; R″ = H_2
6, R = H; R′ = $(CH_3)_2CH$; R″ = H_2
8, R = OCH_3; R′ = H; R″ = O
12, R = H; R′ = $(CH_3)_2CH$; R′ = O



10, R, R‴ = H; R′ = CH_3; R″ = OCH_3
11, R = CH_3; R′, R″ = H; R‴ = $(CH_3)_2CH$



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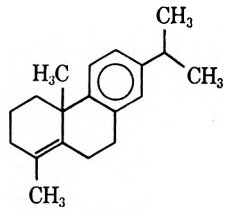

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equatorial.[9] Although the stereochemistry depicted in **8** is that predicted on mechanistic grounds,[4] a cis ketone, with a nonsteroidal conformation (**10**), would show the same spectral properties. The CD curve of the ketone from oxidation of **5** shows a simple negative Cotton effect, θ_{316} − 4620, essentially antipodal to that of the 7 ketone derived from methyl *O*-methylpodocarpate,[10] and in accordance with the predictions of the inverse octant rule.[11] The cis ketone **11**,[12] with a nonsteroidal conformation, shows a multiple Cotton effect θ_{370} − 82, θ_{353} − 132, θ_{322} − 2700, θ_{296} − 5800 as should also a ketone of structure **10**.

Oxidation of the hydrocarbon obtained from acids **2** and **7** gave the oily ketone **12**: ir 5.94 μ; uv $\lambda_{max}^{CH_3OH}$ 258 nm (log ϵ 4.20); M^+ (70 eV) 270. The nmr spectrum of **12** was identical with that of ketone **8**, with the exception of the signals associated with the aromatic ring.

(1) Studies on Resin Acids. VIII. For part VII see J. W. Huffman, *J. Org. Chem.*, **37**, 17 (1972).

(2) B. C. Baguley, R. C. Cambie, W. R. Dive, and R. N. Seelye, *Aust. J. Chem.*, **25**, 1271 (1972).

(3) A. Regnault and P. Canonne, *Tetrahedron*, **25**, 2349 (1969).

(4) H. W. Whitlock and L. E. Overman, *J. Amer. Chem. Soc.*, **93**, 2247 (1971).

(5) J. W. Huffman, *J. Org. Chem.*, **35**, 3154 (1970).

(6) (a) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958); (b) E. Wenkert and J. W. Chamberlin, *ibid.*, **81**, 688 (1959).

(7) All new compounds were characterized by ir, uv, and nmr spectroscopy. Their purity was monitored by glc and/or tlc and the molecular formula confirmed by mass spectrometry.

(8) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy," Holden-Day, San Francisco, Calif., 1964 pp 79–82.

(9) F. Johnson, N. A. Staskousky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965).

(10) A. J. Bose, M. S. Manhas, and R. C. Cambie, *J. Org. Chem.*, **30**, 501 (1965).

(11) G. Snatzke in G. Snatzke, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Heyden and Sons, London, 1967, pp 208–223.

(12) J. W. Huffman, *J. Org. Chem.*, **35**, 478 (1970).

There was also obtained from this oxidation a keto acid (**13**), characterized as the methyl ester [nmr ($CDCl_3$) δ 0.96 (d, J = 6 Hz, 3 H), 1.08 (s, 3 H), 1.18 (d, J = 7 Hz, 6 H), 2.70 (t, J = 6 Hz, 2 H), 3.32 (s, 3 H), 6.60 (br s, 1 H), 6.70 (br d, J = 7 Hz, 1 H), 7.49 (d, J = 7 Hz, 1 H); ir 5.97, 5.84 μ; uv $\lambda_{max}^{CH_3OH}$ 261 nm (log ϵ 4.14); M^+ (70 eV) 316], a substance readily derived from **6** by oxidation at C-10, followed by dehydration and further oxidation, but impossible to rationalize in terms of structure **4**.

It is quite apparent that the structural assignments of Baguley, *et al.*,[2] are incorrect and that those compounds assigned structures **3** and **4** (structures **14** and **15** of ref 2) have in fact structures **5** and **6**, and that the structures of all of the other compounds obtained from these reactions and reported by these authors should be revised accordingly.

The mechanistic path which gives rise to these compounds is probably essentially that suggested by the New Zealand group;[2] however, the initial carbonium ion formed at C-4 must rearrange in a stepwise fashion *via* intermediates similar to those suggested by Whitlock.[4] In agreement with this hypothesis it was found that 18-norabieta-4,8,11,13-tetraene (**14**)[12] gave hydrocarbon **6** on reaction with phosphoryl chloride, although the reaction proceeds somewhat more slowly than with acids **2** and **7**. It was also found that the methyl esters of acids **2** and **7** were smoothly converted to **6** with boron tribromide in methylene chloride at 5°. Although intermolecular hydride transfer reactions involving carbonium ion intermediates are known, they are not common under the relatively mild conditions of these reactions.[13]

Although the examples of the reductive rearrangement reactions cited above are all in the diterpene series, these should prove to be general reactions of appropriately constituted carbonium ions. A detailed investigation of the scope and limitations of these reactions is in progress.

Acknowledgments.—The spectropolarimeter and mass spectrometer used in this work were obtained through National Science Foundation Research Instrument Grants.

(13) (a) R. C. Fuson and L. L. Alexander, *J. Amer. Chem. Soc.*, **58**, 1745 (1936), and earlier papers in this series. (b) J. W. Huffman and J. J. Starnes, *J. Org. Chem.*, **37**, 487 (1972). (c) P. D. Bartlett and J. D. McCollum, *J. Amer. Chem. Soc.*, **78**, 1441 (1956), have reported the use of the triphenylmethylcarbonium ion as a hydride acceptor in the oxidntion of alcohols under mild conditions. See also M. P. Doyle, D. J. DeBruyn, and D. J. Scholten, *J. Org. Chem.*, **38**, 625 (1973), and references therein.

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Synthesis of the Natural Isomer of a Tetrahomoterpene Alcohol Obtained From the Codling Moth

Summary: The synthesis of the four possible stereoisomers of 7-methyl-3-propyl-2,6-decadien-1-ol, a tetrahomoterpene isolated from the codling moth, has been achieved, and spectroscopic and gas chromatographic comparison have established the natural material as the 2*Z*,6*Z* isomer.

Sir: We have recently described[1] the synthesis of (2*Z*,6*E*)-7-methyl-3-propyl-2,6-decadien-1-ol, a tetrahomoterpene alcohol reported[2] to be a pheromone of the codling moth (*Laspeyresia pomonella* L.). Spectroscopic and gas chromatographic comparison established that our synthetic material differed from the natural product; on the basis of nmr chemical shift data and relative retention times upon glpc, we suggested that the natural isomer had the 2*E*,6*Z* configuration. We now report the synthesis of the remaining three isomers of this compound, and the finding that the natural product has the 2*Z*,6*Z* configuration.

The synthesis of the 2*E*,6*Z* (**5**) and the 2*Z*,6*Z* (**7**) isomers proceeded from a common intermediate, the acetylenic ester **3**.[3] This ester was prepared by coupling the allylic bromide **1** with propargyl Grignard, followed by carbethoxylation of the lithio derivative of the acetylene **2**[4] with ethyl chloroformate.[1] Reduction of **3** with lithium aluminum hydride–sodium methoxide (2:1) in refluxing tetrahydrofuran (THF), and iodination of the intermediate alanate (0.5 hr, −78°) after consumption of the excess hydride with ethyl acetate, afforded the iodo alcohol **4**.[5,6] The iodo alcohol coupled cleanly with a fourfold excess of lithium di-*n*-propylcuprate in ether (4 hr, −78°)[7] to give the 2*E*,6*Z*-decadienol **5** in 50% overall yield from **3**.

The stereospecific cis addition of a propyl group and hydrogen to the carbon–carbon triple bond in **3** was effected by treatment with 2 equiv of lithium di-*n*-propylcuprate in THF (5 hr, −78°),[8] followed by

(1) (a) S. B. Bowlus and J. A. Katzenellenbogen, *Tetrahedron Lett.*, 1277 (1973). (b) For another synthesis, see M. P. Cooke, *ibid.*, 1281 (1973).

(2) (a) L. M. McDonough, D. A. George, B. A. Butt, J. M. Ruth, and R. Hill, *Science*, **177**, 177 (1972). (b) The original stereochemical assignment of 2*Z*,6*E*[2a] was based on the nmr chemical shift of the 7-methyl group and on the glpc elution order of a mixture of 7-methyl-3-propyl-2,6-decadien-1-ol isomers. From the results of this study it appears that the misassignment was due to the choice of inappropriate model systems for chemical shift comparison and the unsubstantiated composition and identity of the mixture of isomers. (c) More recent results (L. M. McDonough, personal communication) have established that both natural 3-propyl-7-methyl-2,6-decadien-1-ol and the mixture of four stereoisomers[2a] are inactive as a pheromone in laboratory and field trials. The physiological significance of this substance is thus unknown. On the basis of electroantennogram studies, (8*E*,10*E*)-8,10-dodecadien-1-ol has been proposed to be a pheromone of the codling moth [W. Roelofs, A. Comeau, A. Hall, and G. Milicevic, *Science*, **174**, 297 (1971)]; synthetic material is equally attractive as the compound isolated from the codling moth [C. Descoins and C. A. Henrick, *Tetrahedron Lett.*, 2999 (1972)].

(3) Structural assignments for all new compounds were fully supported by nmr and ir spectroscopy, mass spectrometry, and combustion analysis and/or high resolution mass spectrometry.

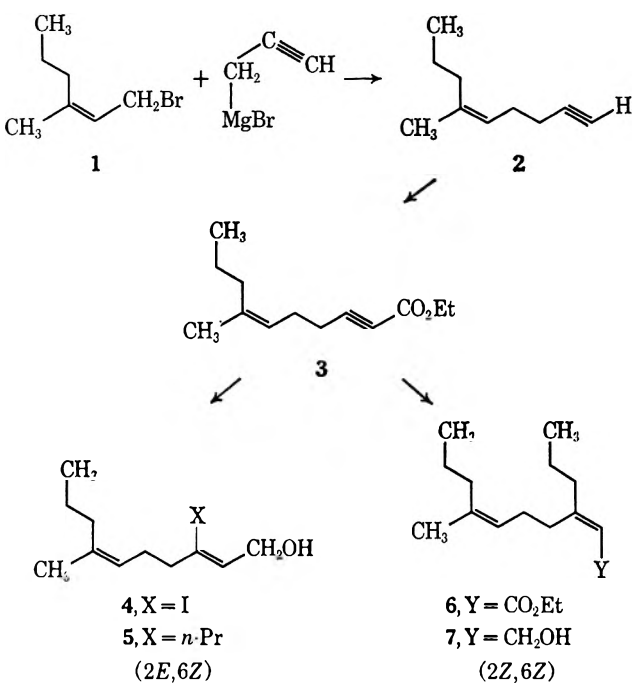
(4) An undetermined amount of the allene corresponding to **2** is found in this reaction, but may be conveniently removed by chromatography following the carbethoxylation reaction.

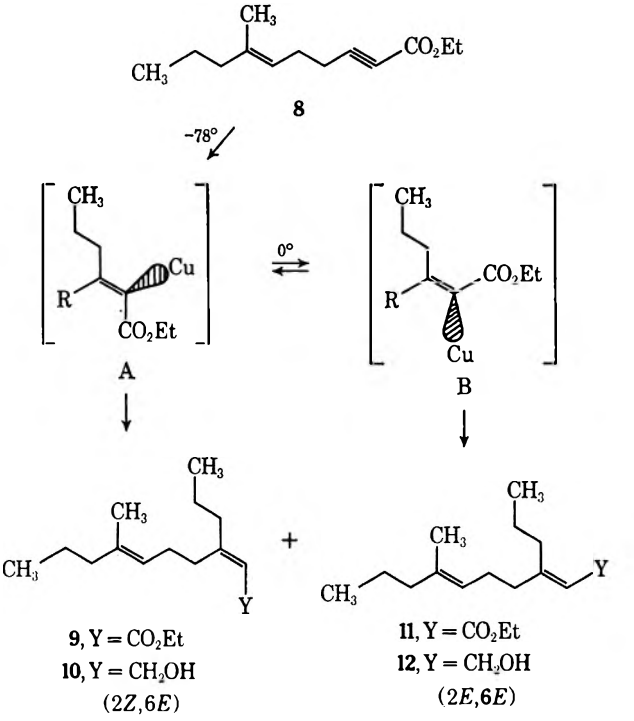
(5) The reaction gives 10–15% 2-iodo alcohol, which may be removed by careful preparative thin layer chromatography.

(6) The reduction–iodination sequence has previously been applied to propargylic alcohols, to give selectively either the 2-iodo or the 3-iodo allylic alcohols: E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 4245 (1967); E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *ibid.*, **90**, 5618 (1968); E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *ibid.*, **91**, 4318 (1969); E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, *ibid.*, **92**, 6314 (1970); E. J. Corey; J. A. Katzenellenbogen, S. A. Roman, and N. W. Gilman, *Tetrahedron Lett.*, 1821 (1971). This application extends the scope of starting materials to propargylic esters.

(7) The coupling of iodo allylic alcohols with lithium dialkylcuprates is described in the references in ref 6.

(8) (a) E. J. Corey and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 1851 (1969); (b) J. B. Siddall, M. Biskup, and J. H. Fried, *ibid.*, **91**, 1853 (1969); (c) J. F. Normant, *Synthesis*, 63 (1972); (d) ref 1a.





quenching with prechilled ethanol at −78°. Aluminum hydride reduction of ester **6** furnished the 2*Z*,6*Z* isomer **7** in 43% overall yield from **3**.

The isomeric alcohols **5** and **7** are spectroscopically indistinguishable (nmr, ir, mass spectra); both show the allylic methyl resonance at δ 1.65. As the corresponding signal in the natural product is reported to be at δ 1.66, and that of the 2*Z*,6*E* isomer at 1.57, this confirms our previous suggestion that the natural material has the 6*Z* configuration.[1a]

Inasmuch as the synthesis of the isomers **5** and **7** established the *Z* configuration at C-6, we felt that it was not profitable to undertake a stereoselective synthesis of the 2*E*,6*E* isomer **12**. For the purpose of glpc comparison, however, we prepared this material as a mixture with the 2*Z*,6*E* isomer **10** by the convenient method described below.

Conjugate addition of lithium di-*n*-propylcuprate to the acetylenic ester **8** at −78° in THF gives exclusively the adduct with the stereochemistry shown in A.[1] Although this enolate is configurationally stable at −78° in THF,[8a] it undergoes facile isomerization at 0°. The mixture of esters **9** and **11** was thus prepared by quenching the enolates A and B after equilibration at 0° for 0.5 hr. The alcohols **10** and **12** were obtained as a mixture after aluminum hydride reduction (overall yield of mixture 57% from **8**).

Glpc analysis of the four isomers on OV-1 established their elution order as 2*Z*,6*Z*, 2*E*,6*Z*, 2*Z*,6*E*, and 2*E*,6*E* (**7**, **5**, **10**, and **12**) with relative retention times of 0.91, 0.96, 1.00 and 1.04. On the basis of the report that the natural product cochromatographed with the second component in a mixture of all possible isomers prepared by a nonselective synthesis,[2a] it was believed that the natural product had the 2*E*,6*Z* configuration.

Subsequent glpc comparisons of our synthetic isomers with the naturally occurring isomer on Carbowax 20M has shown that the natural material cochromatographs with the 2*Z*,6*Z* isomer (**7**).[9] Comparison of our samples with the four-isomer mixture prepared by McDonough[2a,9] indicates that the 2*Z*,6*Z* isomer does indeed elute as the second component; the first peak in the chromatogram of the mixture,[2a] which was originally thought to be the 2*Z*,6*Z* isomer, is actually an unidentified impurity. The third peak consists of the mixed isomers (2*Z*,6*E* and 2*E*,6*Z*), which are not resolved on this phase, and the fourth peak is the 2*E*,6*E* isomer.

It is concluded that the natural material, obtained from the codling moth, is (2*Z*,6*Z*)-7-methyl-3-propyl-2,6-decadien-1-ol (**7**).

(9) These comparisons were carried out by Dr. L. M. McDonough, Agricultural Research Service, Yakima, Wash. Dr. McDouough's cooperation is gratefully acknowledged.

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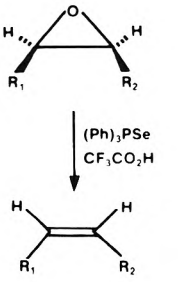
Convert Epoxides to Olefins Stereospecifically

Clive and Denyer[1] have recently demonstrated that triphenylphosphine selenide and trifluoroacetic acid provide a highly effective combination for the stereospecific conversion of epoxides to olefins in good yield. Experimentally, the addition of trifluoroacetic acid (1 equiv) to a solution of epoxide and triphenylphosphine selenide in methylene chloride results in a 53-73% conversion of epoxide to olefin after 1-2.5 hours.



1. D.L.J. Clive and C.V. Denyer, *Chem. Commun.*, 253 (1973).

18,013-0 Triphenylphosphine selenide

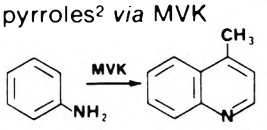
25g 8.50
100g 28.00

MVK

(Methyl vinyl ketone)

$CH_3CCH{=}CH_2$

Quinolines[1] and pyrroles[2] *via* MVK



1. K.N. Campbell and L.J. Schaffner, *J. Amer. Chem. Soc.*, **67**, 86 (1945).
2. A.H. Jackson *et al.*, *Tetrahedron Lett.*, 921 (1962).

HETEROCYCLES

Higher homologs of ketones *via* hydroboration

KETONES

$R_3B \xrightarrow{MVK} RCH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$

A. Suzuki *et al.*, *J. Amer. Chem. Soc.*, **89**, 5708 (1967).

CAROTENOIDS

MVK is used in a key step in Isler's synthesis of vitamin A.

$$HC{\equiv}CH \xrightarrow[Na,\ NH_3]{MVK} CH_2{=}CHC(OH)(CH_3)C{\equiv}CH$$

O. Isler *et al.*, *Helv. Chim. Acta*, **30**, 1911 (1947).

METAL COMPLEXES

$CH_3\overset{O}{\overset{\|}{C}}CH{=}CH_2 \cdot Fe(\pi\text{-}C_5H_5)(CO)_2$

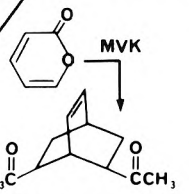
MVK complexes with Ir, Re, Fe, Ni, Pt.

POLYMERS

- Olefins $\xrightarrow{MVK}$ carbonyl-containing copolymers
- Pulp and textile grafting
- Lamination of synthetic film

DIELS-ALDER reactions

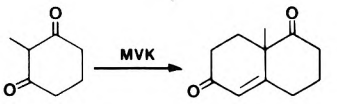
MVK as a reactive dienophile



H.E. Zimmerman and R.M. Paulfer, *J. Amer. Chem. Soc.*, **85**, 1514 (1960).

STEROIDS

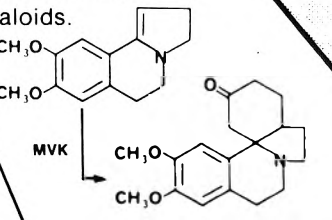
Annelation with MVK through carbanions[1] or enamines[2] is of great value in steroid synthesis.



1. S. Ramachandran and M.S. Newman, *Org. Syn.*, **41**, 38 (1961).
2. G. Stork *et al.*, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

ALKALOIDS

Annelation of an endocyclic enamine is a key step in the synthesis of *Erythrina* alkaloids.



R.V. Stevens and M.P. Wentland, *Chem Commun.*, 1104 (1968)

M8750-9	**Methyl vinyl ketone,** stabilized with 1% hydroquinone **(MVK)**	**100g**	**7.00**		
E5130-9	**Ethyl vinyl ketone**	**8.4g†**	**7.75**	**25g**	**19.50**

† Designates molar unit

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